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# Interleukin-receptor antagonist and tumour necrosis factor inhibitors for the primary and secondary prevention of atherosclerotic cardiovascular diseases (Review)

Martí-Carvajal AJ, Gemmato-Valecillos MA, Monge Martín D, Dayer M, Alegría-Barrero E, De Sanctis JB, Parise Vasco JM, Riera Lizardo RJ, Nicola S, Martí-Amarista CE, Correa-Pérez A

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[Intervention Review]

# Interleukin-receptor antagonist and tumour necrosis factor inhibitors for the primary and secondary prevention of atherosclerotic cardiovascular diseases

Arturo J Martí-Carvajal[1,2,3], Mario A Gemmato-Valecillos[4], Diana Monge Martín[5], Mark Dayer[6,7], Eduardo Alegría-Barrero[5], Juan Bautista De Sanctis[8], Juan Marcos Parise Vasco[1], Ricardo J Riera Lizardo[9], Susana Nicola[1], Cristina Elena Martí-Amarista[10], Andrea Correa-Pérez[5,11]

[1]Universidad UTE, Facultad de Ciencias de la Salud Eugenio Espejo, Centro Asociado Cochrane Ecuador, Centro de Investigación en Salud Pública y Epidemiología Clínica (CISPEC), Quito, Ecuador. [2]Facultad de Medicina (Centro Cochrane Madrid), Universidad Francisco de Vitoria, Madrid, Spain. [3]Cátedra Rectoral de Medicina Basada en la Evidencia, Universidad de Carabobo, Valencia , Venezuela. [4]Icahn School of Medicine at Mount Sinai/ NYCHH Elmhurst Hospital Center, 79-01 Broadway, Elmhurst, New York 11373, USA. [5]Faculty of Medicine, Universidad Francisco de Vitoria, Madrid, Spain. [6]Cardiovascular Research Institute, Mater Private Network, Dublin, Ireland. [7]Faculty of Health, University of Plymouth, Plymouth, UK. [8]Institute of Molecular and Translational Medicine, Palacky University, Faculty of Medicine and Dentistry, Olomouc, Czech Republic. [9]Cátedra Rectoral de Medicina Basada en la Evidencia, Universidad de Carabobo, Valencia, Venezuela. [10]Primary Care - Geriatrics, JenCare Senior Medical Center, Berwyn, Illinois, USA. [11]Hospital Pharmacy and Medical Devices Department, Hospital Central de la Defensa "Gómez Ulla" CSVE, Madrid, Spain

**Contact:** Arturo J Martí-Carvajal, arturo.marti.carvajal@gmail.com.

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## ABSTRACT

### Background

Atherosclerotic cardiovascular disease (ACVD) is worsened by chronic inflammatory diseases. Interleukin receptor antagonists (IL-RAs) and tumour necrosis factor-alpha (TNF) inhibitors have been studied to see if they can prevent cardiovascular events.

### Objectives

The purpose of this study was to assess the clinical benefits and harms of IL-RAs and TNF inhibitors in the primary and secondary prevention of ACVD.

### Search methods

The Cochrane Heart Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE (including In-Process & Other Non-Indexed Citations), Ovid Embase, EBSCO CINAHL plus, and clinical trial registries for ongoing and unpublished studies were searched in February 2024. The reference lists of relevant studies, reviews, meta-analyses and health technology reports were searched to identify additional studies. No limitations on language, date of publication or study type were set.

### Selection criteria

RCTs that recruited people with and without pre-existing ACVD, comparing IL-RAs or TNF inhibitors versus placebo or usual care, were selected. The primary outcomes considered were all-cause mortality, myocardial infarction, unstable angina, and adverse events.

**Data collection and analysis**

Two or more review authors, working independently at each step, selected studies, extracted data, assessed the risk of bias and used GRADE to judge the certainty of evidence.

**Main results**

We included 58 RCTs (22,053 participants; 21,308 analysed), comparing medication efficacy with placebo or usual care. Thirty-four trials focused on primary prevention and 24 on secondary prevention. The interventions included IL-1 RAs (anakinra, canakinumab), IL-6 RA (tocilizumab), TNF-inhibitors (etanercept, infliximab) compared with placebo or usual care. The certainty of evidence was low to very low due to biases and imprecision; all trials had a high risk of bias.

**Primary prevention:**

*IL-1 RAs*

The evidence is very uncertain about the effects of the intervention on all-cause mortality(RR 0.33, 95% CI 0.01 to 7.58, 1 trial), myocardial infarction (RR 0.71, 95% CI 0.04 to 12.48, $I^2$ = 39%, 2 trials), unstable angina (RR 0.24, 95% CI 0.03 to 2.11, $I^2$ = 0%, 2 trials), stroke (RR 2.42, 95% CI 0.12 to 50.15; 1 trial), adverse events (RR 0.85, 95% CI 0.59 to 1.22, $I^2$ = 54%, 3 trials), or infection (rate ratio 0.84, 95% 0.55 to 1.29, $I^2$ = 0%, 4 trials). Evidence is very uncertain about whether anakinra and cankinumab may reduce heart failure (RR 0.21, 95% CI 0.05 to 0.94, $I^2$ = 0%, 3 trials). Peripheral vascular disease (PVD) was not reported as an outcome.

*IL-6 RAs*

The evidence is very uncertain about the effects of the intervention on all-cause mortality (RR 0.68, 95% CI 0.12 to 3.74, $I^2$ = 30%, 3 trials), myocardial infarction (RR 0.27, 95% CI 0.04 to1.68, $I^2$ = 0%, 3 trials), heart failure (RR 1.02, 95% CI 0.11 to 9.63, $I^2$ = 0%, 2 trials), PVD (RR 2.94, 95% CI 0.12 to 71.47, 1 trial), stroke (RR 0.34, 95% CI 0.01 to 8.14, 1 trial), or any infection (rate ratio 1.10, 95% CI: 0.88 to 1.37, $I^2$ = 18%, 5 trials). Adverse events may increase (RR 1.13, 95% CI 1.04 to 1.23, $I^2$ = 33%, 5 trials). No trial assessed unstable angina.

*TNF inhibitors*

The evidence is very uncertain about the effects of the intervention on all-cause mortality (RR 1.78, 95% CI 0.63 to 4.99, $I^2$ = 10%, 3 trials), myocardial infarction (RR 2.61, 95% CI 0.11 to 62.26, 1 trial), stroke (RR 0.46, 95% CI 0.08 to 2.80, $I^2$ = 0%; 3 trials), heart failure (RR 0.85, 95% CI 0.06 to 12.76, 1 trial). Adverse events may increase (RR 1.13, 95% CI 1.01 to 1.25, $I^2$ = 51%, 13 trials). No trial assessed unstable angina or PVD.

**Secondary prevention:**

*IL-1 RAs*

The evidence is very uncertain about the effects of the intervention on all-cause mortality (RR 0.94, 95% CI 0.84 to 1.06, $I^2$ = 0%, 8 trials), unstable angina (RR 0.88, 95% CI 0.65 to 1.19, $I^2$ = 0%, 3 trials), PVD (RR 0.85, 95% CI 0.19 to 3.73, $I^2$ = 38%, 3 trials), stroke (RR 0.94, 95% CI 0.74 to 1.2, $I^2$ = 0%; 7 trials), heart failure (RR 0.91, 95% 0.5 to 1.65, $I^2$ = 0%; 7 trials), or adverse events (RR 0.92, 95% CI 0.78 to 1.09, $I^2$ = 3%, 4 trials). There may be little to no difference between the groups in myocardial infarction (RR 0.88, 95% CI 0.0.75 to 1.04, $I^2$ = 0%, 6 trials).

*IL6-RAs*

The evidence is very uncertain about the effects of the intervention on all-cause mortality (RR 1.09, 95% CI 0.61 to 1.96, $I^2$ = 0%, 2 trials), myocardial infarction (RR 0.46, 95% CI 0.07 to 3.04, $I^2$ = 45%, 3 trials), unstable angina (RR 0.33, 95% CI 0.01 to 8.02, 1 trial), stroke (RR 1.03, 95% CI 0.07 to 16.25, 1 trial), adverse events (RR 0.89, 95% CI 0.76 to 1.05, $I^2$ = 0%, 2 trials), or any infection (rate ratio 0.66, 95% CI 0.32 to 1.36, $I^2$ = 0%, 4 trials). No trial assessed PVD or heart failure.

*TNF inhibitors*

The evidence is very uncertain about the effect of the intervention on all-cause mortality (RR 1.16, 95% CI 0.69 to 1.95, $I^2$ = 47%, 5 trials), heart failure (RR 0.92, 95% 0.75 to 1.14, $I^2$ = 0%, 4 trials), or adverse events (RR 1.15, 95% CI 0.84 to 1.56, $I^2$ = 32%, 2 trials). No trial assessed myocardial infarction, unstable angina, PVD or stroke.

Adverse events may be underestimated and benefits inflated due to inadequate reporting.

**Authors' conclusions**

This Cochrane review assessed the benefits and harms of using interleukin-receptor antagonists and tumour necrosis factor inhibitors for primary and secondary prevention of atherosclerotic diseases compared with placebo or usual care. However, the evidence for the predetermined outcomes was deemed low or very low certainty, so there is still a need to determine whether these interventions provide clinical benefits or cause harm from this perspective. In summary, the different biases and imprecision in the included studies limit their external validity and represent a limitation to determining the effectiveness of the intervention for both primary and secondary prevention of ACVD.

## PLAIN LANGUAGE SUMMARY

**Do drugs that suppress the immune system improve outcomes in those with or at risk from atherosclerosis?**

Do drugs that suppress the immune system improve outcomes in those with or at risk from atherosclerosis?

**Key messages**

- We found some limited evidence that some agents may reduce the risk of developing heart failure, but we are very uncertain about the results.
- We found no difference in death rates or any evidence that these agents reduce the risk of heart attack or stroke.
- Due to the limitations of the available studies, more robust research is needed to draw firm conclusions about the effectiveness of these agents in preventing cardiovascular events.

**What is atherosclerotic vascular disease?**

Atherosclerosis is the process of narrowing and blocking arteries. High blood pressure, high cholesterol, diabetes, and smoking increase the risk of this occurring, as do age and genetic factors. When atherosclerosis develops, arteries can narrow or block, resulting in angina, heart attacks, stroke, and problems with circulation in the feet and legs (peripheral vascular disease). These diseases, which result from narrowing arteries around the body caused by this process, are described broadly as atherosclerotic vascular disease (ACVD). It has also been noted that chronic inflammation can increase the risk too, and many studies have been done to see if drugs which affect the immune system and dampen inflammation can affect this disease process.

**What agents have we studied that affect the immune system?**

Interleukin-1 (IL-1) is a substance that causes an inflammatory process when it binds to its receptor (IL-1R). Anakinra and canakinumab are drugs which block ("antagonise") the binding of IL-1 to the IL-1 receptor and are termed IL-1RAs. Anakinra is used, for example, to treat rheumatoid arthritis.

Interleukin-6 (IL-6) is similar, and a drug called tocilizumab blocks the IL-6 receptor to prevent the inflammatory process from developing.

Tumour necrosis factor-alpha (TNF-a) is a cytokine. A cytokine is a small protein. TNF-a is involved in inflammation. Drugs such as infliximab, etanercept, and adalimumab inhibit TNF activity and dampen inflammation.

**What did we want to find out?**

We wanted to find out if there was any evidence that these drugs, which block inflammation, can affect the progression of ACVD and reduce the risk of dying or having a heart attack, stroke or other complications.

**What did we do?**

We gathered all the data we could on trials which used these agents and reported on outcomes of death, heart attack, stroke, peripheral vascular disease, heart failure, and also infection and side effects more broadly. We looked at 58 trials with over 20,000 participants. Some of those trials (34) looked at preventing the development of ACVD. The remainder (24) looked at the impact of giving these drugs to people who already had ACVD to see if they could prevent further problems from developing.

**What did we find?**

We found, broadly, that these agents have a very limited impact, if at all, on the development or progression of ACVD. We found no conclusive evidence of their effect on the risk of death, heart attack, stroke or peripheral vascular disease. They may have some impact on heart failure, but we are very uncertain about the results.

**What are the limitations of the evidence?**

We found that the trials contained several flaws in the way they were conducted and in the limited number of participants, preventing us from drawing definitive conclusions.

**How up to date is this evidence?**

We searched for studies that were published up to 20 February 2024.

**Summary of findings 1. Interleukin-1 (IL-1) receptor antagonists (anakinra, canakinumab) compared with placebo or usual care for primary prevention of cardiovascular outcomes in adults**

**Interleukin-1 (IL-1) receptor antagonists (anakinra, canakinumab) compared with placebo or usual care for primary prevention of cardiovascular outcomes**

**Patient or population:** primary prevention of cardiovascular outcomes in adults
**Settings:** inpatients or outpatients
**Intervention:** interleukin-1 receptor antagonists (anakinra, canakinumab)
**Comparison:** placebo or usual care

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo or usual care | Interleukin-1 (IL-1) receptor antagonists (anakinra, canakinumab) | | | | |
| **All-cause mortality**<br><br>Follow-up: 14 weeks | **67 per 1000** | **22 per 1000** (1 to 505) | **RR 0.33** (0.01 to 7.58) | 30 (1 study) | ⊕⊝⊝⊝ **very low**[1,2] | The RCT assessed anakinra. |
| **Myocardial infarction (fatal or non-fatal**<br><br>Follow-up: 14 to 16 weeks | **3 per 1000** | **2 per 1000** (0 to 12) | **RR 0.71** (0.04 to 12.48) | 585 (2 studies) | ⊕⊝⊝⊝ **very low**[3,4] | One RCT assessed anakinra; the other assessed canakinumab. |
| **Unstable angina**<br><br>Follow-up: 14 to 16 weeks | **103 per 1000** | **25 per 1000** (3 to 217) | **RR 0.24** (0.03 to 2.11) | 566 (2 studies) | ⊕⊝⊝⊝ **very low**[1,5] | One RCT assessed anakinra; the other assessed canakinumab. |
| **Adverse events**<br><br>by the number of events that people experienced at least once, and the total number of adverse events<br><br>Follow-up: 14 to 16 weeks | **800 per 1000** | **680 per 1000** (472 to 976) | **RR 0.85** (0.59 to 1.22) | 596 (3 studies) | ⊕⊝⊝⊝ **very low**[6,7] | Two RCTs assessed anakinra and one canakinumab.<br><br>Any adverse events as random-effects model<br><br>Rate Ratio: 1.06 (95% CI 0.52 to 2.16); $I^2$ = 75%, 4 studies, 666 participants (Abbate |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | 2010; Abbate 2013; Ebrahimi 2018; Ridker 2012).<br><br>Any infection as random-effects model<br><br>Rate Ratio: 1.46<br>(95% CI 0.50 to 4.30); $I^2$ = 0%, 3 studies, 100 participants (Abbate 2010; Abbate 2013; Ebrahimi 2018). |
| **Peripheral vascular disease**<br><br>Not reported | See comment | See comment | Not estimable | - | . | No trials assessed this outcome. |
| **Stroke (fatal or non-fatal)**<br>Clinical diagnosis with imaging an eligibility criterion.<br><br>Follow-up: 16 weeks | **0 per 1000** | **0 per 1000**<br><br>(0 to 0) | **RR 2.42**<br>(0.12 to 50.15) | 556<br>(1 study) | ⊕⊖⊖⊖<br>**very low**[8,9] | The trial assessed canakinumab. |
| **Heart failure**<br><br>Follow-up: 14 to 16 weeks | **267 per 1000** | **56 per 1000**<br>(13 to 251) | **RR 0.21**<br>(0.05 to 0.94) | 596<br>(3 studies) | ⊕⊖⊖⊖<br>**very low**[10,11] | Two RCTs assessed anakinra and one canakinumab. |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
**High certainty**: we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
**Very low certainty**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded two levels for imprecision: the sample size was small, the number of events was very low, and the relative effect included no effect. Therefore, the 95% CI was extensive.
[2] Downgraded one level for risk of bias: the trial had a high risk of attrition bias and other types of bias.
[3] Downgraded one level for risk of bias: 50% (1/2) of the trials had an unclear risk for random sequence generation, allocation concealment, and blinding of participants and personnel (performance bias).
[4] Downgraded two levels for imprecision: the optimal information size (OIS) was 17,580 (8790 by comparison group), the trial total sample size was 3.33% (585/17580) of the OIS, the total number of events was very low, and the relative effect included no effect. Therefore, the 95% CI was broad.
[5] Downgraded two levels of the certainty of evidence due to risk of bias: both trials had unclear risk for random sequence generation, allocation concealment, and either unclear risk of bias in the blinding of participants and personnel (performance bias) or in the blinding of outcome assessment (detection bias). Additionally, both trials had a high risk of bias in the 'other' biases domain due to bias in the presentation of data, design bias, or other bias; and one of the trials had a high risk of bias for selective reporting.

[6] Downgraded two levels due to risk of bias since 66% (2/3) of the trials had unclear risk for random sequence generation, allocation concealment, and blinding of participants and personnel. One trial had a high risk of attrition bias.
[7] Downgraded two levels for imprecision: OIS was 19,424 (9712 by comparison group), the total (cumulative) sample size was 596, which represents 0.03% (596/19424) of the OIS, the total number of events was fewer than 300, and the 95% CI was wide and included no effect.
[8] Downgraded one level due to risk of bias: the trial had an unclear risk for random sequence generation, allocation concealment, and blinding of participants and personnel.
[9] Downgraded two levels for imprecision: the sample size was small, and the total number of events was fewer than 300 (N = 2), the 95% CI was wide and included no effect.
[10] Downgraded two levels for risk of bias: all trials had a high risk of bias in the other bias domain due to bias in the presentation of data, or design bias; one of the trials had a high risk of attrition bias; and one of the trials had a high risk of selective reporting bias.
[11] Downgraded two levels due to imprecision: the OIS was 630 (315 by comparison group), the total (cumulative) sample size was 596, which represents 94% (596/630) of the OIS, the total number of events was fewer than 300 (N = 8), and the 95% CI was wide.

**Summary of findings 2. IL-6 receptor antagonists (tocilizumab) compared with placebo or usual care for primary prevention of cardiovascular outcomes in adults**

**IL-6 receptor antagonists (tocilizumab) compared with placebo or usual care for primary prevention of cardiovascular outcomes in adults**

**Patient or population:** primary prevention of cardiovascular outcomes in adults
**Settings:** inpatients or outpatients
**Intervention:** interleukin-6 receptor antagonists (tocilizumab)
**Comparison:** placebo or usual care

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo or usual care | IL-6 receptor antagonists (tocilizumab) | | | | |
| **All-cause mortality**<br>Follow-up: 48 to 52 weeks | **28 per 1000** | **19 per 1000** (3 to 105) | **RR 0.68** (0.12 to 3.74) | 329 (3 studies) | ⊕⊖⊖⊖ **very low**[1,2] | Medication study: tocilizumab |
| **Myocardial infarction (fatal or non-fatal)**<br>Follow-up: 48 to 52 weeks | **28 per 1000** | **8 per 1000** (1 to 47) | **RR 0.27** [0.04 to 1.68] | 329 (3 studies) | ⊕⊖⊖⊖ **very low**[1,3] | Medication study: tocilizumab |
| **Unstable angina** | See comment | See comment | Not estimable | See comment | See comment | None of the trials assessed this outcome. |
| **Adverse events** | **700 per 1000** | **791 per 1000** | **RR 1.13** | 1051 | ⊕⊕⊖⊖ | Medication study: tocilizumab |

| | | | | | | |
|---|---|---|---|---|---|---|
| Follow-up: median 48 weeks | | (728 to 861) | (1.04 to 1.23) | (5 studies) | **low**[4] | Incidence rate of adverse events: Rate Ratio: 27.89 (95% CI 19.58 to 39.73); $I^2$ = 0%, 4 studies, 595 participants (Baek 2019; Khanna 2016; Khanna 2020; Villiger 2016)<br><br>Any infection:<br><br>Rate Ratio: 1.10 (95% CI: 0.88 to 1.37); $I^2$ = 18%), 5 studies, 1048 participants (Baek 2019; Khanna 2016; Khanna 2020; Smolen 2008; Villiger 2016) |
| **Peripheral vascular disease**<br><br>Follow-up: 48 weeks | **0 per 1000** | **0 per 1000** (0 to 0) | **RR 2.94** (0.12 to 71.47) | 212 (1 study) | ⊕⊖⊖⊖ **very low**[5,6] | Medication study: tocilizumab |
| **Stroke (fatal or non-fatal).** We included either acute ischaemic stroke or acute cerebral haemorrhage. Clinical diagnosis with imaging was an eligibility criterion.<br><br>Follow-up: 48 weeks | **23 per 1000** | **8 per 1000** (0 to 185) | **RR 0.34** (0.01 to 8.14) | 87 (1 study) | ⊕⊖⊖⊖ **very low**[7,8] | Medication study: tocilizumab |
| **Heart failure**<br><br>Follow-up: 48 weeks | **11 per 1000** | **12 per 1000** (1 to 109) | **RR 1.02** (0.11 to 9.63) | 299 (2 studies) | ⊕⊖⊖⊖ **very low**[9,10] | Medication study: tocilizumab |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
**High certainty**: we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
**Very low certainty**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded two levels due to limitations in risk of bias for the blinding of participants and personnel (one trial), blinding of outcome assessment (two trials) and, in two trials, the loss to follow-up varied between 18% and 23%.

[2] Downgraded two levels for imprecision: optimal information (OIS) size was 17,134 (8567 per comparison group). The total sample size in the meta-analysis was 1.92% (329/17134) of the OIS, the number of events was fewer than 300 (N = 9), and the 95% CI was broad.

[3] Downgraded two levels for imprecision. Due to the absence of the events in the medication study group, it was not possible to estimate the optimal information size, the total sample size of the meta-analysis was small, the number of the events was fewer than 300 (N = 3), and the 95% CI was broad.
[4] Downgraded two levels due to limitations of risk of bias: one trial had unclear risk for generation of random sequence and allocation concealment. Three trials had unclear risk in the blinding of participants and personnel, three had unclear blinding of outcome assessment, and the loss to follow-up had a median of 23.3% (3 trials).
[5] Downgraded one level due to limitations in risk of bias: for the blinding of participants and personnel and blinding of outcome assessment.
[6] Downgraded two levels for imprecision. Due to the absence of the events in the control group, it was not possible to estimate the optimal information size, the total sample size of the meta-analysis was small, the number of the events was fewer than 300 (N = 1), and the 95% CI was very broad.
[7] Downgraded two levels due to limitations in the risk of bias: the follow-up loss was 27.6%.
[8] Downgraded two levels for imprecision. Due to the absence of the events in the medication study group, it was not possible to estimate the optimal information size, the total sample size in the meta-analysis was small, the number of the events was fewer than 300 (N = 1), and the 95% CI was extensive and included no effect.
[9] Downgraded two levels due to limitations in the risk of bias: in the blinding of participants and personnel, blinding of outcome assessment (one trial), and the other trial had a high loss to follow-up (27.6%).
[10] Downgraded two levels for imprecision. The optimal information size was 17,352 (8676 per comparison group), the total sample size in the meta-analysis was 1.72% (299/17,352) of the OIS; the number of events was fewer than 300 (N = 2), and the 95% CI was extensive and included no effect.

**Summary of findings 3. TNF inhibitors (etanercept, infliximab) compared with placebo or usual care for primary prevention of cardiovascular outcomes in adults**

**Tumour necrosis factor inhibitors (etanercept, infliximab) compared with placebo or usual care for primary prevention of cardiovascular outcomes in adults**

**Patient or population:** primary prevention of cardiovascular outcomes in adults
**Settings:** inpatients or outpatients
**Intervention:** tumour necrosis factor inhibitors (etanercept, infliximab)
**Comparison:** placebo or usual care

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo or usual care | TNF inhibitors (etanercept, infliximab) | | | | |
| **All-cause mortality**<br>Follow-up: mean 20 weeks | **34 per 1000** | **60 per 1000** (21 to 169) | **RR 1.78** (0.63 to 4.99) | 609 (3 studies) | ⊕⊖⊖⊖ **very low**[1,2] | Study medication: etanercept |
| **Myocardial infarction (fatal or non-fatal)**<br>Follow-up: 12 weeks | **0 per 1000** | **0 per 1000** (0 to 0) | **RR 2.61** (0.11 to 62.26) | 84 (1 study) | ⊕⊖⊖⊖ **very low**[3,4] | Study medication: etanercept |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Unstable angina**<br><br>Not reported | See comment | See comment | Not estimable | - | See comment | None of the trials assessed this outcome. |
| **Adverse events**<br><br>Follow-up: median 20 weeks | **512 per 1000** | **579 per 1000** (518 to 646) | **RR 1.13** (1.01 to 1.25) | 2654 (13 studies) | ⊕⊕⊖⊖ **low**[5] | Study medications: etanercept (10 RCTs) and infliximab (3 RCTs)<br><br>Any infection:<br><br>Rate Ratio: 1.14 (95% CI: 0.98 to 1.32); $I^2$ = 6%, 22 studies, 5039 participants (Bachelez 2015; Bagel 2012; Bernstein 2006; Boettiche r 2008; Brandt 2003; Don 2010; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; Ralph 2020; Reich 2017; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006) |
| **Peripheral vascular dis ease**<br><br>Not reported | See comment | See comment | Not estimable | - | See comment | None of the trials assessed this outcome. |
| **Stroke (fatal or non-fatal).** We included either acute ischaemic stroke or acute cerebral haemorrhage. Clinical diagnosis with imaging was an eligibility criterion.<br><br>Follow-up: median 24 weeks | **12 per 1000** | **5 per 1000** (1 to 33) | **RR 0.46** (0.08 to 2.80) | 565 (3 studies) | ⊕⊖⊖⊖ **very low**[6,7] | Study medication: etanercept |
| **Heart failure**<br><br>Follow-up: 24 weeks | **45 per 1000** | **39 per 1000** (3 to 580) | **RR 0.85** (0.06 to 12.76) | 48 (1 study) | ⊕⊖⊖⊖ **very low**[8,9] | Study medication: etanercept |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
**High certainty**: we are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
**Very low certainty**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded two levels of the quality of evidence due to risk of bias: 100% had an unclear risk for random sequence generation and allocation concealment, and 66% (2/3) had an unclear risk of bias for blinding personnel and participants. One trial had a high risk of attrition bias from incomplete outcome data.
[2] Downgraded two levels for imprecision. The total sample size of the trials was higher than the optimal information size (609 versus 452, respectively). The number of events was low (N = 22), and the 95% CI was wide and included no effect.
[3] Downgraded one level for risk of bias; unclear risk of bias for random sequence generation and allocation concealment
[4] Downgraded two levels for imprecision. The optimal information size could not be estimated due to the control group's lack of events. The total sample size was small, the number of events was low (N = 1), and the 95% confidence interval was wide and included no effect.
[5] Downgraded two levels due to risk of bias: 38% (5/13) of the trials had an unclear risk for random sequence generation, 54% (7/13) had unclear allocation concealment, 62% (8/13) had unclear blinding of participants and personnel, 77% (10/13) had unclear blinding of outcome assessment, and 46% (6/13) had a high risk from incomplete outcome data due to high loss of the participants during the follow-up.
[6] Downgraded two levels of the quality of evidence due to risk of bias: 66% had an unclear risk for random sequence generation and allocation concealment, and 66% (2/3) had an unclear risk of bias for blinding personnel and participants, and blinding of outcome assessment.
[7] Downgraded two levels for imprecision: the optimal information size was higher than the total sample size (2912 versus 566, respectively), the number of events was low (N = 3), and the 95% confidence interval was wide and included no effect.
[8] Downgraded two levels of the quality of evidence due to risk of bias: one trial had an unclear judgement for the domains: random sequence generation, allocation concealment, and blinding personnel and participants.
[9] Downgraded two levels for imprecision: the optimal information size was 25,486 (12,743 per comparison group), which means that the total size represents 0.18% (48/25,486), the number of events was low (N = 2), and the 95% confidence interval was broad. It included no effect.

## Summary of findings 4. Interleukin-1 (IL-1) receptor antagonists (anakinra, canakinumab) compared with placebo or usual care for secondary prevention of cardiovascular outcomes in adults

**Interleukin-1 receptor antagonists (anakinra, canakinumab) compared with placebo or usual care for secondary prevention of cardiovascular outcomes in adults**

**Patient or population:** secondary prevention of cardiovascular outcomes in adults
**Settings:** inpatient or outpatient
**Intervention:** interleukin-1 receptor antagonists (anakinra, canakinumab)
**Comparison:** placebo or usual care

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo or usual care | Interleukin-1 (IL-1) receptor antago- | | | | |

| | | nists (anakinra, canakinumab) | | | | |
|---|---|---|---|---|---|---|
| **All-cause mortality**<br><br>Follow-up: median 52 weeks | **39 per 1000** | **37 per 1000** (33 to 42) | **RR 0.94** (0.84 to 1.06) | 10743 (8 studies) | ⊕⊖⊖⊖ **very low**[1,2] | Study medications: anakinra (5 trials) and canakinumab (3 trials) |
| **Myocardial infarction (fatal or non-fatal)**<br><br>Follow-up: median 52 weeks | **17 per 1000** | **15 per 1000** (12 to 18) | **RR 0.88** (0.75 to 1.04) | 10,629 (6 studies) | ⊕⊕⊖⊖ **low**[3] | Study medications: anakinra (3 trials) and canakinumab (3 trials) |
| **Unstable angina**<br><br>Follow-up: 52 to 192 weeks | **18 per 1000** | **16 per 1000** (12 to 22) | **RR 0.88** (0.65 to 1.19) | 10,403 (3 studies) | ⊕⊖⊖⊖ **very low**[4,5] | Study medications: anakinra (1 trial) and canakinumab (2 trials) |
| **Adverse events**<br><br>Follow-up: 2-52 weeks (median 28 weeks) | **515 per 1000** | **474 per 1000** (397 to 562) | **RR 0.92** (0.78 to 1.09) | 264 (4 studies) | ⊕⊖⊖⊖ **very low**[6,7] | Medication study: anakinra (2 trials) and canakinumab (2 trials)<br><br>Any infection:<br><br>Rate Ratio: 1.11 (95% CI 1.05 to 1.18); $I^2$ = 0%, 12 studies, 10,249 participants (Abbate 2020; Brucato 2016; Choudhury 2016; Emsley 2005; Krisai 2020; Morton 2015; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018) |
| **Peripheral vascular disease**<br><br>Follow-up: 52 weeks | **1 per 1000** | **1 per 1000** (0 to 4) | **RR 0.85** (0.19 to 3.73) | 10,288 (3 studies) | ⊕⊖⊖⊖ **very low**[8,9] | Medication study: canakinumab |
| **Stroke (fatal or non-fatal)**<br><br>Follow-up: 12 to 192 weeks (median 52 weeks) | **29 per 1000** | **27 per 1000** (21 to 34) | **RR 0.94** (0.74 to 1.2) | 10,705 (7 studies) | ⊕⊖⊖⊖ **very low**[10,11] | Study medications: anakinra (5 trials) and canakinumab (2 trials) |
| **Heart failure** | **114 per 1000** | **104 per 1000** (57 to 189) | **RR 0.91** (0.5 to 1.65) | 10509 (7 studies) | ⊕⊖⊖⊖ **very low**[12,13] | Medication study: anakinra (4 trials) and canakinumab (3 trials) |

| | | | | | |
|---|---|---|---|---|---|
| Follow-up: 2 to 192 weeks (median 52 weeks) | | | | | |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
**High certainty**: we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
**Very low certainty**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded two levels due to limitations of risk of bias: all trials had a high loss of participants during the follow-up. Furthermore, two trials had unclear risks for random sequence generation and allocation concealment and two trials had unclear blinding of participants and personnel.
[2] Downgraded by one level due to lack of precision, as the ideal sample size for optimal information (N = 182,846) exceeds the actual total sample size (N = 10,541) by 5.76 times.
[3] Downgraded two levels due to limitations of risk of bias: all trials had a high loss of follow-up. Furthermore, two trials had unclear risks for random sequence generation and allocation concealment and two trials had unclear blinding of participants and personnel (performance bias).
[4] Downgraded two levels of the due risk of bias: all trials had a high risk of attrition bias (more than 12% of the loss to follow-up). One trial (33%) had an unclear risk of bias for random sequence generation and allocation concealment, and two trials (66%) had unclear risks for blinding participants and personnel.
[5] Downgraded one level for imprecision due to the low number of events.
[6] Downgraded two levels due to risk of bias: 50% of trials had unclear risk for random sequence generation, and three trials (75%) had unclear risk for allocation concealment and blinding of participants and personnel. Two trials (50%) had a high risk of attrition bias (losing more than 12% in follow-up).
[7] Downgraded two levels for imprecision: optimal information size (902 per comparison group) was higher than the total sample size (N = 264), the number of events was fewer than 300, and the 95% confidence interval included no effect.
[8] Downgraded two levels for risk of bias: one trial had unclear risk for random sequence generation and allocation concealment. All trials had a high loss of follow-up of the participants.
[9] Downgraded one level for imprecision: very low number of events (N = 12), 95% confidence interval was wide and included no effect.
[10] Downgraded two levels due to risk of attrition bias. All trials had a high loss of participants during the follow-up.
[11] Downgraded two trials for imprecision: the optimal information size was higher (390,085 per comparison group) than the total sample size (N = 10,705), low number of events (fewer than 300 participants), 95% confidence interval included no effect.
[12] Downgraded two levels for risk of bias. Eighty-five-seven per cent of the trials (6/7) had high loss losses during the follow-up of participants. Forty-two-five per cent of the trials (3/7) indicated unclear risk for random sequence generation, allocation concealment and blinding of participants and personnel.
[13] Downgraded two levels for imprecision: the optimal information size was higher (52,074 participants per comparison group) than the total sample size (N = 10,509), the number of events was low (N = 48), and the 95% confidence interval included no effect.

### Summary of findings 5. Interleukin-6 (IL-6) receptor antagonists (tocilizumab) compared with placebo or usual care for secondary prevention of cardiovascular outcomes in adults

| Interleukin-6 (IL-6) receptor antagonists (tocilizumab) compared to placebo or usual care for secondary prevention of cardiovascular outcomes in adults |
|---|

**Patient or population:** patients with secondary prevention of cardiovascular outcomes in adults
**Settings:** inpatients or outpatients
**Intervention:** interleukin-6 receptor antagonists (tocilizumab)
**Comparison:** placebo or usual care

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo or usual care; | Interleukin-6 (IL-6) receptor antagonists (tocilizumab) | | | | |
| **All-cause mortality**<br><br>Follow-up: median 24.85 weeks | **171 per 1000** | **186 per 1000** (104 to 335) | **RR 1.09** (0.61 to 1.96) | 198 (2 studies) | ⊕⊖⊖⊖ **very low**[1,2] | Medication study: tocilizumab |
| **Myocardial infarction (fatal or non-fatal)**<br><br>Follow-up: median 24 weeks | **63 per 1000** | **29 per 1000** (4 to 190) | **RR 0.46** (0.07 to 3.04) | 345 (3 studies) | ⊕⊖⊖⊖ **very low**[3,4] | Medication study: tocilizumab |
| **Unstable angina**<br><br>Follow-up: 24 weeks | **17 per 1000** | **6 per 1000** (0 to 136) | **RR 0.33** (0.01 to 8.02) | 118 (1 study) | ⊕⊖⊖⊖ **very low**[5,6] | Medication study: tocilizumab |
| **Adverse events**<br><br>Follow-up: 4 to 25 weeks | **528 per 1000** | **470 per 1000** (401 to 554) | **RR 0.89** (0.76 to 1.05) | 113 (2 studies) | ⊕⊖⊖⊖ **very low**[7,8] | Any adverse event (incidence rate):<br><br>Rate Ratio: 0.81 (95% CI 0.45 to 1.44); $I^2$ = 27%, 3 studies, 348 participants (Broch 2021; Carroll 2018; Kleveland 2016)<br><br>Any infection (incidence rate):<br><br>Rate Ratio: 0.66 (95% CI 0.32 to 1.36), $I^2$ = 0%, 4 studies, 433 participants (Broch 2021; Carroll 2018; Kleveland 2016; Meyer 2021) |
| **Peripheral vascular disease** | See comment | See comment | Not estimable | - | See comment | No trial assessed this outcome. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Not reported | | | | | | |
| **Stroke (fatal or non-fatal)**<br><br>Follow-up: 24 weeks | **10 per 1000** | **11 per 1000**<br>(1 to 169) | **RR 1.03**<br>(0.07 to 16.25) | 195<br>(1 study) | ⊕⊖⊖⊖<br>**very low**[7,9] | Medication study: tocilizumab |
| **Heart failure**<br><br>Not reported | See comment | See comment | Not estimable | - | See comment | No trial assessed this outcome. |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
**High certainty**: we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
**Very low certainty**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded one level due to limitations of risk of bias: one trial had unclear risk of bias in the blinding of participants and personnel.
[2] Downgraded two levels for imprecision: the optimal information size was higher (N = 19,461 per comparison group) than the total sample size (N = 198), the number of events was low (N = 29), the 95% confidence interval was wide and included no effect.
[3] Downgraded one level for risk of bias: one trial (1/3) had an unclear risk of bias in random sequence generation, allocation concealment, and high risk for blinding of participants and personnel. Two trials (66%) had an unclear risk of bias for random sequence generation, allocation concealment, and high risk for blinding of participants and personnel.
[4] Downgraded two levels for imprecision: the optimal information size was higher (426 participants per comparison group) than the total sample size, the number of events was low (N = 12), and the 95% confidence interval was wide and included no effect.
[5] Downgraded one level for risk of bias: there was an unclear risk of bias in the blinding of participants and personnel.
[6] Downloaded two levels for imprecision: due to the lack of events in the medication group, it was impossible to estimate the optimal information size. The number of events was low (N = 1), and the 95% confidence interval was broad and included no effect.
[7] Downgraded one level for risk of bias due to one of the two included trials having an unclear risk for random sequence generation and allocation concealment and a high risk for blinding participants and personnel.
[8] Downgraded two levels for imprecision: the optimal information size was 3318 (1659 by comparison group) versus a total sample size of 113 (3.4%), a deficient number of events (N = 78), the 95% CI was broad and included no effect.
[9] Downgraded two levels due to imprecision: RR 1.03 (CI 0.07 to 16.25); the confidence interval was very wide, encompassing the possibility that the intervention may have a very small effect, no effect, or an extremely large effect.

**Summary of findings 6. TNF inhibitors (etanercept, infliximab) compared with placebo or usual care for secondary prevention for cardiovascular diseases in adults**

**Tumour necrosis inhibitors (etanercept, infliximab) compared with placebo or usual care for secondary prevention of cardiovascular outcomes in adults**

**Patient or population:** patients with secondary prevention of cardiovascular outcomes in adults
**Settings:** inpatients or outpatients
**Intervention:** tumour necrosis factor inhibitors (etanercept, infliximab)
**Comparison:** placebo or usual care

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo or usual care | TNF inhibitors (etanercept, infliximab) | | | | |
| **All-cause mortality**<br><br>Follow-up: 12 to 28 weeks (median 24 weeks) | **4 per 1000** | **4 per 1000** (3 to 7) | **RR 1.16** (0.69 to 1.95) | 2780 (5 studies) | ⊕⊖⊖⊖ **very low**[1,2] | Two trials in the etanercept group were not published. Data were extracted from another excluded study.<br><br>Study medication: etanercept (four trials) and infliximab (one trial) |
| **Myocardial infarction (fatal or non-fatal)**<br><br>Not reported | See comment | See comment | Not estimable | - | See comment | None of the trials assessed this outcome. |
| **Unstable angina**<br><br>Not reported | See comment | See comment | Not estimable | - | See comment | None of the trials assessed this outcome. |
| **Adverse events**<br><br>Follow-up: 20 to 28 weeks (median 24 weeks) | **438 per 1000** | **504 per 1000** (368 to 683) | **RR 1.15** (0.84 to 1.56) | 685 (2 studies) | ⊕⊖⊖⊖ **very low**[3,4] | Medication study: etanercept (one trial) and infliximab (one trial)<br><br>Any infection:<br><br>Rate Ratio: 1.23 (95% CI: 1.04 to 1.45); $I^2$ = 0%, 6 studies, 2821 participants (Bozkurt 2001; Chung 2003; Deswal 1999; Ralph 2020; RENAISSANCE 2001; Weisman 2007) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Peripheral vascular disease**<br><br>Not reported | See comment | See comment | Not estimable | - | See comment | None of the trials assessed this outcome. |
| **Stroke (fatal or non-fatal)**<br><br>Not reported | See comment | See comment | Not estimable | - | See comment | None of the trials assessed this outcome. |
| **Heart failure**<br><br>Follow-up: 12-28 weeks (median 24 weeks) | **149 per 1000** | **137 per 1000** (111 to 169) | **RR 0.92** (0.75 to 1.14) | 2245 (4 studies) | ⊕⊖⊖⊖ **very low**[5,6] | Two trials in the etanercept group were not published. Data were extracted from another excluded study.<br><br>Study medication: etanercept (three trials) and infliximab (one trial) |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
**High certainty**: we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
**Very low certainty**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded two levels for risk of bias: all trials had unclear risk of bias in random sequence generation, allocation concealment, and blinding of participants and personnel. Eighty per cent (4/5) had unclear risk bias in the blinding of outcome assessment.
[2] Downgraded two levels for imprecision: the optimal information size was higher (2369 participants per comparison group) than the total sample size (N = 2780), the number of events was fewer than 300 (N = 253), the 95% confidence interval was wide and included no effect.
[3] Downgraded two levels for risk of bias: both trials had unclear risk of bias in random sequence generation, allocation concealment, and blinding of participants and personnel.
[4] Downgraded one level for imprecision: the optimal information size was less (172 participants per comparison group) than the total sample size (N = 618), the number of events was fewer than 300 (N = 168), the 95% confidence interval was wide and included no effect.
[5] Downgraded two levels for risk of bias: all trials had unclear risk of bias in random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.
[6] Downgraded two levels due to imprecision: the optimal information size was larger than the total sample size (23,957 per comparison group). The confidence interval was wide and included no effect.

## BACKGROUND

For a medical glossary, see Appendix 1.

### Description of the condition

#### 1. Definition of atherosclerotic cardiovascular diseases

Atherosclerotic cardiovascular diseases (ACVDs) are clinical conditions resulting from atherosclerotic plaques in arterial beds (Maki 2019). ACVDs encompass coronary artery disease, peripheral arterial disease, and disease affecting the carotid, cerebral, and renal arteries (Maki 2019).

#### 2. Epidemiology of atherosclerotic cardiovascular diseases

Atherosclerotic cardiovascular diseases are the leading cause of mortality in the USA and many countries (Benjamin 2019; Maki 2019). Coronary artery disease and stroke, followed by heart failure and hypertension, are the leading causes of death attributable to ACVDs (Benjamin 2019). According to the World Health Organization, it is estimated that each year approximately 18 million people die from ACVDs, representing approximately 31% of all deaths worldwide (WHO 2020). Although improvements in lifestyle and treatments have reduced the mortality rates associated with acute ACVDs, the prevalence of chronic ACVDs continues to increase (Spitzer 2019). Cardiovascular risk factors, such as obesity and diabetes, continually increase in all ethnic groups in the USA and are the major target for the primary and secondary prevention of ACVDs (Benjamin 2018; Maki 2019).

People with coronary artery disease remain at high risk for acute events such as myocardial infarction (Libby 2018; Shah 2019). Inflammation is central in forming unstable atherosclerotic plaques, leading to acute coronary syndromes (Herder 2017; Libby 2018; Shah 2019). Atherosclerotic plaque formation is also strongly influenced by the immune system, in which B lymphocytes, macrophages, and several interleukins (ILs) are pivotal in enhancing atherogenic inflammatory pathways (Dechkhajorn 2020; Nguyen 2019; Rus 1996; Tsiantoulas 2015). Interestingly, even though high cholesterol is a well-established risk factor in the pathogenesis of atherosclerotic plaques, individuals with controlled low-density lipoprotein levels are not exempt from ACVDs, suggesting that even patients with optimal cholesterol levels may benefit from prevention efforts (Ajala 2020; Lawler 2020).

Peripheral vascular disease (PVD) is another cardiovascular outcome of atherosclerosis (Eid 2021). In 2010, more than 68% of the global cases of PVD were in countries with low and middle incomes (Eid 2021). PVD affects the arteries of the lower limbs and can lead to amputation, especially in black people and those with low socioeconomic status (Eid 2021; Spittel 2004). It also contributes to poor quality of life (Sharma 2016) and increases the risk of cardiovascular mortality by four times (Spittel 2004). As in coronary artery disease, PVD is associated with vascular inflammatory markers like IL-6 (Lee 2006; Nylaende 2006; Nylaende 2006a).

#### 3. Relationship between atherosclerosis and inflammation

Atherosclerosis is not only a disorder of lipid accumulation; it is a dynamic process in which inflammation has a causative role (Brevetti 2010). Atherosclerosis is a complex chronic inflammatory disorder mediated by adaptive and innate immunity (Alexander 1994; Charla 2020; Liberale 2021; Liu 2020; Martinod 2020; Masters 2015; Ross 1999; Rymer 2017; Weber 2023). It is initiated by a macrophage-mediated immune response to lipoprotein and cholesterol accumulation in arterial walls, which results in the formation of plaques (Rahman 2018) that will later manifest as ACVDs (Chang 2013; Jia 2019; Raggi 2018; Wang 2020; Xu 2018; Zheng 2011).

Likewise, ACVDs are also linked to the inflammatory system (Higaki 2019; McMaster 2015; Peiró 2017; Rai 2020; Soehnlein 2021). People with chronic inflammatory diseases have a higher risk of ACVDs compared to the general population (England 2018; Havnaer 2019; Kallinich 2015; Kasselman 2018; Kwon 2020; Liao 2017; Mehta 2023; Van Boheemen 2020; Widdifield 2018). Recent reports suggest a causal relationship between acute infection and myocardial infarction (Musher 2019) due to the role of cytokines in activated inflammatory cells in atherosclerotic plaques (Libby 2005; Mauriello 2005). Several new anti-atherosclerotic treatments have recently been developed, such as cyclodextrins, protein kinase inhibitors, colchicine, inhibitors of p38 mitogen-activated protein kinase (MAPK), lipid dicarbonyl scavengers, a monoclonal antibody targeting interleukin-1β, and P-selectin inhibitors (Gluba-Brzózka 2021). Although colchicine has been shown to be of benefit in those with established ACVD, and has recently gained US Food Drug Administration (FDA) approval, there are as yet, to our knowledge, no prospective randomised controlled clinical trials to demonstrate its benefit in primary prevention of ACVD (Martí-Carvajal 2022). However, further assessment through large, high-quality randomised controlled trials is still necessary to fully determine the clinical efficacy as well as potential harms of these emerging therapies.

Cytokines are soluble hormone-like proteins that allow for communication between leukocytes and between leukocytes and other cells and the external environment (Abbas 2020; Klimov 2019; O'Shea 2019; Tayal 2008). Cytokines encompass the following six subfamilies (Klimov 2019).

- Interleukins (ILs);
- Colony-stimulating factors;
- Interferons;
- Tumour necrosis factor (TNF);
- Transforming growth factors;
- A variety of other proteins.

Several narrative reviews describe the role of cytokines in humans in health and disease (Bartekova 2018; Dayer 2017; Dinarello 2010; Tousoulis 2016; Zhou 2020). Overall, cytokines mediate and regulate cellular communication, immunity, inflammation, and other processes, forming a cytokine network (Ruparelia 2020; Williams 2019). Cytokines have three basic properties (O'Shea 2019; Rider 2016). First, they are pleiotropic, meaning cytokines can have multiple effects in the same cell (O'Shea 2019; Rider 2016). Second, the activity of one cytokine can be compensated by other cytokines, as the cytokine receptor signal-transducing subunit is often shared amongst different receptor complexes (O'Shea 2019; Rider 2016). Third, they can have specific and unique functions, like regulating endothelial cell activation by IL-1 and TNF (O'Shea 2019; Williams 2019). Cytokine receptors have one or more ligand-specific subunits with different affinities. The expression of cytokine receptors is a regulated process dependent on cell stimulation (O'Shea 2019). Hence, dysregulation of the

cytokine network has been linked to impaired immune response, inflammation, and atherosclerosis, as shown in various literature reviews (Adamo 2020; Rider 2016; Tabas 2017; Upadhye 2020; Wang 2020a).

Interleukin-1 (IL-1) is an essential cytokine for local and systemic inflammation (Cavalli 2018; Dayer 2017; Dinarello 2013). A meta-analysis has demonstrated that high IL-1 levels are associated with a high risk of cardiovascular diseases (Herder 2017). There are 11 members of the IL-1 superfamily (Abbate 2020; Dayer 2017; Giuliani 2017). However, when considering the atherothrombotic process, IL-1 is classified into two groups (Ridker 2019). Firstly, there are pro-inflammatory and pro-atherogenic cytokines (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, and IL-36γ). Secondly, there are anti-inflammatory and anti-atherogenic cytokines (IL-1Ra, IL-36Ra, IL-37, and IL-38) (Ait-Oufella 2011; Cavalli 2018; Dayer 2017; Giuliani 2017; Kleemann 2008; Ridker 2019). Likewise, IL-6 is a 'master player' in the cytokine network (Uciechowski 2020). Due to its pro-inflammatory nature, IL-6 induces the expression of various proteins responsible for acute inflammation. IL-6 has pleiotropic activity in various tissues and cells and plays an essential role in cell proliferation and differentiation in humans, and its unregulated expression is responsible for several chronic inflammatory conditions (Kishimoto 2019; Uciechowski 2020).

Interventions with IL-receptor antagonists and TNF inhibitors, and their effect on ACVDs, are the scope of this Cochrane Review. Appendix 2 lists the types of ILs and TNFs, including sources and functions.

#### 4. Molecular links between atherosclerosis and inflammation

There is a strong link between coronary heart disease and IL-6 and IL-1 receptor pathways (Dudbridge 2012; Moriya 2019; Sarwar 2012). So far, the cytokines implicated in the atherothrombotic process are IL-1β, TNF, IL-6, and IL-18 (Libby 2017; Ridker 2019). Many studies have reported the association between acute or chronic heart failure and increased circulating levels of TNF and other cytokines (Briasoulis 2016; Cain 1999; Koller-Strametz 1998; Levine 1990; Monda 2020; Pugliese 2020; Rordorf 2014).

Inflammation is a novel therapeutic target in atherosclerosis (Hanna 2020; Li 2017; Nasonov 2018; Nguyen 2019; Oikonomou 2020; Ruparelia 2020; Zhao 2019). It is hypothesised that anti-cytokine therapies target specific IL signalling pathways and could serve as powerful adjuncts to lipid-lowering therapy in preventing and treating ACVDs (Lim 2020; Montecucco 2017; Ridker 2019). IL-1 receptor antagonist (IL-1Ra) is one of the anti-inflammatory therapies described to date (Ait-Oufella 2019; Tayal 2008). IL-1Ras are monoclonal antibodies (MoAbs). The mechanism of action of MoAbs has been reviewed elsewhere (Cavalli 2018; Mitoma 2018; Varadé 2020).

Three approved biologics for blocking IL-1 are anakinra, rilonacept, and canakinumab (Abbate 2020). However, at present, none of them has an indication for use in ACVD. Anakinra, rilonacept, and canakinumab have been explored in patients with heart disease (Abbate 2020; Buckley 2018). Clinical trials have assessed the impact of IL-Ra antagonists (IL-1 and IL-6) and TNF inhibitors for the prevention of cardiovascular outcomes (Abbate 2010; Abbate 2013; Abbate 2020a; Bozkurt 2001; Carroll 2018; Chung 2003; Deswal 1999; Fichtlscherer 2001; Kleveland 2016; Mann 2004; Morton 2015; Padfield 2013; Ridker 2012; Ridker 2017; Van Tassell 2017; Van Tassell 2016; Van Tassell 2018).

## Description of the intervention

This section only describes the biological agents (IL-Ra and TNF inhibitors) that have been assessed for preventing adverse cardiovascular outcomes. These drugs are also known as immunomodulatory drugs (Thornton 2019) or disease-modifying drugs (Thornton 2019; Visovsky 2019). The biological agents are as follows (Donnenberg 2017).

TNF inhibitors work by blocking the biological activity of a cytokine that plays a role in the destruction of cells. This blockage is essential for curtailing the inflammatory process. For many years, TNF inhibitors have been widely used in the treatment of various autoimmune disorders, making research in this area particularly significant. In addition to monoclonal antibodies, engineered receptor molecules designed to bind with this cytokine are expected to see increased use.

IL-1RAs serve to neutralise surplus IL-1, thereby mitigating inflammation. Clinical studies have shown that using receptor antagonists or antibodies to prevent the cytokine from attaching to its specific receptors is generally more effective than directly targeting the cytokine. Notably, therapies targeting the IL-6 receptor and IL-1RAs are more successful at reducing inflammation compared to those targeting IL-1 and IL-6 directly. In conclusion, biological therapies offer a more targeted approach to managing excessive inflammation. For detailed insights into the unique characteristics and depth of these drugs, please refer to Appendix 1, Appendix 2, Appendix 3, and Appendix 4.

### Interleukin-receptor antagonists

#### *Interleukin-1 receptor antagonists*

- Anakinra is a recombinant human IL-1 receptor antagonist protein that inhibits signalling by IL-1α and IL-1β (EMA 2020; Rider 2016). It is the recombinant form of the natural IL-1Ra (Cavalli 2018). It is available as a solution for subcutaneous injection (EMA 2020). It should be used with caution in patients who have severely reduced liver function or moderately reduced kidney function (EMA 2020). In patients with severely reduced kidney function, the clinician should consider giving anakinra every other day (EMA 2020). Anakinra has a short half-life of about six hours; treatment, therefore, requires frequent subcutaneous injections (Rider 2016). The most common side effect of anakinra is injection site reaction. Anakinra's short half-life allows immediate treatment withdrawal if needed (Rider 2016).
- Canakinumab is a human monoclonal anti-IL-1β antibody with a longer half-life than anakinra. Canakinumab is a human monoclonal antibody produced by recombinant DNA technology, and it is administered subcutaneously (EMA 2020a).

#### *Interleukin-6 receptor antagonists*

- Tocilizumab is a humanised monoclonal antibody directed against soluble and membrane-bound IL-6 receptors, produced by recombinant DNA technology (Carroll 2018b; EMA 2020b; Sheppard 2017; Varadé 2020).

**Tumour necrosis factor inhibitors**

- Etanercept is a dimer of a chimeric protein genetically engineered by fusing the extracellular ligand-binding domain of human TNF receptor-2 (TNFR2) to the fragment crystallisable (Fc) region of the human immunoglobulin G1 (IgG1) (EMA 2020c; Mitoma 2018; Moreland 2004; Tracey 2008). Etanercept is produced by recombinant DNA technology (EMA 2020c). Etanercept has a mean elimination half-life of approximately 70 hours (range of 7 to 300 hours) (Combe 2008; EMA 2020c).
- Infliximab is a chimeric human-murine IgG1 monoclonal antibody produced by recombinant DNA technology (EMA 2020d; Moreland 2004; Varadé 2020).

For a pharmacological summary and primary clinical applications of these biological agents, see Appendix 3 (EMA 2020; EMA 2020a; EMA 2020b; EMA 2020c; EMA 2020d; FDA 2020). Appendix 4 lists warnings and precautions for IL-receptor antagonist therapy.

## How the intervention might work

Both IL-receptor antagonists and TNF inhibitors are specific MoAbs (EMA 2020; EMA 2020a; EMA 2020b; EMA 2020c; EMA 2020d; FDA 2020a; FDA 2020c; FDA 2020b; FDA 2020; Moreland 2004). The principal sources of information about these drugs are on disorders for which they have been used, such as rheumatological, infectious, and immunological disorders and cancer (Abbas 2020; Cavalli 2018; Combe 2008; Dinarello 2010; Dinarello 2013; Giuliani 2017; Havnaer 2019; Kallinich 2015; Kishimoto 2019; Klimov 2019; Kwon 2020; Liao 2017; Liu 2020a; Martinod 2020; Masters 2015; Mitoma 2018; Moreland 2004; O'Shea 2019; Rider 2016; Sheppard 2017; Singh 2018; Tayal 2008; Tracey 2008; Uciechowski 2020; Varadé 2020).

In rheumatoid arthritis, inflammation is associated with heart disorders; therefore, the intervention is an alternative strategy to attenuate inflammation and subsequent inflammation-driven comorbidities in rheumatoid arthritis (Chen 2021; Fragoulis 2020). Inflammation is a risk factor for cardiotoxicity (Campana 2021). The intervention can reduce inflammation, minimising ventricular arrhythmogenesis by blocking the cardiac macrophages and macrophage-secreted inflammatory cytokines (Chen 2020). This outcome has been demonstrated, with a decrease in chronic inflammation resulting in a reduction in time from the start of the Q wave to the end of the T wave adjusted or corrected by heart rate (QTc) in people with rheumatoid arthritis (Adlan 2015; Levine 2018), which parallels C-reactive protein (CRP) reduction (Kobayashi 2018). In addition to anti-arrhythmic benefits, intervention therapy increases ejection fraction and reduces left ventricular mass index associated with rheumatic disease activity (Kobayashi 2014).

**Interleukin-receptor antagonists**

***Interleukin-1 receptor antagonists***

- Anakinra is a recombinant human IL-1 receptor antagonist (EMA 2020). Anakinra binds to IL-1, thereby blocking the binding of IL-1 to its receptor, preventing cell activation. A blockade of IL-1 activity may inhibit the cascade of downstream secretion of pro-angiogenic factors such as vascular endothelial cell growth factor, TNF alpha (TNFα), and IL-6, inhibiting tumour angiogenesis (NCI 2020a).
- Canakinumab is a human recombinant polypeptide that acts as a receptor antagonist to IL-1β. Canakinumab neutralises the action of human IL-1β (Singh 2018; EMA 2020a). This event suppresses the inflammatory responses mediated by IL-1β (NCI 2020b).

***Interleukin-6 receptor antagonists***

- Tocilizumab is a human IL-6 receptor antagonist (Sheppard 2017; Singh 2018). Tocilizumab selectively binds to soluble and membrane-bound human IL-6 receptors, thereby inhibiting the binding of IL-6 to its receptors and blocking the subsequent signalling cascade of IL-6 (EMA 2020b; FDA 2020a).

**Tumour necrosis factor inhibitors**

- Etanercept acts as a soluble TNF receptor and binds TNFα and TNF-beta (TNFβ) (EMA 2020c; Pan 2020; Tracey 2008). It binds solubilised and cell-surface TNFα, thus neutralising its ability to interact with its cell-surface receptor to promote inflammation (Moreland 2004). The receptor moiety of etanercept binds to circulating TNF (two molecules of TNF per receptor) and inhibits its attachment to endogenous TNF-cell surface receptors, thereby rendering TNF inactive and inhibiting TNF-mediated mechanisms of inflammation (NCI 2020c).
- Infliximab neutralises the biological activity of soluble and cell-surface TNFα by inhibiting its interaction with the TNF receptor. Moreover, TNFα upregulates IL-6 production (Moreland 2004).

## Why it is important to do this review

Heritable and non-heritable links between atherosclerosis and inflammation may explain residual cardiovascular risk after accounting for traditional risk factors (Bazeley 2020; Fang 2020; Jung 2020; Sano 2018). Several molecular mechanisms are essential in the development of ACVDs (Holte 2017; Kleveland 2018; Ueland 2018). The biological agents described above have been approved for non-ACVD medical conditions, and their effects on the cardiovascular system have not been systematically reviewed. This review aims to synthesise the current knowledge on the clinical benefits and harms of IL-receptor antagonists and TNF inhibitors in preventing ACVDs (FDA 2020c; Liu 2020a; Rider 2016; Singh 2018; Visovsky 2019). Evidence from clinical trials has also highlighted other serious adverse events, such as pulmonary hypertension, interstitial lung disease, pulmonary alveolar proteinosis, hypertension, hyperlipidaemia, and increased risk for developing severe infections, such as the reactivation of tuberculosis (Liu 2020a; Rider 2016; Singh 2018; Visovsky 2019). Some of these adverse effects may increase rather than reduce cardiovascular risk. Therefore, a careful analysis of the risk/benefit ratio is essential.

To date, despite the potential benefits of IL-receptor antagonists and TNF inhibitors in decreasing primary and secondary cardiovascular events, there are no guidelines regarding their use in patients with ACVDs (Arnett 2019; Virani 2020). Therefore, this Cochrane Review could inform decision-making and improve healthcare quality. This Cochrane Review presents valuable insights that will be of great interest to epidemiologists and healthcare policymakers seeking to make evidence-based decisions.

# OBJECTIVES

1. To assess the clinical benefits and harms of interleukin-receptor antagonists and tumour necrosis factor (TNF) inhibitors

for the primary and secondary prevention of atherosclerotic cardiovascular diseases.

# METHODS

## Criteria for considering studies for this review

### Types of studies

We included randomised controlled trials (RCTs). We excluded non-randomised clinical trials. We included studies reported as full-text, those published as an abstract only, and unpublished data, if available. Furthermore, we did not apply any language, country, or follow-up duration limitations. We only included studies with a parallel design. Due to the nature of the clinical condition and the intervention's pharmacodynamic properties, we considered cross-over and cluster-randomised trials unsuitable.

IL-receptor antagonists and TNF inhibitors had to meet all three of the following conditions:

- They are utilised for a new indication (medications were started in the last five years);
- They have been approved for use in the condition in question;
- They are compared with a placebo or usual care in the trial for inclusion in the review.

### Types of participants

This Cochrane review encompassed adults aged 18 and older, irrespective of their cardiovascular disease history, including conditions like myocardial infarction, unstable angina, heart failure, stroke, and peripheral vascular disease. We considered individuals with or without comorbidities such as hypertension, diabetes mellitus, and chronic kidney disease. Moreover, we included individuals affected by a range of chronic inflammatory conditions, including but not limited to rheumatoid arthritis, psoriasis, and inflammatory bowel disease.

If a trial included at least ten participants that met our inclusion criteria, and it had a clear subgroup analysis, it was included in the calculation. Otherwise, we excluded from the analysis any study with a mixed population. For example, if a trial included both adults and children, with no clear subgroup analysis according to the age of the participants, it was excluded from our analysis. Nonetheless, before making the final decision, we tried to obtain the data for the participants of interest from the trialists.

### Types of interventions

We included trials comparing IL-receptor antagonists or TNF inhibitors with placebo or usual care. For the purposes of the review, and in the absence of a standard definition of usual care, we accepted the following: "It can include the routine care received by patients for prevention or treatment of diseases" (Gellman 2013). We included interventions given at any dosage and administration route, as follows.

#### *Interventions*

- Interleukin-1 (IL-1) receptor antagonists (anakinra, canakinumab);
- Interleukin-6 (IL-6) receptor antagonists (tocilizumab);
- Tumour necrosis factor inhibitors (etanercept, infliximab).

#### *Comparisons*

- Placebo
- Usual care

For the analysis, comparisons were treated separately. This means there were three comparison groups, organised by the level of prevention, as follows.

Primary prevention:

- IL-1 receptor antagonists (anakinra, canakinumab) compared with placebo or usual care;
- IL-6 receptor antagonists (tocilizumab) compared with placebo or usual care;
- TNF inhibitors (etanercept, infliximab) compared with placebo or usual care.

Secondary prevention:

- IL-1 receptor antagonists (anakinra, canakinumab) compared with placebo or usual care;
- IL-6 receptor antagonists (tocilizumab) compared with placebo or usual care;
- TNF inhibitors (etanercept, infliximab) compared with placebo or usual care.

We accepted co-medication use (such as lipid-lowering medication, antihypertensives, anticoagulants, or antithrombotic therapies) if all participants had equal access to these co-medications.

### Types of outcome measures

Reporting one or more of the outcomes listed below in the trial was not an inclusion criterion for the review. We tried to access the trial protocol or contacted the trial authors to ascertain all measured outcomes, even if unreported. Relevant trials that measured these outcomes but did not report the data at all or not in a usable format were included in the narrative. We did not exclude an RCT solely based on the reporting of the outcome data.

For outcomes that can occur more than once during follow-up, we were interested in the number of participants with at least one event. All outcomes were assessed at maximum follow-up.

#### *Primary outcomes*

1. All-cause mortality;
2. Myocardial infarction (fatal or non-fatal);
3. Unstable angina;
4. Adverse events. We analysed adverse events by the number of people that experienced at least one event and the total number of adverse events· We reported these analyses separately. We prioritised reporting infections.

#### *Secondary outcomes*

1. Peripheral vascular disease;
2. Stroke (fatal or non-fatal). We included either acute ischaemic stroke or acute cerebral haemorrhage. Clinical diagnosis with imaging was an eligibility criterion;
3. Quality of life, measured by validated scales such as the WHO quality of life assessment instrument (WHOQOL), Medical Outcomes Study 36-item Short-Form health survey

(SF-36), Nottingham Health Profile (NHP), Euro-Quality of life questionnaire (EuroQol, EQ-5D), etc. (Gierlaszyńska 2016);
4. Heart failure.

Economic costs were excluded as an outcome of this Cochrane Review. However, if data were available, economic costs were narratively discussed in the Discussion section of the review.

## Search methods for identification of studies

### Electronic searches

We identified trials through systematic searches of the following bibliographic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2024, Issue 2) in the Cochrane Library;
- MEDLINE (Ovid, from 1946 to 20 February 2024);
- Embase (Ovid, from 1980 to 20 February 2024). From 2022 to 2024, we utilised the non-Ovid version of Embase. As a result, we adapted the original search strategy to be compatible with the platform we had access to during this period;
- Web of Science CPCI-S (Conference Proceedings Citation Index-Science) (Clarivate Analytics, from 1990 to 20 February 2024).

The preliminary search strategy for MEDLINE (Ovid) was adapted for use in the other databases. The search strategies and results are presented in Appendix 5. The preliminary search strategy is reported in Martí-Carvajal 2021. The Cochrane sensitivity-precision maximising RCT filter (Lefebvre 2019) was applied to MEDLINE (Ovid) and adaptations of it to the other databases, except CENTRAL. We searched all databases from their inception to February 2024. We did not restrict the language of publication or publication status. We also searched the following ongoing trial registries.

- ClinicalTrials.gov (www.ClinicalTrials.gov);
- WHO International Clinical Trials Registry Platform (www.who.int/ictrp/en/).

We also searched the following regulatory data websites.

- European Medicines Agency (EMA) (www.ema.europa.eu/en);
- Food and Drug Administration (FDA) (www.fda.gov/Drugs).

### Searching other resources

We checked reference lists of all included studies and any relevant systematic reviews identified for additional trial references. We also examined all pertinent retraction statements and errata for included studies. We contacted study authors for missing data and ongoing trials.

We searched relevant manufacturers' websites for trial information on the interventions, as follows.

- Anakinra;
- Canakinumab;
- Tocilizumab;
- Etanercept;
- Infliximab.

## Data collection and analysis

We followed the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008).

### Selection of studies

Two pairs of review authors (AMC/SN; DM/ACP) independently and in duplicate screened titles and abstracts of all the potential studies we identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. Any disagreement was solved by arbitration (MD, EA). We retrieved the full-text study reports/publications, and two review authors (RRL, MGV) independently screened the full text, identified studies for inclusion, and identified and recorded reasons for excluding the ineligible studies. We resolved any disagreement through discussion or, if required, we consulted two review authors (MD, JBDS). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Page 2021).

### Data extraction and management

We used a data collection form for study characteristics and outcome data piloted on at least one study in the review. AMC and MGV independently extracted outcome data from the included studies. We resolved disagreements by consensus or by involving two authors (RRL). One review author (AMC) transferred data into Review Manager software (RevMan Web 2019). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the data extraction form. A second review author (RRL) spot-checked study characteristics for accuracy against the trial report. We extracted the following study characteristics.

1. Methods: study design, the total duration of the study, follow-up period, details of any 'run-in' period, number of study centres and location, study setting, type of trial (superiority, equivalence, or non-inferiority trial), and date of the study;
2. Participants: number (N) randomised, number lost to follow-up/withdrawn, number analysed, mean age, age range, gender, the severity of the condition (i.e. New York Heart Association (NYHA) functional classification, etc.), diagnostic criteria (e.g. how stroke was diagnosed), history of cardiovascular disease (myocardial infarction (fatal or non-fatal), unstable angina, heart failure, stroke (fatal or non-fatal), peripheral vascular disease), comorbidities (hypertension, diabetes mellitus, and chronic kidney disease), other cardiovascular risk factors (smoking, dyslipidaemia), inclusion criteria, and exclusion criteria;
3. Interventions: intervention, comparison, concomitant medications, and excluded medications. Appendix 6 shows details of the intervention description (Hoffmann 2014; Hoffmann 2017). Appendix 7 shows details of collecting adverse events' information with an Excel spreadsheet (Li 2019);
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported;
5. Notes: trial registration number, date trial was conducted, a priori sample estimation, financial disclosures, other disclosures, and funding/support.

### Assessment of risk of bias in included studies

One review author (AMC) assessed the risk of bias in each trial, using the original version of Cochrane's 'Risk of bias' tool and following the domain-based evaluation described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Other review authors (MG, MD, JBDeS) independently re-checked the risk of bias in each trial. We discussed any discrepancies between review authors and achieved consensus on the final assessment.
We assessed the following domains as 'Yes' (i.e. low risk of bias), 'Unclear' (uncertain risk of bias), or 'No' (i.e. high risk of bias).

1. Randomisation;
2. Concealment of allocation;
3. Blinding (of participants, personnel and outcome assessors);
4. Incomplete outcome data;
5. Selective outcome reporting;
6. Free of other bias (baseline imbalance, early stopping, academic fraud, drug company involvement) (Gurusamy 2009; Ioannidis 2008a Ioannidis 2008b).

We used the following definitions.

#### *Generation of the allocation sequence*

- Yes (low risk of bias) if a computer or random number table generated the allocation sequence. Drawing lots, tossing a coin, shuffling cards, or throwing dice will be considered adequate if a person, who was not otherwise involved in the recruitment of participants, performed the procedure.
- Unclear (uncertain risk of bias) if the trial was described as randomised, but the method used for the allocation sequence generation was not explained.
- No (high risk of bias) if a system involving dates, names, or admittance numbers was used to allocate patients. These studies are known as quasi-randomised and were excluded from the present review.

#### *Allocation concealment*

- Yes (low risk of bias) if the allocation of patients involved a central independent unit, on-site locked computer, identical appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
- Unclear (uncertain risk of bias) if the trial was described as randomised, but the method used to conceal the allocation was not explained.
- No (high risk of bias) if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised. The latter were excluded from the present review.

#### *Incomplete outcome data*

- Yes (low risk of bias); the numbers and reasons for dropouts and withdrawals in all intervention groups were described, or it was specified that there were no dropouts or withdrawals.
- Unclear (uncertain risk of bias), the report gave the impression that there had been no dropouts or withdrawals, but this was not explicitly stated.
- No (high risk of bias), and the number of reasons for dropouts and withdrawals were not described. We examined the percentages of dropouts overall in each trial and per randomisation arm.

We evaluated whether intention-to-treat (ITT) analysis could have been performed (based on the published information).

#### *Were all randomised participants analysed in the group to which they were allocated? (ITT analysis)*

- Yes (low risk of bias): reported explicitly by authors that intention-to-treat analysis (ITT) was undertaken, and this was confirmed on the study assessment, or not stated but evident from the study assessment that all randomised participants were reported and analysed in the group to which they were allocated for the most critical time point of outcome measurement (minus missing values) irrespective of non-compliance and co-interventions.
- No (high risk of bias): lack of ITT confirmed on study assessment (randomised patients were not included in the analysis because they did not receive the study intervention, withdrew from the study, or were not included because of protocol violation) regardless of whether ITT was reported or not. Per protocol analysis done with the substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
- Unclear (uncertain risk of bias): Described as ITT analysis, but unable to confirm on study assessment, or not reported and unable to verify by study assessment.

#### *Selective outcome reporting*

- Yes: good, pre-defined, or clinically relevant and reasonably expected outcomes were reported.
- Unclear: not all pre-defined or clinically relevant and reasonably expected outcomes were reported on or reported fully, or it was unclear whether data on these outcomes were recorded.
- No, inadequate, one or more clinically relevant and reasonably expected outcomes were not reported; data on these outcomes were likely to have been recorded.

#### *Free of other bias (baseline imbalance, stopping early for benefit, academic fraud, drug company involvement)*

- Yes (low risk of bias); the trial appears to be free of other components that could put it at risk of bias.
- Unclear (uncertain risk of bias), the trial may or may not be free of other components that could put it at risk of bias.
- No (high risk of bias); other factors in the trial could put it at risk of bias, e.g. academic fraud, stopping early, industry involvement, or extreme baseline imbalance.

#### *Overall risk of bias*

We made explicit judgements about whether the RCTs were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We assessed the risk of bias as being high if any of the above domains were assessed as being at unclear or high risk of bias.
Trials that had an adequate generation of allocation sequence, allocation concealment, blinding, handling of incomplete outcome data, and no selective outcome reporting and without other risks of bias were considered to be trials with a low risk of bias.

We assessed the risk of bias for the outcomes of the included trials in our 'Summary of findings' table (Schünemann 2019).

### Measures of treatment effect

We analysed dichotomous data (all-cause mortality, myocardial infarction, unstable angina, adverse events, heart failure, and stroke) with risk ratios and 95% confidence intervals (CIs). For outcomes measuring incidence rates, e.g. counts of the number of adverse events occurring or number of infections occurring (sometimes this happens more than once per person), then we estimated the rate ratio and 95% CIs. We also estimated the mean difference (MD) with 95% CI for measuring quality of life.

For future updates, if different scales are used for measuring the quality of life, we plan to use the standardised mean difference (SMD) with 95% CIs. We will also estimate the ratio of means (RoM), with 95% CIs, from the mean difference (Friedrich 2011). As RoM can only be used when outcome measurements are positive, we will use RoM for single (post-intervention) assessments and not for change-from-baseline measures, which could be negative (Higgins 2008).

Due to practitioners' understanding and preference for dichotomous presentations of continuous outcomes, which they perceive to be the most useful (Johnston 2016), we will estimate odds ratios (ORs) with 95% CIs and the number needed to treat for an additional beneficial outcome (NNTB) from the SMD using Furukawa's method (Furukawa 1999; Furukawa 2011). The NNTB is a measure of assessment of the clinical usefulness of the consequences of treatment (Laupacis 1988). We will estimate the NNTB with GraphPad software and the Cochrane Stroke Group NNT calculator.

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008), if necessary, we multiplied the mean values from one set of studies by −1 to ensure that all the scales pointed in the same direction (Higgins 2008). We narratively described skewed data reported as medians and interquartile ranges. If statistical information was missing (such as standard deviations), we tried to extract it from other relevant information in the paper, such as P values and CIs.

### Unit of analysis issues

The unit of analysis in this Cochrane Review was the participant. The time of the analysis was the longest follow-up time established in each trial. In the case of multiple-armed trials, we combined the groups to yield a single pairwise comparison (Higgins 2008). For future updates, we will divide the control group denominator by two for continuous outcomes to have two pairwise comparisons. This approach will avoid double-counting participants.

### Dealing with missing data

This Cochrane review found that most meta-analyses included a small number of trials, which often showed high attrition bias. For future updates, we will assess the percentage of dropouts for each included trial and intervention group. We will evaluate whether an intention-to-treat (ITT) analysis was performed or could be performed using the available published information. If necessary, we will attempt to contact the study authors to answer any questions arising from this issue.

To undertake an ITT analysis, we will seek data from the trial authors about the number of participants in the treatment groups, irrespective of their compliance and whether they will later be thought to be ineligible, otherwise excluded from treatment, or lost to follow-up. We will perform a 'per protocol' analysis of those who will complete the study, aware that it may be biased. We will include participants with incomplete or missing data in sensitivity analyses by imputing them according to the following scenarios.

Extreme-case analysis favouring the experimental intervention ('best-worst' case scenario): none of the dropouts/participants lost from the experimental arm, but all the dropouts/participants lost from the control arm will experience the outcome, including all randomised participants in the denominator.

Extreme-case analysis favouring the control ('worst-best' case scenario): all dropouts/participants lost from the experimental arm, but none from the control arm ill experience the outcome, including all randomised participants in the denominator (Hollis 1999).

Gamble-Hollis analysis, which will take account of the uncertainty and will generate uncertainty intervals for a trial incorporating both sampling error and the potential impact of missing data (Gamble 2005). This method will increase the trials' uncertainty using the best-case and worst-case analyses (Chaimani 2014). We will perform no Gamble-Hollis analysis for the incidence rate. We will use STATA statistical software, version 18, to conduct the 'best-worst' case scenario, 'worst-best' case scenario, and Gamble-Hollis analysis for dichotomous data.

### Assessment of heterogeneity

We quantified statistical heterogeneity using the $I^2$ statistic, which describes the percentage of total variation across trials due to heterogeneity rather than sampling error (Higgins 2003). We assumed 50% to 90% may represent substantial heterogeneity (Deeks 2019). For a proper interpretation of $I^2$, we followed these recommendations: "The importance of the observed value of $I^2$ depends on (1) magnitude and direction of effects, and (2) strength of evidence for heterogeneity (e.g. P value from the $Chi^2$ test, or a confidence interval for $I^2$: uncertainty in the value of $I^2$ is substantial when the number of studies is small)" (Deeks 2019). However, we considered statistical heterogeneity present if $I^2$ was 70% or above (Deeks 2019). We will quantify the 95% CI or uncertainty interval of $I^2$ for future updates with STATA statistical software (Kontopantelis 2010).

For future updates, if there is statistical heterogeneity and three or more RCTs, we will determine the 95% prediction interval, which considers the whole distribution of the effects (Riley 2011). Prediction intervals in meta-analysis show similar studies' expected range of true effects (IntHout 2016). We will estimate the 95% prediction interval with STATA. If there are ten or more RCTs and the $I^2$ value is 70% or greater, we will conduct a meta-regression with STATA in future updates. The outcome variable will be predicted for the following explanatory variables (the potential effect modifiers): diabetes mellitus, chronic kidney disease, and receptor antagonist type. We plan to conduct the potential meta-regression analyses by prevention level.

### Assessment of reporting biases

We conducted only one funnel plot with RevMan Web's tools. There were technical issues with performing a contour-enhanced funnel plot as planned.

For future updates, if there are 10 or more RCTs, we will use a contour-enhanced funnel plot to differentiate asymmetry that is due to publication bias from that due to other factors (Peters 2008). We will assess the likelihood of publication bias with Harbord's and Peter's tests (Sterne 2011). We will use STATA to produce conventional and contour funnel plots.

### Data synthesis

We performed meta-analyses with 95% CIs using a random-effects model. We conducted the meta-analyses using RevMan Web (RevMan Web 2019). Following the recommendation of the Cochrane Handbook, we reported the results of both random-effects and fixed-effect models within the text of the review for those meta-analyses with more than five trials (Bender 2018; Schulz 2022). For future updates, we will report the prediction interval in the case of statistical heterogeneity ($I^2$ value of 70% or greater) (Deeks 2019; IntHout 2016; Riley 2011).

### Subgroup analysis and investigation of heterogeneity

For future updates, we will conduct subgroup analyses for primary or secondary prevention. If we identify enough trials (five or more), we will conduct the following subgroup analyses for any outcomes with substantial heterogeneity.

1. Adult participants (18 to 64 years old) versus older participants (65 years old or more) (hypothesis: older participants have a higher risk of developing cardiovascular outcomes).
2. Male participants compared to female participants (hypothesis: females have a higher risk of cardiovascular outcomes due to the high prevalence of rheumatic disorders).
3. Participants with diabetes mellitus versus participants without diabetes mellitus (hypothesis: people with diabetes mellitus have an additional risk factor for developing cardiovascular outcomes).
4. Participants with chronic kidney disease versus participants without chronic kidney disease. We will follow the classification based on the estimated glomerular filtration rate (mL/min/1.73 $m^2$) (Grams 2019) (hypothesis: chronic kidney disease is an additional risk factor for developing a cardiovascular outcome).
5. Trials with 200 participants or fewer by group versus trials with more than 200 participants per group; 200 is an arbitrary threshold or cut-off point (hypothesis: trials with a small sample size show an overestimation of effect size).
6. Trials supported by pharmaceutical companies compared to trials not supported by pharmaceutical companies (hypothesis: pharmaceutical-supported trials are associated with a positive effect).

We will use the formal test for subgroup differences in RevMan Web (RevMan Web 2019) and base our interpretation on this. We will conduct a subgroup analysis for all outcomes.

### Sensitivity analysis

For future updates, we plan to conduct sensitivity analyses as follows, comparing the results with the original analyses:

1. We will compare trials with a low risk of bias to those with unclear and high risk of bias. In this first version, all included trials had high or unclear risk of bias, so we did not conduct this sensitivity analysis.
2. We will compare trials without missing data to trials with missing data. For the current version, we determined this would be redundant, as we had already conducted:
   a. An extreme-case analysis favouring the experimental intervention ('best-worst' case scenario)
   b. An extreme-case analysis favouring control ('worst-best' case scenario)
   c. The Gamble-Hollis analysis

In this first version, most meta-analyses included few studies and showed high attrition bias.

We will use the overall risk of bias judgement for studies rather than specific domains. To assess differences between primary and sensitivity analyses, we will compare changes in P values.

We will conduct these analyses only for the primary outcomes.

For future updates, we will also assess the percentage of dropouts for each included trial and intervention group. We will evaluate whether an intention-to-treat (ITT) analysis was performed or could be performed using the available published information. If necessary, we will attempt to contact the study authors to answer any questions arising from this issue.

### Summary of findings and assessment of the certainty of the evidence

We created six 'Summary of findings' tables using the following outcomes: all-cause mortality, myocardial infarction, unstable angina, adverse events, peripheral vascular disease, stroke, and heart failure (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it related to the studies which contributed data to the meta-analyses for the prespecified outcomes (Atkins 2004; Guyatt 2008). We used the methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019) using GRADEpro software. Each comparison (as listed in Types of interventions) was according to the protocol of this Cochrane review (Martí-Carvajal 2021). We justified all decisions to downgrade the quality of the evidence using footnotes, and we made comments to aid the reader's understanding of the review, where necessary.

We used www.stat.ubc.ca/~rollin/stats/ssize/b2.html to estimate the optimal information size to assess imprecision as recommended in Guyatt 2011.

Judgements about evidence quality were made by two review authors (AMC, JMPV) working independently, with disagreements resolved by discussion or involving three authors (MGV, EA, DM). Judgements were justified, documented, and incorporated into the reporting of results for each outcome. We communicated the findings of interventions following the GRADE Working Group's recommendations (Santesso 2020).

# RESULTS

## Description of studies

This Cochrane review conducted two searches for trials: one in February 2022 and another in February 2024. The latter search was carried out during the first editorial review. A total of 3563 records were identified by database searches up to January 2022. An additional 514 records were collected from February 2022 to February 2024. In addition, 31 records were identified through other sources, resulting in a total of 4108 records before removal of duplicates. After deduplication, the number was reduced to 900 unique records, of which 899 were from the period up to January 2022 and one from the period February 2022 to February 2024. Screening of the 900 records by title and abstract led to the exclusion of 762 records as they did not meet the pre-defined inclusion criteria. The remaining 138 records were reviewed in full text and 20 records corresponding to 17 studies were excluded for various specific reasons: one study for duplicate participant data (Antoni 2005) in three records, one non-randomised clinical trial (Chaudhari 2001) in one record, three studies for other reasons (Bissonnette 2011; Martínez-Taboada 2008; Reich 2005) in three records, three trials were classified as awaiting classification (Gottlieb 2011, Parry-Jones 2023, Strober 2011) in three records, and nine studies in ten records were identified as ongoing (see the 'Ongoing studies' section below).

We identified 118 records corresponding to 58 trials published between 1999 and 2023 (Abbate 2010; Abbate 2013; Abbate 2020; Bachelez 2015; Baek 2019; Bagel 2012; Bernstein 2006; Boetticher 2008; Bozkurt 2001; Brandt 2003; Broch 2021; Brucato 2016; Butchart 2015; Calin 2004; Carroll 2018; Choudhury 2016; Chung 2003; Davis 2003; Deswal 1999; Don 2010; Ebrahimi 2018; Emsley 2005; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Kleveland 2016; Kreiner 2010; Krisai 2020; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Meyer 2021; Micali 2015; Morton 2015; Padfield 2013; Papp 2005; Ralph 2020; RECOVER 2000; Reich 2017; RENAISSANCE 2001; Ridker 2012; Ridker 2017; Russel 2019; Smith 2018; Smolen 2008; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Villiger 2016; Weisman 2007).

Figure 1 shows details of the flow of study selection. Please also see Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

**Figure 1.**

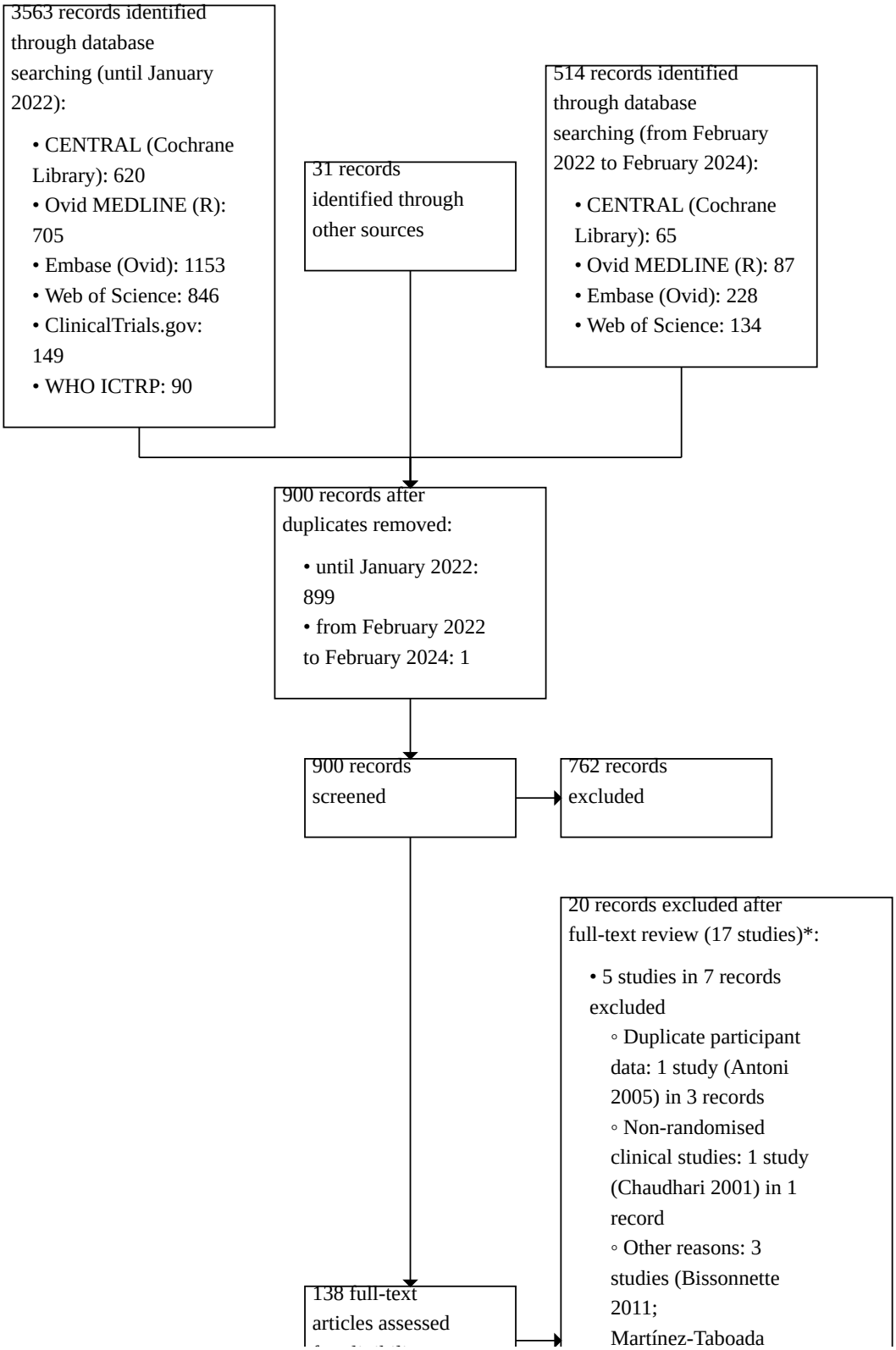
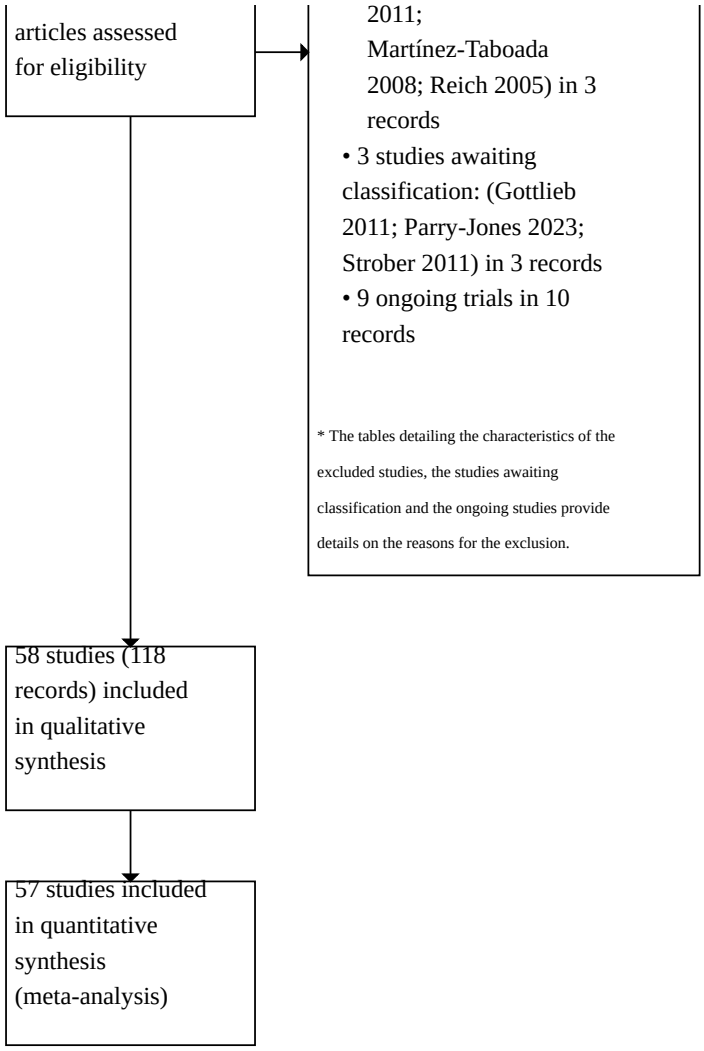


**Figure 1. (Continued)**




### Results of the search

All trials are described in the section Characteristics of included studies. The trials varied in size, characteristics of participant populations, duration, study setting, drug dosage, and experimental design. Figure 1 shows details of the flow of study selection.

### Included studies

#### *1. Methods*

##### 1.1. Design

The parallel-group trial design was used in all trials, as it was required by the criteria for inclusion.

##### 1.2 Number of comparison groups

The number of comparison groups ranged between two and five: forty trials compared two arms (Abbate 2010; Abbate 2013; Bachelez 2015; Baek 2019; Bagel 2012; Bernstein 2006; Boetticher 2008; Brandt 2003; Broch 2021; Brucato 2016; Butchart 2015; Calin 2004; Carroll 2018; Choudhury 2016; Davis 2003; Don 2010; Ebrahimi 2018; Emsley 2005; Gorman 2002; Gottlieb 2003; Khanna 2016; Khanna 2020; Kleveland 2016; Krisai 2020; Mease 2000; Mease 2004; Meyer 2021; Micali 2015; Morton 2015; Padfield 2013; Ralph 2020; Russel 2019; Smith 2018; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van Tassell 2016; Van Tassell 2018; Villiger 2016; Weisman 2007), twelve had three arms (Abbate 2020; Bozkurt 2001; Chung 2003; Gottlieb 2004; Menter 2007; Papp 2005; RECOVER 2000; RENAISSANCE 2001; Reich 2017; Smolen 2008; Van Tassell 2017; Van der Heijde 2006), five had four arms (Bachelez 2015; Deswal 1999; Kreiner 2010; Leonardi 2003; Ridker 2017), and one had five comparison groups (Ridker 2012).

##### 1.3 Country setting for trials

The mean number of countries by trial was 4.45 (SD 7.51, minimum 1, maximum 40; 95% CI 2.51 to 6.39), and the median was 1 (Q1: 1 and Q3: 5). The United States of America was the country with the most published trials. Table 1 shows complete details.

#### 1.4 Follow-up

The mean follow-up duration for all trials was 27.3 weeks (SD 28.5, min: 0.14, max: 192, 95% CI 19.8 to 34.8), and the median was 24 weeks (Interquartile range: 12 to 29).

#### 1.5 Run-in-period

Five trials reported a run-in-period (Brucato 2016; Micali 2015; Ridker 2012; Russel 2019; Villiger 2016).

#### 1.6 Type of prevention

Thirty-four trials focused on primary prevention (Abbate 2010; Abbate 2013; Bachelez 2015; Baek 2019; Bagel 2012; Bernstein 2006; Boetticher 2008; Brandt 2003; Butchart 2015; Calin 2004; Davis 2003; Don 2010; Ebrahimi 2018; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; Reich 2017; Ridker 2012; Smolen 2008; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006; Villiger 2016). The follow-up mean was 25.28 weeks (SD 19.53, 95% CI 18.7 to 31.9, median 24 (Q1: 14 and Q3: 28)).

Twenty-four trials aimed at secondary prevention (Abbate 2020; Bozkurt 2001; Broch 2021; Brucato 2016; Carroll 2018; Choudhury 2016; Chung 2003; Deswal 1999; Emsley 2005; Kleveland 2016; Krisai 2020; Meyer 2021; Morton 2015; Padfield 2013; Ralph 2020; RECOVER 2000; RENAISSANCE 2001; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Weisman 2007). The follow-up mean was 36.51 weeks (SD 48.8, 95% CI 17 to 56, median 24 (Q1: 12 Q3: 42))

#### 1.7 Internationally collaborative trials

There were twenty-one internationally collaborative trials (Bachelez 2015; Bagel 2012; Calin 2004; Choudhury 2016; Davis 2003; Khanna 2016; Khanna 2020; Krisai 2020; Menter 2007; Micali 2015; Papp 2005; RECOVER 2000; RENAISSANCE 2001; Reich 2017; Ridker 2012; Ridker 2017; Russel 2019; Smolen 2008; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006). See Table 2 for details.

#### 1.8 Number of study centres

Fifty-three trials reported the number of study centres where they were conducted (Abbate 2010; Abbate 2013; Abbate 2020; Bachelez 2015; Baek 2019; Bernstein 2006; Boetticher 2008; Bozkurt 2001; Brucato 2016; Butchart 2015; Calin 2004; Carroll 2018; Choudhury 2016; Chung 2003; Davis 2003; Deswal 1999; Don 2010; Ebrahimi 2018; Emsley 2005; Gottlieb 2004; Khanna 2016; Khanna 2020; Kleveland 2016; Kreiner 2010; Krisai 2020; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Meyer 2021; Micali 2015; Morton 2015; Padfield 2013; Papp 2005; Ralph 2020; RECOVER 2000; Reich 2017; RENAISSANCE 2001; Ridker 2012; Ridker 2017; Russel 2019; Smith 2018; Smolen 2008; Stanley 2011; Torii 2010; Tyring 2006; Van der Heijde 2006; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Villiger 2016; Weisman 2007). The mean of the study centres was 46 (SD 154.24, the range was 1 to 1113, 95% CI was 6.3 to 85.7). Five trials didn't report this information (Bagel 2012; Brandt 2003; Gorman 2002; Gottlieb 2003; Van de Kerkhof 2008).

Forty-one trials were multicentre trials (Abbate 2020; Bachelez 2015; Baek 2019; Bagel 2012; Bernstein 2006; Boetticher 2008; Bozkurt 2001; Brandt 2003; Broch 2021; Brucato 2016; Calin 2004; Choudhury 2016; Chung 2003; Davis 2003; Don 2010; Ebrahimi 2018; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Kleveland 2016; Krisai 2020; Leonardi 2003; Mease 2004; Menter 2007; Micali 2015; Morton 2015; Papp 2005; RECOVER 2000; RENAISSANCE 2001; Reich 2017; Ridker 2012; Ridker 2017; Russel 2019; Smolen 2008; Torii 2010; Tyring 2006; Weisman 2007; Van de Kerkhof 2008; Van der Heijde 2006).

There were seventeen single-centre trials conducted in the following countries: Australia (Ralph 2020), Denmark (Kreiner 2010; Meyer 2021), Switzerland (Villiger 2016), the United Kingdom (Butchart 2015; Emsley 2005; Padfield 2013; Smith 2018), and the United States of America (Abbate 2010; Abbate 2013; Carroll 2018; Deswal 1999; Mease 2000; Stanley 2011; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018).

#### 1.9 Trial settings

There were three types of study settings (inpatient settings, outpatient settings and both inpatient and outpatient settings). Nine trials had both inpatient and outpatient settings (Abbate 2010; Abbate 2013; Abbate 2020; Brucato 2016; Carroll 2018; Emsley 2005; Krisai 2020; Van Tassell 2016; Van Tassell 2017); forty-three had an outpatient setting (Bachelez 2015; Baek 2019; Bagel 2012; Bernstein 2006; Boetticher 2008; Bozkurt 2001; Brandt 2003; Butchart 2015; Calin 2004; Choudhury 2016; Chung 2003; Davis 2003; Deswal 1999; Don 2010; Ebrahimi 2018; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; RECOVER 2000; RENAISSANCE 2001; Ralph 2020; Reich 2017; Ridker 2012; Ridker 2017; Russel 2019; Smolen 2008; Stanley 2011; Torii 2010; Tyring 2006; Van Tassell 2018; Villiger 2016; Weisman 2007; Van de Kerkhof 2008; Van der Heijde 2006) and six had an inpatient setting (Broch 2021; Kleveland 2016; Meyer 2021; Morton 2015; Padfield 2013; Smith 2018).

#### 1.10 Type of trial

One trial was a superiority trial (Ridker 2017), and three were reported as non-inferiority trials (Bachelez 2015; Carroll 2018; Van der Heijde 2006). Type of trial was not reported in fifty-four trials (Abbate 2010; Abbate 2013; Abbate 2020; Baek 2019; Bagel 2012; Bernstein 2006; Boetticher 2008; Bozkurt 2001; Brandt 2003; Broch 2021; Brucato 2016; Butchart 2015; Calin 2004; Choudhury 2016; Chung 2003; Davis 2003; Deswal 1999; Don 2010; Ebrahimi 2018; Emsley 2005; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Kleveland 2016; Kreiner 2010; Krisai 2020; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Meyer 2021; Micali 2015; Morton 2015; Padfield 2013; Papp 2005; Ralph 2020; RECOVER 2000; Reich 2017; RENAISSANCE 2001; Ridker 2012; Russel 2019; Smith 2018; Smolen 2008; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Villiger 2016; Weisman 2007).

### *2. Participants*

#### 2.1 Type of disease

We identified thirty trials related to cardiovascular diseases, either primary or secondary prevention (Abbate 2010; Abbate 2013; Abbate 2020; Bernstein 2006; Bozkurt 2001; Broch 2021; Brucato 2016; Carroll 2018; Choudhury 2016; Chung 2003; Deswal 1999; Don 2010; Ebrahimi 2018; Emsley 2005; Kleveland 2016; Krisai 2020; Meyer 2021; Morton 2015; Padfield 2013; RECOVER 2000; RENAISSANCE 2001; Ralph 2020; Ridker 2012 Ridker 2017; Russel 2019; Smith 2018; Stanley 2011; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018). Twenty-eight were related to soft tissue and

musculoskeletal disorders (Bachelez 2015; Baek 2019; Bagel 2012; Boetticher 2008; Brandt 2003; Butchart 2015; Calin 2004; Davis 2003; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; Reich 2017; Smolen 2008; Torii 2010; Tyring 2006; Villiger 2016; Weisman 2007; Van de Kerkhof 2008; Van der Heijde 2006).

#### 2.2 Type of participants

Fifty-seven studies only included participants that had the condition investigated in the trial (Abbate 2010; Abbate 2013; Abbate 2020; Bachelez 2015; Baek 2019; Bagel 2012; Bernstein 2006; Boetticher 2008; Bozkurt 2001; Brandt 2003; Broch 2021; Brucato 2016; Butchart 2015; Calin 2004; Carroll 2018; Choudhury 2016; Chung 2003; Davis 2003; Deswal 1999; Don 2010; Ebrahimi 2018; Emsley 2005; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Kleveland 2016; Krisai 2020; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Meyer 2021; Micali 2015; Morton 2015; Padfield 2013; Papp 2005; Ralph 2020; RECOVER 2000; Reich 2017; RENAISSANCE 2001; Ridker 2012; Ridker 2017; Russel 2019; Smith 2018; Smolen 2008; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Villiger 2016; Weisman 2007). One study (Kreiner 2010) included participants with and without the disease investigated in the trial; however, we only used the data from the participants with the condition assessed.

#### 2.3. Randomised groups

The fifty-eight trials included 22,053 randomised participants; however, due to some studies having more than two arms using interventions not included in our protocol, the total number of participants who met our inclusion criteria was 21,308, and these were the ones analysed in this review. The mean was 367 (SD: 1320; minimum: 10; maximum: 10,061, 95% CI: 20 to 714), and the median was 86 (quartile 1 (Q1): 34 and quartile 3 (Q3): 212) (Abbate 2010; Abbate 2013; Abbate 2020; Bachelez 2015; Baek 2019; Bagel 2012; Bernstein 2006; Boetticher 2008; Bozkurt 2001; Brandt 2003; Broch 2021; Brucato 2016; Butchart 2015; Calin 2004; Carroll 2018; Choudhury 2016; Chung 2003; Davis 2003; Deswal 1999; Don 2010; Ebrahimi 2018; Emsley 2005; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Kleveland 2016; Kreiner 2010; Krisai 2020; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Meyer 2021; Micali 2015; Morton 2015; Padfield 2013; Papp 2005; Ralph 2020; RECOVER 2000; Reich 2017; RENAISSANCE 2001; Ridker 2012; Ridker 2017; Russel 2019; Smith 2018; Smolen 2008; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Villiger 2016; Weisman 2007).

Regardless of either primary or secondary prevention, in cardiovascular disease trials, the mean was 479 (SD: 1829; minimum: 10; maximum: 10,061; 95% CI -204 to 1162), and the median was 52 (Q1: 28, Q3: 150) (Abbate 2010; Abbate 2013; Abbate 2020; Bernstein 2006; Bozkurt 2001; Broch 2021; Brucato 2016; Carroll 2018; Choudhury 2016; Chung 2003; Deswal 1999; Don 2010; Ebrahimi 2018; Emsley 2005; Kleveland 2016; Krisai 2020; Meyer 2021; Morton 2015; Padfield 2013; RECOVER 2000; RENAISSANCE 2001; Ralph 2020; Ridker 2012 Ridker 2017; Russel 2019; Smith 2018; Stanley 2011; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018). In non-cardiovascular disorders, the mean was 248 (SD: 242; minimum: 22; maximum: 835; 95% CI: 242 to 253), and the median was 133.5 (Q1: 57 and Q3: 400) (Bachelez 2015; Baek 2019; Bagel 2012; Boetticher 2008; Brandt 2003; Butchart 2015; Calin 2004; Davis 2003: Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; Reich 2017; Smolen 2008; Torii 2010; Tyring 2006; Villiger 2016; Weisman 2007; Van de Kerkhof 2008; Van der Heijde 2006).

As for primary prevention, regardless of the type of disease, the participants' mean was 210 (SD: 233; minimum: 10; maximum: 835; 95% CI: 129 to 291), and the median was 109 (Q1: 41 and Q3: 277) (Abbate 2010; Abbate 2013; Bachelez 2015; Baek 2019; Bagel 2012; Bernstein 2006; Boetticher 2008; Brandt 2003; Butchart 2015; Calin 2004; Davis 2003; Don 2010; Ebrahimi 2018; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; Reich 2017; Ridker 2012; Smolen 2008; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006; Villiger 2016). As for secondary prevention, the mean was 590 (SD: 2038; minimum: 18; maximum: 10,061; 95% CI -270 to 1451), and the median was 70 (Q1: 29 and Q3: 186) (Abbate 2020; Bozkurt 2001; Broch 2021; Brucato 2016; Carroll 2018; Choudhury 2016; Chung 2003; Deswal 1999; Emsley 2005; Kleveland 2016; Krisai 2020; Meyer 2021; Morton 2015; Padfield 2013; Ralph 2020; RECOVER 2000; RENAISSANCE 2001; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Weisman 2007)

#### 2.4. Loss of participants

There were 13.4% (2853/21,308) lost participants in all trials. The trials assessing cardiovascular disorders lost 14.51% of participants (2085/14,370). For the trials studying non-cardiovascular diseases, the total loss of participants was 11.1% (768/6938).

#### 2.5. Comorbidities

##### 2.5.1 Hypertension

Twenty-eight trials included participants with hypertension. Regarding primary prevention, there were seven trials (Abbate 2010; Abbate 2013; Bernstein 2006; Ebrahimi 2018; Kreiner 2010; Ridker 2012; Stanley 2011) and twenty-one trials in secondary prevention (Abbate 2020; Broch 2021; Brucato 2016; Carroll 2018; Choudhury 2016; Chung 2003; Emsley 2005; Kleveland 2016; Krisai 2020; Meyer 2021; Morton 2015; Padfield 2013; RECOVER 2000; RENAISSANCE 2001; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Weisman 2007).

##### 2.5.2 Diabetes mellitus

Twenty-four trials had participants with this condition. Five trials were related to primary prevention (Abbate 2010; Abbate 2013; Ebrahimi 2018; Ridker 2012; Van der Heijde 2006), and nineteen to secondary prevention (Abbate 2020; Broch 2021; Carroll 2018; Choudhury 2016; Chung 2003; Emsley 2005; Kleveland 2016; Krisai 2020; Meyer 2021; Morton 2015; Padfield 2013; RECOVER 2000; RENAISSANCE 2001; Ridker 2017; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Weisman 2007).

##### 2.5.3 Chronic kidney disease

Five trials covered this comorbidity: one in primary prevention (Don 2010) and four in secondary prevention (Carroll 2018; Meyer 2021; Ridker 2017; Van Tassell 2016).

#### 2.5.4 Smoking

Nineteen trials stated they included patients with current or previous smoking habits. Six related to primary prevention (Baek 2019; Ebrahimi 2018; Khanna 2020; Kreiner 2010; Ridker 2012; Stanley 2011); and thirteen to secondary prevention (Broch 2021; Carroll 2018; Choudhury 2016; Emsley 2005; Kleveland 2016; Krisai 2020; Meyer 2021; Morton 2015; Padfield 2013; Ridker 2017; Smith 2018; Van Tassell 2016; Van Tassell 2018).

#### 2.5.5 Hyperlipidaemia

Eighteen trials reported having included participants with this condition. Seven were from primary prevention (Baek 2019; Bernstein 2006; Ebrahimi 2018; Kreiner 2010; Ridker 2012; Smolen 2008; Stanley 2011), and eleven from secondary prevention trials (Broch 2021; Brucato 2016; Carroll 2018; Choudhury 2016; Emsley 2005; Kleveland 2016; Morton 2015; Padfield 2013; Ridker 2017; Smith 2018; Van Tassell 2016)

### 2.6 C-reactive protein

Sixty-six per cent of the trials (38/58) reported information about C-reactive protein levels, either related to primary or secondary prevention (Abbate 2010; Abbate 2013; Abbate 2020; Baek 2019; Bernstein 2006; Brandt 2003; Broch 2021; Brucato 2016; Butchart 2015; Calin 2004; Carroll 2018; Choudhury 2016; Chung 2003; Davis 2003; Don 2010; Ebrahimi 2018; Emsley 2005; Gorman 2002; Khanna 2016; Khanna 2020; Kleveland 2016; Kreiner 2010; Krisai 2020; Mease 2000; Mease 2004; Meyer 2021; Morton 2015; Ridker 2012; Ridker 2017; Russel 2019; Smith 2018; Smolen 2008; Stanley 2011; Van der Heijde 2006; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Villiger 2016).

Regardless of primary or secondary prevention, thirty-six per cent of trials (21/58) reported non-high sensitivity C-reactive protein levels (Baek 2019; Bernstein 2006; Brandt 2003; Brucato 2016; Butchart 2015; Calin 2004; Carroll 2018; Davis 2003; Don 2010; Ebrahimi 2018; Emsley 2005; Gorman 2002; Khanna 2016; Khanna 2020; Kreiner 2010; Mease 2000; Mease 2004; Smith 2018; Smolen 2008; Van der Heijde 2006; Villiger 2016). Twenty-nine per cent of the trials (17/58) reported high sensitivity C-reactive protein levels (Abbate 2010; Abbate 2013; Abbate 2020; Broch 2021; Choudhury 2016; Chung 2003; Kleveland 2016; Krisai 2020; Meyer 2021; Morton 2015; Ridker 2012; Ridker 2017; Russel 2019; Stanley 2011; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018). Information about C-reactive protein levels remains unknown in 20 trials (Bachelez 2015; Bagel 2012; Boetticher 2008; Bozkurt 2001; Deswal 1999; Gottlieb 2003; Gottlieb 2004; Leonardi 2003; Menter 2007; Micali 2015; Padfield 2013; Papp 2005; Ralph 2020; RECOVER 2000; Reich 2017; RENAISSANCE 2001; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Weisman 2007).

Concerning the primary prevention aim, eighteen trials reported C-reactive protein levels (Baek 2019; Bernstein 2006; Brandt 2003; Butchart 2015; Calin 2004; Davis 2003; Don 2010; Ebrahimi 2018; Gorman 2002; Khanna 2016; Khanna 2020; Kreiner 2010; Mease 2000; Mease 2004; Smolen 2008; Stanley 2011; Van der Heijde 2006; Villiger 2016).

Fifteen trials recorded basal non-high sensitivity C-reactive protein levels, and the mean was 4.43 mg/dL (SD 6.6 min: 0.21, max: 23.81, 95% CI 1.09 to 7.77, and the median was 2.0) (Baek 2019; Bernstein 2006; Butchart 2015; Calin 2004; Don 2010; Davis 2003; Ebrahimi 2018; Gorman 2002; Khanna 2016; Khanna 2020; Kreiner 2010; Mease 2000; Smolen 2008; Van der Heijde 2006; Villiger 2016). However, only ten trials reported that biomarker at the end of the trial, and the mean was 3.02 mg/dL (SD 5.9, 95% CI -0.622 to 6.659, min: 0.15 max: 19.27, median 0.7) (Butchart 2015; Calin 2004; Don 2010; Davis 2003; Ebrahimi 2018; Gorman 2002; Khanna 2020; Kreiner 2010; Mease 2000; Smolen 2008). One trial aiming at primary prevention reported high-sensitivity C-reactive protein, but only the basal levels (Stanley 2011).

Regarding secondary prevention targets, twenty trials reported basal C-reactive protein levels (Abbate 2010; Abbate 2013; Broch 2021; Brucato 2016; Carroll 2018; Choudhury 2016; Chung 2003; Kleveland 2016; Meyer 2021; Morton 2015; Ridker 2012; Ridker 2017; Russel 2019; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018).

Two trials reported basal non-high sensitivity C-reactive protein levels, and the mean was 1.1 mg/dL (SD 1.3 minimum: 0.2, maximum: 2.09, 95% CI -0.707 to 2.997, median: 0.45) (Brucato 2016; Carroll 2018). Fourteen trials reported high-sensitivity C-reactive protein basal levels (Abbate 2010; Abbate 2013; Broch 2021; Choudhury 2016; Chung 2003; Kleveland 2016; Meyer 2021; Morton 2015; Ridker 2012; Ridker 2017; Russel 2019; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018). The mean was 10.25 mg/L (SD 13.2 min: 0.28 max: 44.8, 95% CI 3.35 to 17.2). The median was 5.1 mg/L (Q1: 2.6 Q3: 9.7).

## *3. Interventions*

### 3.1. Types of interventions

#### 3.1.1 Interleukin-1 (IL-1) receptor antagonists (anakinra, canakinumab)

Sixteen trials used an interleukin-1 receptor antagonist. Eleven trials assessed anakinra (Abbate 2010; Abbate 2013; Abbate 2020; Brucato 2016; Ebrahimi 2018; Emsley 2005; Morton 2015; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018). Five trials assessed canakinumab (Choudhury 2016; Krisai 2020; Ridker 2012; Ridker 2017; Russel 2019).

#### 3.1.2 Interleukin-6 (IL-6) receptor antagonists (tocilizumab)

Nine trials assessed tocilizumab (Baek 2019; Broch 2021; Carroll 2018; Khanna 2016; Khanna 2020; Kleveland 2016; Meyer 2021; Smolen 2008; Villiger 2016).

#### 3.1.3 Tumour necrosis factor inhibitors (etanercept, infliximab)

Thirty-three trials assessed a TNF inhibitor as a study medication. Twenty-nine trials evaluated etanercept (Bachelez 2015; Bagel 2012; Bernstein 2006; Boetticher 2008; Bozkurt 2001; Brandt 2003; Butchart 2015; Calin 2004; Davis 2003; Deswal 1999; Don 2010; Gorman 2002; Gottlieb 2003; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Micali 2015; Padfield 2013; Papp 2005; RECOVER 2000; RENAISSANCE 2001; Ralph 2020; Reich 2017; Stanley 2011; Tyring 2006; Weisman 2007; Van de Kerkhof 2008; Van der Heijde 2006). Four trials assessed infliximab (Chung 2003; Gottlieb 2004; Menter 2007; Torii 2010).

### 3.2. Intervention doses

All trials reported the dose of medication they used. Table 3 shows details of this information.

#### 3.2.1 Interleukin-1 (IL-1) receptor antagonists (anakinra, canakinumab)

*3.2.1.1 Anakinra*

Ten out of eleven studies using anakinra reported the same dose of 100 mg (Abbate 2010; Abbate 2013; Abbate 2020; Brucato 2016; Ebrahimi 2018; Morton 2015; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018). One trial used another dose (Emsley 2005).

*3.2.2.1 Canakinumab*

Sixty per cent (3/5) of the trials reported canakinumab use at 150 mg (Choudhury 2016; Krisai 2020; Russel 2019). Two other trials reported other doses (Ridker 2012; Ridker 2017). See Table 3 for more information.

#### 3.2.2 Interleukin-6 (IL-6) receptor antagonists (tocilizumab)

The nine trials using tocilizumab reported diverse doses. Three trials used a dose of 162 mg (Carroll 2018; Khanna 2016; Khanna 2020). Another three trials used 8 mg/kg as their dose (Baek 2019; Smolen 2008; Villiger 2016)

#### 3.2.3 Tumour necrosis factor inhibitors (etanercept, infliximab)

Fifty-eight per cent of the studies using etanercept (17/29) reported a dose of 25 mg (Boetticher 2008; Brandt 2003; Calin 2004; Davis 2003; Don 2010; Gorman 2002; Gottlieb 2003; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Papp 2005; Ralph 2020; RECOVER 2000; RENAISSANCE 2001; Van der Heijde 2006; Weisman 2007). Eleven studies (38%) declared using a dose of 50 mg (Bachelez 2015; Bagel 2012; Bernstein 2006; Butchart 2015; Leonardi 2003; Micali 2015; Papp 2005; Reich 2017; Van de Kerkhof 2008; Van der Heijde 2006; Stanley 2011; Tyring 2006). One study used another dosage (Deswal 1999).

### 3.3 Frequency of administration

All trials reported frequency of administration. Table 3 shows details regarding the frequency of administration for all trials.

### 3.4 Intervention administration's route

#### 3.4.1 Intravenous

Thirteen trials used the intravenous route for four study medications: anakinra (Emsley 2005), etanercept (Deswal 1999; Padfield 2013), infliximab (Chung 2003; Gottlieb 2004; Menter 2007; Torii 2010) and tocilizumab (Baek 2019; Broch 2021; Kleveland 2016; Meyer 2021; Smolen 2008; Villiger 2016).

#### 3.4.2 Subcutaneous

Forty-four trials used the subcutaneous administration route: etanercept (Bachelez 2015; Bagel 2012; Bernstein 2006; Boetticher 2008; Bozkurt 2001; Brandt 2003; Butchart 2015; Calin 2004; Davis 2003; Don 2010; Gorman 2002; Gottlieb 2003; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Micali 2015; Papp 2005; RECOVER 2000; RENAISSANCE 2001; Reich 2017; Stanley 2011; Tyring 2006; Weisman 2007; Van de Kerkhof 2008; Van der Heijde 2006), anakinra (Abbate 2010; Abbate 2013; Abbate 2020; Brucato 2016; Ebrahimi 2018; Morton 2015; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018), canakinumab (Choudhury 2016; Krisai 2020; Ridker 2012; Ridker 2017; Russel 2019), and tocilizumab (Carroll 2018; Khanna 2016; Khanna 2020).

#### 3.4.3 Perispinal

One trial used this administration route for etanercept (Ralph 2020).

### 3.5 Comparison

All trials reported placebo use as the comparison group. Seventy-four per cent of the trials (43/58) didn't specify the placebo composition (Abbate 2020; Bachelez 2015; Baek 2019; Bagel 2012; Bernstein 2006; Boetticher 2008; Bozkurt 2001; Brucato 2016; Calin 2004; Choudhury 2016; Chung 2003; Davis 2003; Deswal 1999; Emsley 2005; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Krisai 2020; Leonardi 2003; Mease 2004; Menter 2007; Micali 2015; Morton 2015; Papp 2005; RECOVER 2000; RENAISSANCE 2001; Ridker 2012; Ridker 2017; Russel 2019; Smith 2018; Smolen 2008; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Villiger 2016; Weisman 2007). Twelve trials reported saline solution as a placebo (Abbate 2010; Abbate 2013; Broch 2021; Carroll 2018; Don 2010; Ebrahimi 2018; Kleveland 2016; Kreiner 2010; Meyer 2021; Padfield 2013; Ralph 2020; Reich 2017). Table 4 shows details related to miscellaneous compositions.

#### Co-interventions

The co-interventions ranged from low-potency topical corticosteroids to more systemic treatments, such as immunomodulatory therapy, antihypertensives, statins, and various anti-inflammatory drugs. Each of these interventions can independently influence cardiovascular outcomes.

Thirty-two trials prescribed the standard of care as a co-intervention (Abbate 2010; Abbate 2013; Abbate 2020; Baek 2019; Boetticher 2008; Bozkurt 2001; Broch 2021; Calin 2004; Carroll 2018; Choudhury 2016; Chung 2003; Davis 2003; Deswal 1999; Don 2010; Ebrahimi 2018; Emsley 2005; Gorman 2002; Kleveland 2016; Krisai 2020; Meyer 2021; Morton 2015; RECOVER 2000; RENAISSANCE 2001; Ralph 2020; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Weisman 2007; Van der Heijde 2006). In contrast, twenty-three trials investigated thirteen different interventions, either alone or in combination, as documented in references (Bagel 2012; Bachelez 2015; Bernstein 2006; Brandt 2003; Brucato 2016; Butchart 2015; Gottlieb 2003; Khanna 2016; Khanna 2020; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; Reich 2017; Ridker 2012; Smolen 2008; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Villiger 2016). These co-interventions are detailed in Table 5, offering insight into the varied co-interventions explored. Three trials did not provide information on their co-intervention strategies, posing a challenge for comprehensive analysis (Gottlieb 2004; Padfield 2013; Stanley 2011).

## *4. Outcomes*

Regardless of the type of prevention, the included trials had a predefined outcome mean of 6.64 (SD 2.81, minimum 1, maximum 15; 95% CI 5.93 to 7.36), and the median was 6 (Q1: 5 and Q3: 8). Fifty-seven trials stated primary outcomes. The mean number was 1.3 (SD 0.83, minimum: 1, maximum: 6; 95% CI 1.1 to 1.5), and the median was 1 (Q1: 1 and Q3: 1). Fifty-six trials declared secondary outcomes, and the mean number was 5.4 (SD 2.82, minimum: 1, maximum: 12; 95% CI 4.66 to 6.14), and the median was 5 (Q1: 3 and Q3: 7).

The following information relates to the predefined outcomes for this Cochrane review in the included trials.

#### 4.1 Primary

##### 4.1.1 All-cause mortality

Thirty-eight studies reported information about all-cause mortality (Abbate 2013; Abbate 2020; Bachelez 2015; Baek 2019; Bagel 2012; Boetticher 2008; Bozkurt 2001; Broch 2021; Carroll 2018; Choudhury 2016; Chung 2003; Don 2010; Emsley 2005; Khanna 2016; Khanna 2020; Kleveland 2016; Krisai 2020; Mease 2004; Menter 2007; Meyer 2021; Micali 2015; Morton 2015; RECOVER 2000; Reich 2017; RENAISSANCE 2001; Ridker 2012; Ridker 2017; Russel 2019; Smith 2018; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Villiger 2016; Weisman 2007).

##### 4.1.2. Myocardial infarction (fatal or non-fatal)

Nineteen trials conveyed information about this outcome (Abbate 2010; Abbate 2013; Abbate 2020; Bachelez 2015; Broch 2021; Calin 2004; Carroll 2018; Choudhury 2016; Khanna 2016; Khanna 2020; Kleveland 2016; Krisai 2020; Menter 2007; Morton 2015; Ridker 2012; Ridker 2017; Russel 2019; Van Tassell 2017; Villiger 2016).

##### 4.1.3 Unstable angina

Six trials documented this outcome (Abbate 2010; Abbate 2020; Choudhury 2016; Ridker 2012; Ridker 2017; Van Tassell 2017).

##### 4.1.4. Adverse events

Ninety-eight per cent of the trials (57/58) published information about adverse events (Abbate 2010; Abbate 2013; Abbate 2020; Bachelez 2015; Baek 2019; Bagel 2012; Bernstein 2006; Boetticher 2008; Bozkurt 2001; Brandt 2003; Broch 2021; Brucato 2016; Butchart 2015; Calin 2004; Carroll 2018; Choudhury 2016; Chung 2003; Davis 2003; Deswal 1999; Don 2010; Ebrahimi 2018; Emsley 2005; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Kleveland 2016; Kreiner 2010; Krisai 2020; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Meyer 2021; Micali 2015; Morton 2015; Papp 2005; Ralph 2020; RECOVER 2000; Reich 2017; RENAISSANCE 2001; Ridker 2012; Ridker 2017; Russel 2019; Smith 2018; Smolen 2008; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Villiger 2016; Weisman 2007). Table 6 and Table 7 show the approaches for reporting adverse events, including infections.

#### 4.2 Secondary

##### 4.2.1 Peripheral vascular disease

Six trials stated information about this outcome (Choudhury 2016; Khanna 2016; Khanna 2020; Reich 2017; Ridker 2017; Russel 2019).

##### 4.2.2 Stroke (fatal or non-fatal)

Fifteen trials conveyed information about this outcome (Abbate 2020; Bachelez 2015; Broch 2021; Choudhury 2016; Don 2010; Emsley 2005; Gottlieb 2003; Khanna 2016; Khanna 2020; Krisai 2020; Morton 2015; Ridker 2012; Ridker 2017; Smith 2018; Van Tassell 2017).

##### 4.2.3 Quality of life

Twenty-two trials published data about that outcome (Bachelez 2015; Baek 2019; Brandt 2003; Chung 2003; Deswal 1999; Don 2010; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Leonardi 2003; Mease 2004; Menter 2007; Micali 2015; Reich 2017; Smolen 2008; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van Tassell 2017; Van Tassell 2018).

##### 4.2.4 Heart failure

Twenty-one trials informed about this outcome (Abbate 2010; Abbate 2013; Abbate 2020; Boetticher 2008; Bozkurt 2001; Broch 2021; Choudhury 2016; Chung 2003; Khanna 2016; Khanna 2020; Kleveland 2016; Krisai 2020; RECOVER 2000; RENAISSANCE 2001; Ridker 2012; Ridker 2017; Russel 2019; Torii 2010; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018).

### *5. Notes*

#### 5.1 Trial registration number

Nineteen trials reported no trial registration number (Bernstein 2006; Boetticher 2008; Bozkurt 2001; Brandt 2003; Calin 2004; Chung 2003; Davis 2003; Deswal 1999; Emsley 2005; Gorman 2002; Gottlieb 2003; Leonardi 2003; Mease 2000; Padfield 2013; Papp 2005; RECOVER 2000; RENAISSANCE 2001; Torii 2010; Van der Heijde 2006). Five trials were published after it became mandatory to submit the clinical trial registration (ICMJE 2006).

#### 5.2 Date of study closure

Ten per cent (6/58) of trials reported no trial dates (Bozkurt 2001; Deswal 1999; Mease 2000; Padfield 2013; Torii 2010; Van der Heijde 2006). Two trials did not state the trial's end date (Brandt 2003; Gottlieb 2003).

#### 5.3 A priori sample size estimation

Fifteen point fifty-one per cent (9/58) trials reported no sample size estimation (Bozkurt 2001; Deswal 1999; Gottlieb 2004; Krisai 2020; Micali 2015; Padfield 2013; Ridker 2012; Stanley 2011; Torii 2010).

#### 5.4 Financial disclosure

One trial reported no financial disclosure (Torii 2010).

#### 5.5 Ethical committee approval

All trials reported ethical committee approval.

#### 5.6 Sponsorship by drug companies

Fifty-one and seven per cent (30/58), respectively, were funded by companies producing drugs and medical devices (Bachelez 2015; Baek 2019; Bagel 2012; Brucato 2016; Butchart 2015; Calin 2004; Chung 2003; Davis 2003; Don 2010; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015 Papp 2005; RECOVER 2000; RENAISSANCE 2001; Reich 2017; Ridker 2012; Ridker 2017; Russel 2019; Smolen 2008; Tyring 2006; Weisman 2007; Van de Kerkhof 2008; Van der Heijde 2006). Seventy-six percent (23/30) were trials of primary prevention (Bachelez 2015; Baek 2019; Bagel 2012; Butchart 2015;Calin 2004;Davis 2003;Don 2010;Gottlieb 2003;Gottlieb 2004; Khanna 2016; Khanna 2020; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; Reich 2017; Ridker 2012;Smolen 2008; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006). Seven trials (23.3%) were conducted for secondary prevention (Brucato 2016; Chung 2003; RECOVER 2000; RENAISSANCE 2001; Ridker 2017; Russel 2019; Weisman 2007).

### Excluded studies

We excluded five studies (7 records) after checking their full texts. Four of the five studies were randomised controlled trials. However, their methods and results showed shortcomings that led to exclusion. For example, the reasons for exclusion were participants being counted twice (Antoni 2005), the trial likely not a randomised clinical trial after reading the random sequence generation (Chaudhari 2001), and miscellaneous reasons (Bissonnette 2011; Martínez-Taboada 2008; Reich 2005). The table of Excluded studies shows the details of study exclusion. Figure 1 shows details of the flow of study selection.

#### *Awaiting classification*

Three trials are awaiting classification (Gottlieb 2011; Parry-Jones 2023; Strober 2011). Two have different clinical trial registration numbers (NCT00691964 & NCT00710580) (Gottlieb 2011; Strober 2011). However, the trials have an identical protocol. The same drug company (Abbott) sponsored both trials. The sponsor employs the last two authors of both papers. The medical writing support was provided by the same person who was an employee of the sponsor. Both articles reference each other's results, even though both trials were sent and accepted for publication on the same dates, in the same journal, and published sequentially (pp. 652-660 & pp. 661-8). The sample size differed by three (347 and 350). The baseline demographics and clinical characteristics are very close. We have emailed the leading authors and journal Editor-in-Chief. We received a reply from Dr John Ingram, Editor-in-Chief of the British Journal of Dermatologists "On taking a careful and close look, they report two parallel and separate trials (often this is done to meet regulatory requirements). The two studies have different trial registration numbers, and within the text they refer to each other and include the other trial in their reference list. So, no issue with duplicate publication and the results of both can be included in systematic reviews." (4 March 2023 at 11:00:54 GMT). The trial authors have not replied yet.

We updated the search on February 20, 2024, identifying one other RCT meeting the inclusion criteria (Parry-Jones 2023). It is a small trial with a duration of three months. Therefore, including this trial would not likely change the current conclusions. This section, Characteristics of studies awaiting classification, shows details for all three trials (Gottlieb 2011; Parry-Jones 2023; Strober 2011). Figure 1 shows details of the flow of study selection.

#### Duplicate publication

We identified one duplicate trial sharing the registration number (NCT01532869) with another trial with the same leading author. The second publication reported the participants transitioned to the open-label period (Khanna 2016). We emailed the leading author (02 March 2023) who answered, "The first study provides data from a double-blind study, and the second one presents data from an open-label extension. Same trial but two different reporting periods."

#### *Ongoing trials*

We identified nine ongoing trials (10 references), five with the aim of primary prevention (ISRCTN12961797; NCT01423591; NCT02902731; NCT04017936; Kerneis 2023). Four trials assessed secondary prevention (NCT03644667; NCT03797001; NCT04834388; NCT05177822). Seven trials assessed anakinra (ISRCTN12961797; Kerneis 2023; NCT02902731; NCT03797001; NCT04017936; NCT04834388; NCT05177822), one with infliximab (NCT01423591), and one tocilizumab (NCT03644667). Four trials were multicentre (ISRCTN12961797; NCT04017936; NCT05177822; NCT03644667). Six trials were related to cardiovascular disease (NCT04017936; Kerneis 2023; NCT03644667; NCT04834388; NCT05177822; NCT03797001). The section, Characteristics of ongoing studies, shows details of all the studies. Figure 1 shows details of the flow of study.selection.

### Risk of bias in included studies

We summarised the risks of bias in the included trials in Figure 2 and Figure 3, and we provided more details in the Characteristics of included studies.

**Figure 2.**

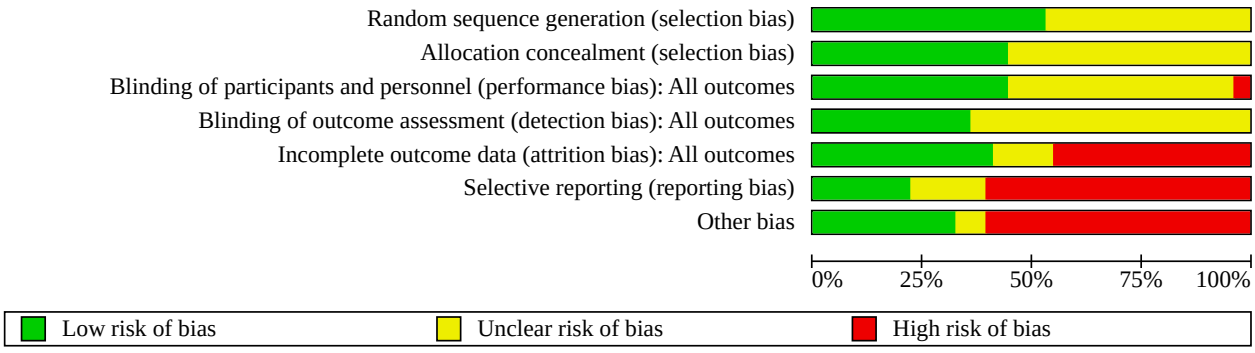


**Figure 3.**

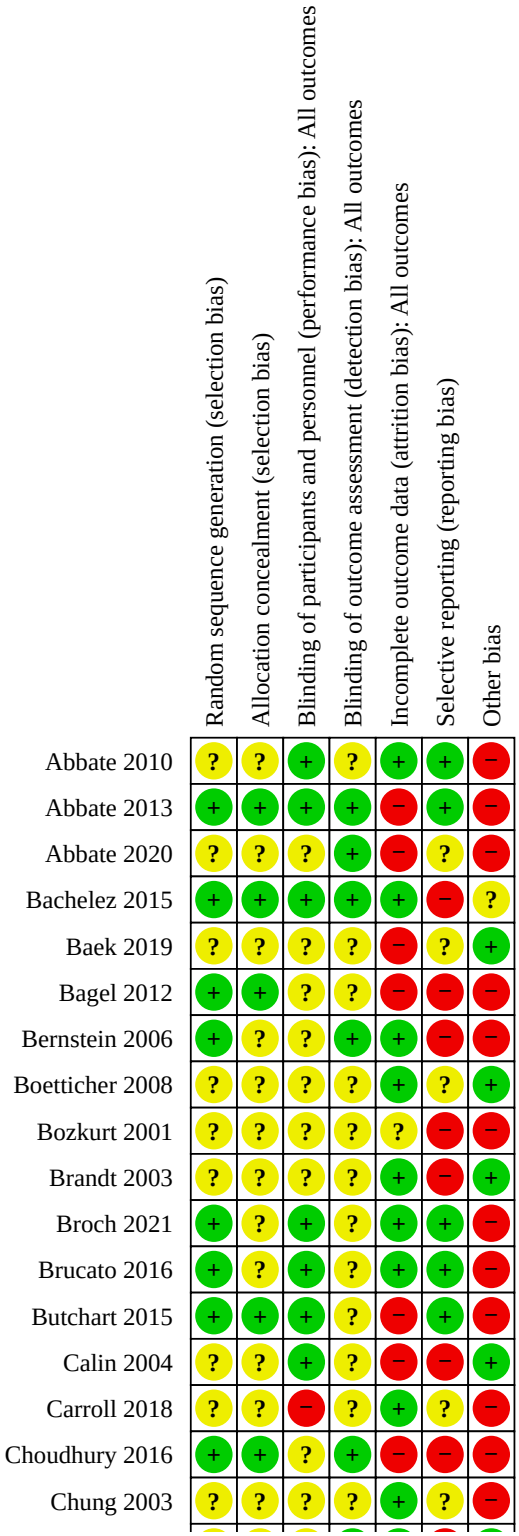


**Figure 3. (Continued)**

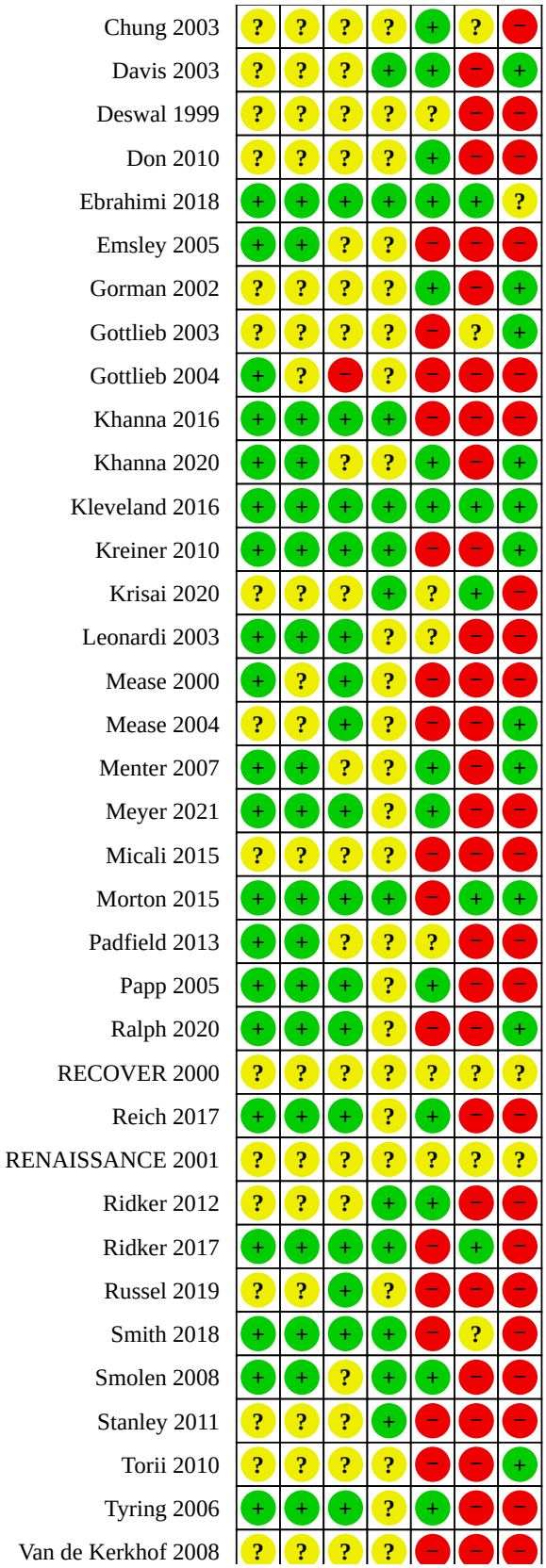
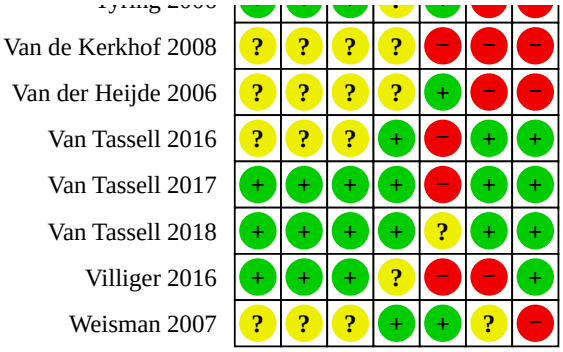


**Figure 3. (Continued)**




### Allocation

#### *Random sequence generation*

Thirty-one trials had a low risk of selection bias due to using an appropriate procedure to conduct the random sequence generation (Abbate 2013; Bachelez 2015; Bagel 2012; Bernstein 2006; Broch 2021; Brucato 2016; Butchart 2015; Choudhury 2016; Ebrahimi 2018; Emsley 2005; Gottlieb 2004; Khanna 2016; Khanna 2020; Kleveland 2016; Kreiner 2010; Leonardi 2003; Mease 2000; Menter 2007; Meyer 2021; Morton 2015; Padfield 2013; Papp 2005; Ralph 2020; Reich 2017; Ridker 2017; Smith 2018; Smolen 2008; Tyring 2006; Van Tassell 2017; Van Tassell 2018; Villiger 2016). Twenty-seven trials had an unclear risk of bias for this domain due to the lack of a clear description of how the random sequence generation was conducted.

Regarding primary prevention, 60% of trials (18/30) had a low risk of bias (Abbate 2013; Bachelez 2015; Bagel 2012; Bernstein 2006; Butchart 2015; Ebrahimi 2018; Gottlieb 2004; Khanna 2016; Khanna 2020; Kreiner 2010; Leonardi 2003; Mease 2000; Menter 2007; Papp 2005; Reich 2017; Smolen 2008; Tyring 2006; Villiger 2016). In secondary prevention, 40% of trials (12/30) had low risk of bias (Broch 2021; Brucato 2016; Choudhury 2016; Emsley 2005; Kleveland 2016; Meyer 2021; Morton 2015; Padfield 2013; Ridker 2017; Smith 2018; Van Tassell 2017; Van Tassell 2018).

#### *Allocation concealment*

We considered the risk of bias arising from the method of allocation concealment to be low in twenty-six trials (Abbate 2013; Bachelez 2015; Bagel 2012; Butchart 2015; Choudhury 2016; Ebrahimi 2018; Emsley 2005; Khanna 2016; Khanna 2020; Kleveland 2016; Kreiner 2010; Leonardi 2003; Menter 2007; Meyer 2021; Morton 2015; Padfield 2013; Papp 2005; Ralph 2020; Reich 2017; Ridker 2017; Smith 2018; Smolen 2008; Tyring 2006; Van Tassell 2017; Van Tassell 2018; Villiger 2016). Thirty-two trials did not report the allocation concealment methodology: thus, we considered the risk of bias arising from the method of allocation concealment to be unclear.

In primary prevention, 55.5% (15/27) had a low risk of bias regarding the method of allocation concealment (Abbate 2013; Bachelez 2015; Bagel 2012; Butchart 2015; Ebrahimi 2018; Khanna 2016; Khanna 2020; Kreiner 2010; Leonardi 2003; Menter 2007; Papp 2005; Reich 2017; Smolen 2008; Tyring 2006; Villiger 2016). In secondary prevention, 42.3% of trials (11/26) had low risk for this domain (Choudhury 2016; Emsley 2005; Kleveland 2016; Meyer 2021; Morton 2015; Padfield 2013; Ralph 2020; Ridker 2017; Smith 2018; Van Tassell 2017; Van Tassell 2018).

### Blinding

The risk of bias due to the lack of blinding of participants and personnel was rated as low in 27 trials (Abbate 2010; Abbate 2013; Bachelez 2015; Broch 2021; Brucato 2016; Butchart 2015; Calin 2004; Ebrahimi 2018; Gottlieb 2004; Khanna 2016; Kleveland 2016; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Meyer 2021; Morton 2015; Papp 2005; Ralph 2020; Reich 2017; Ridker 2017; Russel 2019; Smith 2018; Tyring 2006; Van Tassell 2017; Van Tassell 2018; Villiger 2016). Thirty trials had an unclear risk of performance bias. One trial had a high risk of performance bias (Carroll 2018).

In primary prevention, there were 59.2% of trials (16/27) with a low risk of bias in this domain (Abbate 2010; Abbate 2013; Bachelez 2015; Butchart 2015; Calin 2004; Ebrahimi 2018; Gottlieb 2004; Khanna 2016; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Papp 2005; Reich 2017; Tyring 2006; Villiger 2016). In secondary prevention, there were 40.7% of trials (11/27) with a low risk of bias (Broch 2021; Brucato 2016; Kleveland 2016; Meyer 2021; Morton 2015; Ralph 2020; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2017; Van Tassell 2018).

Twenty-one trials appropriately reported the outcome assessment and the risk of detection bias was considered low (Abbate 2013; Abbate 2020; Bachelez 2015; Bernstein 2006; Choudhury 2016; Davis 2003; Ebrahimi 2018; Khanna 2016; Kleveland 2016; Kreiner 2010; Krisai 2020; Morton 2015; Ridker 2012; Ridker 2017; Smith 2018; Smolen 2008; Stanley 2011; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Weisman 2007). The blinding of outcome assessors was either unclear or not performed in the remaining 38 trials, so the overall risk of detection bias was considered high.

In primary prevention, 47.61% of trials (10/21) had a low risk of bias (Abbate 2013; Bachelez 2015; Bernstein 2006; Davis 2003; Ebrahimi 2018; Khanna 2016; Kreiner 2010; Ridker 2012; Smolen 2008; Stanley 2011). In secondary prevention, 55% of trials (11/20) had low risk of bias (Abbate 2020; Choudhury 2016; Kleveland 2016; Krisai 2020; Morton 2015; Ridker 2017; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Weisman 2007).

### Incomplete outcome data

The risk of attrition bias was low in 25 trials (Abbate 2010; Bachelez 2015; Bernstein 2006; Boetticher 2008; Brandt 2003; Broch 2021; Brucato 2016; Calin 2004; Carroll 2018; Chung 2003; Davis 2003;

Don 2010; Ebrahimi 2018; Gorman 2002; Khanna 2020; Kleveland 2016; Menter 2007; Meyer 2021; Papp 2005; Reich 2017; Ridker 2012; Smolen 2008; Tyring 2006; Weisman 2007; Van der Heijde 2006). The risk of attrition bias was either unclear or high in the remaining 33 trials.

In primary prevention, 72% of trials (18/25) had a low risk of bias (Abbate 2010; Bachelez 2015; Bernstein 2006; Boetticher 2008; Brandt 2003 Calin 2004; Davis 2003; Don 2010; Ebrahimi 2018; Gorman 2002; Khanna 2020; Menter 2007; Papp 2005; Reich 2017; Ridker 2012; Smolen 2008; Tyring 2006; Van der Heijde 2006). In secondary prevention, 28% of the trials (7/25) had a low risk of bias (Broch 2021; Brucato 2016; Carroll 2018; Chung 2003; Kleveland 2016; Meyer 2021; Weisman 2007).

#### Selective reporting

The risk of selective outcome reporting bias was rated as low in 13 trials (Abbate 2010; Abbate 2013; Broch 2021; Brucato 2016; Butchart 2015; Ebrahimi 2018; Kleveland 2016; Krisai 2020; Morton 2015; Ridker 2017; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018). The risk of selective outcome reporting was rated as unclear or high in the remaining 45 trials, as these trials neither measured nor reported major cardiovascular or adverse event data.

In primary prevention, we identified four low-risk trials in this domain (Abbate 2010; Abbate 2013; Butchart 2015; Ebrahimi 2018). In secondary prevention, we found nine trials with a low risk of selective outcome reporting (Broch 2021; Brucato 2016; Kleveland 2016; Krisai 2020; Morton 2015; Ridker 2017; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018).

#### Other potential sources of bias

The risk of other biases was rated as low in 18 trials (Baek 2019; Boetticher 2008; Brandt 2003; Calin 2004; Davis 2003; Gorman 2002; Gottlieb 2003; Khanna 2020; Kleveland 2016; Kreiner 2010; Mease 2004; Morton 2015; Ralph 2020; Torii 2010; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Villiger 2016), and high or unclear in the remaining 40 trials due to bias in the presentation of data, design bias, or financial conflict of interest. There was a significant design bias in the included studies, primarily due to the lack of a priori sample size estimation. Additionally, the family-wise error rate substantially exceeded the standard 5% threshold. This is concerning because the family-wise error rate acts as a safeguard when scientists are testing multiple hypotheses simultaneously. It helps prevent researchers from erroneously concluding that an effect exists when it doesn't, especially when analysing numerous outcomes or making multiple comparisons (Delorme 2016; Porta 2014).

#### *Overall risk of bias*

Given the considerations noted above, all trials were considered at high risk of bias. See Risk of bias in included studies.

## Effects of interventions

See: **Summary of findings 1** Interleukin-1 (IL-1) receptor antagonists (anakinra, canakinumab) compared with placebo or usual care for primary prevention of cardiovascular outcomes in adults; **Summary of findings 2** IL-6 receptor antagonists (tocilizumab) compared with placebo or usual care for primary prevention of cardiovascular outcomes in adults; **Summary of findings 3** TNF inhibitors (etanercept, infliximab) compared with placebo or usual care for primary prevention of cardiovascular outcomes in adults; **Summary of findings 4** Interleukin-1 (IL-1) receptor antagonists (anakinra, canakinumab) compared with placebo or usual care for secondary prevention of cardiovascular outcomes in adults; **Summary of findings 5** Interleukin-6 (IL-6) receptor antagonists (tocilizumab) compared with placebo or usual care for secondary prevention of cardiovascular outcomes in adults; **Summary of findings 6** TNF inhibitors (etanercept, infliximab) compared with placebo or usual care for secondary prevention for cardiovascular diseases in adults

### A) Primary prevention

#### *A.1. Interleukin- 1 receptor antagonists (anakinra, canakinumab) compared with placebo or usual care*

##### Primary outcomes

##### A.1.1 All-cause mortality

The evidence of one trial assessing the interleukin-1 receptor antagonist (anakinra) compared with placebo or usual care suggests little to no difference in all-cause mortality in primary prevention, (0/15 (0%) versus 1/15 (6.7%)) (risk ratio 0.33, 95% CI 0.01 to 7.58); P = 0.49; $I^2$ = NA; 1 study, 30 participants, very low certainty of the evidence; Analysis 1.1). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Abbate 2013).

##### A.1.2. Myocardial infarction (fatal or non-fatal)

Meta-analysis assessing interleukin-1 receptor antagonists (anakinra and canakinumab) compared with placebo or usual care suggests that both medication drugs may have little to no effect on the outcome in primary prevention, but the evidence is very uncertain (1/390 (0.26%) versus 1/195 (0.51%)) (risk ratio 0.71, 95% CI 0.04 to 12.48; P = 0.81; $I^2$ = 39%; 2 studies, 585 participants, very low certainty of the evidence; Analysis 1.2). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Abbate 2013; Ridker 2012).

##### A.1.3 Unstable angina

Meta-analysis assessing interleukin-1 receptor antagonists (anakinra and canakinumab) compared with placebo or usual care suggests that both medication drugs may have little to no effect on the outcome in primary prevention, but the evidence is very uncertain (0/380 (0%) versus 2/186 (1.1%)) (risk ratio 0.24, 95% CI 0.03 to 2.11; P = 0.20; $I^2$ = 0%, 2 studies, 566 participants, very low certainty of the evidence; Analysis 1.3). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Abbate 2010; Ridker 2012).

##### A.1.4 Adverse events

Meta-analysis assessing interleukin-1 receptor antagonists (anakinra and canakinumab) compared with placebo or usual care suggests that both medication drugs may have little to no effect on the outcome in primary prevention, but the evidence is very uncertain (176/395 (44.6%) versus 94/201 (46.8%)) (risk ratio 0.85, 95% CI 0.59 to 1.22; P = 0.37; $I^2$ = 54%, 3 trials, 596 participants; very low certainty of the evidence; Analysis 1.4). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Abbate 2010; Abbate 2013; Ridker 2012).

*A.1.4.1. Adverse events (incidence rate)*

Meta-analysis assessing interleukin-1 receptor antagonists (anakinra and canakinumab) compared with placebo or usual care to report the rate ratio of adverse events suggests that both medication drugs may have little to no effect on the incidence rate of the outcome in primary prevention, but the evidence is very uncertain, as shown in meta-analysis with binary data (rate ratio 1.06, 95% 0.52 to 2.16; P = 0.87; $I^2$ = 75%; 4 studies, 666 participants; very low certainty of the evidence; Analysis 1.5) (Abbate 2010; Abbate 2013; Ebrahimi 2018; Ridker 2012). The rate ratio in three trials testing anakinra versus placebo was 1.17, 95% CI 0.38 to 3.67; $I^2$ = 80%, 110 participants (Abbate 2010; Abbate 2013; Ebrahimi 2018). Furthermore, in one trial assessing canakinumab, the rate ratio was 0.83 (95% CI 0.83 (0.56 to 1.22); 556 participants) (Ridker 2012). Tests for subgroup differences did not find evidence of differences: $Chi^2$ = 0.33, df = 1 (P = 0.57), $I^2$ = 0%.

*A.1.4.2 Any infection (incidence rate)*

Meta-analysis assessing interleukin-1 receptor antagonists (anakinra and canakinumab) compared with placebo or usual care to report the rate ratio of any infection suggest that both medication drugs may have little to no effect on the incidence rate of the outcome in primary prevention, but the evidence is very uncertain, as shown in meta-analysis with binary data (rate ratio 0.84, 95% 0.55 to 1.29; P = 0.43; $I^2$ = 0%; 4 studies, 666 participants; very low certainty of the evidence; Analysis 1.6). Due to a lack of substantial statistical heterogeneity, we did not show data by intervention. There was no evidence of subgroup differences: $Chi^2$ = 1.21, df = 1 (P = 0.27), $I^2$ = 17.5% (Abbate 2010; Abbate 2013; Ebrahimi 2018; Ridker 2012).

**Secondary outcomes**

**A.1.5 Peripheral vascular disease**

None of the trials assessed this outcome.

**A.1.6 Stroke (fatal or non-fatal)**

The evidence of one trial assessing interleukin-1 receptor antagonist canakinumab compared with placebo or usual care suggests that the medication drug may have little to no effect on the outcome in primary prevention, but the evidence is very uncertain (2/375 (0.53%) versus 0/181 (0%)) (risk ratio 2.42, 95% CI 0.12 to 50.15; P = 0.57; $I^2$ = NA; 1 study, 556 participants; very low certainty of the evidence; Analysis 1.7). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Ridker 2012).

**A.1.7 Quality of life**

Due to lack of uniformity in the baseline and the end of follow-up reports for this outcome, we were unable to undertake a statistical synthesis. Therefore, the quality of life results for each trial are summarised in Table 8.

**A.1.8 Heart failure**

Meta-analysis assessing interleukin-1 receptor antagonists (anakinra and canakinumab) compared with placebo or usual care shows very uncertain evidence about the effect of both medication drugs on the outcome in primary prevention (1/395 (0.25%) versus 7/201 (3.5%)) (risk ratio 0.21, 95% CI 0.05 to 0.94; P = 0.04; $I^2$ = 0%, 3 studies, 596 participants; very low certainty of the evidence; Analysis 1.8). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Abbate 2010; Abbate 2013; Ridker 2012).

***A.2. Interleukin-6 receptor antagonists (tocilizumab) compared with placebo or usual care***

**Primary outcomes**

**A. 2.1 All-cause mortality**

The evidence of the meta-analysis assessing tocilizumab compared with placebo or usual care is very uncertain about the effect of tocilizumab on the outcome of primary prevention. The certainty of the evidence is very low (4/168 (2.4%) versus 5/161 (3.1%)) (risk ratio 0.68, 95% CI 0.12 to 3.74; P = 0.65; $I^2$ = 30%, 3 studies, 329 participants; very low certainty of the evidence; Analysis 2.1). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Khanna 2016; Khanna 2020; Villiger 2016).

**A.2.2 Myocardial infarction (fatal or non-fatal)**

The evidence of the meta-analysis assessing tocilizumab compared with placebo or usual care is very uncertain about the effect of tocilizumab on the outcome (0/168 (0%) versus 3/161 (1.9%)) (risk ratio 0.27, 95% CI 0.04 to 1.68; P = 0.16; $I^2$ = 0%, 3 studies, 329 participants; very low certainty of the evidence; Analysis 2.2). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Khanna 2016; Khanna 2020; Villiger 2016).

**A.2.3 Unstable angina**

None of the trials assessed this outcome.

**A.2.4 Adverse events**

Tocilizumab may increase adverse events slightly: (483/635 (76.1%) versus 289/416 (69.5%)); (risk ratio 1.13, 95% CI 1.04 to 1.23; P = 0.006; $I^2$ = 33%, 5 studies, 1051 participants, low-certainty of the evidence; Analysis 2.3) The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Baek 2019; Khanna 2016; Khanna 2020; Smolen 2008; Villiger 2016).

*A.2.4.1 Adverse events (incidence rate)*

The evidence suggests that tocilizumab is associated with a significant increase in the incidence rate of adverse events when used for primary prevention, as seen in the meta-analysis comparing tocilizumab with placebo or usual care (rate ratio 27.89, 95% CI 19.58 to 39.73; $I^2$ = 0%; 4 studies; 621 participants; Analysis 2.4) (Baek 2019; Khanna 2016; Khanna 2020; Villiger 2016). However, it is essential to note that the certainty of this evidence is low, as shown in the meta-analysis with binary data (see above).

*A.2.4.2 Any infection (incidence rate)*

The evidence suggests that tocilizumab, compared with placebo or usual care, may result in little to no difference in the incidence rate of any infection in primary prevention (rate ratio 1.10, 95% CI 0.88 to 1.37; $I^2$ = 18%, 5 studies, 1048 participants; Analysis 2.5) (Baek 2019; Khanna 2016; Khanna 2020; Smolen 2008; Villiger 2016). However, it is essential to note that the certainty of this evidence is low, as shown in the meta-analysis with binary data (see above).

**Secondary outcomes**

**A.2.5 Peripheral vascular disease**

Tocilizumab may have little to no effect on the outcome, but the evidence is very uncertain regarding primary prevention: 1/107 (0.93%) versus 0/105 (0%) (risk ratio 2.94, 95% CI 0.12 to 71.47); P = 0.51; $I^2$ = NA; 1 study, 312 participants; very low of certainty of the evidence; Analysis 2.6). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Khanna 2020).

**A.2.6 Stroke (fatal or non-fatal)**

The evidence is very uncertain about the effect of tocilizumab on the outcome in primary prevention. One trial compared tocilizumab with placebo or usual care: 0/43 (0%) versus 1/44 (2.3%) (risk ratio 0.34, 95% CI 0.01 to 8.14; P = 0.51; $I^2$ = NA, 1 trial, 87 participants; very low certainty of the evidence; Analysis 2.7). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Khanna 2016).

**A.2.7 Quality of life**

Due to the lack of uniformity in the baseline and the end of follow-up reports for this outcome, we were unable to undertake a statistical synthesis. Therefore, the quality of life results for each trial are summarised in Table 8.

**A.2.8 Heart failure**

The evidence is very uncertain about the effect of tocilizumab on the outcome related to primary prevention. Meta-analysis of two trials assessing tocilizumab compared with placebo or usual care suggests the medication may have little to no effect on outcome in primary prevention, but the evidence is very uncertain (1/148 (0.68%) versus 1/151 (0.66%)) (risk ratio 1.02, 95% CI 0.11 to 9.63; P = 0.99; $I^2$ = 0%, 2 studies, 309 participants; very low certainty of the evidence; Analysis 2.8). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Khanna 2016; Khanna 2020).

***A.3. Tumour necrosis factor inhibitors (etanercept, infliximab) compared with placebo or usual care***

**Primary outcomes**

**A.3.1 All-cause mortality**

Meta-analysis assessing etanercept compared with placebo or usual care suggests the medication may have little to no effect on outcome (16/432 (3.7%) versus 6/177 (3.44%)) (risk ratio 1.78, 95% CI 0.63 to 4.99; P = 0.27; $I^2$ = 10%; 3 studies, 609 participants; very low certainty of the evidence; Analysis 3.1). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Boetticher 2008; Mease 2004; Van der Heijde 2006).

**A.3.2. Myocardial infarction (fatal or non-fatal)**

Etanercept may have little to no effect on the outcome, but the evidence is very uncertain regarding primary prevention: 1/45 (2.2%) versus 0/39 (0%) (risk ratio 2.61; 95% CI 0.11 to 62.26; P = 0.57; $I^2$ = NA; 1 study, 84 participants; very low of certainty of the evidence; Analysis 3.2). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Calin 2004).

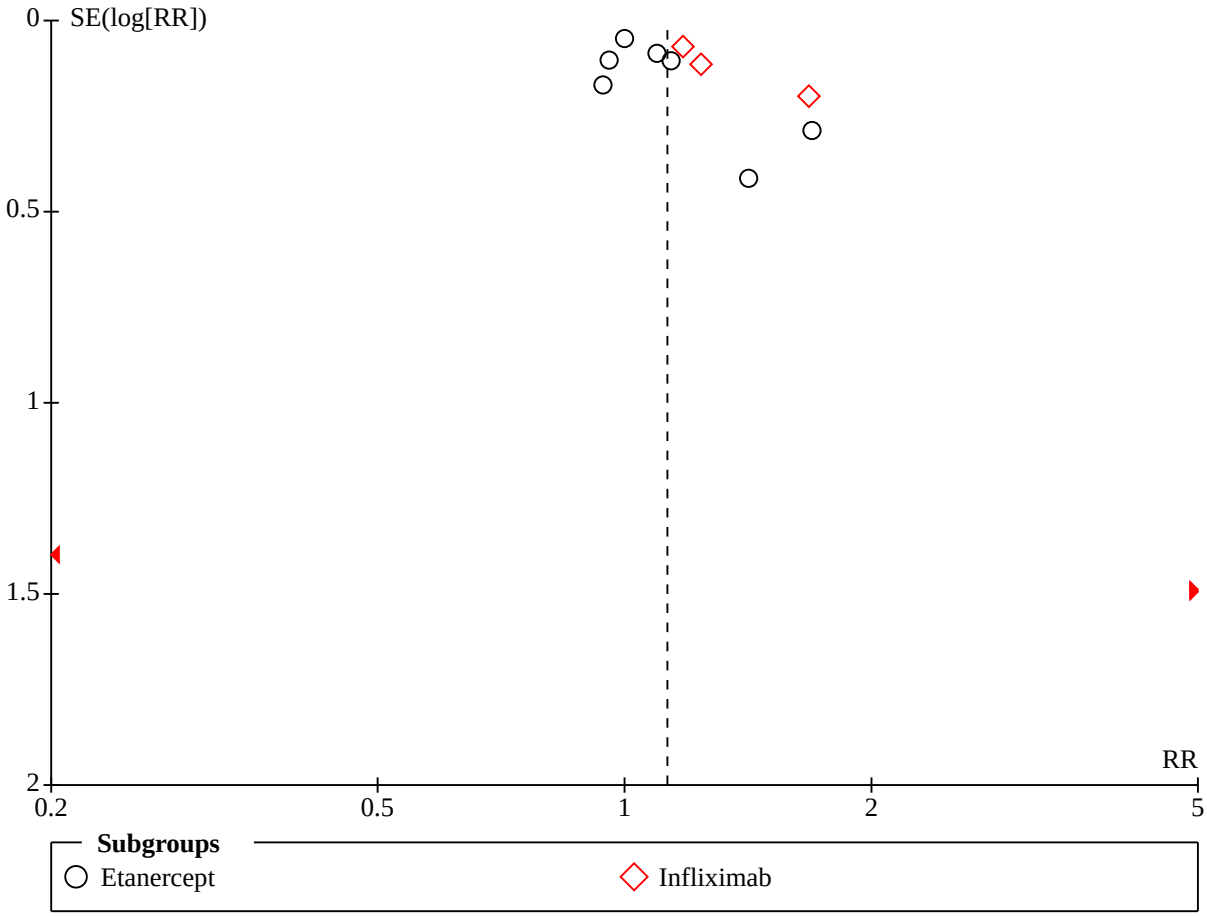
**A.3.3. Unstable angina**

None of the trials assessed this outcome.

**A.3.4. Adverse events**

The evidence suggests that tumour necrosis factor inhibitors etanercept (10 trials) and infliximab (3 trials) may increase this outcome slightly: 1074/1773 (60.6%) versus 472/921 (51.2%) (risk ratio 1.13, 95% CI 1.01 to 1.25; P = 0.03; $I^2$ = 51%; 13 studies, 2654 participants; low certainty of the evidence; Analysis 3.3). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size. The funnel plot shows clear evidence of asymmetry, and two smaller trials show a tendency to yield bigger effect sizes (high variability), favouring the adverse events of intervention (Figure 4). Egger's test for small-study effects suggests uncertainty regarding smaller trials, which tended to give different results when compared with larger trials (intercept 0.453, 95% CI -0.285 to 0.59: P = 0.308) (Bachelez 2015; Bagel 2012; Bernstein 2006; Boetticher 2008; Brandt 2003; Butchart 2015; Don 2010; Gottlieb 2004; Kreiner 2010; Menter 2007; Micali 2015; Torii 2010; Tyring 2006).

**Figure 4. Funnel plot of the 13 trials comparing tumour necrosis factor inhibitors (etanercept and infliximab) and placebo or usual care for any adverse events in primary prevention.**
**The vertical line means the summary log(RR) as estimated from the random-effects model (RiR, risk ratio).**
**The large trials are located at the top. The small trials show high standard error.**




*A.3.4.1. Adverse events: incidence rate of any infection*
The evidence suggests that tumour necrosis factor inhibitors etanercept (20 trials) and infliximab (2 trials) may increase the outcome when related to primary prevention (identical results for both models) (rate ratio 1.32, 95% CI 1.16 to 1.49; $Tau^2$ = 0.04; $I^2$ = 56%; low-certainty evidence; Analysis 3.4). There were concerns about the risk of bias and imprecision. There was no evidence of differences according to subgroups (both models: P = 0.68, $I^2$ = 0%) (Bachelez 2015; Bagel 2012; Bernstein 2006; Boetticher 2008; Brandt 2003; Don 2010; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; Ralph 2020; Reich 2017; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006).

*A.3.4.2. Adverse events: incidence rate of severe infection*
The evidence suggests that tumour necrosis factor inhibitors etanercept (19 trials) and infliximab (3 trials) may result in little to no difference in this outcome when related to primary prevention: random-effects model (rate ratio 1.14, 95% CI 0.98 to 1.32; $Tau^2$ = 0.01; $I^2$ = 6%) and fixed-effect model (rate ratio 1.14, 95% CI 0.99 to 1.31; $I^2$ = 6%), both low-certainty evidence (Analysis 3.5). There were concerns about the risk of bias and imprecision. There was no evidence of a difference between subgroups (random-effects model: P = 0.23, $I^2$ = 30%; and fixed-effect model: P = 0.08; $I^2$ = 0%) (Bachelez 2015; Bagel 2012; Bernstein 2006; Boetticher 2008; Brandt 2003; Don 2010; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; Ralph 2020; Reich 2017; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006).

**Secondary outcomes**

**A.3.5. Peripheral vascular disease**

None of the trials assessed this outcome.

**A.3.6 Stroke (fatal or non-fatal)**

Meta-analysis assessing etanercept compared with placebo or usual care suggests the medication may have little to no effect on outcome in primary prevention, but the evidence is very uncertain (1/398 (0.95%) versus 2/168 (1.2%)) (risk ratio 0.46, 95% CI 0.08 to 2.8; P = 0.40; $I^2$ = 0%; 3 studies, 566 participants; very low certainty of the evidence; Analysis 3.6). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Bachelez 2015; Don 2010; Gottlieb 2003).

#### A.3.7. Quality of life

Due to the lack of uniformity on the baseline and the end of follow-up reports for this outcome, we were unable to do a statistical synthesis. Therefore, the quality of life results for each trial are summarised in Table 8.

### 3.8. Heart failure

The evidence is very uncertain about the effect of etanercept on this outcome in primary prevention. One trial compared etanercept with placebo or usual care: 1/26 (3.8%) versus 1/22 (4.5%) (risk ratio 0.85, 95% CI 0.06 to 12.76; P = 0.90; $I^2$ = NA; 1 trial, 46 participants; very low certainty of the evidence; Analysis 3.7). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Boetticher 2008).

## B) Secondary prevention

### *B.1. Interleukin-1 receptor antagonists (anakinra, canakinumab) compared with placebo or usual care*

#### Primary outcomes

#### B.1.1. All-cause mortality

Meta-analysis comparing anakinra and canakinumab with placebo or usual care showed very uncertain evidence about the effect of these interleukin-1 receptor antagonists on the outcome in secondary prevention: 722/7083 (10.2%) versus 388/3660 (10.6%) (risk ratio 0.94, 95% CI 0.84 to 1.06; P = 0.31, $I^2$ = 0%; 8 studies, 10,743 participants; very low-certainty evidence; Analysis 4.1). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Abbate 2020; Choudhury 2016; Emsley 2005; Morton 2015; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2017).

#### B.1.2. Myocardial infarction (fatal or non-fatal)

The evidence of one meta-analysis assessing interleukin-1 receptor antagonists (anakinra and canakinumab) compared with placebo or usual care suggests little to no difference in myocardial infarction (fatal or non-fatal) in secondary prevention: 516/7027 (7.3%) versus 296/3602 (8.2%) (risk ratio 0.88, 95% CI 0.75 to 1.04; P = 0.13; $I^2$ = 0%); 6 studies, 10,089 participants; low-certainty evidence; Analysis 4.2). The evidence was downgraded due to the risk of bias (Abbate 2020; Choudhury 2016; Morton 2015; Ridker 2017; Russel 2019; Van Tassell 2017).

#### B.1.3. Unstable angina

The evidence is very uncertain about the effect of anakinra and canakinumab on this outcome for secondary prevention. Meta-analysis of three trials comparing these interleukin-1 receptor antagonists with placebo or usual care shows medication may have little to no effect on the outcome, but the evidence is very uncertain: 112/6930 (0.17%) versus 63/3473 (1.8%) (risk ratio 0.88, 95% CI 0.65 to 1.19; P = 0.40; $I^2$ = 0%; 3 studies, 10,403 participants; very low certainty of the evidence; Analysis 4.3). The evidence was downgraded due to the risk of bias and a low number of events (Abbate 2020; Choudhury 2016; Ridker 2017).

#### B.1.4. Adverse events

The evidence is very uncertain about the effect of anakinra and canakinumab on this outcome in secondary prevention. Meta-analysis comparing these interleukin-1 receptor antagonists with placebo or usual care showed study medication may have little to no effect on the outcome, but the evidence is very uncertain: 88/132 (66.6%) versus 95/132 (72%) (risk ratio 0.92, 95% CI 0.78 to 1.09; P = 0.35; $I^2$ = 3%; 4 studies, 264 participants; very low certainty of the evidence; Analysis 4.4). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Brucato 2016; Choudhury 2016; Krisai 2020; Van Tassell 2016).

*B.1.4.1 Adverse events by incidence rate*

The evidence suggests that the effect of anakinra (8 trials) and canakinumab (4 trials) on this outcome may result in little to no difference for secondary prevention (rate ratio 0.98, 95% CI 0.85 to 1.14; P = 0.84; $I^2$ = 56%; 12 studies, 10,849; low-certainty of the evidence; Analysis 4.5). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Abbate 2020; Brucato 2016; Choudhury 2016; Emsley 2005; Krisai 2020; Morton 2015; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018).

*B.1.4.2 Adverse events: serious infection by incidence rate*

The evidence suggests the effect of anakinra (8 trials) and canakinumab (4 trials) on this outcome may increase the outcome slightly in secondary prevention (rate ratio 1.11, 95% CI 1.05 to 1.18; P = 0.0003; $I^2$ = 0%; 12 studies, 10,849; low-certainty of the evidence; Analysis 4.6). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size. The tests for subgroup differences did not show evidence of differences (P = 0.83; $I^2$ = 0%) (Abbate 2020; Brucato 2016; Choudhury 2016; Emsley 2005; Krisai 2020; Morton 2015; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018).

#### Secondary outcomes

#### B.1.5 Peripheral vascular disease

Meta-analysis comparing canakinumab with placebo or usual care shows very uncertain evidence of the effect of the intervention on the outcome related to secondary prevention (6/6830 (0.009%) versus 6/3458 (0.7%)) (risk ratio 0.85, 95% CI 0.19 to 3.73; P = 0.82; $I^2$ = 38%; 3 studies, 10,288 participants; very low certainty of the evidence; Analysis 4.7). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Choudhury 2016; Ridker 2017; Russel 2019).

#### B. 1.6 Stroke (fatal or non-fatal)

Meta-analysis comparing anakinra and canakinumab with placebo or usual care showed very uncertain evidence of the effect of these interventions on the outcome related to secondary prevention (179/7065 (2.5%) versus 97/3640 (2.7%)) (risk ratio 0.94, 95% CI 0.74 to 1.2; P = 0.62; $I^2$ = 0%; 7 studies, 10,706 participants; very low certainty of the evidence; Analysis 4.8). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Abbate 2020; Choudhury 2016; Emsley 2005; Morton 2015; Smith 2018; Ridker 2017; Van Tassell 2017).

#### B.1.7. Quality of life

One trial compared anakinra with placebo to assess the quality of life with the Duke Activity Status Index and the Minnesota Living With Heart Failure scale. Trial authors suggested that there were improvements in the participants exposed to anakinra on both scales (Van Tassell 2017). See additional Table 9 for details.

One trial comparing anakinra with placebo or usual care showed the results using a narrative approach; "none of the differences in

anakinra versus placebo changes reached statistical significance for any of the changes in questionnaires over time (all P > 0.05 for time × group interaction...)" (Van Tassell 2018).

#### B.1.8 Heart failure

Meta-analysis of trials comparing anakinra (four trials) and canakinumab (three trials) with placebo or usual care showed very uncertain evidence of the effect of these interventions on the outcome related to secondary prevention (29/6971 (0.42%) versus 19/3538 (0.54%)) (risk ratio 0.91, 95% CI 0.5 to 1.65; P = 0.75; $I^2$ = 0%; 7 studies, 10,705 participants; very low certainty of the evidence; Analysis 4.9). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Abbate 2020; Choudhury 2016; Ridker 2017; Russel 2019; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018). There was no indication of subgroup differences: $Chi^2$ = 1.92, df = 1 (P = 0.17), $I^2$ = 48.0%.

### *B.2. Interleukin-6 receptor antagonists (tocilizumab) compared with placebo or usual care*

#### Primary outcomes

#### B.2.1 All-cause mortality

Meta-analysis comparing tocilizumab with placebo or usual care showed very uncertain evidence of the effect of the intervention on all-cause mortality (15/98 (15.3%) versus 14/100 (14%)) (risk ratio 1.09, 95% CI 0.61 to1.96; P = 0.77; $I^2$ = 0%; 2 studies, 198 participants; very low certainty of the evidence; Analysis 5.1). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Kleveland 2016; Meyer 2021).

#### B.2.2. Myocardial infarction (fatal or non-fatal)

Meta-analysis comparing tocilizumab with placebo or usual care showed very uncertain evidence of the effect of the intervention on this outcome (3/172 (1.7%) versus 9/173 (5.2%)) (risk ratio 0.46, 95% CI 0.07 to 3.04; P = 0.42; $I^2$ = 45%; 3 studies, 345 participants; very low certainty of the evidence; Analysis 5.2). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Broch 2021; Carroll 2018; Kleveland 2016).

#### B.2.3. Unstable angina

One trial comparing tocilizumab with placebo or usual care showed very uncertain evidence of the effect of the intervention on the outcome related to secondary prevention (0/59 (0%) versus 1/59 (1.7%)) (risk ratio 0.33, 95% CI 0.01 to 8.02 $I^2$ = NA; 1 study, 118 participants; very low certainty of the evidence; Analysis 5.3). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Kleveland 2016).

#### B.2.4. Adverse events

Meta-analysis comparing tocilizumab with placebo or usual care showed very uncertain evidence of the effect of the intervention on the outcome related to secondary prevention (36/54 (66.7%) versus 42/59 (71.2%)) (risk ratio 0.89, 95% CI 0.76 to 1.05; P = 0.17; $I^2$ = 0%; 2 studies, 113 participants; very low certainty of the evidence; Analysis 5.4). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Carroll 2018; Meyer 2021).

*Adverse events (incidence rate)*
Meta-analysis comparing tocilizumab with placebo or usual care showed a very uncertain effect of the intervention on the incidence rate of adverse events in secondary prevention (rate ratio 0.81, 95% CI 0.45 to 1.44; P = 0.47; $I^2$ = 27%; 2 studies, 348 participants; very low certainty of the evidence; Analysis 5.5). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Carroll 2018; Meyer 2021).

*Adverse events: infection (incidence rate)*
Meta-analysis comparing tocilizumab with placebo or usual care showed a very uncertain effect of the intervention on the incidence rate of the infection in secondary prevention (rate ratio 0.66, 95% CI 0.32 to 1.36; P = 0.26; $I^2$ = 0%; 4 studies, 533 participants; very low certainty of the evidence; Analysis 5.6). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Broch 2021; Carroll 2018; Kleveland 2016; Meyer 2021).

#### Secondary outcomes

#### B.2.5. Peripheral vascular disease

None of the trials assessed this outcome.

#### B.2.6. Stroke (fatal or non-fatal)

The evidence is very uncertain about the effect of tocilizumab on this outcome for secondary prevention (1/96 (1%) versus 1/99 (1%)) (risk ratio 1.03, 95% CI 0.07 to 16.25; P = 0.98; $I^2$ = NA; 1 study, 195 participants; very low certainty of the evidence; Analysis 5.7). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Broch 2021).

#### B.2.7 Quality of life

None of the trials assessed this outcome.

#### B.2.8 Heart failure

One trial assessed this outcome; however, it did report any events in either group (Kleveland 2016).

### *B.3. Tumour necrosis factor inhibitors (etanercept, infliximab) compared with placebo or usual care*

#### Primary outcomes

#### B.3.1 All-cause mortality

Tumour necrosis factor inhibitors (etanercept and infliximab) may have little to no effect on the outcome for secondary prevention, but the evidence is very uncertain. Meta-analysis comparing tumour necrosis factor inhibitors with placebo or usual care showed very low certainty of the evidence (175/1764 (9.9%) versus 78/1016 (7.7%)) (risk ratio 1.16, 95% CI 0.69 to 1.95; P = 0.57; $I^2$ = 47%; 5 studies, 2780 participants; very low certainty of the evidence; Analysis 6.1). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Bozkurt 2001; Chung 2003; RECOVER 2000; RENAISSANCE 2001; Weisman 2007).

#### B.3.2. Myocardial infarction (fatal or non-fatal)

None of the trials assessed this outcome.

#### B.3.3. Unstable angina

No trial assessed this outcome.

#### B.3.4. Adverse events

Tumour necrosis factor inhibitors (etanercept and infliximab) may have little to no effect on the outcome for secondary prevention,

but the evidence is very uncertain. Meta-analysis comparing tumour necrosis factor inhibitors with placebo or usual care shows very low certainty of the evidence (112/367 (30.5%) versus 56/318 (17.6%)) (risk ratio 1.15, 95% CI 0.84 to 1.56; P = 0.39; $I^2$ = 32%; 2 studies, 685 participants; very low certainty of the evidence; Analysis 6.2). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Chung 2003; Weisman 2007).

*B.3.4.2 Adverse events by incidence rate*

Medications may increase the outcome, but the evidence is very uncertain. This conclusion is derived from a meta-analysis encompassing six trials, with five trials investigating etanercept and one examining infliximab (rate ratio 1.17, 95% CI 1.08 to 1.28; P = 0.0003; $I^2$ = 0%; 6 studies; 2283 participants; very low certainty of the evidence; Analysis 6.3). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size. Additionally, subgroup analyses did not reveal significant differences (P = 0.93; $I^2$ = 0%) (Bozkurt 2001; Chung 2003; Deswal 1999; Ralph 2020; RECOVER 2000; RENAISSANCE 2001).

*B.3.4.3 Adverse events: incidence rate of serious infection*

Medications may increase the outcome, but the evidence is very uncertain. This conclusion is derived from a meta-analysis encompassing seven trials, with six trials investigating etanercept and one examining infliximab (rate ratio 1.23, 95% CI 1.04 to 1.45; P = 0.01; $I^2$ = 0%; 7 studies; 2821 participants; very low certainty of the evidence; Analysis 6.4). The evidence was downgraded due to the risk of bias and small sample size. Subgroup analyses conducted revealed no significant differences (P = 0.58; $I^2$ = 0%) (Bozkurt 2001; Chung 2003; Deswal 1999; Ralph 2020; RECOVER 2000; RENAISSANCE 2001; Weisman 2007).

#### Secondary outcomes

#### B.3.5 Peripheral vascular disease

None of the trials assessed the outcome.

#### B.3.6 Stroke (fatal or non-fatal)

The trials didn't assess the outcome.

#### B.3.7. Quality of life

One trial compared etanercept with placebo in people with heart failure for secondary prevention. However, the evidence is very uncertain (MD 18.93, 95% CI 95% -7.10 to 4.96; P = 0.15; $I^2$ = NA; 1 study, 18 participants, very low certainty of evidence; Analysis 6.5). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Deswal 1999).

One trial compared infliximab with placebo or usual care to assess the quality of life with the Minnesota Living With Heart Failure scale. The trial showed no changes in the quality of life scores at 14 weeks or 28 weeks, between 150 participants receiving a placebo, 5 mg/kg infliximab, and 10 mg/kg infliximab (Chung 2003). See additional Table 9 for details.

#### B.3.8. Heart failure

Tumour necrosis factor inhibitors (etanercept and infliximab) may have little to no effect on the outcome regarding secondary prevention, but the evidence is very uncertain. Meta-analysis comparing tumour necrosis factor inhibitors with placebo or usual care shows very low certainty of the evidence (209/1498 (14%) versus 111/747 (14.9%)) (risk ratio 0.92, 95% CI 0.75 to 1.14; P = 0.45; $I^2$ = 0%; 4 studies, 2245 participants; very low certainty of the evidence; Analysis 6.6). The evidence was downgraded due to the risk of bias and imprecision as a result of the small sample size (Bozkurt 2001; Chung 2003; RECOVER 2000; RENAISSANCE 2001).

#### Summary of findings tables

Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6 shows details of the results.

## DISCUSSION

### Summary of main results

This Cochrane review thoroughly examines the clinical benefits and harms of interleukin-receptor antagonists and tumour necrosis factor inhibitors to prevent primary and secondary atherosclerotic cardiovascular disease outcomes. The review included a total of 58 randomised controlled trials, including 21,308 randomised participants, assessing five types of biological agents: anakinra, canakinumab (interleukin-1 receptor antagonists), tocilizumab (interleukin-6 receptor antagonist), and etanercept and infliximab (tumour necrosis factor inhibitors). These trials used placebo or usual care as a control comparison. However, it is essential to note that the trials were found to have a high overall risk of bias, with only one large-scale trial evaluating canakinumab for secondary prevention (Ridker 2017).

Table 2 clearly shows that the USA had the highest number of published trials, with a total of 58. Of these, 21 were conducted internationally, accounting for 36.3%. On average, each study had 46 centres, with a standard deviation of 154.24. Most trials (70.6%) were multicentre, and most settings (74.1%) were outpatients. C-reactive protein levels were reported in 66% of the primary or secondary prevention trials. As shown in Table 3, all trials provided information on the frequency of administration, with subcutaneous administration being the most common route (used in 75.8% or 44 trials). Adverse events were the most frequently reported outcome in 98% of the trials, with detailed information provided in Table 6 and Table 7. Unstable angina and peripheral vascular disease were the least reported outcomes. Quality of life was reported in 22 trials (37.9%), but meta-analyses were not conducted due to unsuitable reporting of the information; instead, we used a narrative approach to report quality of life. Most trials (86.2%, 50/58) reported an a priori sample size estimation. Finally, 51.7% (30/58) of the trials were sponsored by drug and medical device companies.

The Cochrane Review permitted comprehensive meta-analyses of biological agents utilised for primary and secondary prevention, but it only encompassed specific predetermined outcomes from the trials. Furthermore, numerous outcomes required further information. As per the imprecision domain for GRADE, it was determined that almost all meta-analyses lacked sufficient power.

For primary prevention, eleven meta-analyses were conducted. The majority (73%) of these studies displayed low or very low certainty of the evidence according to GRADE standards. While the most extensive study included 2694 participants, a few meta-analyses had only a limited number of studies with few participants. On average, each meta-analysis had only three trials. For a comprehensive understanding of the factors contributing to the very low-certainty GRADE ratings across most variables,

please refer to Summary of findings 1, Summary of findings 2 and Summary of findings 3.

In terms of secondary prevention, thirteen meta-analyses were conducted. We found that 92.3% (12/13) of these meta-analyses had a very low certainty of evidence, in GRADE ratings, across most variables. These meta-analyses included a median of four trials and 2780 participants. For a better understanding of the factors contributing to the very low-certainty GRADE ratings across most variables, please refer to Summary of findings 4, Summary of findings 5 and Summary of findings 6. In summary, there was a predominance of meta-analyses with few studies.

Regarding the comprehensive understanding of the factors contributing to the certainty of judgement GRADE ratings across most variables, please refer to Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6.

**A) Primary prevention**

***A1. Interleukin-1 receptor antagonists compared with placebo or usual care***

Four meta-analyses looked at anakinra and canakinumab, compared with placebo or usual care. However, the medications studied had little to no effect on myocardial infarction (two trials, 585 participants), unstable angina (two trials, 566 participants), adverse events (three trials, 596 participants), or heart failure (three trials, 596 participants). It should be noted that the evidence was very uncertain due to limitations in design and execution, as well as the imprecision of the included trials (Summary of findings 1).

***A2. IL-6 receptor antagonists (tocilizumab) compared with placebo or usual care***

Four meta-analyses compared tocilizumab with placebo or usual care. However, the medication studied had little to no effect on all-cause mortality (two trials, 329 participants), myocardial infarction (fatal or non-fatal) (three trials, 329 participants), or heart failure (two trials, 299 participants). It should be noted that the evidence was very uncertain due to limitations in design and execution, as well as imprecision in the included trials. Regarding adverse events (five trials, 1051 participants), the evidence suggested that tocilizumab may worsen outcomes. However, the certainty of the evidence was judged as low due to limitations in the design and execution of the included trials (Summary of findings 2).

***A3. TNF inhibitors (etanercept, infliximab) compared with placebo or usual care***

Three meta-analyses compared tumour necrosis factor inhibitors (etanercept, infliximab) with placebo or usual care. However, the medications studied had little to no effect on all-cause mortality (three trials, 609 participants), stroke (fatal or non-fatal) (three trials, 565 participants), or heart failure (one trial, 48 participants). The evidence was very uncertain due to limitations in design and execution and imprecision in the included trials. Regarding adverse events (thirteen trials, 2654 participants), the evidence suggested that the medication studied may worsen the outcome slightly. However, the certainty of the evidence was judged as low due to limitations in the design and execution of the included trials (Summary of findings 3).

**B) Secondary prevention**

***B1. Interleukin-1 receptor antagonists compared with placebo or usual care***

Seven meta-analyses assessed anakinra and canakinumab compared with placebo or usual care. In six meta-analyses, the medications studied had little to no effect on all-cause mortality (eight trials, 10,743 participants), unstable angina (three trials, 10,403 participants), adverse events (four trials, 264 participants), peripheral vascular disease (three trials, 10,288 participants), stroke (seven trials, 10,705 participants) or heart failure (seven trials, 10,509 participants). It should be noted that the evidence was very uncertain due to limitations in design and execution, as well as imprecision in the trials included in these meta-analyses. Evidence from a meta-analysis about myocardial infarction (six trials, 10,629 participants) suggested interleukin-1 receptor antagonists had little to no effect on secondary prevention. The low certainty of the evidence is due to the limitation in the design and execution of the trials (Summary of findings 4).

***B2. IL-6 receptor antagonists (tocilizumab) compared with placebo or usual care***

Three meta-analyses were conducted to compare tocilizumab with placebo or usual care. The results showed that tocilizumab had minimal or no impact on all-cause mortality (based on two trials involving 198 participants), myocardial infarction (fatal or non-fatal) (based on three trials involving 345 participants), and adverse events (based on two trials involving 113 participants). However, the evidence was very uncertain due to limitations in design and execution and imprecision in the trials included in these meta-analyses (Summary of findings 5).

***B3. Tumour necrosis factor inhibitors (etanercept, infliximab) compared with placebo or usual care***

After conducting three meta-analyses, the medications etanercept and infliximab had little to no impact on all-cause mortality (based on five trials with 2780 participants), adverse events (based on two trials with 685 participants), and heart failure (based on four trials with 2245 participants) when compared to placebo or usual care. The trials included in these meta-analyses had limitations in their design, execution, and imprecision, so the evidence was very uncertain (Summary of findings 6).

To sum up, using the GRADE approach, we found that in 91.2% (22/24) of the meta-analyses, whether for primary or secondary prevention, the evidence was very uncertain.

## Overall completeness and applicability of evidence

This Cochrane Review has demonstrated that interleukin-receptor antagonists (either interleukin-1 antagonists, anakinra and canakinumab, or interleukin-6 antagonists, tocilizumab) and tumour necrosis factor inhibitors (etanercept or infliximab) have little to no impact on clinical benefits for the primary or secondary prevention of atherosclerotic cardiovascular disease outcomes.

Two types of interventions (interleukin-6 receptor antagonists and tumour necrosis factor inhibitors) may slightly increase harm. The result is mainly based on meta-analyses of trials that reported results on these outcomes. However, this conclusion is based on trials at high risk of bias due to flaws in design and execution and

underpowered meta-analyses (imprecision). Thus, the certainty of the evidence ranged from low to very low.

Therefore, based on these GRADE findings (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6), future research is needed to better understand the clinical benefits of these interventions for the primary or secondary prevention of atherosclerotic cardiovascular disease outcomes.

**Factors influencing the certainty of the evidence for the outcomes**

This review shows that, for the three groups of interventions (five biological agents), the evidence was low- to very low-certainty. This is due to the trials being at high risk of bias due to flaws in design and execution. Furthermore, the meta-analyses were either underpowered or not pooled, resulting in imprecision. The results presented in this Cochrane Review are based on data from trials that included a broad range of participants with different comorbidities who received different treatments.

We identified twenty-seven trials with a high risk of selective reporting of primary prevention outcomes (Bachelez 2015; Bagel 2012; Bernstein 2006; Brandt 2003; Calin 2004; Davis 2003; Don 2010; Gorman 2002; Gottlieb 2004; Khanna 2016; Khanna 2020; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; Reich 2017; Ridker 2012; Smolen 2008; Stanley 2011; Torii 2010; Tyring 2006; Villiger 2016; Van de Kerkhof 2008; Van der Heijde 2006) and seven reporting secondary prevention outcomes (Bozkurt 2001; Choudhury 2016; Emsley 2005; Meyer 2021; Padfield 2013; Ralph 2020; Russel 2019). The high proportion of trials with a high risk of bias when reporting outcomes in these studies could be explained by the lack of awareness amongst rheumatologists and dermatologists that soft tissue diseases are associated with a high risk of cardiovascular disease (Berna-Rico 2023). It is possible that the trial's follow-up duration may be insufficient to ensure the proper development of cardiovascular outcomes.

Another important finding of this review was that 70.7% (41/58) of the trials had fewer than 200 participants. Small sample sizes in clinical trials can cause confusion and bias due to the allocation of unknown prognostic factors being affected by the small sample size, resulting in an imbalance of covariates between comparison groups. The resulting variability in distribution can create complexity and contradiction in clinical trial research (Berger 2005; Horwitz 1987; Martí-Carvajal 2018). Recently, Van Zwet and colleagues identified issues with simplistic P value interpretations, inflated effect sizes, and imprecision, which are common in fields with low statistical power. To address these problems, they proposed an empirical guide for interpreting P values from clinical trials, which estimates the overestimation of reported effects, the probability of incorrect effect directions, and the trial's predictive power (Van Zwet 2024). It is imperative to address this issue to ensure accurate and reliable clinical trial results.

In primary prevention trials, we identified 16 trials at high risk of bias in random sequence generation (Abbate 2010; Baek 2019; Boetticher 2008; Brandt 2003; Calin 2004; Davis 2003; Don 2010; Gorman 2002; Gottlieb 2003; Mease 2004; Micali 2015; Ridker 2012; Stanley 2011; Torii 2010; Van de Kerkhof 2008; Van der Heijde 2006). Regarding secondary prevention, 75% (9/12) of trials had a high risk of bias concerning random sequence generation (Abbate 2020; Bozkurt 2001; Carroll 2018; Chung 2003; Deswal 1999; Krisai 2020; Ralph 2020; Russel 2019; Van Tassell 2016).

Trials without proper allocation concealment can potentially inflate clinical benefits compared to trials with adequate allocation concealment (Viera 2005; ). There were 31 trials with a high risk of bias in allocation concealment (primary prevention (19 trials: Abbate 2010; Baek 2019Zeraatkar 2023; Bernstein 2006; Boetticher 2008; Brandt 2003; Calin 2004; Davis 2003; Don 2010; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Mease 2000; Mease 2004; Micali 2015; Ridker 2012; Stanley 2011; Torii 2010; Van de Kerkhof 2008; Van der Heijde 2006; secondary prevention (12 trials: Abbate 2020; Bozkurt 2001; Brucato 2016; Carroll 2018; Chung 2003; Deswal 1999; Krisai 2020; RECOVER 2000; RENAISSANCE 2001; Russel 2019; Van Tassell 2016; Weisman 2007).

The review identified many drawbacks concerning the reporting of adverse events, quality of life, and high-sensitivity C-reactive protein levels. Due to inconsistencies in data reporting, we were compelled to report adverse events using two different methods (risk ratio and rate ratio). Furthermore, certain trials presented data that could not be combined. These factors and the low number of events resulted in sparse data bias for that crucial variable (Greenland 2016).

**Adverse events**

Table 10 summarises the percentage of missing data for adverse events, classified by the intervention and prevention method used. We identified pitfalls related to harm reporting in the 50 included trials, with a mean of 16.65% (95% CI 12.97 to 20.34) of missing data. Therefore, we must consider the underestimation of this result. This situation forced us to assess the risk ratio and rate ratio with and without evaluation of the missing data, demonstrating the subgroup differences according to the approach used to evaluate the outcome.

For primary prevention, 34 trials reported any adverse events, twenty-six reported serious adverse events, and twenty-five reported non-serious adverse events. Regarding the incidence of infection, thirty trials reported any infection, twenty-two reported severe infections, and twenty-two reported non-serious infections. It has been suggested that adverse events in randomised trials can be "neglected", "restricted", "distorted", and "silenced" (Ioannidis 2009).

Regarding secondary prevention, 23 trials reported data on any adverse event, 17 trials reported severe adverse events, 15 reported non-serious adverse events, 22 reported any infection, 17 reported severe infections, and 11 reported non-serious infections. However, the trials reported data on adverse events or infections using two approaches simultaneously, either by participants with the outcome or by the number of outcomes. This precluded a single estimate of those critical results, and uncertainty remains, which affects the external validity of these results (Ioannidis 2022).

The dispersion of data could yield an "artificial reduction" in the number of events, resulting in sparse data bias (Greenland 2016). Due to these difficulties, trial authors should follow the Consolidated Standards of Reporting Trials (CONSORT) recommendations when reporting harms in future randomised trials (Junqueira 2023a; Junqueira 2023b).

### Quality of life

Reporting appropriate information on the quality of life in randomised clinical trials in people with autoimmune disease and cardiovascular diseases is critical for several reasons (Conrad 2022; Farhat 2022). Firstly, quality of life is an important patient-reported outcome that reflects the impact of treatments on five dimensions: physical, material, social, emotional well-being and development, and activity (Felce 1995). Secondly, quality of life can be affected by the index condition and comorbidities, which are common in this population (Strand 2008). Thirdly, quality of life can inform the cost-effectiveness and value of different interventions for patients, clinicians, and policymakers (Kievit 2017).

Therefore, rigorously and in a standardised fashion, collecting and analysing quality of life data is essential in randomised clinical trials involving people with autoimmune and cardiovascular diseases. Studies demonstrate the proper methodology for studying and reporting quality of life in clinical trials (Aaronson 1989; Sedaghat 2019; Watt 2021; Zeng 2023). Various strategies were found in the trials, but they did not permit a meta-analysis; almost all reported the information narratively (Table 8; Table 9).

### C-reactive protein levels

Some trials reported CRP levels, but did not specify whether or not a high-sensitivity assay was used. In some trials, reported CRP levels were not elevated. Baseline information was reported in some trials but not at the end, and vice versa. These gaps make it difficult to evaluate the impact of treatment on this recognised risk biomarker for cardiovascular outcomes (Denegri 2021). It is also concerning that twenty trials did not report this crucial information (Fernández Pinto 2019; Smith 2016).

### Co-interventions

Another finding that requires mention is the key role of co-interventions. Antihypertensives and statins are well-documented for their roles in reducing cardiovascular risk. Their inclusion as co-interventions could potentially confound the outcomes of studies focused on cardiovascular health. Similarly, the use of anti-inflammatory drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunomodulatory therapies, could also potentially influence cardiovascular outcomes (Conrad 2022; Farhat 2022).

The inclusion of these co-interventions underscores the importance of carefully considering and adjusting for their potential effects when analysing study outcomes. It highlights the need for a comprehensive understanding of how these treatments might interact with the primary interventions under investigation and their overall impact on cardiovascular health. Discussing the potential impact of these co-interventions provides a more nuanced understanding of the variables affecting study outcomes, thereby strengthening the paper's overall impact by acknowledging the complexity of managing patients with cardiovascular diseases and the multifaceted nature of the interventions they receive (Felce 1995; Strand 2008; Kievit 2017).

### Cost-effectiveness

We reviewed several biological disease-modifying antirheumatic drugs, such as anakinra, canakinumab, tocilizumab, etanercept, and infliximab targeting the cytokines responsible for inflammation and their effects on atherogenesis. Notably, these biological agents are high-cost (Prieto-Peña 2021; Sarzi-Puttini 2019). Given the uncertain findings of this review, it makes it unlikely based on the current evidence that the drugs would be cost-effective for either primary or secondary prevention of cardiovascular disease. However, we have not conducted a formal economic evaluation.

## Quality of the evidence

We conducted GRADE assessments on outcomes of both meta-analysis and non-pooled trials. The certainty of the evidence was graded as low or very low across these outcomes. This low-certainty conclusion is based on the small sample sizes (even after meta-analysis), which generate wide confidence intervals with low precision of the estimate of the intervention effects. It is also based on the high risk of bias due to a lack of adequate randomisation methods, lack of blinding, high attrition, unclear reporting of outcomes, and considerable loss of follow-up. These issues are associated with the inflation of intervention effect size estimates and between-trial inconsistency in trials reporting subjectively assessed outcomes (Pereira 2011; Savovic 2012).

Looking more specifically at each GRADE domain for the certainty of the evidence:

**Risk of bias:** The certainty of the evidence was downgraded to low/very low because most included studies suffered from high risk of bias stemming from inadequate randomisation methods, lack of blinding of participants and assessors, high attrition with incomplete outcome data, and unclear or selective reporting of measured outcomes.

**Precision:** The certainty of evidence was also downgraded due to wide confidence intervals and imprecise effect estimates, even in the meta-analyses. This was primarily driven by small sample sizes in the included studies.

**Consistency:** Heterogeneity was assessed but was not a factor in downgrading certainty levels. Effects estimates were consistent enough across studies.

**Directness:** Reported outcomes aligned directly with the stated objectives, so there was no downgrading based on concerns over directness or applicability.

The quality of the evidence is a measure of how confident we can be in the results of a study or a synthesis of studies. It is based on several factors, such as the risk of bias, consistency, precision, and directness of the evidence (Schünemann 2019). When the judgement of certainty is very low in almost all of these factors, the evidence is very uncertain and unreliable. This Cochrane review found seven variables graded as very low and three as low in the judgement of certainty in eleven meta-analyses related to primary prevention of cardiovascular outcomes in any medication study compared with placebo or usual care. Regarding secondary prevention, twelve meta-analyses had a very low judgement of certainty for seven variables and one low in any intervention compared with placebo or usual care.

We cannot draw any firm conclusions from such evidence, and we should be very cautious of using it to inform decisions or policies. The quality of the evidence can be improved by conducting more rigorous and relevant studies that address the sources of

uncertainty and provide more accurate and consistent estimates of the effects of an intervention (Santesso 2020; Schünemann 2019).

See the Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6 for complete assessment and rationale for ratings.

### Potential biases in the review process

Publication bias poses a significant problem in research studies (Howland 2011). The publication of results is often based on their direction and strength rather than their quality or other essential factors. This can lead to a distorted representation of evidence in any scientific field, but clinical trials are particularly vulnerable (Turner 2013). Adverse events are an outcome commonly affected by publication bias, and are not always reported accurately in clinical trials. Such events provide crucial information about an intervention's safety, tolerability, and potential risks and benefits. This review of 58 trials found that drug and medical companies sponsored 30 studies, and only one trial failed to report adverse event information. However, the reported information about adverse events varied amongst the included trials. This can result in underestimating the harms and overestimating the benefits of an intervention, which can mislead readers and decision-makers.

Amongst the 24 meta-analyses conducted, only one could assess the potential for publication bias due to the availability of essential data. This particular analysis specifically examined the adverse effects of tumour necrosis factor inhibitors for primary prevention compared to either placebo or usual care (Figure 4). The remaining 23 meta-analyses did not contain a sufficient number of trials to identify any possible publication bias.

It is crucial to emphasise that the included trials often failed to note significant findings about heart failure, peripheral vascular disease, unstable angina, and quality of life. This strongly implies that outcome reporting bias may exist, leading to limited availability of information (Ioannidis 2010). Furthermore, there was no consistent definition or reporting of heart failure, peripheral vascular disease and unstable angina used in the trials.

Furthermore, analysing the trials' follow-up periods and the low number of cardiovascular outcomes reported, we determined that this Cochrane Review is limited in the evaluation of the risks and benefits of the biologics studied. Therefore, it is strongly recommended that the duration of trials for atherosclerosis should be as long as practically feasible, given the low annual event rates (Insull 2009). This limitation has been previously discussed and acknowledged in our review.

We updated the search on February 20, 2024, identifying one RCT meeting the inclusion criteria (Parry-Jones 2023). However, it is a small trial with a duration of three months. Therefore, including this trial will likely not change the current conclusion. The Studies awaiting classification section provides the details for Parry-Jones 2023.

### Agreements and disagreements with other studies or reviews

According to our knowledge, we have conducted the first systematic review and meta-analysis on the clinical benefits and harms of interleukin-receptor antagonists and tumour necrosis factor inhibitors for preventing atherosclerotic cardiovascular outcomes. The only mega trial with over 10,000 participants supports the review's findings on the rise in infections with canakinumab (Ridker 2017). However, the ad hoc meta-analysis of this Cochrane Review heavily depends on this study; yet, the judgement of certainty was very low due to imprecision and the high risk of bias. Concerning adverse events, this Cochrane review yielded findings similar to those reported by Westergren and colleagues. The review discovered inconsistencies in disease definitions, reporting thresholds, and incomplete reporting (Westergren 2022). A Cochrane review on biologic monotherapy for rheumatoid arthritis has also raised concerns about adverse events (Singh 2016).

## AUTHORS' CONCLUSIONS

### Implications for practice

This Cochrane Review assessed the benefits and harms of interleukin-receptor antagonists and tumour necrosis factor inhibitors for primary and secondary prevention of cardiovascular disease compared to placebo or usual care. However, the certainty of evidence for the predetermined outcomes was low to very low. Biases and imprecision in the studies limited its external validity and the ability to determine the effectiveness of the interventions for both primary and secondary prevention of cardiovascular outcomes. Further research is needed to establish the clinical benefits and potential harms of these treatments.

### Implications for research

This Cochrane review highlights the need for well-designed and adequately powered randomised controlled trials to evaluate the effects of interleukin receptor antagonists and tumour necrosis factor inhibitors on cardiovascular atherosclerotic outcomes from a primary and secondary prevention perspective.

The review recommends that future trials should be designed to consistently report on definitions of peripheral vascular disease, heart failure, infection, and quality of life. We also suggest that composite outcomes should be reported individually to ensure accuracy in meta-analyses. In addition, trials need to limit confounding and attrition biases to ensure reliable results.

Another critical point is that primary prevention studies have not extensively researched the impact of biological interventions on cardiovascular outcomes, except for a few exceptions (Abbate 2010; Abbate 2013; Ridker 2012). Several references about people with autoimmune diseases suggest an increased risk of cardiovascular disease compared to the general population (Agca 2017). However, the lack of evidence in this area does not necessarily mean that such evidence does not exist. This Cochrane review suggests that the current evidence base is limited and that more high-quality randomised controlled trials are needed to determine the effects of interventions on cardiovascular outcomes in people with autoimmune diseases.

Trials in the soft tissue and autoimmune disease population should focus on cardiovascular clinical outcomes (such as myocardial infarction, stroke, the incidence of heart failure, and peripheral vascular disease) and quality of life, with reports including the name of the scale and continuous measurements. Studies have mainly focused on rheumatological and dermatological diseases. There is a need for more research on the impact of these interventions in these conditions on cardiovascular outcomes.

Trials should adopt an agreed set of core outcomes to reduce outcome reporting bias (Clarke 2007). The trials should also be designed and reported according to established standards to improve the quality of reporting of the effects of the interventions and any adverse events encountered (Kirkham 2010; Parry 2021).

The trials should be designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (Chan 2013a; Chan 2013b; Tunn 2024) and reported according to the CONSORT statement to improve the quality of reporting of efficacy; the trials should also provide better reports of harms/adverse events encountered during their conduct (Butcher 2022; Junqueira 2023a; Junqueira 2023b; Tunn 2024). Future trials should be planned following the Foundation of Patient-Centered Outcomes Research recommendations (Parry 2021). The implementation of this strategy is crucial in reducing the production of low-quality biomedical research (Chalmers 2009; Ioannidis 2014).

Therefore, for the reasons outlined above, the conclusions of this review are limited to determining the effectiveness of interleukin-receptor antagonists and tumour necrosis factor inhibitors for primary and secondary prevention of ACVD.

It is imperative that new immunotherapies are developed to effectively treat the inflammatory mechanisms responsible for atherosclerotic cardiovascular disease (Amadori 2023).

In 2015, Roberts and colleagues published a paper titled "The knowledge system underpinning healthcare is not fit for purpose and must change. The medical literature is biased and inundated with poor quality trials" (Roberts 2015). Our review shows evidence of that.

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**Editorial contributions**:

Cochrane Heart Group supported the authors in the development of this systematic review.

The following people conducted the editorial process for this article:

**Sign-off Editor** (final editorial decision): Rui Providencia, St Bartholomew's Hospital, London; **Managing Editor** (edited the article, collated peer-reviewer comments, and provided editorial guidance to authors): Marwah Anas El-Wegoud, Cochrane Central Editorial Service; **Editorial Assistant** (conducted editorial policy checks, selected peer reviewers, and supported editorial team): Sara Hales-Brittain, Cochrane Central Editorial Service; **Copy Editor** (copy editing and production): Anne Lethaby, Cochrane Central Production Service.

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* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Abbate 2010**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 1 year<br>4. Follow-up period: 14 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no |

**Abbate 2010** *(Continued)*

8. Multicentre (number of centres): N/A
9. Country: United States
10. Study setting: inpatient and outpatient
11. Type trial: not stated
12. Type of prevention: primary

| | |
|---|---|
| Participants | 1. Type of disease: acute myocardial infarction<br>2. Diagnosis criteria: < 24 hours of the onset of chest pain, new or presumably new ST-segment elevation ≥ 1 mm in ≥ 2 anatomically contiguous leads<br>3. Severity: not stated<br>4. Total randomised: 10 participants<br>a. Anakinra: 5<br>b. Placebo: 5<br>5. Number lost to follow-up/withdrawn (%): 0<br>a. Anakinra: 0<br>b. Placebo: 0<br>6. Total analysed<br>a. Anakinra: 5<br>b. Placebo: 5<br>7. Age, years, participants<br>a. Anakinra: 34, 35, 40, 59, 59<br>b. Placebo: 28, 45, 53, 60, 65<br>8. Gender, male% (males/total)<br>a. Anakinra: 60 (3/5)<br>b. Placebo: 100 (5/5)<br>9. C-reactive protein basal level, mg/dL, measure not specified (range)<br>a. Anakinra: 15.4 (13.0 to 16.6)<br>b. Placebo: 2.3 (1.9 to 2.7)<br>10. Inclusion criteria:<br>a. Age ≥ 18 years;<br>b. Acute (24 hours) onset of chest pain;<br>c. New or presumably new ST-segment elevation (≥ 1 mm) in ≥ 2 anatomically contiguous leads;<br>d. Planned or completed angiography for urgent percutaneous coronary intervention.<br>11. Exclusion criteria:<br>• Inability to give informed consent;<br>• Late presentation (> 24 hours);<br>• Unsuccessful revascularisation or urgent coronary bypass surgery;<br>• Haemodynamic instability;<br>• End-stage congestive heart failure;<br>• Pre-existing severe LV dysfunction or severe valvular disease;<br>• Severe asthma;<br>• Pregnancy;<br>• Contraindications to cardiac MRI or cardiac angiography;<br>• Severe coagulopathy;<br>• Severe renal insufficiency;<br>• Recent (< 14 days) use of anti-inflammatory drugs (NSAIDs excluded);<br>• Chronic inflammatory disease. |
| Interventions | 1. Intervention<br>a. Anakinra (Kineret®)<br>b. Pharmaceutical laboratory: Amgen (Thousand Oaks, California, USA)<br>c. Dose: 100 mg, once daily for 14 days<br>d. Administration route: subcutaneous |

**Abbate 2010** *(Continued)*

2. Control
   a. Placebo (sodium chloride 0.9%), once daily for 14 days
   b. Administration route: subcutaneous
3. Co-intervention: standard of care for the condition

| | |
|---|---|
| Outcomes | 1. Primary (baseline, 72 hours, 14 days, and 10 to 14 weeks)<br>a. Difference in interval changes in the LV end-systolic volume index (LVESVi) assessed by CMR imaging<br>2. Secondary (baseline, 72 hours, 14 days, and 10 to 14 weeks)<br>a. Difference in interval changes in the LVESVi, by echocardiography<br>b. Difference interval changes in the LV end-diastolic volume index, LV ejection fraction, LV mass, infarct size, wall motion score index, and estimated cardiac index, assessed by CMR or echocardiography<br>c. CPR, white blood cell count, BNP, troponin I, creatine kinase-MB, creatinine<br>d. Adverse events |
| Notes | 1. Trial registration number: NCT00789724<br>2. Trial dates: November 2008–August 2009<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: grants from the Virginia Commonwealth University “A.D. Williams Fund,” the Virginia Commonwealth University General Clinical Research Center Funds for Pilot Clinical Research given to Dr Abbate, and the VCU Pauley Heart Center funds (Richmond, Virginia) funded this study<br>5. Disclosure comment: not stated<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Randomization was performed by the investigational pharmacist using a dedicated randomization algorithm (available online at www.metcardio.org). The investigator in charge of randomization was not involved in patient care, data gathering, or data analysis." (p. 1372).<br><br>Comment: There is a difference of median/mean of 13.1 in the CRP basal levels between the study groups, having the intervention study at a considerably higher level. (p.1374)<br><br>Note: Add email communication |
| Allocation concealment (selection bias) | Unclear risk | Quote: "Randomization was performed by the investigational pharmacist using a dedicated randomization algorithm (available on-line at www.metcardio.org). The investigator in charge of randomization was not involved in patient care, data gathering, or data analysis." (p. 1372).<br><br>Comment: There is a difference of median/mean of 13.1 in the CRP basal levels between the study groups, having the intervention study at a considerably higher level. (p.1374) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "For each patient, the pharmacist prepared a set of 14 syringes containing 100 mg of anakinra in 0.67 mL or matching syringes containing sodium chloride 0.9% placebo that were indistinguishable from the treatment syringes." (p. 1372). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | We considered it an unclear risk citing "some differences in blood results and unclear if investigators were aware of these during the trial." |

**Abbate 2010** *(Continued)*

| | | |
|---|---|---|
| | | Comment: Some differences in blood results were noted between groups. It is unclear whether investigators were aware of these differences during the trial. Insufficient information provided to determine if this knowledge could have influenced outcome assessment. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | 1. Randomised: 10<br>a. Anakinra: 5<br>b. Placebo: 5<br>2. Study completion:<br>a. Anakinra: 5<br>b. Placebo: 5 |
| Selective reporting (reporting bias) | Low risk | The trial reported the main cardiovascular outcomes and adverse events. |
| Other bias | High risk | Other bias: imbalance of basal levels of CRP between comparison groups |

**Abbate 2013**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 2 years<br>4. Follow-up period: 14 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): N/A<br>9. Country: United States<br>10. Study setting: inpatient and outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: ST-elevation myocardial infarction<br>2. Diagnosis criteria: new or presumably new ST-segment elevation (> 1 mm) in ≥ 2 anatomically contiguous leads<br>3. Severity: not stated<br>4. Total randomised: 30 participants<br>a. Anakinra: 15<br>b. Placebo: 15<br>5. Number lost to follow-up/withdrawn (%): 5 (16.6)<br>a. Anakinra: 4 (26.6)<br>b. Placebo: 1 (6.6)<br>6. Total analysed: 25<br>a. Anakinra: 11<br>b. Placebo: 14<br>7. Age, years, median (range)<br>a. Anakinra: 57 (46-86)<br>b. Placebo: 58 (35-83)<br>8. Gender, male% (males/total)<br>a. Anakinra: 60 (9/15)<br>b. Placebo: 86.6 (13/15) |

**Abbate 2013** *(Continued)*

9. C-reactive protein basal level, mg/dL, measure not stated (range)
   a. Anakinra: 7.0 (2.3-8.7)
   b. Placebo: 4.3 (2.2-7.5)
10. Inclusion criteria:
   a. Age: 18 years and older;
   b. Acute (< 24 hours) onset of chest pain;
   c. New or presumably new elevation (< 24 hours) onset of chest pain, new or presumably new ST-segment elevation (> 1 mm) of the ST-segment in ≥ 2 anatomically contiguous leads;
   d. Planned or completed angiography for urgent percutaneous coronary intervention.
11. Exclusion criteria:
   a. Inability to give informed consent;
   b. Late presentation;
   c. Unsuccessful revascularisation procedure;
   d. Haemodynamic instability;
   e. Prior Q-wave infarction;
   f. End-stage congestive heart failure, severe left ventricular dysfunction (EF < 20%), severe valvular heart disease;
   g. Pregnancy, dye allergy or contraindications to cardiac angiography or magnetic resonance imaging, coagulopathy;
   h. Recent (< 14 days) use of anti-inflammatory drugs (not including NSAIDs);
   i. Chronic inflammatory disease, malignancy, or any comorbidity limiting survival or conditions predict the inability to complete the study.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Anakinra (Kineret®)<br>b. Pharmaceutical laboratory: Swedish Orphan Biovitrum, Stockholm, Sweden<br>c. Dose: 100 mg once daily for 14 days<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (sodium chloride at 0.9%) once daily for 14 days<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline, 72 hours, 14 days, and 10 to 14 weeks)<br>a. Difference in interval changes in the LV end-systolic volume index (LVESVi)<br>2. Secondary (baseline, 72 hours, 14 days, and 10 to 14 weeks)<br>a. Difference interval changes in the LV end-diastolic volume index, LV ejection fraction, infarct size<br>b. hsCPR, white blood cell count, BNP, troponin I, creatine kinase-MB, creatinine<br>c. Adverse events |
| Notes | 1. Trial registration number: NCT01175018<br>2. Trial dates: September 2010-September 2012<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: a grant to Dr Abbate from the American Heart Association, a Presidential Research Incentive Program of the Virginia Commonwealth University, and the internal funds of the VCU Pauley Heart Center and Victoria Johnson Research Laboratories funded this study. Dr Van Tassell was supported by institutional K12 award KL2RR031989 from the National Institutes of Health, and Dr Dinarello was supported by grant AI15614 from the National Institutes of Health.<br>5. Disclosure comment: several authors claimed to have received research funding or acted as advisors or consultants for several privately owned companies in the health area, including the one that makes the medication in this study.<br>6. Ethical committee approved: yes |
| ***Risk of bias*** | |

**Abbate 2013** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The investigational pharmacist performed randomization using a dedicated randomization algorithm obtained from randomization.com (seed no. 7408, created July 23, 2010)." (p. 1395). |
| Allocation concealment (selection bias) | Low risk | Quote: "The investigational pharmacist performed randomization using a dedicated randomization algorithm obtained from randomization.com (seed no. 7408, created July 23, 2010)." (p. 1395). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "For each patient, the pharmacist prepared a set of 14 syringes with the content of 100 mg of anakinra (...) in 0.67 ml or matching NaCl 0.9% placebo. The syringes were indistinguishable." (p. 1395). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "The clinical events were adjudicated by 3 investigators unaware of treatment allocation and based on the documentation available in the chart, and consensus was needed for all determinations." (p. 1397). |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 30<br>a. Anakinra: 15<br>b. Placebo: 15<br>2. Withdrawal:<br>a. Anakinra: 26.66% (4/15)<br>b. Placebo: 6.66% (1/15)<br>c. Overall: 16.66% (5/30)<br>3. Reason for withdrawal:<br>a. Death (1) in the placebo group<br>b. Withdrew (5) in the anakinra group<br>4. Completed study:<br>a. Anakinra:11/15<br>b. Placebo: 14 /15<br>c. Overall: 83% (25/30) |
| Selective reporting (reporting bias) | Low risk | The trial reported cardiovascular outcomes and adverse events. |
| Other bias | High risk | Conflict of interests: Dr Abbate received money from the lab making the drug and combined his previous work with this one to get more statistical significance. |

**Abbate 2020**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 3 arms<br>3. Duration: 4 years<br>4. Follow-up period: 12 months<br>5. Run-in period: N/A<br>6. Run-in period time: N/A<br>7. International: no<br>8. Multicentre (number of centres): yes (3) |

**Abbate 2020** *(Continued)*

9. Country: United States
10. Study setting: inpatient and outpatient
11. Type trial: not stated
12. Type of prevention: secondary

| | |
|---|---|
| Participants | 1. Type of disease: ST-elevation myocardial infarction<br>2. Diagnosis criteria: chest pain or equivalent with electrocardiographic evidence of new or presumably new ST-segment elevation (> 1 mm) in ≥ 2 anatomically contiguous leads<br>3. Severity: not stated<br>4. Total randomised: 99 participants<br>a. Anakinra (once daily): 33<br>b. Anakinra (twice daily): 31<br>c. Placebo: 35<br>5. Number lost to follow-up/withdrawn (%): 22 (22.2)<br>a. Anakinra (once daily): 11 (33.3)<br>b. Anakinra (twice daily): 4 (12.9)<br>c. Placebo: 7 (20)<br>6. Total analysed: 77<br>a. Anakinra (once daily): 22<br>b. Anakinra (twice daily): 27<br>c. Placebo: 28<br>7. Age, years, median (IQR)<br>a. Anakinra (once daily): 53 (49–62)<br>b. Anakinra (twice daily): 55 (45–61)<br>c. Placebo: 56 (51–65)<br>8. Gender, male% (males/total)<br>a. Anakinra (once daily): 73 (24/33)<br>b. Anakinra (twice daily): 84 (26/31)<br>c. Placebo: 86 (30/35)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. Age > 21;<br>b. Acute STEMI defined as chest pain (or equivalent) with an onset within 12 hours and ECG evidence of ST-segment elevation (> 1 mm) in 2 or more anatomically contiguous leads that is new or presumably new;<br>c. Planned or completed coronary angiogram for potential intervention.<br>11. Exclusion criteria:<br>a. Inability to give informed consent;<br>b. Pregnancy;<br>c. Pre-existing congestive heart failure, pre-existing severe left ventricular dysfunction (EF < 20%), pre-existing severe valvular heart disease;<br>d. Active infections (acute or chronic) - excluding Hepatitis C Virus (HCV)+ with undetectable RNA;<br>e. Recent (< 14 days) or active use of anti-inflammatory drugs (not including NSAIDs or corticosteroids used for IV dye allergy only);<br>f. Chronic inflammatory disease;<br>g. Active malignancy, excluding carcinoma in situ (any organ) and non-melanoma skin cancer;<br>h. Anticipated need for cardiac surgery;<br>i. Neutropenia. |
| Interventions | 1. Intervention<br>a. Anakinra (Kineret®)<br>b. Pharmaceutical laboratory: Swedish Orphan Biovitrum LLC (Stockholm, Sweden)<br>c. Dose: 100 mg, once daily for 14 days<br>d. Administration route: subcutaneous |

**Abbate 2020** *(Continued)*

2. Intervention
   a. Drug (Kineret®)
   b. Pharmaceutical laboratory: Swedish Orphan Biovitrum LLC (Stockholm, Sweden)
   c. Dose: 100 mg, twice daily for 14 days
   d. Administration route: subcutaneous
3. Control
   a. Placebo (composition not stated) twice daily for 14 days
   b. Administration route: subcutaneous
4. Co-intervention: standard of care for the condition

Outcomes

1. Primary (baseline, 72 hours, and day 14)
   a. Area under the curve for hsCRP
2. Secondary (baseline through month 12)
   a. Interval changes in LV end-systolic volume and ejection fraction
   b. Incidence of heart failure
   c. All-cause mortality
   d. Adverse events

Notes

1. Trial registration number: NCT01950299
2. Trial dates: July 2014-December 2018
3. A priori sample size estimation: yes
4. Financial disclosure: a grant from the National Institutes of Health (1R34HL121402-01) to Dr Abbate and Dr Van Tassell supported the study. Swedish Orphan Biovitrum LLC provided the interventions free of cost.
5. Disclosure comment: "Dr Abbate and Dr Van Tassell have served as consultants to Swedish Orphan Biovitrum LLC. The remaining authors have no disclosures to report." Swedish Orphan Biovitrum LLC did not participate in the investigation.
6. Ethical committee approved: yes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "... randomization log was prepared and maintained at the investigational pharmacy at VCU. The syringes were sequentially numbered from 1 to 28 to maintain allocation concealment, and patients were instructed to inject the syringes sequentially so to alternate odd-numbered syringes in the morning and even-numbered syringes in the evening" (p. 2). |
| Allocation concealment (selection bias) | Unclear risk | Quote: "... randomization log was prepared and maintained at the investigational pharmacy at VCU. The syringes were sequentially numbered from 1 to 28 to maintain allocation concealment, and patients were instructed to inject the syringes sequentially so to alternate odd-numbered syringes in the morning and even-numbered syringes in the evening" (p. 2). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "Anakinra and identical matching placebo syringes were handled by the investigational pharmacy at the coordinating center (VCU). ... The investigational drug was prepared at VCU and shipped to the other centers in blocks of 5." (p. 2). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "LV ejection fraction occurred offline at the end of the study by a core laboratory with 2 separate operators blinded to group allocations." (p. 3). |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 99<br>a. Anakinra (once daily): 33<br>b. Anakinra (twice daily): 31 |

**Abbate 2020** *(Continued)*

| | | |
|---|---|---|
| | | c. Placebo: 35<br>2. Withdrawal:<br>a. Anakinra (once daily): 27.27% (9/33)<br>b. Anakinra (twice daily): 12.90% (4/31)<br>c. Placebo: 37.5% (9/35)<br>d. Overall: 22.22% (22/99)<br>3. Completed study:<br>a. Anakinra (once daily): 73% (24/33)<br>b. Anakinra (twice daily): 87.09% (27/31)<br>c. Placebo: 69% (24/35)<br>d. Overall: 76% (75/99) |
| Selective reporting (reporting bias) | Unclear risk | Inappropriate report of individual cardiovascular outcome |
| Other bias | High risk | Conflict of interest: the pharmaceutical company that produces Anakinra provided the drug and has paid the researchers. |

**Bachelez 2015**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 4 arms*<br>3. Duration: 2 years<br>4. Follow-up period: 16 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (112)<br>9. Country: Argentina, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Chile, Colombia, Croatia, Czechia, Denmark, France, Germany, Hong Kong, Hungary, Israel, Korea (Republic of), the Netherlands, Poland, Russian Federation, Singapore, Slovakia, Spain, Sweden, Switzerland, Türkiye, and the United Kingdom<br>10. Study setting: outpatient<br>11. Type trial: non-inferiority<br>12. Type of prevention: primary<br><br>*Included data from etanercept and placebo arms only as per protocol. |
| Participants | 1. Type of disease: plaque psoriasis<br>2. Diagnosis criteria: PASI ≥ 12, BSA affected ≥ 10%, Physician Global Assessment of moderate-to-severe<br>3. Severity: moderate-to-severe<br>4. Total randomised: 1106 participants<br>a. Etanercept: 336*<br>b. Placebo: 108*<br>5. Number lost to follow-up/withdrawn (%)*<br>a. Etanercept: 23 (6.84)<br>b. Placebo: 13 (12)<br>6. Total analysed*<br>a. Etanercept: 335<br>b. Placebo: 107<br>7. Age, years, median (range)* |

**Bachelez 2015** *(Continued)*

a. Etanercept: 42 (18–74)
b. Placebo: 46 (21–81)

8. Gender, male% (males/total)*
   a. Etanercept: 70 (233/335)
   b. Placebo: 66 (71/107)
9. C-reactive protein basal level: not stated
10. Inclusion criteria:
    a. Age: 18 years or older;
    b. Chronic stable plaque psoriasis;
    c. Candidates for systemic or phototherapy;
    d. PASI score of 12 or higher and a Physician's Global Assessment of moderate or severe;
    e. Psoriasis involving at least 10% of the body's surface area;
    f. Failed to respond to, had a contraindication to, or were intolerant to at least one conventional systemic therapy (including ultraviolet therapy) approved for plaque psoriasis treatment.
11. Exclusion criteria:
    a. Non-plaque or drug-induced forms of psoriasis;
    b. Inability to discontinue systemic therapies;
    c. Previously treated with or had a contraindication to etanercept, previously not responded to treatment with any tumour necrosis factor inhibitors;
    d. Evidence of active infection;
    e. Previously participated in studies involving oral tofacitinib;
    f. Clinically significant infections within six months before the study or a history of infection that needed antimicrobial therapy within two weeks before the study.

*Included data from etanercept and placebo arms only as per protocol

| | |
|---|---|
| Interventions | 1. Intervention*<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 50 mg twice-weekly for 12 weeks<br>d. Administration route: subcutaneous<br>2. Control*<br>a. Placebo (composition not stated), twice-weekly for 12 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: tofacitinib<br><br>*Included data from etanercept and placebo arms only as per protocol |
| Outcomes | 1. Primary (baseline to week 12)<br>a. Proportion achieving PASI75<br>b. Proportion achieving a Physician's Global Assessment of "clear" or "almost clear."<br>2. Secondary (baseline to week 12)<br>a. Proportion achieving PASI50 and PASI90<br>b. Itch severity item score<br>c. Dermatology Life Quality Index (DLQI)<br>d. See the appendix of the study for additional outcomes |
| Notes | 1. Trial registration number: NCT01241591<br>2. Trial dates: November 2010-September 2012<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Pfizer Inc. funded the study.<br>5. Disclosure comment: several authors declared they have received funding or served as consultants or advisors for several privately owned companies in the health area, including the one that sponsored the study. "JPa, JPr, PG, HT, MT, HV, and RW are employees of Pfizer Inc. AK, J-HL, and VY declare no competing interests." |

**Bachelez 2015** *(Continued)*

6. Ethical committee approved: yes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "computer-generated randomisation schedule was used to assign patients to the treatment groups. (...) Randomisation was done at the country level. The study site contacted an interactive voice response system or web-based interactive response system, which associated that patient and their identification number with the next available randomisation number on the randomisation schedule." (p. 53-54). |
| Allocation concealment (selection bias) | Low risk | Quote: "computer-generated randomisation schedule was used to assign patients to the treatment groups. (...) Randomisation was done at the country level. The study site contacted an interactive voice response system or web-based interactive response system, which associated that patient and their identification number with the next available randomisation number on the randomisation schedule." (p. 53-54). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Patients and study personnel were masked to treatment assignment: the study drug packaging was labelled such that the patient and staff could not establish to which treatment group each patient was assigned. Placebo was provided as oral tablets matching those of tofacitinib to be given to the etanercept and placebo groups, and as prefilled syringes for subcutaneous injection matching those of etanercept, to be given to the tofacitinib and placebo groups." (p. 554). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "Cardiovascular events were adjudicated by an independent, masked cardiovascular safety endpoint adjudication committee consisting of external experts. All available histological material from potentially malignant tumours was reviewed by a central laboratory (...), by prospective, masked over-read of local histopathology data, to confirm the findings." (p. 554). |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Randomised: 1106<br>a. 330 to tofacitinib 5 mg twice daily<br>b. 332 to tofacitinib 10 mg twice daily<br>c. 336 to etanercept 50 mg twice-weekly<br>d. 108 to placebo<br>2. Received medication study:<br>a. 329 received treatment and were analysed for primary outcome<br>b. 330 received treatment and were analysed for primary outcome<br>c. 335 received treatment and were analysed for primary outcome<br>d. 107 received treatment and were analysed for primary outcome<br>3. Withdrawals (discontinued treatment with exposed reasons)<br>a. Tofacitinib 5 mg twice daily: 6.99% (23/329)<br>b. Tofacitinib 10 mg twice daily: 7.27% (24/330)<br>c. Etanercept 50 mg twice-weekly: 6.56% (22/335)<br>d. Placebo (12/107): 11.21%<br>e. Total: 7.32% (81/1101)<br>4. Completed study:<br>a. Tofacitinib 5 mg twice daily: 93.01%% (306/329)<br>b. Tofacitinib 10 mg twice daily: 92.73%% (306/330)<br>c. Etanercept 50 mg twice-weekly: 93.44% (313/335)<br>d. Placebo: 88.78% (95/107) |

**Bachelez 2015** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | High risk | Trial reported only adverse events and quality of life (see additional reference). |
| Other bias | Unclear risk | Conflict of interest: the company funding the study (Pfizer) was involved in the design of the study and the writing of the manuscript. |

**Baek 2019**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 1 year<br>4. Follow-up period: 24 weeks*<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (11)<br>9. Country: Korea (Republic of)<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary<br><br>*Data from the "main" section of the trial (first 24 weeks) |
| Participants | 1. Type of disease: rheumatoid arthritis<br>2. Diagnosis criteria: 1987 American College of Rheumatology criteria<br>3. Severity: "active disease refractory to methotrexate"<br>4. Total randomised: 99 participants<br>a. Tocilizumab: 48<br>b. Placebo: 51<br>5. Number lost to follow-up/withdrawn (%): 19 (19.2)<br>a. Tocilizumab: 8 (16.67)<br>b. Placebo: 11 (21.57)<br>6. Total analysed: 99<br>a. Tocilizumab: 48<br>b. Placebo: 51<br>7. Age, years, mean (SD)<br>a. Tocilizumab: 52.6 (10.4)<br>b. Placebo: 52 (12.2)<br>8. Gender, male% (males/total)<br>a. Tocilizumab: 10.6 (5/47)<br>b. Placebo: 12.5 (6/48)<br>9. C-reactive protein basal level, mg/dL, mean (SD)<br>a. Tocilizumab: 3 (2.7)<br>b. Placebo: 2.7 (2.5)<br>10. Inclusion criteria:<br>a. Age ≥ 18 years;<br>b. Rheumatoid Arthritis, according to the 1987 American College of Rheumatology criteria;<br>c. Active disease refractory to Methotrexate with or without other conventional DMARDs;<br>d. A stable dose of DMARDs was required for at least eight weeks before study entry.<br>11. Exclusion criteria: |

**Baek 2019** *(Continued)*

a. Concurrent active infections or malignancies;
b. History of hypersensitivity or contraindication to monoclonal antibodies;
c. Latent tuberculosis and rejection of anti-tuberculosis treatment.

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|---|---|
| Interventions | 1. Intervention<br>a. Tocilizumab (RoActemra®/Actemra®)<br>b. Pharmaceutical laboratory: JW Pharmaceutical<br>c. Dose: 8 mg/kg every four weeks for 24 weeks<br>d. Administration route: intravenous<br>2. Control<br>a. Placebo (composition not stated), every four weeks for 24 weeks<br>b. Administration route: intravenous<br>3. Co-intervention: DMARDs, oral and intra-articular glucocorticoids |
| Outcomes | 1. Primary (baseline to week 24)<br>a. Proportion achieving ACR20<br>2. Secondary (baseline to week 24)<br>a. Proportion achieving ACR50 and ACR70<br>b. DAS28 and EULAR response<br>c. Health Assessment Questionnaire - Disability Index (HAQ-DI)<br>d. Lack of efficacy and use of rescue medication<br>e. Adverse events |
| Notes | 1. Trial registration number: NCT01211834<br>2. Trial dates: October 2009-October 2010<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: JW Pharmaceutical Co. Ltd. supported the study.<br>5. Disclosure comment: not stated<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "99 patients were randomly assigned to either the TCZ group or placebo group. Randomization was stratified according to whether patients used MTX alone or in combination with other DMARDs." (p. 918) |
| Allocation concealment (selection bias) | Unclear risk | Comment: insufficient information to judge "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "TCZ at a dose of 8 mg/kg or placebo was administered intravenously in a blinded manner." (p. 918)<br><br>Comment: insufficient information to judge "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: insufficient information to judge "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 99<br>a. Tocilizumab: 48<br>b. Placebo: 51<br>2. Withdrawals: 19.2% (19/99)<br>a. Tocilizumab: 16.67% (8/48)<br>b. Placebo: 21.57% (11/51) |

**Baek 2019** *(Continued)*

| | | |
|---|---|---|
| | | 3. Main reasons for withdrawing:<br>a. Adverse events (N = 7): 36.8% (6/7 in the tocilizumab group)<br>b. Lack of efficacy (N = 5): 26.31% (5/5 in the placebo group) |
| Selective reporting (reporting bias) | Unclear risk | Comment: insufficient information to judge "high" or "low" risk of bias |
| Other bias | Low risk | No other bias identified |

**Bagel 2012**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 2 years<br>4. Follow-up period: 24 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (not stated)<br>9. Country: Canada and the United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: plaque psoriasis<br>2. Diagnosis criteria: PASI score ≥ 10, BSA involved ≥ 10%<br>3. Severity: moderate-to-severe<br>4. Total randomised: 124 participants<br>a. Etanercept: 62<br>b. Placebo: 62<br>5. Number lost to follow-up/withdrawn (%): 26 (20.96)<br>a. Etanercept: 13 (20.96)<br>b. Placebo: 13 (20.96)<br>6. Total analysed: 124<br>a. Etanercept: 62<br>b. Placebo: 62<br>7. Age, years, median (min-max)<br>a. Etanercept: 39 (18-71)<br>b. Placebo: 42 (18-70)<br>8. Gender, male% (males/total)<br>a. Etanercept: 53.2 (33/62)<br>b. Placebo: 58.1 (36/62)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. Age: 18 years and older;<br>b. Stable moderate-to-severe plaque psoriasis;<br>c. Involvement of 10% or more of BSA for ≥ 6 months and PASI scores of 10 or higher;<br>d. 30% or higher of the scalp surface area (SSA) affected, with Psoriasis Scalp Severity Index scores of 15 or higher;<br>e. Candidates for phototherapy or systemic therapy. |

**Bagel 2012** *(Continued)*

11. Exclusion criteria:
    a. Guttate, erythrodermic, or pustular psoriasis;
    b. Significant medical problems, history of tuberculosis, history of cancer five years or less before enrolment;
    c. Discontinue the use of topical cyclosporine, calcineurin inhibitors, or tar shampoos 14 days or more before enrolment;
    d. Intravenous or oral cyclosporine, phototherapies, oral retinoids, topical vitamin A or D analogues, anthralin, cyclophosphamide, sulfasalazine, topical steroids, steroid shampoos, and anakinra 28 days or more before enrolment;
    e. Alefacept, efalizumab, and tumour necrosis factor (TNF) inhibitors biologic therapies were discontinued three months before study entry. Interleukin (IL) 12/IL-23 inhibitor was suspended six months before study entry.

| | |
|---|---|
| Interventions | 1. Intervention*<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Immunex Corporation<br>c. Dose: 50 mg twice-weekly for 12 weeks<br>d. Administration route: subcutaneous<br>2. Control*<br>a. Placebo (composition not stated), twice-weekly for 12 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: low-potency topical corticosteroids<br><br>*Data collected from the first 12 weeks of the study. After that period, all participants received etanercept. |
| Outcomes | 1. Primary (baseline to week 12)<br>a. Change in PSSI score<br>2. Secondary (baseline, weeks 12 and 24)<br>a. Change in the PSSI score<br>b. Proportion achieving PSSI 75 improvement<br>c. Patient satisfaction with treatment (quality of life reported in a separate publication)<br>d. Adverse events<br>e. Change in SSA involvement<br>f. Proportion achieving PASI 50/75/90 improvement<br>g. Static Physician's Global Assessment of Psoriasis (sPGA)<br>h. Change in BSA involvement |
| Notes | 1. Trial registration number: NCT00791765[a]<br>2. Trial dates: October 2008-March 2010<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Immunex Corporation, a wholly-owned subsidiary of Amgen Inc. (Thousand Oaks, California), funded the study.<br>5. Disclosure comment: several authors informed that they have received funding and honoraries or had worked as consultants or advisors for several privately owned companies in the health area, including the one that funded the study. Dr Kricorian, Yifei Shi, and Dr Klekotka are employees of Amgen Inc. and have received Amgen stock/stock options.<br>6. Ethical committee approved: yes<br><br>[a]Number not stated in the publications, retrieved by the authors of this review<br><br>Note: This trial was a parallel-trial design until 12 weeks. After week 12, all participants received etanercept. |
| ***Risk of bias*** | |

**Bagel 2012** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "randomized assignment from an Interactive Web Response System..." (p. 87) |
| Allocation concealment (selection bias) | Low risk | Quote: "randomized assignment from an Interactive Web Response System..." (p. 87) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "patients and clinicians were blinded throughout the study as to treatment assignments..." (p. 87).<br>Comment: insufficient information to judge "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: insufficient information to judge "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 124<br>a. Etanercept: 62<br>b. Placebo: 62<br>2. Withdrawals:<br>a. Etanercept: 20.96% (13/62)<br>b. Placebo: 20.96% (13/62)<br>3. Main reasons for withdrawing:<br>a. Adverse events (N = 5): 38.46% (5/13) in the etanercept group<br>b. Withdrawal of consent (N = 6): Etanercept: 1, placebo: 5<br>4. Completed study (at 24 weeks):<br>a. Etanercept: 79% (49/62)<br>b. Placebo: 79% (49/62) |
| Selective reporting (reporting bias) | High risk | The trial reported no cardiovascular outcomes. |
| Other bias | High risk | Amgen funded the study and the writing of the manuscript (p. 92). |

**Bernstein 2006**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 1 year<br>4. Follow-up period: 25 day<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (2)<br>9. Country: United States<br>10.Study setting: outpatient<br>11.Type trial: not stated<br>12.Type of prevention: primary |
| Participants | 1. Type of disease: metabolic syndrome |

**Bernstein 2006** *(Continued)*

2. Diagnosis criteria: modified World Health Organization (WHO) criteria for metabolic syndrome
3. Severity: not stated
4. Total randomised: 56 participants
   a. Etanercept: 28
   b. Placebo: 28
5. Number lost to follow-up/withdrawn (%): 4 (7.14)
   a. Etanercept: 2 (7.14)
   b. Placebo: 2 (7.14)
6. Total analysed: 55
   a. Etanercept: 28
   b. Placebo: 27
7. Age, years, mean (SD)
   a. Etanercept: 45.1 (8.7)
   b. Placebo: 46.2 (8.3)
8. Gender, male% (males/total)
   a. Etanercept: 53.5 (15/28)
   b. Placebo: 53.5 (15/28)
9. C-reactive protein basal level, mg/L, mean (SD)
   a. Etanercept: 7.0 (3.9)
   b. Placebo: 5.1 (3.5)
10. Inclusion criteria:
    a. Age: 18 to 55 years old;
    b. Met the modified World Health Organization (WHO) criteria of metabolic syndrome, with either hyperinsulinemia or impaired glucose tolerance and 2 of 3 additional criteria:
       i. Waist-hip ratio (WHR) greater than 0.90 for men and greater than 0.85 for women or body mass index greater than 30
       ii. Serum triglyceride level of 150 mg/dL or higher or high-density lipoprotein cholesterol level less than 35 mg/dL for men and less than 39 mg/dL for women;
       iii. Blood pressure of 140/90 mm Hg or higher or receiving antihypertensive medication.
11. Exclusion criteria:
    a. History of known coronary artery disease or diabetes mellitus and/or were taking insulin or any antihyperglycaemic medication, niacin or fibrates, or immunosuppressant medication, including oral steroids;
    b. History of chronic infection (including tuberculosis, human immunodeficiency virus, and chronic hepatitis), malignancy, organ transplantation, blood dyscrasia, congestive heart failure classes I to IV, central nervous system demyelinating disorder, and any other known autoimmune or inflammatory condition;
    c. Pregnancy.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Amgen Inc (Thousand Oaks, California, USA)<br>c. Dose: 50 mg once weekly for 4 weeks<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated), once weekly for 4 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to day 25)<br>a. CRP levels<br>2. Secondary (baseline to day 25)<br>a. Inflammatory markers<br>b. Body composition and nutritional markers<br>c. Adverse events |

**Bernstein 2006** *(Continued)*

d. Lipids and insulin sensitivity
e. TNF receptors level

| | |
|---|---|
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: April 2004-March 2005<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Amgen Inc. and the grants NIH M01-RR01066 and NIH F32 DK068902-01 from the National Institutes of Health funded the study.<br>5. Disclosure comment: "Dr. Grinspoon has previously received research grant support on an unrelated project but has not served as a consultant or advisor or received any lecture fees or other support from Amgen Inc. Dr. Bernstein was awarded the Endocrine Society Lilly Fellowship award for the study to cover her salary in part. Dr. Bernstein was also supported by a National Institutes of Health training grant to the Endocrine Division and subsequently an individual National Research Service Award for salary support."<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The MGH Research Pharmacy performed the randomization based on sequential enrolment numbers using a permuted block algorithm and kept the randomization code. Randomization was stratified by sex. The allocation was concealed" (p. 904). |
| Allocation concealment (selection bias) | Unclear risk | Quote: "The allocation was concealed" (p. 904).<br>However, the process was not described. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "All investigators, study staff, and subjects were blinded to drug assignment throughout the entire study." (p. 904).<br><br>Comments: The authors state that all investigators, study staff, and subjects were blinded to drug assignment throughout the entire study. However, they did not provide details on how this blinding was achieved or maintained. Specifically, there is no description of the placebo's appearance or other measures taken to ensure proper blinding. Without this information, it is not possible to confidently judge whether the risk of performance bias is low or high. More details about the blinding process would be needed to make a proper assessment. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | The trials' outcomes were objective. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Randomised: 56<br>a. Etanercept: 28<br>b. Placebo: 28<br>2. Withdrawals:<br>a. Etanercept: 12.5% (1/28)<br>b. Placebo: 12.5% (1/28)<br>3. Overall: 3.57% (2/56) |
| Selective reporting (reporting bias) | High risk | There was a narrative report about a few adverse events. |
| Other bias | High risk | Conflict of interest: the company making the drug funded the study. |

**Boetticher 2008**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 4 years<br>4. Follow-up period: 6 months<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (7)<br>9. Country: United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: alcoholic hepatitis<br>2. Diagnosis criteria: "clinical evaluation and testing supporting a diagnosis of alcoholic hepatitis... exclusion of other causes of hepatitis..." (p. 1954)<br>3. Severity: moderate-to-severe<br>4. Total randomised: 48 participants<br>a. Etanercept: 26<br>b. Placebo: 22<br>5. Number lost to follow-up/withdrawn (%): 19 (39.58)<br>a. Etanercept: 13 (50)<br>b. Placebo: 6 (27.3)<br>6. Total analysed: 48<br>a. Etanercept: 26<br>b. Placebo: 22<br>7. Age, years, mean (SD)<br>a. Etanercept: 52.8 (9.3)<br>b. Placebo: 49.1 (9.2)<br>8. Gender, male% (males/total)<br>a. Etanercept: 69 (18/26)<br>b. Placebo: 77 (17/22)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. 18 years or older;<br>b. Alcoholic hepatitis in the setting of compatible alcohol consumption.<br>11. Exclusion criteria:<br>a. Hypersensitivity to etanercept;<br>b. Presence of infection;<br>c. History of autoimmune disease;<br>d. Use of corticosteroids, pentoxifylline, propylthiouracil, or thalidomide in the preceding four weeks before evaluation;<br>e. Pregnancy or breastfeeding. |
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Amgen Inc.<br>c. Dose: 25 mg on days 1, 4, 8, 11, 15, and 18<br>d. Administration route: subcutaneous |

**Boetticher 2008** *(Continued)*

| | |
|---|---|
| | 2. Control<br>a. Placebo (composition not stated) on days 1, 4, 8, 11, 15, and 18<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to month 1 and 6)<br>a. Mortality<br>2. Secondary (baseline through month 6)<br>a. Prevalence of infections<br>b. Cause of death<br>c. Adverse events |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: June 2004-June 2007<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: A grant from the National Institutes of Health and Amgen sponsored the study.<br>5. Disclosure comment: "All analyses and writing were conducted at the Mayo Clinic. Authors have no other conflicts of interest to disclose." (p.1960)<br>6. Ethical committee approved: yes<br>7. Other disclosure if noted: "recruitment was terminated at the completion of the fourth year because of lack of further funding, and analysis was performed with the 48 recruited patients." (p.1956) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Randomization was conducted through the use of logbooks in the study pharmacy at each individual site, in which randomly generated numbers (blocks of 4) for each strata were recorded. Enrolled patients were entered sequentially to receive the assigned treatment" (p. 1954).<br><br>Comment: Entering participants in a sequential fashion in groups of 4 could introduce bias to the randomisation and allocation in a study with a small sample. |
| Allocation concealment (selection bias) | Unclear risk | Quote: "Randomization was conducted through the use of logbooks in the study pharmacy at each individual site, in which randomly generated numbers (blocks of 4) for each strata were recorded. Enrolled patients were entered sequentially to receive the assigned treatment" (p. 1954).<br><br>Comment: Entering participants in a sequential fashion in groups of 4 could introduce bias to the randomisation and allocation in a study with a small sample. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "Patient, coordinator, and physician were blinded to randomisation group" (p. 1954).<br><br>Comment: not enough information to be labelled "high" or "low" risk |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quotes:<br><br>1. "Patient, coordinator, and physician were blinded to randomization group" (p. 1954).<br>2. "Patients were evaluated in person or by telephone visit by a nurse coordinator or coinvestigator on days 1, 4, 8, 11, 15, and 18, as well as at 1, 3, and 6 months." (p.1954)<br><br>Comment: not enough information to labelled "high" or "low" risk |

**Boetticher 2008** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | Low risk | 1. Total randomised: 48 participants<br>a. Etanercept: 26<br>b. Placebo: 22<br>2. Number lost to follow-up/withdrawn (%): 19 (39.58)<br>a. Etanercept: 13 (50)<br>b. Placebo: 6 (27.3)<br>3. Main reasons for withdrawing:<br>a. Death (N = 7): 36.84% (5/7 in the etanercept group)<br>b. Withdrawal of consent/voluntary discontinuation (N = 7): 36.84%<br>c. Adverse events (N = 4): 21.1% (4/4 in the etanercept group)<br><br>Comment: the main endpoint of this study is mortality. Therefore, deaths could not count as incomplete data. Also, the safety analysis used an intention-to-treat analysis. |
| Selective reporting (reporting bias) | Unclear risk | Quote: "Patients were evaluated in person or by telephone visit by a nurse coordinator or coinvestigator on days 1, 4, 8, 11, 15, and 18, as well as at 1, 3, and 6 months." (p. 1954)<br><br>Comment: not enough information to be labelled "high" or "low" risk |
| Other bias | Low risk | Found no other bias |

**Bozkurt 2001**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | 1. Study design: parallel<br>2. Number of arms: 3 arms<br>3. Duration: 3 months<br>4. Follow-up period: 3 months<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (2)<br>9. Country: United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: secondary |
| Participants | 1. Type of disease: heart failure<br>2. Diagnosis criteria: New York Heart Association (NYHA) functional class III to IV and left ventricular ejection fraction (LVEF) < 35%<br>3. Severity: "advanced"<br>4. Total randomised: 47 participants<br>a. Etanercept (5 mg/m$^2$): 16<br>b. Etanercept (12 mg/m$^2$) 15<br>c. Placebo: 16<br>5. Number lost to follow-up/withdrawn (%): 4 (8.51)<br>a. Etanercept (5 mg/m$^2$): 4 (25)<br>b. Etanercept (12 mg/m$^2$): 0<br>c. Placebo: 0 |

**Bozkurt 2001** *(Continued)*

6. Total analysed: 47
   a. Etanercept (5 mg/m$^2$): 16
   b. Etanercept (12 mg/m$^2$): 15
   c. Placebo: 16
7. Age, years, mean (SD)
   a. Etanercept (5 mg/m$^2$): 54 (2.7)
   b. Etanercept (12 mg/m$^2$): 53.2 (2.6)
   c. Placebo: 57.6 (2.4)
8. Gender, male% (males/total)
   a. Etanercept (5 mg/m$^2$): 75 (12/16)
   b. Etanercept (12 mg/m$^2$): 80 (12/15)
   c. Placebo: 88 (14/16)
9. C-reactive protein basal level: not stated
10. Inclusion criteria:
    a. Stable New York Heart Association (NYHA) functional class III to IV heart failure;
    b. LVEF < 35%;
    c. Have stable doses of ACEI, digoxin, and oral diuretics for 30 days before enrolment. ACEI-intolerant patients were on hydralazine/isosorbide or losartan. The use of β-blockers was permitted on stable doses for three months before enrolment;
    d. Able to walk ≥ 100 metres during a 6-minute walk test.
11. Exclusion criteria: Not stated

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Immunex Corporation<br>c. Dose: 5 mg/m$^2$ twice-weekly for 3 months<br>d. Administration route: subcutaneous<br>2. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Immunex Corporation<br>c. Dose: 12 mg/m$^2$ twice-weekly for 3 months<br>d. Administration route: subcutaneous<br>3. Control<br>a. Placebo (composition not stated) twice-weekly for 3 months<br>b. Administration route: subcutaneous<br>4. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to month 3)<br>a. "Safety and tolerability of etanercept"<br>2. Secondary (baseline to month 3)<br>a. Improvement in LV function and structure<br>b. Improvement in functional and clinical status<br>c. Adverse events |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: not stated<br>3. A priori sample size estimation: no<br>4. Financial disclosure: the National Institutes of Health (P50 HL-O6H) and Immunex Corporation funded the study.<br>5. Disclosure comment: "Dr Mann serves as an unpaid consultant to Immunex Corporation; Dr Feldman is an Immunex Corporation stockholder."<br>6. Ethical committee approved: yes |

**Bozkurt 2001** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Patients were randomized to receive..." (p. 1044).<br>Comment: insufficient information to judge as "high" or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "This study (...) double-blind, placebo-controlled, multidose..." (p. 1044)<br>Comment: insufficient information to judge as "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "Doppler echocardiographic readings were performed at baseline and after 3 months of therapy, and they were interpreted by a single qualified reader who was blinded to the treatment protocol" (p. 1045). |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Randomised: 47<br>Etanercept (5 mg/$m^2$): 16<br>Etanercept (12/$m^2$): 15<br>Placebo: 16<br><br>Withdrawal: 8.5% (4/47)<br>Etanercept (5 mg/$m^2$):25% (4/16)<br>Etanercept (12/$m^2$): 0% (0/15<br>Placebo: 0% (0/16) |
| Selective reporting (reporting bias) | High risk | This trial assessed "Safety and tolerability of etanercept." (p. 1044). |
| Other bias | High risk | Design bias: no information about a priori sample size estimation<br><br>Conflict of interest: the company making the drug funded the study. |

**Brandt 2003**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel*<br>2. Number of arms: 2 arms*<br>3. Duration: 6 weeks*<br>4. Follow-up period: 6 weeks*<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (not stated)<br>9. Country: Germany<br>10.Study setting: outpatient<br>11.Type trial: not stated<br>12.Type of prevention: primary<br><br>*Data from the first 6 weeks of the study only, as per protocol |

**Brandt 2003** *(Continued)*

| | |
|---|---|
| Participants | 1. Type of disease: ankylosing spondylitis<br>2. Diagnosis criteria: modified New York criteria for ankylosing spondylitis<br>3. Severity: active disease (defined by a Bath AS Disease Activity Index)<br>4. Total randomised: 33 participants<br>a. Etanercept: 16<br>b. Placebo: 17<br>5. Number lost to follow-up/withdrawn (%): 4 (12.1)*<br>a. Etanercept: 2 (12.5)<br>b. Placebo: 2 (11.8)<br>6. Total analysed: 30*<br>a. Etanercept: 14<br>b. Placebo: 16<br>7. Age, years, mean (SD)<br>a. Etanercept: 39.8 (9.1)<br>b. Placebo: 32 (7.5)<br>8. Gender, male% (males/total)<br>a. Etanercept: 71.4 (10/14)<br>b. Placebo: 75 (12/16)<br>9. C-reactive protein basal level: unclear<br>10. Inclusion criteria:<br>a. Ankylosing spondylitis according to the modified New York criteria;<br>b. Active disease according to Bath ankylosing spondylitis disease activity index (BASDAI) and spinal pain ≥ 4 on a 0-10 scale.<br>11. Exclusion criteria:<br>a. Active tuberculosis in the previous three years;<br>b. Serious infection in the previous two months;<br>c. Lymphoproliferative disease or other malignancies in the previous five years;<br>d. Multiple sclerosis or related diseases;<br>e. Signs or symptoms of severe disease.<br>*Data from the first 6 weeks of the study only, as per protocol |
| Interventions | 1. Intervention*<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Wyeth Pharma<br>c. Dose: 25 mg twice-weekly for 6 weeks<br>d. Administration route: subcutaneous<br>2. Control*<br>a. Placebo (bacteriostatic water) twice-weekly for 6 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: NSAIDs<br>*Data from the first 6 weeks of the study only, as per protocol |
| Outcomes | 1. Primary (baseline to week 6)<br>a. Proportion achieving ≥ 50% improvement on the BASDAI<br>2. Secondary (baseline through week 24)<br>a. Bath ankylosing spondylitis functional index (BASFI)<br>b. Bath ankylosing spondylitis metrology index (BASMI)<br>c. Spinal pain<br>d. Quality of life: SF-36<br>e. Ankylosing Spondylitis (ASAS) Working Group response criteria<br>f. CRP and ESR |

**Brandt 2003** *(Continued)*

| | |
|---|---|
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: March 2001-not stated<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: a grant (Kompetenznetz Rheuma) from the German Ministry of Research and Wyeth Pharma supported the study.<br>5. Disclosure comment: not stated<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Patients were randomly allocated to one of the treatment groups." (p. 1668)<br><br>Comment: insufficient information to judge as a "high" or "low" risk |
| Allocation concealment (selection bias) | Unclear risk | Quote: "Patients were randomly allocated to one of the treatment groups." (p. 1668).<br><br>Comment: insufficient information to judge as a "high" or "low" risk |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Comment: trial was reported as double-blind. However, there was no information about how to conduct the blinding process and the medication study and placebo's appearance. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: insufficient information to judge as a "high" or "low" risk |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Total sample: 33<br>2. Withdrawal: 12.1% (4/33)<br>a. Etanercept: 12.5% (2/16), due to not having received medication as allocated.<br>b. Placebo: 11.76% (2/17), due to compliance issues and not receiving medication as allocated. |
| Selective reporting (reporting bias) | High risk | Reported only quality of life and adverse events |
| Other bias | Low risk | Found no other bias |

**Broch 2021**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 3 years<br>4. Follow-up period: 6 months<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no |

**Broch 2021** *(Continued)*

8. Multicentre (number of centres): yes (3)
9. Country: Norway
10. Study setting: inpatient
11. Type trial: not stated
12. Type of prevention: secondary

| | |
|---|---|
| Participants | 1. Type of disease: ST-elevation myocardial infarction (MI)<br>2. Diagnosis criteria: ST-segment elevation in 2 contiguous electrocardiogram leads<br>3. Severity: not stated<br>4. Total randomised: 200 participants<br>a. Tocilizumab: 101<br>b. Placebo: 98<br>5. Number lost to follow-up/withdrawn (%): 10 (5)<br>a. Tocilizumab: 4 (3.96)<br>b. Placebo: 5 (5.1)<br>c. Other: 1<br>6. Total analysed<br>a. Tocilizumab: varies with the outcome<br>b. Placebo: varies with the outcome<br>7. Age, years, mean (SD)<br>a. Tocilizumab: 62 (10)<br>b. Placebo: 60 (9)<br>8. Gender, male% (males/total)<br>a. Tocilizumab: 79 (80/101)<br>b. Placebo: 89 (87/98)<br>9. C-reactive protein basal level, mg/L, median (IQR)<br>a. Tocilizumab: 2.4 (0.9–5.0)<br>b. Placebo: 2.9 (1.4–5.0)<br>10. Inclusion criteria:<br>a. Aged between 18 and 80 years;<br>b. Presenting with chest pain within 6 hours of symptom onset;<br>c. ST-segment elevation in 2 contiguous ECG leads consistent with acute transmural MI.<br>11. Exclusion criteria:<br>a. Previous MI, left bundle branch block, cardiogenic shock, resuscitated cardiac arrest, or fibrinolytic therapy within the last 72 hours;<br>b. History of severe renal failure, liver failure, malignant disease, chronic infection, or chronic autoimmune or inflammatory disease; uncontrolled bowel disease; ongoing infectious or immunologic disease; major surgery within the past 8 weeks; or treatment with immunosuppressants other than low-dose steroids. |
| Interventions | 1. Intervention<br>a. Tocilizumab (Actemra®/Roactemra®)<br>b. Pharmaceutical laboratory: Roche<br>c. Dose: 280 mg, single dose<br>d. Administration route: intravenous<br>2. Control<br>a. Placebo (NaCl 0.9%), single dose<br>b. Administration route: intravenous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline, days 3-7, month 6)<br>a. Myocardial salvage index by cardiac magnetic resonance (CMR)<br>2. Secondary (baseline to month 6)<br>a. Final infarct size (in% of left ventricular mass) by CMR |

**Broch 2021** *(Continued)*

b. Microvascular obstruction
c. Area under the curve for troponin T
d. CRP during index hospitalisation
e. NT-proBNP
f. Baseline-adjusted left ventricular end-diastolic volume
g. Safety and tolerability

Notes

1. Trial registration number: NCT03004703
2. Trial dates: March 2017-February 13, 2020
3. A priori sample size estimation: yes
4. Financial disclosure: the South-Eastern Norway Regional Health Authority, the Central Norway Regional Health Authority, and Roche funded this study.
5. Disclosure comment: "Dr Gullestad has received lecture fees from AstraZeneca, Boehringer Ingelheim, Novartis, and Amgen; and has been a member of the local advisory board in AstraZeneca and Boehringer Ingelheim. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose."
6. Ethical committee approved: yes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The Research Support Unit at Oslo University Hospital generated a balanced, permuted block randomization list with varying block sizes. The randomization was stratified by center and by whether the time from symptom onset was shorter or longer than 3 h." (p. 1848). |
| Allocation concealment (selection bias) | Unclear risk | Quote: "The Research Support Unit at Oslo University Hospital generated a balanced, permuted block randomization list with varying block sizes. The randomization was stratified by center and by whether the time from symptom onset was shorter or longer than 3 h." (p. 1848). However, the authors did not provide information on how it was concealed. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Patients, study personnel, and caretakers were blinded to treatment allocation." (p. 1848).<br>Quote: "Patients allocated to placebo received an identical-looking intravenous infusion of 100 ml NaCl 0.9% (...) Unblinded personnel pre-prepared identical-looking infusion bottles containing the active study drug or placebo." (p. 1848). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "Patients, study personnel, and caretakers were blinded to treatment allocation." (p. 1848).<br>Quote: "Patients allocated to placebo received an identical-looking intravenous infusion of 100 ml NaCl 0.9% (...) Unblinded personnel pre-prepared identical-looking infusion bottles containing the active study drug or placebo." (p. 1848). However, the study did not mention outcome assessors. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Randomised: 200 (one participant withdrew consent)<br>a. Tocilizumab: 101<br>b. Placebo: 98<br>2. Withdrawals: 4.52% (9/200)<br>a. Tocilizumab: 3.96% (4/101)<br>b. Placebo: 5.01% (5/98)<br>3. Reason for withdrawing:<br>a. Tocilizumab: lack of cardiac resonance imaging (N = 4)<br>b. Placebo: lack of cardiac resonance imaging (N = 5).<br>4. Analysed for final infarct size (6-month follow-up visit): |

**Broch 2021** *(Continued)*

| | | |
|---|---|---|
| | | a. Tocilizumab: 96.03% (97/101)<br>b. Placebo: 94.89% (93/98) |
| Selective reporting (reporting bias) | Low risk | Trial reported information about cardiovascular outcome and adverse events. |
| Other bias | High risk | Conflict of interest: the company making the drug funded the study. |

**Brucato 2016**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 8 months<br>4. Follow-up period: 8 months<br>5. Run-in period: yes<br>6. Run-in period time: 60 days<br>7. International: no<br>8. Multicentre (number of centres): yes (3)<br>9. Country: Italy<br>10. Study setting: inpatient and outpatient<br>11. Type trial: not stated<br>12. Type of prevention: secondary |
| Participants | 1. Type of disease: recurrent pericarditis<br>2. Diagnosis criteria: pericarditis followed by recurrences (with ≥ 3 previous recurrences)<br>3. Severity: "corticosteroid dependent and colchicine resistant"<br>4. Total randomised: 21 participants*<br>a. Anakinra: 11<br>b. Placebo: 10<br>5. Number lost to follow-up/withdrawn (%): 0*<br>a. Anakinra: 0<br>b. Placebo: 0<br>6. Total analysed: 21*<br>a. Anakinra: 11<br>b. Placebo: 10<br>7. Age, years, mean (SD)*<br>a. Anakinra: 46.5 (16.3)<br>b. Placebo: 44 (12.5)<br>8. Gender, male% (males/total)*<br>a. Anakinra: 36.4 (4/11)<br>b. Placebo: 30 (3/10)<br>9. C-reactive protein basal level, mg/dL, mean (SD)*<br>a. Anakinra: 0.2 (0.2)<br>b. Placebo: 0.3 (0.2)<br>10. Inclusion criteria:<br>a. Recurrent idiopathic pericarditis;<br>b. Older than 2 years and younger than 70 years;<br>c. The first episode of pericarditis was diagnosed when at least the following criteria were present: pericarditic-typical chest pain, pericardial friction rubs, widespread ST-segment elevation or PR depressions not previously reported, and new or worsening pericardial effusion; |

**Brucato 2016** *(Continued)*

d. Recurrence was diagnosed when chest pain re-occurred along with 1 or more of the following signs: fever, pericardial friction rub, ECG changes, or echocardiographic evidence of worsening pericardial effusion;
e. Increased concentration of CRP, greater than 1mg/dL;
f. Treatment with corticosteroids.

11. Exclusion criteria:
a. Pericarditis that was secondary to specific aetiologies;
b. Pregnant or lactating;
c. History of immunodepression, including a positive human immunodeficiency virus test result;
d. Positive QuantiFERON test result or positive purified protein derivative test result (≥ 5 mm induration) after the first attack of pericarditis;
e. Any live vaccinations within 3 months prior to the start of the trial;
f. History of malignancy of any organ system, treated or untreated, within the past 5 years;
g. History of other significant medical conditions that, in the investigator's opinion, would exclude participants.

*Data gathered from the double-blinded portion of the study only, as per protocol

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Anakinra (Kineret®)<br>b. Pharmaceutical laboratory: SOBI (Sweden)<br>c. Dose+: 100 mg once daily for 6 months<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated) once daily for 6 months<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for the condition<br>+Data only from the patients able to receive the adult dose |
| Outcomes | 1. Primary (baseline to month 8)<br>a. Pericarditis recurrence rate<br>b. Time to recurrence of pericarditis from the baseline<br>2. Secondary (baseline to day 60, week 6, and month 8)<br>a. Time to respond in the open-label phase<br>b. Percentage of patients with corticosteroid withdrawal<br>c. Adverse events |
| Notes | 1. Trial registration number: NCT02219828<br>2. Trial dates: June 2014-October 2015<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: "SOBI (Sweden) provided anakinra and placebo as part of an unrestricted institutional grant."<br>5. Disclosure comment: several authors reported having received grants or fees or have acted as speakers for several privately owned companies in the health area.<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Participants were randomly (...) by a computer-based automated sequence..." (p. 1908). |

**Brucato 2016** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Placebo was delivered by a syringe with identical appearance to the study drug. (...) and patients and physicians were blinded." (p. 1908). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Randomised: 21<br>a. Anakinra: 11<br>b. Placebo: 10<br>2. Analysed:<br>a. Anakinra: 11<br>b. Placebo: 10 |
| Selective reporting (reporting bias) | Low risk | This trial focused on "Recurrent Pericarditis Among Patients With Colchicine Resistance and Corticosteroid Dependence." Reported adverse events |
| Other bias | High risk | Design bias: they randomised people after responding to anakinra in the run-in period; therefore, the patients included were those who tolerated and responded to anakinra already. |

**Butchart 2015**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 2 years<br>4. Follow-up period: 28 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): no<br>9. Country: United Kingdom<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: Alzheimer's disease<br>2. Diagnosis criteria: National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria<br>3. Severity: mild-to-moderate<br>4. Total randomised: 41 participants<br>a. Etanercept: 20<br>b. Placebo: 21<br>5. Number lost to follow-up/withdrawn (%): 8 (14.63)<br>a. Etanercept: 2 (10)<br>b. Placebo: 6 (28.57) |

**Butchart 2015** *(Continued)*

6. Total analysed
   a. Etanercept: varies with the outcome
   b. Placebo: varies with the outcome
7. Age, years, mean (SE)
   a. Etanercept: 72 (2.1)
   b. Placebo: 72.9 (2.2)
8. Gender, male% (males/total)
   a. Etanercept: 75 (15/20)
   b. Placebo: 48 (10/21)
9. C-reactive protein basal level, µg/mL, median (IQR)
   a. Etanercept: 1.8 (0.7-3.6)
   b. Placebo: 1.1 (0.5-3.6)
10. Inclusion criteria:
   a. Sex: all;
   b. Age: 55 years or older;
   c. Diagnosis of probable Alzheimer's disease defined by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria;
   d. Modified Hachinski Ischaemic Scale score ≤ 5 points,
   e. Mini-Mental State Examination (MMSE) score > 10 and < 27 points;
   f. Have an informant spending at least 24 hours per week with the participant;
   g. Capable of giving informed consent;
   h. Been on cholinesterase inhibitor, memantine, or antidepressant medication for a minimum period of 90 days before baseline, if they were using them.
11. Exclusion criteria:
   a. Prior exposure to amyloid vaccines, monoclonal antibodies, or IV immunoglobulins for the treatment of Alzheimer's disease;
   b. Rheumatoid arthritis, psoriasis, psoriatic arthritis, or ankylosing spondylitis;
   c. Use of anti–TNF-α agents, immunosuppressive drugs, and/or oral prednisone > 10 mg/day within the 90 days before screening;
   d. Known contraindications (active infections) or cautions (previous significant exposure to tuberculosis, herpes zoster, hepatitis B, heart failure, demyelination disorders, and active malignancy within the past five years) to the use of etanercept.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Pfizer<br>c. Dose: 50 mg, once weekly for 24 weeks<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (water for injection) once weekly for 24 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to week 24)<br>a. Compliance<br>b. Adverse events<br>2. Secondary (baseline, weeks 12, 24, and 28)<br>a. Psychometric measures<br>b. Adverse events<br>c. Inflammation biomarkers |
| Notes | 1. Trial registration number: NCT01068353<br>2. Trial dates: January 2011-February 2013<br>3. A priori sample size estimation: yes |

**Butchart 2015** *(Continued)*

4. Financial disclosure: the study was funded as an independent investigator-initiated grant awarded by Pfizer Pharmaceuticals to Prof. Clive Holmes.
5. Disclosure comment: "C. Holmes reports receiving an independent investigator-initiated grant from Pfizer to fund this study." The rest of the authors had nothing to disclose about this study.
6. Ethical committee approved: yes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "They used a computer to generate a simple random allocation sequence (1:1), stratified in blocks of 4, to ensure 20 patients in the treatment group (subcutaneous etanercept 50 mg) and 20 patients in the placebo group (water for injection). The investigators had no knowledge of the allocation sequence, which remained concealed throughout the study." (p. 2163) |
| Allocation concealment (selection bias) | Low risk | Quote: "ACE Pharmaceuticals loaded etanercept or placebo vials into serially numbered containers according to the allocation sequence." (p. 2163). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | The loaded containers, and the interventions inside them, were identical in appearance and consistency to ensure concealment of the allocation sequence from the investigators." (p. 2163) |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 41<br>a. Etanercept: 20<br>b. Placebo: 21<br>2. Withdrawals: (mainly adverse events)<br>a. Etanercept: 10% (2/20)<br>b. Placebo: 28.57% (6/21)<br>c. Overall: 19.51% (8/41) |
| Selective reporting (reporting bias) | Low risk | This trial was phase II. Reported adverse events |
| Other bias | High risk | Conflict of interest: the company funding the study was the same one that produced the drug that was used. |

**Calin 2004**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 5 months<br>4. Follow-up period: 12 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (14) |

**Calin 2004** *(Continued)*

| | |
|---|---|
| | 9. Country: Belgium, Finland, France, Germany, Italy, The Netherlands, Spain, and the United Kingdom<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: ankylosing spondylitis<br>2. Diagnosis criteria: modified New York criteria for ankylosing spondylitis<br>3. Severity: active disease<br>4. Total randomised: 84 participants<br>a. Etanercept: 45<br>b. Placebo: 39<br>5. Number lost to follow-up/withdrawn (%): 2 (2.4)<br>a. Etanercept: 2 (4.44)<br>b. Placebo: 0<br>6. Total analysed: 84<br>a. Etanercept: 45<br>b. Placebo: 39<br>7. Age, years, mean (SD):<br>a. Etanercept: 45.3 (9.5)<br>b. Placebo: 40.7 (11.4)<br>8. Gender, male% (males/total):<br>a. Etanercept: 80 (36/45)<br>b. Placebo: 77 (30/39)<br>9. C-reactive protein basal level, mg/L, median:<br>a. Etanercept: 154<br>b. Placebo: 97<br>10. Inclusion criteria:<br>a. Age 18-70 years;<br>b. Ankylosing spondylitis according to modified New York criteria and active disease.<br>11. Exclusion criteria:<br>a. Complete ankylosing of the spine;<br>b. Previous use of TNFα inhibitors;<br>c. Use of DMARDs other than hydroxychloroquine, sulfasalazine, or methotrexate in the previous four weeks;<br>d. Use multiple NSAIDs or > 10 mg prednisone or change of doses of NSAIDs or prednisone in the previous two weeks. |
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Wyeth Pharma<br>c. Dose: 25 mg twice-weekly for 12 weeks<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated) twice-weekly for 12 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: hydroxychloroquine, sulfasalazine, or methotrexate |
| Outcomes | 1. Primary (baseline to week 12)<br>a. Proportion achieving 20% improvement in the ASAS Working Group response criteria (ASAS20)<br>2. Secondary (baseline and weeks 2, 4, 8, 12)<br>a. ASAS20, 50 and 70<br>b. BASDAI<br>c. CRP and ESR<br>d. Spinal mobility |

**Calin 2004** *(Continued)*

e. Adverse events

| | |
|---|---|
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: March 2002-August 2002<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Wyeth Research funded the study.<br>5. Disclosure comment: "Ron Pedersen, an employee of Wyeth, is acknowledged for his study design advice and statistical analysis. Susan Coyle, an employee of Wyeth, is acknowledged for her writing support."<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "(...), randomised, placebo controlled study..." p. 1595.<br>Comment: insufficient information to judge a "high risk" or "low" risk |
| Allocation concealment (selection bias) | Unclear risk | Quote: "(...), randomised, placebo controlled study..." p. 1595.<br>Comment: insufficient information to judge a "high risk" or "low" risk |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Patients self administered the product and were given individual packages containing injection supplies and instructions for storage and use. To preserve the integrity of the blind study, placebo and etanercept supplies were similar in appearance." p. 1670 |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: The trial authors did not report on how the blinding of outcome assessment was conducted. There is a lack of information regarding the methods used to ensure that outcome assessors remained unaware of the treatment allocation. Without these details, it is not possible to determine whether the risk of detection bias is low or high. Additional information about the procedures for blinding outcome assessors would be necessary to make a proper assessment. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Total sample: 84<br>2. Total withdrawal: 2.38% (2/84)<br>a. Etanercept: 4.44% (2/45) for for non-safety reasons<br>b. Placebo: zero |
| Selective reporting (reporting bias) | High risk | Reported no major cardiovascular outcomes |
| Other bias | Low risk | Found no other bias |

**Carroll 2018**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 1 year<br>4. Follow-up period: 30 days<br>5. Run-in period: not stated |

**Carroll 2018** *(Continued)*

6. Run-in period time: not applicable
7. International: no
8. Multicentre (number of centres): no
9. Country: United States
10. Study setting: inpatient and outpatient
11. Type trial: non-inferiority trial
12. Type of prevention: secondary

| | |
|---|---|
| Participants | 1. Type of disease: myocardial infarction (MI)<br>2. Diagnosis criteria: not stated<br>3. Severity: not stated<br>4. Total randomised: 28 participants<br>a. Tocilizumab: 12<br>b. Placebo: 16<br>5. Number lost to follow-up/withdrawn (%): 1 (3.57)<br>a. Tocilizumab: 1 (8.33)<br>b. Placebo: 0<br>6. Total analysed: 27<br>a. Tocilizumab: 11<br>b. Placebo: 16<br>7. Age, years, mean (SD)<br>a. Tocilizumab: 70.7 (10.0)<br>b. Placebo: 67.7 (9.5)<br>8. Gender, male% (males/total)<br>a. Tocilizumab: 83.3 (10/12)<br>b. Placebo: 87.5 (14/16)<br>9. C-reactive protein basal level, mg/L, mean (SD)<br>a. Tocilizumab: 20.9 (20)<br>b. Placebo: 6.0 (9.2)<br>10. Inclusion criteria:<br>a. 18 years of age or older;<br>b. Presented or developed clinical, physical examination, serologic, and/or electrocardiographic evidence of an acute MI, including non-ST segment elevation MI (NSTEMI) and ST-segment elevation MI (STEMI).<br>11. Exclusion criteria:<br>a. Evidence of or treatment for an acute infection;<br>b. Immunocompromised (such as transplant subjects, subjects with human immunodeficiency virus, etc.);<br>c. Clinical or radiographic evidence of active tuberculosis (TB);<br>d. Allergy to the study medication;<br>e. Malignancy (not including non-melanoma skin cancer);<br>f. Pregnancy or breastfeeding. |
| Interventions | 1. Intervention<br>a. Tocilizumab (Actemra®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 162 mg, single dose<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (saline), single dose<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to day 30) |

**Carroll 2018** *(Continued)*

a. Difference in major adverse cardiac events
2. Secondary (baseline to day 30)
   a. Change in CPR
   b. Change in QT/QTc interval
   c. Adverse events

| | |
|---|---|
| Notes | 1. Trial registration number: NCT02419937<br>2. Trial dates: May 2015-September 2016<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Keesler Air Force Base Medical Center<br>5. Disclosure comment: "We affirm that we have no financial support or other benefits from commercial sources to disclose. The authors have received no pharmaceutical or industry support in writing this manuscript."<br>6. Ethical committee approved: yes<br>7. Other disclosures: due to a slowing down in enrolment, the study was suspended in February 2017, and they performed a futility analysis (p. 61) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Randomization was performed using the website http://www.randomizer.org... (p. 61).<br><br>Comment: there was an imbalance in the CRP basal levels between the groups of the study (a difference of 14.9 mg/L). |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to judge a "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "our placebo was not matched, thus preventing complete blinding of everyone involved in the trial. Though unlikely, it is conceivable subjects. . . may have been aware of whether placebo or tocilizumab was administered, and this could have biased the results obtained." (p. 64).<br><br>Comment: The authors have explicitly stated that the placebo was not matched to the active treatment (tocilizumab), which prevented complete blinding of all parties involved in the trial. They acknowledge that this could have potentially compromised the blinding of participants, which may have influenced the results. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Randomised: 28<br>   a. Tocilizumab: 12<br>   b. Placebo: 16<br>2. Withdrawal: 3.57% (1/28)<br>   a. Tocilizumab: 8.33% (1/12)<br>   b. Placebo: 0 (0/16)<br>3. Completed: 96.42% (27/28)<br>   a. Tocilizumab: 42.85% (12/28)<br>   b. Placebo: 53.57% (15/28) |
| Selective reporting (reporting bias) | Unclear risk | Reported few types of cardiovascular outcomes, and adverse events |

**Carroll 2018** *(Continued)*

| | | |
|---|---|---|
| Other bias | High risk | Quote: "...we calculated that we would need a total of 98 subjects. Anticipating that potentially up to 25% could be lost to follow-up, we requested a total number for enrollment of 125 subjects. We planned on performing an interim analysis of available study data after 50 subjects had been enrolled; however, recruitment significantly slowed down, and in February 2017, the decision was made to perform a futility analysis." (p. 3) |

**Choudhury 2016**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 5 years<br>4. Follow-up period: 52 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (9)<br>9. Country: Canada, Germany, Israel, the United Kingdom, and the United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: secondary |
| Participants | 1. Type of disease: atherosclerotic vascular disease and type 2 diabetes mellitus or impaired glucose tolerance<br>2. Diagnosis criteria: previous carotid stenosis, myocardial infarction, peripheral vascular diseases, or stroke<br>3. Severity: not stated<br>4. Total randomised: 189 participants<br>a. Canakinumab: 95<br>b. Placebo: 94<br>5. Number lost to follow-up/withdrawn (%): 49 (25.9)<br>a. Canakinumab: 28 (29.5)<br>b. Placebo: 21 (22.3)<br>6. Total analysed<br>a. Canakinumab: varies with the outcome<br>b. Placebo: varies with the outcome<br>7. Age, years, mean (SD)<br>a. Canakinumab: 61.7 (7.8)<br>b. Placebo: 61.9 (6.9)<br>8. Gender, male% (males/total)<br>a. Canakinumab: 86 (82/95)<br>b. Placebo: 85 (80/94)<br>9. High-sensitive C-reactive protein basal level, mg/L, median (IQR)<br>a. Canakinumab: 1.77 (0.84-3.74)<br>b. Placebo: 1.85 (0.83-3.88)<br>10. Inclusion criteria:<br>a. Ages 18 to 74;<br>b. Clinically evident atherosclerotic vascular disease: previous myocardial infarction; history of angina; carotid stenosis (> 30%); peripheral vascular disease (ankle-brachial index < 0.9); endarterectomy > 3 months previously; or transient ischaemic attack or stroke; |

**Choudhury 2016** *(Continued)*

c. Type 2 diabetes mellitus (for ≤ 14 years and glycosylated haemoglobin [HbA1c] levels between 6% and 10%) or impaired glucose tolerance (defined as a peak 2-h glucose reading ≥ 140 mg/dL but < 200 mg/dL after an oral glucose tolerance test during screening);
d. Stable statin therapy for a period of ≥ 6 weeks before screening or having physician-documented statin intolerance.

11. Exclusion criteria:
a. Pregnancy;
b. Systemic steroid use;
c. Baseline high-sensitivity C-reactive protein (hs-CRP) levels > 30 mg/L;
d. History of significant multiple drug allergies;
e. History or evidence of chronic infection, including tuberculosis and liver disease;
f. Standard contraindication to MRI.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Canakinumab (Ilaris®)<br>b. Pharmaceutical laboratory: Novartis Pharmaceuticals (Cambridge, Massachusetts, USA)<br>c. Dose: 150 mg, once monthly for 12 months<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated) once monthly for 12 months<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for the conditions |
| Outcomes | 1. Primary (baseline to months 3 and 12)<br>a. Change in aortic distensibility<br>b. Change in total plaque burden in the aorta and carotid arteries<br>c. Adverse events<br>2. Secondary (baseline to months 3 and 12)<br>a. Change in aortic pulse wave velocity<br>b. Change in hs-CRP, HbA1c, homeostasis model assessment (HOMA)–insulin resistance, and peak blood glucose level 2 hours after an oral glucose challenge<br>c. Peripheral biomarkers of inflammation (IL-6, serum amyloid A, and plasma lipoproteins) |
| Notes | 1. Trial registration number: NCT00995930<br>2. Trial dates: December 2009-February 2014<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Novartis Pharmaceuticals (Cambridge, Massachusetts, USA) and the National Institute for Health Research Oxford Biomedical Research Centre funded the study.<br>5. Disclosure comment: several authors have reported they worked as advisors/consultants or have received grants and research funding from several privately owned companies in the healthcare area, including the one that funded this study. "Drs. Basson, Svensson, Zhang, and Yates are employees of and hold equity shares in Novartis" (p. 1769)<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "...centrally according to a validated computer-generated randomization code, stratified according to glycemic status..." (p. 1771) |
| Allocation concealment (selection bias) | Low risk | Quote: "...centrally according to a validated computer-generated randomization code, stratified according to glycemic status..." (p. 1771) |

**Choudhury 2016** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "initiated this Phase II, double-blind..." (p. 1770)<br>Comment: insufficient information to judge whether "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "3 adjudication committees made blinded assessments of adverse events in relation to cardiac, malignant, and infection-related events." (p. 1771) |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Participants: 189<br>a. Canakinumab: 95<br>b. Placebo: 94<br>2. Completed: 140 (74.1%)<br>a. Canakinumab: 67 (70.5%)<br>b. Placebo: 73 (77.7%)<br>3. Withdrawal: 49 (25.9%)<br>a. Canakinumab: 28 (29.5%)<br>i. Main reasons for withdrawal: adverse events: 14 (14.7%), consent withdrawal: 4 (4.2%), loss to follow-up: 2 (2.1%), death: 1 (1.1%), protocol deviation: 5 (5.3%)<br>b. Placebo: 21 (22.3%)<br>i. Main reasons for withdrawal: adverse events: 11 (11.7%), consent withdrawal: 3 (3.2%), loss to follow-up: 1 (1.1%), protocol deviation: 2 (2.1%)<br><br>Comments: Withdrawals in this trial were 26% of the sample. |
| Selective reporting (reporting bias) | High risk | Trial authors only reported information about adverse events. |
| Other bias | High risk | Conflict of interest: the company funding the study initiated, supervised, and partially wrote the study. |

**Chung 2003**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 3 arms<br>3. Duration: 1 year<br>4. Follow-up period: 28 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not apply<br>7. International: no<br>8. Multicentre (number of centres): yes (32)<br>9. Country: United States<br>10.Study setting: outpatient<br>11.Type trial: not stated<br>12.Type of prevention: secondary |
| Participants | 1. Type of disease: heart failure<br>2. Diagnosis criteria: left ventricular ejection fraction (LVEF) ≤ 35%<br>3. Severity: NYHA class III or IV<br>4. Total randomised: 150 participants |

**Chung 2003** *(Continued)*

a. Infliximab (5 mg/kg): 50
b. Infliximab (10 mg/kg): 51
c. Placebo: 49

5. Number lost to follow-up/withdrawn (%): 8 (5.33)
   a. Infliximab (5 mg/kg): 2 (4)
   b. Infliximab (10 mg/kg): 5 (9.8)
   c. Placebo: 1 (2.04)
6. Total analysed: 150
   a. Infliximab (5 mg/kg): 50
   b. Infliximab (10 mg/kg): 51
   c. Placebo: 49
7. Age, years, mean (SD)
   a. Infliximab (5 mg/kg): 62 (15)
   b. Infliximab (10 mg/kg): 62 (13)
   c. Placebo: 60 (12)
8. Gender, male% (males/total)
   a. Infliximab (5 mg/kg): 86 (43/50)
   b. Infliximab (10 mg/kg): 84 (43/50)
   c. Placebo: 76 (37/49)
9. High-sensitive C-reactive protein basal level, mg/L, mean:
   a. Infliximab (5 mg/kg): 2.2
   b. Infliximab (10 mg/kg): 4.4
   c. Placebo: 6.2
10. Inclusion criteria:
    a. 18 years or older;
    b. Stable NYHA class III or IV heart failure associated with an LVEF ≤ 35%;
    c. Have received treatment with a diuretic and ACE inhibitor (or an angiotensin II receptor blocker) during the prior 3 months;
    d. β-Blockers, digoxin, and spironolactone were allowed if they were started ≥ 3 months before screening;
    e. Treatment with vasodilators or nitrates was permitted but not required;
    f. Doses of all cardiac medications were to be constant for at least 2 weeks before and during the screening;
    g. Adequate immunisation against *Streptococcus pneumoniae* ≥ 2 weeks before randomisation.
11. Exclusion criteria:
    a. Haemodynamically significant obstructive valvular disease, cor pulmonale, restrictive or hypertrophic cardiomyopathy, constrictive pericarditis, or congenital heart disease;
    b. Acute myocardial infarction or coronary revascularisation procedure within 2 months, or were likely to undergo coronary revascularisation or heart transplant during the anticipated duration of the study;
    c. Had been resuscitated from sudden death or had a therapeutic discharge of an implanted implantable cardioverter defibrillator within 3 months;
    d. Had received within 2 weeks or were likely to receive within the following 28 weeks any of the following: a class IC or III antiarrhythmic other than amiodarone; a calcium channel blocker other than amlodipine for hypertension or angina; a positive inotrope other than digoxin; or an NSAID other than aspirin;
    e. Serious infection within 2 months;
    f. Had latent tuberculosis or had tuberculosis within 3 years;
    g. Had a documented human immunodeficiency virus infection; or had any other opportunistic infection within 6 months;
    h. Had been treated with infliximab or other therapeutic agents that could interfere with the actions of TNFα.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Infliximab (Remicade®) |

**Chung 2003** *(Continued)*

| | |
|---|---|
| | b. Pharmaceutical laboratory: not stated<br>c. Dose: 5 mg/kg at weeks 0, 2 and 6<br>d. Administration route: intravenous<br>2. Intervention<br>a. Infliximab (Remicade®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 10 mg/kg at weeks 0, 2 and 6<br>d. Administration route: intravenous<br>3. Control<br>a. Placebo (composition not stated) at weeks 0, 2 and 6<br>b. Administration route: intravenous<br>4. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to week 14)<br>a. Change in clinical status of heart failure<br>2. Secondary (baseline, weeks 14 and 28)<br>a. Inflammatory markers<br>b. Change in LVEF<br>c. Combined risk of death or hospitalisation for worsening heart failure<br>d. Change in Minnesota Living With Heart Failure score<br>e. Major clinical events |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: August 2000-April 2001<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Centocor Inc. funded the study.<br>5. Disclosure comment: "Dr. Packer is a consultant to and Drs Lo and Fasanmade are employees of Centocor, Inc., which provided support for this study."<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Eligible patients were randomly assigned (...) receive infliximab 5 mg/kg, infliximab 10 mg/kg (to maximum of 1 g), or placebo immediately after randomization... " (p. 3133).<br>Comment: Insufficient information to judge as "high" or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: " ...a double-blind fashion...". (p. 3133).<br>Insufficient information to judge as "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Randomised: 150<br>Infliximab (5 mg/kg): 51<br>Infliximab (10 mg/kg): 50<br>Placebo 49<br>Withdrawals: 5.33% (8/150) |

**Chung 2003** *(Continued)*

| | | |
|---|---|---|
| | | Infliximab (5 mg/kg): 3.93% (2/51)<br>Infliximab (10 mg/kg): 10% (5/50)<br>Placebo: 2% (1/49)<br>Main reason for withdrawing: :<br>Adverse events: 75% (6/8). There was no information by comparison group.<br><br>Analysed study:<br><br>Infliximab (5 mg/kg): 51<br>Infliximab (10 mg/kg): 50<br>Placebo: 49 |
| Selective reporting (reporting bias) | Unclear risk | Comment: insufficient information to judge as "high" or "low" risk of bias |
| Other bias | High risk | Conflict of interest: Centocor funded the study, and several authors are company employees. |

**Davis 2003**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 1 year<br>4. Follow-up period: 24 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (28)<br>9. Country: Canada, France, Germany, The Netherlands, and the United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: ankylosing spondylitis<br>2. Diagnosis criteria: modified New York criteria for ankylosing spondylitis<br>3. Severity: active disease<br>4. Total randomised: 277 participants<br>a. Etanercept: 138<br>b. Placebo: 139<br>5. Number lost to follow-up/withdrawn (%): 31 (11.2)<br>a. Etanercept: 12 (8.7)<br>b. Placebo: 19 (13.7)<br>6. Total analysed: 277<br>a. Etanercept: 138<br>b. Placebo: 139<br>7. Age, years, mean (range)<br>a. Etanercept: 42.1 (24-70)<br>b. Placebo: 41.9 (18-65)<br>8. Gender, male% (males/total)<br>a. Etanercept: 76 (105/138)<br>b. Placebo: 76 (105/139)<br>9. C-reactive protein basal level, mg/dL, mean (SEM) |

**Davis 2003** *(Continued)*

a. Etanercept: 1.9 (0.2)
b. Placebo: 2.0 (0.2)

10. Inclusion criteria:
    a. Sex: all;
    b. Age: 18 to 70 years old;
    c. Ankylosing spondylitis according to modified New York criteria;
    d. Active disease.
11. Exclusion criteria:
    a. Complete ankylosis of the spine;
    b. Previous treatment with TNF inhibitors;
    c. Serious infections in the previous four weeks;
    d. Pregnancy;
    e. Use of DMARDs other than hydroxychloroquine, methotrexate or sulfasalazine;
    f. Doses of prednisone and NSAIDs stable for two weeks;
    g. Analgesics, including acetaminophen, codeine, hydrocodone, oxycodone, and tramadol, were permitted in standard dosages.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Immunex-Wyeth Research (Seattle, Washington, USA)<br>c. Dose: 25 mg twice-weekly for 24 weeks<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated) twice-weekly for 24 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: corticosteroids, NSAIDs, hydroxychloroquine, methotrexate, sulfasalazine |
| Outcomes | 1. Primary (baseline to week 12)<br>a. Proportion achieving 20% of response in the Ankylosing Spondylitis Assessment (ASAS20)<br>2. Secondary (baseline to weeks 12 and 24)<br>a. ASAS 50 and 70<br>b. Disease activity and partial remission<br>c. BASDAI<br>d. Spinal mobility<br>e. CPR and ESR<br>f. Peripheral joint count<br>g. Assessor's global assessment<br>h. Adverse events |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: December 2001-October 2002<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Immunex Corporation (Seattle, Washington, a wholly owned subsidiary of Amgen Inc., Thousand Oaks, California) supported the study.<br>5. Disclosure comment: not stated<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: #1:"Patients, investigators, assessors, other study site personnel, and representatives of the sponsor were blinded to the randomization schedule and to treatment assignment until completion of the trial." |

**Davis 2003** *(Continued)*

| | | |
|---|---|---|
| | | Quote: #2: "Patients were randomized in a 1:1 ratio to receive either etanercept or placebo, in blocks of 2 within each of the 2 strata." (p. 3231).<br><br>Comment: random sequence generation process was not described. Insufficient information to judge a "high" or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to judge a "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "Patients, investigators, assessors, other study site personnel, and representatives of the sponsor were blinded to the randomization schedule and to treatment assignment until completion of the trial."(p. 3231).<br><br>Comments:<br><br>• Whilst the authors assert that blinding was maintained for all relevant parties throughout the trial, they did not describe the process by which this blinding was achieved and maintained.<br>• Crucially, there was no information provided about the appearance of the study medication and the placebo. Without this information, it is impossible to determine whether the treatments were visually indistinguishable, which is a key aspect of effective blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "...to prevent influencing the assessments due to events such as injection-site reactions, assessors who were not otherwise involved in study-related patient care evaluated all non-patient–reported efficacy measures in a blinded manner. (p. 3231). |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Total sample: 277<br>2. Withdrawal from a full 24-week study: 10.8% (30/277)<br>a. Etanercept: 8.69% (12/138) due to adverse events (7/12), low efficacy (3/12), and loss of follow-up (2/12).<br>b. Placebo: 12.9% (18/139) mainly due to lack of efficacy (13/18). |
| Selective reporting (reporting bias) | High risk | Team authors reported no major cardiovascular outcomes. |
| Other bias | Low risk | Found no other bias |

**Deswal 1999**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 4 arms<br>3. Duration: 14 days<br>4. Follow-up period: 14 days<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): no<br>9. Country: United States<br>10.Study setting: outpatient<br>11.Type trial: not stated<br>12.Type of prevention: secondary |

**Deswal 1999** *(Continued)*

| | |
|---|---|
| Participants | 1. Type of disease: heart failure<br>2. Diagnosis criteria: LVEF < 35%<br>3. Severity: NYHA class III<br>4. Total randomised: 18 participants*<br>a. Etanercept (1 mg/m$^2$): 4<br>b. Etanercept (4 mg/m$^2$): 4<br>c. Etanercept (10 mg/m$^2$): 4<br>d. Placebo: 6<br>5. Number lost to follow-up/withdrawn (%): not stated<br>a. Etanercept: not stated<br>b. Placebo: not stated<br>6. Total analysed<br>a. Etanercept: unclear<br>b. Placebo: unclear<br>7. Age, years, mean (SEM)<br>a. Etanercept: 63.3 (3.0)<br>b. Placebo: 63.3 (3.9)<br>8. Gender, male% (males/total)<br>a. Etanercept: 100 (12/12)<br>b. Placebo: 83.3 (5/6)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. NYHA class III heart failure;<br>b. LVEF < 35%;<br>c. Elevated circulating plasma levels of TNF > 3.0 pg/mL.<br>11. Exclusion criteria: not stated<br><br>*The participants were randomised into four arms. However, in the publications, all the reports divided the sample into those who received the drugs and those who got the placebo (two arms). |
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 1, 4 or 10 mg/m$^2$ in a single dose<br>d. Administration route: intravenous<br>2. Control<br>a. Placebo ("diluent" p. 3234) in a single dose<br>b. Administration route: intravenous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to day 14)<br>a. Adverse events<br>b. LVEF<br>c. Functional status (quality of life and uncoached walk test)<br>2. Secondary (baseline to day 14)<br>a. Levels of type 2 soluble TNF receptor |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: not stated<br>3. A priori sample size estimation: not stated<br>4. Financial disclosure: NIH (research fund P50-HL-O6H) and Immunex Corp. funded the study.<br>5. Disclosure comment: F.A.H. and C.B. are employees of Immunex Corp. Other disclosure comments were not stated. |

**Deswal 1999** *(Continued)*

6. Ethical committee approved: yes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "The study was a randomized..." (p. 3224).<br>Comment: insufficient information to judge as "high" or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Comment: insufficient information to judge as "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "The study was double-blind, placebo-controlled,..." (p. 3224).<br>Comment: insufficient information to judge as "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "Changes in quality of life were measured by the visual analogue scale in which the patient assesses his or her overall feeling of well-being on an ordinal scale ranging from 0 to 100, with 100 as the best possible score" (p. 3226).<br>Comments: Insufficient information to judge as "high" or "low" risk of bias. The trial team did not report the appearance of the study medication and placebo. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | 1. Total randomised: 18 participants*<br>a. Etanercept (1 mg/m$^2$): 4<br>b. Etanercept (4 mg/m$^2$): 4<br>c. Etanercept (10 mg/m$^2$): 4<br>d. Placebo: 6<br>2. Number lost to follow-up/withdrawn (%): not stated<br>a. Etanercept: not stated<br>b. Placebo: not stated<br>3. Total analysed<br>a. Etanercept: unclear<br>b. Placebo: unclear<br>*The participants were randomised into four arms. However, in the publications, all the reports divided the sample into those who received the drugs and those who got the placebo (two arms). |
| Selective reporting (reporting bias) | High risk | The author reported only quality of life and adverse events. |
| Other bias | High risk | Design bias due to lack of a priori sample size estimation |

**Don 2010**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 5 years<br>4. Follow-up period: 52 weeks<br>5. Run-in period: not stated |

**Don 2010** *(Continued)*

6. Run-in period time: not applicable
7. International: no
8. Multicentre (number of centres): yes (4)
9. Country: United States
10. Study setting: outpatient
11. Type trial: not stated
12. Type of prevention: primary

| | |
|---|---|
| Participants | 1. Type of disease: end-stage renal disease<br>2. Diagnosis criteria: not stated<br>3. Severity: not stated<br>4. Total randomised: 10 participants<br>a. Etanercept: 5<br>b. Placebo: 5<br>5. Number lost to follow-up/withdrawn: 5 (50%)<br>a. Etanercept: 3 (60%)<br>b. Placebo: 2 (40%)<br>6. Total analysed: 10<br>a. Etanercept: 5<br>b. Placebo: 5<br>7. Age, years, median (SD)<br>a. Etanercept: 51 (16.73)<br>b. Placebo: 55 (15.20)<br>8. Gender, male% (males/total)<br>a. Etanercept: 80% (4/5)<br>b. Placebo: 60% (3/5)<br>9. C-reactive protein basal level, mg/dL, mean (SD)<br>a. Etanercept: 23.81 (15.1)<br>b. Placebo: 10.38 (6.2)<br>10. Inclusion criteria:<br>a. End-stage renal disease participants<br>11. Exclusion criteria:<br>a. History of tuberculosis;<br>b. History of recurrent infection;<br>c. Recent acute myocardial infarction;<br>d. Cancer within the previous five years;<br>e. Presence of hepatitis B, hepatitis C, HIV, systemic lupus erythematosus;<br>f. Presence of transcutaneous access (external catheter). |
| Interventions | 1. Intervention:<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 25 mg, twice-weekly for 44 weeks<br>d. Administration route: subcutaneous<br>2. Control:<br>a. Placebo (saline) twice-weekly for 44 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to week 44)<br>a. C-reactive protein (CRP)<br>b. Interleukin-6 (IL-6)<br>c. Albumin<br>d. Prealbumin |

**Don 2010** *(Continued)*

e. Vascular endothelial growth factor (VEGF)
f. Soluble interstitial cell adhesion molecules (sICAM)

2. Secondary
   a. Quality of life (assessed with Medical Outcomes Study Short-Form Health Survey-36-Item (MOS SF-36)
   b. Adverse events

| | |
|---|---|
| Notes | 1. Trial registration number: NCT00293202<br>2. Trial dates: January 2005-June 2010<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Kaysen, George A., M.D., PhD, sponsored the study. Collaborators: Amgen and Dialysis Clinic, Inc.<br>5. Disclosure comment: none<br>6. Ethical committee approved: yes<br>7. Other disclosure if noted: "Only 10 out of 40 subjects recruited. Only 5 out of 10 subjects randomized completed the study. The study has been slow to accrue patients due to the large number and stringent inclusion and exclusion criteria so as to optimize safety." |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "The study was designed as a double-blind randomized prospective study..". (p. 432)<br>Comment: insufficient information to judge a "high" or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Quote: "The study was designed as a double-blind randomized prospective study.." (p. 432)<br>Comment: insufficient information to judge a "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "The study was designed as a double-blind" ... (p. 432)<br>Comment: insufficient information to judge a "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: insufficient information to judge a "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Authors reported no withdrawals. |
| Selective reporting (reporting bias) | High risk | This trial only reported information about quality of life and adverse events. |
| Other bias | High risk | The study lacked a reported a priori sample size calculation. This omission raises concerns about:<br>1. Statistical power: It's unclear if the study was adequately powered to detect meaningful differences.<br>2. Scientific rigour: Without a predefined sample size, the study's design and stopping rules are ambiguous.<br>3. Ethical considerations: Exposing participants to a trial without a clear justification for the sample size is ethically questionable.<br>Therefore, the absence of a reported a priori sample size calculation in this study introduces significant issues, including: |

**Don 2010** *(Continued)*

1. Design bias: Without a predetermined sample size, the study lacks a clear stopping point, potentially leading to premature termination or unnecessary continuation.
2. The lack of a prespecified sample size makes it difficult to interpret the results confidently, as it is unclear whether the study was adequately powered to detect meaningful effects."

**Ebrahimi 2018**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 1 year<br>4. Follow-up period: 4 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (2)<br>9. Country: Switzerland<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: metabolic syndrome and low testosterone<br>2. Diagnosis criteria: see p. 3467 of the study<br>3. Severity: not stated<br>4. Total randomised: 70 participants<br>a. Anakinra: 35<br>b. Placebo: 35<br>5. Number lost to follow-up/withdrawn (%): 3 (4.3)<br>a. Anakinra: 2 (5.7)<br>b. Placebo: 1 (2.9)<br>6. Total analysed: 67<br>a. Anakinra: 33<br>b. Placebo: 34<br>7. Age, years, mean (SD)<br>a. Anakinra: 54.4 (13.7)<br>b. Placebo: 54.1 (13.8)<br>8. Gender, male%: 100 (only males in the study)<br>9. C-reactive protein basal level, mg/L, mean (SD)<br>a. Anakinra: 3.7 (2.5)<br>b. Placebo: 5.3 (8.5)<br>10. Inclusion criteria:<br>a. Sex: male;<br>b. Age: 18-75 years old;<br>c. Two serum morning total testosterone levels < 2 nmol/L in fasting;<br>d. BMI > 30 kg/$m^2$ and at least one additional parameter for metabolic syndrome.<br>11. Exclusion criteria:<br>a. Previous or concurrent testosterone treatment;<br>b. Primary or secondary hypogonadism of other aetiologies;<br>c. Antiandrogen medication; |

**Ebrahimi 2018** *(Continued)*

| | |
|---|---|
| | d. Drug abuse;<br>e. Infections during the last two months;<br>f. Immunocompromised state. |
| Interventions | 1. Intervention<br>a. Anakinra (Kineret®)<br>b. Pharmaceutical laboratory: Swedish Orphan Biovitrum<br>c. Dose: 100 mg twice daily for four weeks<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (sodium chloride 0.9%) twice daily for four weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for metabolic syndrome |
| Outcomes | 1. Primary (baseline to week 4)<br>a. Change in morning testosterone level<br>2. Secondary (baseline to week 4)<br>a. Laboratory parameters:<br>i. Free testosterone<br>ii. Sex hormone-binding globulin (SHBG)<br>iii. Oestradiol<br>iv. LH/FSH ratio<br>v. Prolactin<br>vi. CRP<br>b. Clinical variables:<br>i. International Index for Erectile Function (IIEF) score<br>ii. Fatigue scale for motor and cognitive functions (FSMC) questionnaire<br>iii. Quantitative androgen deficiency in the ageing male (qADAM) score<br>iv. Blood pressure<br>v. Hand grip |
| Notes | 1. Trial registration number: NCT02672592<br>2. Trial dates: January 2016-June 2017<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: the Swiss National Foundation Grant, the “Wissenschaftspool” of the University Hospital Basel, a grant of the University of Basel, and the Young Talents in Clinical Research programme by the Bangerter Foundation and the Swiss Academy of Medical Sciences supported the study.<br>5. Disclosure comment: "M.Y.D. is an inventor on patent WO 2004002512 A1. The remaining authors have nothing to disclose." (p. 3575)<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was done with variable block sizes of four to six. Allocation was concealed with a prespecified computer-generated randomization list, which was centrally kept at the Hospital Pharmacy, University of Basel Hospital." (p. 3467) |
| Allocation concealment (selection bias) | Low risk | Quote: "Allocation was concealed with a prespecified computer-generated randomization list, which was centrally kept at the Hospital Pharmacy, University of Basel Hospital." (p. 3467) |

**Ebrahimi 2018** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Patients were randomly assigned to receive a set of study medication that was prepared prior to the initiation of the study and packed into identical containers according to the randomization list by the Hospital Pharmacy, University of Basel Hospital. Patients, treating physicians, investigators, and data assessors were masked to treatment allocation." (p. 3467) |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "Patients were randomly assigned to receive a set of study medication that was prepared prior to the initiation of the study and packed into identical containers according to the randomization list by the Hospital Pharmacy, University of Basel Hospital. Patients, treating physicians, investigators, and data assessors were masked to treatment allocation." (p. 3467) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Total randomised: 70 participants<br>a. Anakinra: 35<br>b. Placebo: 35<br>2. Number lost to follow-up/withdrawn (%): 3 (4.3)<br>a. Anakinra: 2 (5.7)<br>b. Placebo: 1 (2.9)<br>3. Reasons for lost to follow-up/withdrawn:<br>a. Blinded post-randomisation exclusion: 2<br>b. Withdrew consent: 1 |
| Selective reporting (reporting bias) | Low risk | The trial reported major outcomes. |
| Other bias | Unclear risk | The sample size seemed inconsistent with the number of outcomes. |

**Emsley 2005**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 2 years<br>4. Follow-up period: 3 months<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): no<br>9. Country: United Kingdom<br>10. Study setting: inpatient and outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: acute stroke<br>2. Diagnosis criteria: not stated<br>3. Severity: not stated<br>4. Total randomised: 34 participants<br>a. Anakinra: 17<br>b. Placebo: 17<br>5. Number lost to follow-up/withdrawn (%): 9 (26.47)<br>a. Anakinra: 5 (29.41)<br>b. Placebo: 4 (23.52) |

**Emsley 2005** *(Continued)*

6. Total analysed: 34
   a. Anakinra: 17
   b. Placebo: 17
7. Age, years, median (IQR)
   a. Anakinra: 71 (56-78)
   b. Placebo: 74 (62-78)
8. Gender, male% (males/total)
   a. Anakinra: 59 (10/17)
   b. Placebo: 41 (7/17)
9. C-reactive protein basal level: not stated
10. Inclusion criteria:
    a. Age #18 years;
    b. Written informed consent/assent;
    c. Within 6 hours of the onset of symptoms of acute stroke.
11. Exclusion criteria:
    a. A clinically significant concurrent medical condition affecting the evaluation of tolerability, safety, or efficacy;
    b. Rapid clinical improvement;
    c. National Institutes of Health Stroke Scale (NIHSS) score ≤ 4;
    d. Pre-stroke modified Rankin score (MRS) ≥ 4;
    e. Previous inclusion in the current study;
    f. Investigational drug or device within the previous 30 days;
    g. Pregnancy or breastfeeding.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Anakinra (Kineret®)<br>b. Pharmaceutical laboratory: Amgen (Thousand Oaks, California, USA)<br>c. Dose: 100 mg loading dose, followed by consecutive 2 mg/kg/h over 72 hours<br>d. Administration route: intravenous<br>2. Control<br>a. Placebo (composition not stated), loading dose, and a consecutive infusion over 72 hours<br>b. Administration route: intravenous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to hour 72)<br>a. Serious adverse events<br>b. Increase in NIHSS score > 4 points<br>2. Secondary (baseline, day 5-7, to month 3)<br>a. Adverse events<br>b. Markers of biological activity (WBC count, ESR, CRP, and IL-6)<br>c. CT brain infarct volume<br>d. Clinical outcomes (survival to 3 months, NIHSS, Barthel Index, and modified Rankin score) |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: February 2001-July 2003<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: a grant from Research into Ageing, provided by the UK Community Fund and the Salford Royal Hospitals National Health Service (NHS) Trust Research and Development Directorate supported the trial.<br>5. Disclosure comment: the authors reported they were funded by the NHS and/or public universities.<br>6. Ethical committee approved: yes |
| ***Risk of bias*** | |

**Emsley 2005** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Treatment group assignment (rhIL1ra or matching placebo) was performed by an independent, interactive voice response service (...). Restricted block randomisation balanced the groups..." (p. 1367) |
| Allocation concealment (selection bias) | Low risk | Quote: "Treatment group assignment (rhIL1ra or matching placebo) was performed by an independent, interactive voice response service (...). Restricted block randomisation balanced the groups.." (p. 1367) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "We have undertaken the first randomised, double-blind, placebo controlled study..." (p. 1366)<br>Comment: Insufficient information to judge as "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 34<br>a. Anakinra: 17<br>b. Placebo: 17<br>2. Withdrawals: 26.47% (9/34)<br>a. Anakinra: 29.41% (5/17)<br>b. Placebo: 23.52% (4/17)<br>3. Main reason for withdrawing:<br>a. Death (3) and withdrew consent (2) in anakinra<br>b. Death (4) in the placebo<br>4. Assessed at 3 months:<br>a. Anakinra: 70.58% (12/17)<br>b. Placebo: 76.47%% (13/17) |
| Selective reporting (reporting bias) | High risk | The trial only reported death and adverse events. |
| Other bias | High risk | Design bias due to lack of a priori sample size estimation. |

**Gorman 2002**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 1 year<br>4. Follow-up period: 4 months<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (not specified)<br>9. Country: United States<br>10.Study setting: outpatient<br>11.Type trial: not stated<br>12.Type of prevention: primary |

**Gorman 2002** *(Continued)*

| | |
|---|---|
| Participants | 1. Type of disease: ankylosing spondylitis<br>2. Diagnosis criteria: modified New York criteria<br>3. Severity: active disease<br>4. Total randomised: 40 participants<br>a. Etanercept: 20<br>b. Placebo: 20<br>5. Number lost to follow-up/withdrawn (%): 3 (7.5)<br>a. Etanercept: 1 (5)<br>b. Placebo: 2 (10)<br>6. Total analysed: 40<br>a. Etanercept: 20<br>b. Placebo: 20<br>7. Age, years, median (SD)<br>a. Etanercept: 38 (10)<br>b. Placebo: 39 (10)<br>8. Gender, male% (males/total)<br>a. Etanercept: 65 (13/20)<br>b. Placebo: 90 (18/20)<br>9. C-reactive protein basal level, mg/dL, median (SD)<br>a. Etanercept: 2.0 (1.8)<br>b. Placebo: 1.5 (1.2)<br>10. Inclusion criteria:<br>a. Age: over 18 years old;<br>b. Ankylosing spondylitis according to modified New York criteria;<br>c. Active disease;<br>d. Drugs prescribed before the trial were accepted as long the doses hadn't been changed four weeks before the start of the trial.<br>11. Exclusion criteria:<br>a. Spondylitis other than ankylosing spondylitis;<br>b. Complete ankylosis of the spine;<br>c. History of recurrent infections or cancer;<br>d. Serious liver, renal, haematologic, or neurologic disorder. |
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Immunex<br>c. Dose: 25 mg twice-weekly for 4 months<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated) twice-weekly for 4 months<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to month 4)<br>a. Improvement of at least 20% in the Assessments in Ankylosing Spondylitis Working Group (ASAS20)<br>2. Secondary (baseline to month 4)<br>a. Physician's global assessment<br>b. Spinal mobility<br>c. Enthesitis<br>d. Peripheral-joint tenderness<br>e. ESR and CRP<br>f. Adverse events |

**Gorman 2002** *(Continued)*

| | |
|---|---|
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: July 1999-December 2001<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: the National Institute of Arthritis and Musculoskeletal and Skin Diseases and Immunex supported the study.<br>5. Disclosure comment: "Dr Davis has served as a consultant to Immunex." (p. 1355)<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "A statistician not otherwise involved with the study randomly assigned patients to the study groups, using computer-generated, random blocks of two and four." (p. 1350)<br><br>Comment: there was an imbalance regarding the sex variable (table 2, p. 135). |
| Allocation concealment (selection bias) | Unclear risk | Quote: "Cards with the group assignments were placed in sequentially numbered envelopes that were opened by the study pharmacist as each patient was enrolled." (p. 1350)<br><br>Comment: trial authors did not mention whether envelopes were opaque. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "The patients and study investigators were unaware of the group assignments." (p. 1350)<br><br>Comment: there was no information regarding the placebo and study medication's appearance. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge as a "high" or "low" risk |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Total sample: 40<br>Total withdrawal: 7.5% (3/40)<br>Etanercept: 5% (1/20) for personal reasons<br>Placebo: 10% (2/20) for lack of efficacy |
| Selective reporting (reporting bias) | High risk | Trial authors only reported adverse events. |
| Other bias | Low risk | Found no other bias |

**Gottlieb 2003**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 24 weeks<br>4. Follow-up period: 24 weeks<br>5. Run-in period: no stated<br>6. Run-in period time: not applicable<br>7. International: no |

**Gottlieb 2003** *(Continued)*

8. Multicentre (number of centres): yes (not specified)
9. Country: United States
10. Study setting: outpatient
11. Type trial: not stated
12. Type of prevention: primary

| | |
|---|---|
| Participants | 1. Type of disease: plaque psoriasis<br>2. Diagnosis criteria: not stated<br>3. Severity: moderate-to-severe<br>4. Total randomised: 118 participants ("6 patients received randomization numbers but withdrew before receiving the study drug," p. 1628)<br>a. Etanercept: 57 participants<br>b. Placebo: 55 participants<br>5. Total analysed: 112<br>a. Etanercept: 57<br>b. Placebo: 55<br>6. Number lost to follow-up/withdrawn (%): 52 (46.42)<br>a. Etanercept: 9 (15.78)<br>b. Placebo: 43 (78.18)<br>7. Age, years, mean (range)<br>a. Etanercept: 48.2 (25-72)<br>b. Placebo: 46.5 (18-77)<br>8. Gender, male% (males/total)<br>a. Etanercept: 58 (33/57)<br>b. Placebo: 67 (37/55)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. 18 years of age;<br>b. Sex: all;<br>c. Active, stable plaque psoriasis involving 10% or more of body surface area;<br>d. One previous systemic psoriasis therapy or phototherapy (methoxsalen plus UV-A, UV-B, oral retinoids, cyclosporine, or methotrexate).<br>11. Exclusion criteria:<br>a. Guttate, erythrodermic, or pustular psoriasis;<br>b. Other skin conditions or other significant medical conditions that might interfere with evaluations of the effect of study medications on psoriasis. |
| Interventions | 1. Intervention:<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Immunex Corporation (Seattle, Washington, USA)<br>c. Dose: 25 mg, twice-weekly for 24 weeks<br>d. Administration route: subcutaneous<br>2. Control:<br>a. Placebo ("vehicle material without the active drug" p. 1628), twice-weekly for 24 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: low-potency topical corticosteroids |
| Outcomes | 1. Primary (baseline and weeks 4, 8, 12, and 24)<br>a. 75% improvement in the Psoriasis Area and Severity Index (PASI 75)<br>2. Secondary (baseline and weeks 4, 8, 12, and 24)<br>a. Psoriasis Area and Severity Index with 50% and 90% improvement (PASI 50, PASI 90)<br>b. Physician's global score<br>c. Patient's global score<br>d. Body surface area affected |

**Gottlieb 2003** *(Continued)*

e. Quality of life (Composite Dermatology Life Quality Index)

| | |
|---|---|
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: August 2000-end not specified<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Immunex Corp, a subsidiary of Amgen, Inc., sponsored the study.<br>5. Disclosure comment: One of the authors, Dr Zitnik, was an employee of Amgen at the time of the study.<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Insufficient information to judge whether "high" risk or "low" risk (p. 1628) |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to judge whether "high" risk or "low" risk (p. 1628) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Insufficient information to judge whether "high" risk or "low" risk (p. 1628) |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge whether "high" risk or "low" risk (p. 1628) |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 112<br>a. Etanercept: 57<br>b. Placebo: 55<br>2. Withdrawals (at the primary endpoint analysis: 12 weeks)<br>a. Etanercept: 7% (4/57)<br>b. Placebo: 27.27% (15/55)<br>c. Overall: 16.96% (19/112)<br>d. Imbalance: 20.27% (27.27%-7%)<br>3. Withdrawals (At the final: 24-week)<br>a. Etanercept: 9.43% (5/53)<br>b. Placebo: 70% (28/40)<br>c. Overall: 35.5% (33/93)<br>d. Imbalance: 60.57% (70%-9.43%)<br>4. Total completed study:<br>a. Etanercept: 84.2% (48/57)<br>b. Placebo: 21.8% (12/55)<br>c. Overall: 49.2% (60/112)<br>d. Imbalance: 62.4% (84.2% - 21.8%)<br>5. The main reason for withdrawals:<br>a. Lack of efficacy in etanercept: 62.5% (5/9)<br>b. Lack of efficacy in placebo: 76.74% (33/43) |
| Selective reporting (reporting bias) | Unclear risk | Trial only reported adverse events and quality of life. The trial author reported no data regarding quality of life (p. 1630). |
| Other bias | Low risk | No other bias identified |

**Gottlieb 2004**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 3 arms<br>3. Duration: 2 years<br>4. Follow-up period: 20 weeks<br>5. Run-in period: no stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (24)<br>9. Country: United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: plaque psoriasis<br>2. Diagnosis criteria: Psoriasis Area and Severity Index (PASI) score of 12 or more and psoriatic plaques covering at least 10% of the body surface<br>3. Severity: Severe<br>4. Total randomised: 249 participants<br>a. Infliximab (3 mg/kg): 99<br>b. Infliximab (5 mg/kg): 99<br>c. Placebo: 51<br>5. Number lost to follow-up/withdrawn (%): 85 (34.13)<br>a. Infliximab (3 mg/kg): 30 (30.30)<br>b. Infliximab (5 mg/kg): 18 (18.18)<br>c. Placebo: 37 (72.54)<br>6. Total analysed: 249<br>a. Infliximab (3 mg/kg): 99<br>b. Infliximab (5 mg/kg): 99<br>c. Placebo: 51<br>7. Age, years, median (IQR),<br>a. Infliximab (3 mg/kg): 45 (37, 55)<br>b. Infliximab (5 mg/kg): 44 (34, 53)<br>c. Placebo: 45 (30, 52)<br>8. Gender, male% (males/total):<br>a. Infliximab (3 mg/kg): 70.7% (70/99)<br>b. Infliximab (5 mg/kg): 73.4% (73/99)<br>c. Placebo: 60.8% (31/51)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. 18 years or older;<br>b. Sex: all;<br>c. Plaque-type psoriasis for at least 6 months before screening;<br>d. Plaque-type psoriasis covering at least 10% of total body surface area at baseline;<br>e. Received psoralen + ultraviolet light (UV) A and/or other systemic treatment for psoriasis.<br>11. Exclusion criteria:<br>a. Non-plaque forms of psoriasis;<br>b. History of drug-induced psoriasis;<br>c. Pregnant, nursing, or planning pregnancy within 12 months of enrolment; |

**Gottlieb 2004** *(Continued)*

| | |
|---|---|
| | d. Chronic infectious disease or opportunistic infection, serious infection within 2 months, active or latent tuberculosis;<br>e. History of lymphoproliferative disease, active malignancy, or history of malignancy within the previous 5 years;<br>f. Any previous treatment with infliximab or any therapeutic agent. |
| Interventions | 1. Intervention:<br>a. Infliximab (Remicade®)<br>b. Pharmaceutical laboratory: Centocor Inc (Malvern, Pennsylvania, USA)<br>c. Dose: 3 mg/kg every two weeks, for 3-4 doses*<br>d. Administration route: intravenous<br>2. Intervention:<br>a. Infliximab (Remicade®)<br>b. Name of the pharmaceutical laboratory: Centocor Inc (Malvern, Pennsylvania, USA)<br>c. Dose: 5 mg/kg every two weeks, for 3-4 doses*<br>d. Administration route: intravenous<br>3. Control:<br>a. Placebo ("infliximab and placebo infusions were identically formulated, except the latter contained no infliximab" p. 535), every two weeks, for 3-4 doses*.<br>b. Administration route: intravenous infusions<br>4. Co-intervention: none<br><br>*Participants with significant psoriasis at week 26 received a fourth additional infusion. |
| Outcomes | 1. Primary (baseline to week 10)<br>a. Participants achieving a 75% improvement in PASI score<br>2. Secondary (baseline, biweekly the first 10 weeks, every 4 weeks through week 30)<br>a. Participants achieving a 50, 75 and 90% improvement in PASI score<br>b. Physician's Global Assessment<br>c. Adverse effects, infections, infusion reactions<br>d. Newly positive antinuclear antibodies (ANA), anti-double-stranded DNA antibodies (anti-dsDNA), and anti-infliximab antibodies<br>e. Quality of life (by DLQI score) |
| Notes | 1. Trial registration number: NCT00230529<br>2. Trial dates: 2001-January 2003<br>3. A priori sample size estimation: no<br>4. Financial disclosure: Centocor Inc. sponsored the study.<br>5. Disclosure comment: Drs Gottlieb and Menter have received research support from and served as consultants for Centocor Inc. Drs Baker, Bala, Dooley, Evans, Guzzo, and Marano, and Ms Li, are employees of Centocor Inc.<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was carried out using adaptive treatment allocation" (p. 535). |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias) | High risk | Quote: "Patients and investigators were unaware of treatment assignments. Double blinding was achieved and maintained by using an independent phar- |

**Gottlieb 2004** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | macist or staff member to prepare all study infusions. The infliximab and placebo infusions were identically formulated ..." (p. 535). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 249<br>a. Infliximab (3 mg/kg): 99<br>b. Infliximab (5 mg/kg): 99<br>c. Placebo: 51<br>2. Withdrawals:<br>a. Infliximab (3 mg/kg): 30.30% (30/99)<br>b. Infliximab (5 mg/kg): 18.18% (18/99)<br>c. Placebo: 72.54% (37/51)<br>d. Overall: 34.13% (85/249)<br>3. Main reason for withdrawing:<br>a. Lack of efficacy in infliximab (3 mg/kg): 27.77% (5/18)<br>b. Lack of efficacy in infliximab (5 mg/kg): 29.72% (11/37)<br>c. Lack of efficacy in placebo: 70.27% (26/37)<br>4. Completed study (at 30-week):<br>a. Infliximab (3 mg/kg): 76.76% (76/99)<br>b. Infliximab (5 mg/kg): 82.82% (82/99)<br>c. Placebo: 31.30% (16/51)<br>d. Overall: 69.87% (174/249) |
| Selective reporting (reporting bias) | High risk | Trial authors reported adverse events and quality of life. |
| Other bias | High risk | Design bias due to a lack of a priori sample size estimation |

**Khanna 2016**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 48 weeks*<br>4. Follow-up period: 48 weeks*<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (35)<br>9. Country: Canada, France, Germany, United Kingdom, and the United States<br>10.Study setting: outpatient<br>11.Type trial: not stated<br>12.Type of prevention: primary<br><br>*Includes only data from the study's double-blinded phase (first 48 weeks), as per protocol |
| Participants | 1. Type of disease: systemic sclerosis<br>2. Diagnosis criteria: 1980 ACR criteria for systemic sclerosis<br>3. Severity: not stated |

**Khanna 2016** *(Continued)*

4. Total randomised: 87 participants
   a. Tocilizumab: 43
   b. Placebo: 44
5. Number lost to follow-up/withdrawn (%): 24 (27.6)
   a. Tocilizumab: 13 (30.2)
   b. Placebo: 11 (25)
6. Total analysed: 87
   a. Tocilizumab: 43
   b. Placebo: 44
7. Age, years, mean (SD)
   a. Tocilizumab: 51 (11.7)
   b. Placebo: 48 (12.9)
8. Gender, male % (males/total)
   a. Tocilizumab: 26 (11/43)
   b. Placebo: 20 (9/44)
9. C-reactive protein basal level, mg/L, mean (SD)
   a. Tocilizumab: 10 (13.5)
   b. Placebo: 10 (13.5)
10. Inclusion criteria:
    a. Adult patients ≥ 18 years of age;
    b. Systemic sclerosis, as defined by the American College of Rheumatology 1980 criteria;
    c. Disease duration of ≤ 60 months (defined as the time from the first non-Raynaud phenomenon manifestation);
    d. Modified Rodnan skin score between 15-40;
    e. Active disease;
    f. Uninvolved skin at injection sites;
    g. Negative pregnancy test for a female subject of childbearing potential.
11. Exclusion criteria:
    - Major surgery (including joint surgery) within eight weeks before and/or during study enrolment;
    - Rheumatic autoimmune disease other than systemic sclerosis;
    - Skin thickening (scleroderma) limited to areas distal to the elbows or knees at screening;
    - Previous treatment with tocilizumab;
    - History of severe allergic or anaphylactic reactions to human, humanised, or murine monoclonal antibodies;
    - Severe cardiopulmonary disease;
    - Known active current or history of recurrent infections;
    - Use of any investigational, biologic, or immunosuppressive therapies, including intra-articular or parenteral corticosteroids, before study enrolment;
    - Current or past medical condition or medical history involving but not limited to the nervous, renal, pulmonary, endocrine, and gastrointestinal organ systems determined by the Principal Investigator to pose a significant safety risk to any subject while participating in the study;
    - Primary or secondary immunodeficiency.

| | |
|---|---|
| Interventions | 1. Intervention*<br>a. Tocilizumab (Actemra®/RoActemra®)<br>b. Pharmaceutical laboratory: F Hoffmann-La Roche<br>c. Dose: 162 mg once weekly for 48 weeks<br>d. Administration route: subcutaneous<br>2. Control*<br>a. Placebo (composition not stated) once weekly for 48 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: methotrexate, hydroxychloroquine, or mycophenolate mofetil after week 24<br><br>*Includes only data from the study's double-blinded phase (first 48 weeks), as per protocol |

**Khanna 2016** *(Continued)*

| | |
|---|---|
| Outcomes | 1. Primary (baseline to week 24)<br>a. Change in modified Rodnan skin score<br>2. Secondary (baseline to weeks 24 and 48)<br>a. Change in modified Rodnan skin score<br>b. HAQ-DI<br>c. Patient's global visual analogue scale<br>d. Physician's global vial analogue scale<br>e. Functional Assessment of Chronic Illness Therapy (FACIT)<br>f. Fatigue score<br>g. Pruritus 5-D itch score<br>h. Tender joint count 28<br>i. Adverse events<br>j. Serum IL-6<br>k. Serum-soluble IL-6 receptor<br>l. Anti-tocilizumab antibody |
| Notes | 1. Trial registration number: NCT01532869<br>2. Trial dates: March 2012-May 2014<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: F Hoffmann-La Roche and Genentech funded the study.<br>5. Disclosure comment: Several authors declared having received grants or honoraria from several privately owned companies in the healthcare sector, including the ones funding this study. (see p. 10-11)<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients were randomly assigned (1:1) using an interactive voice and web response system to receive weekly. . ." (p. 2631) |
| Allocation concealment (selection bias) | Low risk | Quote: "Patients were randomly assigned (1:1) using an interactive voice and web response system to receive weekly. . ." (p. 2631) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Investigators, patients, and sponsor personnel were masked to treatment assignment. To prevent unmasking, separate assessors evaluated efficacy and safety." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "The efficacy assessor did not have access to safety data during the double-blind phase of the trial, but the safety assessor had access to both efficacy and safety data. Although some sponsor personnel were unmasked after the primary analysis at 24 weeks, personnel interacting with sites and site staff remained masked to treatment assignment until the database lock at 48 weeks." |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Total sample: 87<br>2. Total withdrawal: 18.39% (16/87)<br>a. Tocilizumab: 18.60% (8/43)<br>b. Placebo: 18.18% (8/44)<br>c. Authors reported the reasons for withdrawing at 24 weeks. |
| Selective reporting (reporting bias) | High risk | There was no information about major cardiovascular outcomes. |

**Khanna 2016** *(Continued)*

| | | |
|---|---|---|
| Other bias | High risk | Financial conflict of interest: The company funding the study designed the study. Several authors work or have stock options in the company funding the study. |

**Khanna 2020**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 48 weeks*<br>4. Follow-up period: 48 weeks*<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (75)<br>9. Country: Argentina, Belgium, Bulgaria, Canada, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Lithuania, Mexico, the Netherlands, Poland, Portugal, Puerto Rico, Romania, Spain, Switzerland, United Kingdom, and the United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary<br><br>*Includes only data from the study's double-blinded phase (first 48 weeks), as per protocol |
| Participants | 1. Type of disease: systemic sclerosis<br>2. Diagnosis criteria: 2013 American College of Rheumatology/ European League Against Rheumatism criteria<br>3. Severity: active disease<br>4. Total randomised: 212 participants<br>a. Tocilizumab: 105<br>b. Placebo: 107<br>5. Number lost to follow-up/withdrawn (%): 24 (11.3)<br>a. Tocilizumab: 10 (9.5)<br>b. Placebo: 14 (13.1)<br>6. Total analysed: 210<br>a. Tocilizumab: 104<br>b. Placebo: 106<br>7. Age, years, mean (SD)<br>a. Tocilizumab: 47 (12.2)<br>b. Placebo: 49.3 (12.6)<br>8. Gender, male% (males/total)<br>a. Tocilizumab: 22 (23/104)<br>b. Placebo: 15 (16/106)<br>9. C-reactive protein basal level, mg/mL, mean (SD)<br>a. Tocilizumab: 7.0 (11.1)<br>b. Placebo: 8.9 (14.8)<br>10. Inclusion criteria:<br>a. Systemic sclerosis according to the 2013 American College of Rheumatology/ European League Against Rheumatism criteria;<br>b. Active disease;<br>c. Total disease duration ≤ 60 months; |

**Khanna 2020** *(Continued)*

d. Modified Rodnan skin score between 10-35;
e. Agreement to use effective contraceptives amongst participants of childbearing potential.

11. Exclusion criteria:
a. Pregnancy or breastfeeding;
b. Major surgery within eight weeks before screening;
c. Scleroderma limited to the face or areas distal to the elbows or knees;
d. Other rheumatic autoimmune diseases;
e. Immunisation with a live or attenuated vaccine within four weeks before the baseline;
f. Known hypersensitivity to human, humanised, or murine monoclonal antibodies;
g. Moderately severe nervous system, renal, endocrine, pulmonary, cardiovascular, or gastrointestinal (GI) disease not related to systemic sclerosis;
h. Active or significant history of infection, including treatment with IV antibiotics within four weeks or oral antibiotics within two weeks before screening;
i. Significant history of tuberculosis (TB);
j. Primary or secondary immunodeficiency;
k. Malignant disease, except for excised/cured local basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix;
l. History of drug or alcohol abuse.

| | |
|---|---|
| Interventions | 1. Intervention*<br>a. Tocilizumab (Actemra®/RoActemra®)<br>b. Pharmaceutical laboratory: F Hoffmann-La Roche Ltd.<br>c. Dose: 162 mg once weekly for 48 weeks<br>d. Administration route: subcutaneous<br>2. Control*<br>a. Placebo (composition not stated) once weekly for 48 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: "immunomodulatory therapy" after week 16<br><br>*Includes only data from the study's double-blinded phase (first 48 weeks), as per protocol |
| Outcomes | 1. Primary (baseline to week 48)<br>a. Change in modified Rodnan skin score<br>2. Secondary (baseline to weeks 8, 16, 24, and 48)<br>a. Participants with ≥ 20%, 40%, or 60% improvement in modified Rodnan skin score<br>b. Percent predicted FVC (ppFVC)<br>c. Forced vital capacity (FVC)<br>d. HAQ-DI score<br>e. Patient's Global Assessment Score<br>f. Physician's Global Assessment Score<br>g. Time to treatment failure<br>h. Adverse events<br>i. Serious systemic sclerosis-related complications<br>j. Digital ulcer count<br>k. Anti-tocilizumab antibodies<br>l. ESR, CRP, serum IL-6 and soluble IL-6 receptor |
| Notes | 1. Trial registration number: NCT02453256<br>2. Trial dates: November 2015-February 2019<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: F Hoffmann-La Roche Ltd. funded the study.<br>5. Disclosure comment: Several authors declared having received grants or honoraria from several privately owned companies in the healthcare sector, including the one funding this study. (p. 11) |

**Khanna 2020** *(Continued)*

6. Ethical committee approved: yes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "... interactive voice-based or web-based response system...." (p. 964). |
| Allocation concealment (selection bias) | Low risk | Quote: "... interactive voice-based or web-based response system...." (p. 964). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "Participants and study funder personnel were masked to study treament." (pp. 964-5)<br><br>Comment: trial authors reported no information about the study medication and placebo's appearance. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "Efficacy or clinical assessors were responsible for assessing efficacy measures, including mRSS and lung function, but did not have access to laboratory data" (p. 965).<br><br>Comment: insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Total sample: 212<br>a. Tocilizumab: 105 (one participant received no drug).<br>b. Placebo: 107 (one participant received no placebo).<br>2. Withdrawals:<br>a. Total: 10.47% (22/210)<br>b. Tocilizumab: 8.65% (9/104) for adverse events (two people), death (one person), patient decision (five people), and other reasons (one person)<br>c. Placebo: 12.26% (13/106) for adverse events (three people), death (one person), and patient decision (nine people) |
| Selective reporting (reporting bias) | High risk | No information about major cardiovascular outcomes |
| Other bias | Low risk | Found no other bias |

**Kleveland 2016**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 3 years<br>4. Follow-up period: 6 months<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (2)<br>9. Country: Norway<br>10.Study setting: inpatient<br>11.Type trial: not stated |

**Kleveland 2016** *(Continued)*

12. Type of prevention: secondary

| | |
|---|---|
| Participants | 1. Type of disease: non-ST-elevation myocardial infarction<br>2. Diagnosis criteria: European Society of Cardiology universal definition of MI<br>3. Severity: not stated<br>4. Total randomised: 121 participants<br>a. Tocilizumab: 60<br>b. Placebo: 61<br>5. Number lost to follow-up/withdrawn (%): 6 (4.95)<br>a. Tocilizumab: 3 (5)<br>b. Placebo: 3 (4.9)<br>6. Total analysed: 117<br>a. Tocilizumab: 58<br>b. Placebo: 59<br>7. Age, years, mean (SD)<br>a. Tocilizumab: 59.8 (7.7)<br>b. Placebo: 60.1 (9.9)<br>8. Gender, male% (males/total)<br>a. Tocilizumab: 84.5 (49/58)<br>b. Placebo: 91.5 (54/59)<br>9. High-sensitive C-reactive protein basal level, mg/L, geometric mean (95% CI)<br>a. Tocilizumab: 3.76 (1.97-7.19)<br>b. Placebo: 3.26 (1.91-5.56)<br>10. Inclusion criteria:<br>• NSTEMI (European Society of Cardiology Type 1);<br>• Age 18-80 years;<br>• Troponin T ≥ 30 ng/mL;<br>• Informed consent to participation.<br>11. Exclusion criteria:<br>• STEMI;<br>• Known cardiac disease, except coronary disease (cardiomyopathy, heart failure with known EF < 45%, severe valvular heart disease attending regular follow-up, recent PCI/ACB (< 3 months));<br>• Haemodynamic and/or respiratory instability;<br>• Cardiac arrest in the acute phase;<br>• Concurrent condition affecting/potentially affecting CRP (infection, malignancy, autoimmune disease);<br>• Recent major surgery (< 3 months);<br>• Recent/concurrent immunosuppressant treatment (< 2 weeks, except NSAIDs);<br>• Severe renal failure (eGFR < 30 mL/min);<br>• Pregnancy;<br>• Contraindications to any study investigations and/or medication;<br>• Expected non-adherence to study protocol. |
| Interventions | 1. Intervention<br>a. Tocilizumab (RoActemra®)<br>b. Pharmaceutical laboratory: Roche<br>c. Dose: 280 mg, single dose<br>d. Administration route: intravenous<br>2. Control<br>a. Placebo (NaCl 0.9%), single dose<br>b. Administration route: intravenous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to day 3) |

**Kleveland 2016** *(Continued)*

a. Area under the curve (AUC) for high-sensitivity C-reactive protein

2. Secondary (baseline, day 3, and month 6)
   a. AUC for high-sensitivity TnT (hsTnT)
   b. IL-6-related parameters
   c. NT-proBNP
   d. Routine clinical biochemistry (safety analyses)
   e. Echocardiographic LVEF and dimensions
   f. Serious adverse events

| | |
|---|---|
| Notes | 1. Trial registration number: NCT01491074<br>2. Trial dates: August 2011-April 2014<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: the South-Eastern Norway Regional Health Authorities, Oslo, Norway (grant number 2011124) supported the study.<br>5. Disclosure comment: "L.G. has participated in an expert meeting sponsored by F. Hoffman-La Roche AG in 2014. The other authors declare no conflicts of interest."<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The randomization list was generated using a computerized procedure" (p. 2).<br>Quote: "the randomisation list was generated using a computerised procedure by Unit for Applied Clinical Research (UACR), Norwegian University of Science and Technology, Trondheim, Norway. UACR had no involvement in the rest of the trial" (Supplementary Material). |
| Allocation concealment (selection bias) | Low risk | Quote: "...personnel from a separate ward not involved in patient treatment or follow-up opened a sealed opaque envelope with treatment allocation..." (Supplementary Material). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "to ensure double-blindness to treatment allocation for patients, clinicians and trial personnel, personnel from a separate ward not involved in patient treatment or follow-up opened a sealed opaque envelope with treatment allocation and prepared either the tocilizumab or placebo infusion bag. The tocilizumab and placebo solutions had similar appearances. The study drug infusion bag was labelled with time, date, patient initials and the inscription: “this bag contains either tocilizumab 280 mg or NaCl 0.9%". The nurse in charge of the patient ward, blinded to treatment allocation, administered the study drug. Both patients and trial personnel remained blinded throughout the whole trial period beyond follow-up of the last included patient"(Supplementary Material). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "...personnel from a separate ward not involved in patient treatment or follow-up..." |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Randomised: 121<br>a. Tocilizumab: 60<br>b. Placebo: 61<br>2. Withdrawals: 4.95% (6/121)<br>a. Tocilizumab: 5% (3/60)<br>b. Placebo: 4.91% (3/61)<br>3. Analysed at 6-month: 95% (115/121)<br>a. Tocilizumab: 95% (57/60) |

**Kleveland 2016** *(Continued)*

| | | |
|---|---|---|
| | | b. Placebo: 95.08% (58/61) |
| Selective reporting (reporting bias) | Low risk | The trial reported cardiovascular outcomes and adverse events. |
| Other bias | Low risk | Found no other bias |

**Kreiner 2010**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 4 arms*<br>3. Duration: 2 years<br>4. Follow-up period: 2 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): no<br>9. Country: Denmark<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary<br><br>*We included only the 22 patients with PMR for analyses. |
| Participants | 1. Type of disease: polymyalgia rheumatica (PMR)<br>2. Diagnosis criteria: Chuang criteria<br>3. Severity: not stated<br>4. Total randomised: 22 participants*<br>a. Etanercept: 10<br>b. Placebo: 12<br>5. Number lost to follow-up/withdrawn (%): 2 (9.1)*<br>a. Etanercept (with PMR): 0<br>b. Placebo (with PMR): 2 (16.67)<br>6. Total analysed: 20 participants*<br>a. Etanercept (with PMR): 10<br>b. Placebo (with PMR): 10<br>7. Age, years, mean (SEM)<br>a. Etanercept (with PMR): 72.6 (2.6)<br>b. Placebo (with PMR): 71.4 (3.6)<br>8. Gender, male% (males/total)<br>a. Etanercept (with PMR): 40 (4/10)<br>b. Placebo (with PMR): 30 (3/10)<br>9. C-reactive protein basal level, mg/dL, mean (SE)<br>a. Etanercept (with PMR): 7.46<br>b. Placebo (with PMR): 3.5<br>10. Inclusion criteria:<br>a. Diagnosis of PMR according to Chuang criteria<br>11. Exclusion criteria:<br>a. Prior or current use of glucocorticoids or other immunosuppressive drugs;<br>b. Signs of giant cell arteritis; |

**Kreiner 2010** *(Continued)*

| | |
|---|---|
| | c. Infections with systemic impact; hepatitis B or C infection; positive tuberculosis screening tests; positive blood or urine culture;<br>d. Uncontrolled diabetes mellitus;<br>e. Uncontrolled hypertension;<br>f. Severe heart failure;<br>g. Other inflammatory diseases than PMR;<br>h. Cancer in the past five years;<br>i. Neuromuscular disease, thyroid disease, disturbance of calcium homeostasis;<br>j. Diagnosis of PMR (for control subjects only).<br><br>*We included only the 22 patients with PMR for analyses. |
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Wyeth Pharmaceutical (New Lane, Hampshire, UK)<br>c. Dose: 25 mg, twice-weekly for 2 weeks<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (saline), twice-weekly for 2 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention:<br>a. Tramadol, 50 mg, oral (Mandolgin, Sandoz A/S, Odense, Denmark)<br>b. "Subjects were allowed to take their usual medication, if any, in the morning before the examination but abstained from analgesics." (p. 3) |
| Outcomes | 1. Primary (baseline to day 15)<br>a. Change in PMR activity score<br>2. Secondary (baseline to day 15)<br>a. Changes in ESR<br>b. Cumulative intake of tramadol<br>c. Plasma TNF-a and IL-6 concentrations<br>d. Functional status using HAQ<br>e. Adverse events |
| Notes | 1. Trial registration number: NCT00524381<br>2. Trial dates: July 2007-May 2009<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: grants from The Danish Rheumatism Association (grant number 233-463-14.10.05) and The Danish Medical Research Council (grant number 271-06-0311) supported the study.<br>5. Disclosure comment: "The authors declare that they have no competing interests."<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "A five-block randomization scheme was generated using the web site... by two trial-associated senior nurses, who were also responsible for drug preparation and who had no contact with the participants" (p. 3/9). |
| Allocation concealment (selection bias) | Low risk | Quote: "A five-block randomization scheme was generated using the web site... by two trial-associated senior nurses, who were also responsible for drug preparation and who had no contact with the participants" (p. 3/9). |

**Kreiner 2010** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Physicians and technicians in direct contact with participants or those responsible for data and plasma analysis including staff that administered the medication were blinded to group assignment."<br><br>Quote: "To ensure proper blinding, etanercept and placebo, which were both colorless solutions, were prepared in indistinguishable syringes by nurses, who had no interaction with the subjects" (p. 3/9). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "Physicians and technicians in direct contact with participants or those responsible for data and plasma analysis including staff that administered the medication were blinded to group assignment." |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Total sample: 22<br>2. Total withdrawals: 9% (2/22)<br>a. Etanercept: zero<br>b. Placebo: 16.66% (2/12) (one suspected malignancy) and one (non-compliance)<br><br>Comment: even though the investigators randomised 43 participants, only 22 had a pathology that could benefit from the drug. Therefore, those were the ones that we used in this review. |
| Selective reporting (reporting bias) | High risk | No information about major cardiovascular outcomes |
| Other bias | Low risk | No other bias identified |

**Krisai 2020**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 3 years<br>4. Follow-up period: 6 months<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (5)<br>9. Country: Germany and Switzerland<br>10. Study setting: inpatient and outpatient<br>11. Type trial: not stated<br>12. Type of prevention: secondary |
| Participants | 1. Type of disease: atrial fibrillation<br>2. Diagnosis criteria: ECG-documented atrial fibrillation<br>3. Severity: persistent<br>4. Total randomised: 24 participants<br>a. Canakinumab: 11<br>b. Placebo: 13<br>5. Number lost to follow-up/withdrawn (%): not stated<br>a. Canakinumab: not stated<br>b. Placebo: not stated<br>6. Total analysed: 24 |

**Krisai 2020** *(Continued)*

a. Canakinumab: 11
b. Placebo: 13

7. Age, years, mean (SD)
   a. Canakinumab: 64.9 (8.5)
   b. Placebo: 66.8 (7.8)
8. Gender, male% (males/total)
   a. Canakinumab: 81.8 (9/11)
   b. Placebo: 76.9 (10/13)
9. C-reactive protein basal level: not stated
10. Inclusion criteria:
    a. EKG documented atrial fibrillation before electrical cardioversion;
    b. Age ≥ 50 years old;
    c. hs-CRP ≥ 1.25 mg/L;
    d. Ability to give informed consent.
11. Exclusion criteria:
    a. Atrial fibrillation persistent after electrical cardioversion;
    b. Atrial fibrillation recurrence before randomisation;
    c. Use of amiodarone in the last six months.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Canakinumab (Ilaris®)<br>b. Pharmaceutical laboratory: Novartis Pharma Ag<br>c. Dose: 150 mg, single dose<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated) single dose<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to month 6)<br>a. Atrial fibrillation recurrence<br>2. Secondary (baseline to month 6)<br>a. Time to first redo-electrical cardioversion<br>b. Hospitalisation-free survival<br>c. Antiarrhythmic drug use<br>d. hs-CRP<br>e. Infections<br>f. Infection-related hospitalisation |
| Notes | 1. Trial registration number: NCT01805960*<br>2. Trial dates: June 2013-December 2016<br>3. A priori sample size estimation: not stated<br>4. Financial disclosure: Novartis Pharma Ag, the University of Basel, the Mach-Gaensslen Foundation, and the Bangerter-Rhyner Foundation funded the study.<br>5. Disclosure comment: Drs Schnabel and Kühne have received professional fees from several privately owned companies in the healthcare sector. The rest of the authors reported no conflicts.<br>6. Ethical committee approved: yes<br>7. Other disclosures: the study is labelled as "Terminated" on the registrations site. https://clinicaltrials.gov/ct2/show/NCT01805960<br><br>*Number not stated in any of the publications. The authors of this review retrieved the number. |
| ***Risk of bias*** | |

**Krisai 2020** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "...patients were randomly assigned..." (p. 701).<br><br>Comment: insufficient information to judge a "high" or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Quote: "...patients were randomly assigned..." (p. 701).<br><br>Comment: insufficient information to judge a "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "Patients, healthcare providers, data collectors, and outcome adjudicators were blinded to treatment allocation."<br><br>Comment: insufficient information to judge a "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "Patients, healthcare providers, data collectors, and outcome adjudicators were blinded to treatment allocation."<br><br>Comment: insufficient information to judge a "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Total sample: 24<br>Total withdrawals: not stated |
| Selective reporting (reporting bias) | Low risk | This trial reported information related to the predefined outcomes of this Cochrane review. |
| Other bias | High risk | Design bias due to a lack of a priori sample size estimation |

**Leonardi 2003**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 4 arms<br>3. Duration: 1 year<br>4. Follow-up period: 24 weeks*<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (47)<br>9. Country: United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary<br><br>*Included data from the first 12 weeks. After that, all patients received etanercept. |
| Participants | 1. Type of disease: plaque psoriasis<br>2. Diagnosis criteria: active but clinically stable plaque psoriasis involving ≥ 10% of the body surface area, had a PASI ≥ 10<br>3. Severity: moderate-to-severe<br>4. Total randomised: 672 participants<br>a. Etanercept low dose (25 mg once weekly): 169<br>b. Etanercept medium dose (25 mg twice-weekly): 167 |

**Leonardi 2003** *(Continued)*

c. Etanercept high dose (50 mg twice-weekly): 168
d. Placebo: 168

5. Number lost to follow-up/withdrawn (%): 20 (3)
   a. Etanercept low dose (25 mg once weekly): 9 (5.3)
   b. Etanercept medium dose (25 mg twice-weekly): 5 (3)
   c. Etanercept high dose (50 mg twice-weekly): 4 (2.4)
   d. Placebo: 2 (1.2)
6. Total analysed: 652
   a. Etanercept low dose (25 mg once weekly): 160
   b. Etanercept medium dose (25 mg twice-weekly): 162
   c. Etanercept high dose (50 mg twice-weekly): 164
   d. Placebo: 166
7. Age, years, mean (SD)
   a. Etanercept low dose (25 mg once weekly): 44.4 (0.9)
   b. Etanercept medium dose (25 mg twice-weekly): 45.4 (1.0)
   c. Etanercept high dose (50 mg twice-weekly): 44.8 (0.8)
   d. Placebo: 45.6 (1.0)
8. Gender, male% (males/total)
   a. Etanercept low dose (25 mg once weekly): 74 (118/160)
   b. Etanercept medium dose (25 mg twice-weekly): 67 (109/162)
   c. Etanercept high dose (50 mg twice-weekly): 65 (107/164)
   d. Placebo: 63 (105/166)
9. C-reactive protein basal level: not stated
10. Inclusion criteria:
    a. 18 years of age;
    b. Sex: all;
    c. Active, clinically stable plaque psoriasis involving at least 10% of the body surface area;
    d. PASI of 10 (indicating moderate-to-severe psoriasis;
    e. Previous phototherapy or systemic psoriasis therapy at least once or had been a candidate for such therapy.
11. Exclusion criteria:
    a. Guttate, erythrodermic, or pustular psoriasis;
    b. Other active skin conditions that would interfere with evaluations;
    c. Previously received etanercept or antibody to TNF;
    d. Received anti-CD4 antibodies or interleukin-2–diphtheria-toxin fusion protein within the previous six months;
    e. Received any biological or investigational drug, psoralen–ultraviolet A phototherapy, systemic corticosteroids, or systemic psoriasis therapy within the previous four weeks;
    f. Received ultraviolet B phototherapy, topical corticosteroids, vitamin A or D analogues, or anthralin within the previous two weeks;
    g. Took antibiotics within the previous week.

| | |
|---|---|
| Interventions | 1. Intervention:<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Immunex–Wyeth<br>c. Dose: 25 mg, once weekly for 12 weeks<br>d. Administration route: subcutaneous<br>2. Intervention:<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Immunex–Wyeth<br>c. Dose: 25 mg, twice-weekly for 12 weeks<br>d. Administration route: subcutaneous<br>3. Intervention: |

**Leonardi 2003** *(Continued)*

a. Etanercept (Enbrel®)
b. Pharmaceutical laboratory: Immunex–Wyeth
c. Dose: 50 mg, twice-weekly for 12 weeks
d. Administration route: subcutaneous

4. Control*:
   a. Placebo (composition not stated), once or twice-weekly for 12 weeks
   b. Administration route: subcutaneous
5. Co-intervention: low-potency topical steroids

*Included data from the first 12 weeks. After that, all patients received etanercept.

| | |
|---|---|
| Outcomes | 1. Primary (baseline to week 12)<br>a. Proportion achieving 75% improvement in the PASI<br>2. Secondary (baseline and weeks 2, 4, 8, 12, 16, 20, 24)<br>a. The proportion of participants achieving 50%, 75%, and 90% improvement in the PASI<br>b. Physician's Static Global Assessment of Psoriasis<br>c. Participants' outcomes: DLQI and Patient's Global Assessment of Psoriasis<br>d. Adverse events |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: December 2001-October 2002<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Immunex (Seattle), a wholly-owned subsidiary of Amgen (Thousand Oaks, California), supported the study.<br>5. Disclosure comment: Several authors report having served as consultants or paid lecturers for the funding company and other privately owned companies in the health field. Dr Zitnik and Ms Wang report owning equity in Amgen.<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients underwent central randomization with the use of a permuted block randomization list, with equal allocation to each of the four treatment groups" (p. 2016). |
| Allocation concealment (selection bias) | Low risk | Quote: "Patients underwent central randomization with the use of a permuted block randomization list, with equal allocation to each of the four treatment groups" (p. 2016). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "In order to maintain masking with respect to the treatment assignments, all patients received two injections per dose of study drug, with placebo making up the balance of injections for patients assigned to the low-dose–etanercept regimen or the medium-dose–etanercept regimen" (p. 2015). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge a "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Quote: "Overall, 94 percent of the patients completed 12 weeks of treatment and 88 percent completed 24 weeks, with similar proportions of patients completing treatment in each group" (p. 2017).<br><br>Comments: |

**Leonardi 2003** *(Continued)*

| | | |
|---|---|---|
| | | 1. Authors reported overall completion rates but did not provide group-specific attrition data.<br>2. A participant flowchart is missing, which would have clarified the progression of participants through the trial.<br>3. Lack of information on reasons for dropouts and handling of missing data prevents a thorough assessment of attrition bias. |
| Selective reporting (reporting bias) | High risk | The trial assessed only adverse events and quality of life. |
| Other bias | High risk | Several authors reported having served as consultants or paid lecturers for the funding company and other privately owned companies in the health field. Dr Zitnik and Ms Wang reported owning equity in Amgen. |

**Mease 2000**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 12 weeks<br>4. Follow-up period: 12 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): no<br>9. Country: United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: psoriasis, psoriatic arthritis<br>2. Diagnosis criteria: active psoriatic arthritis, defined as ≥ 3 swollen joints and ≥ 3 tender or painful joints<br>3. Severity: not stated<br>4. Total randomised: 60 participants<br>a. Etanercept: 30<br>b. Placebo: 30<br>5. Number lost to follow-up/withdrawn: 4 (6.7%)<br>a. Etanercept: 0 (0%)<br>b. Placebo: 4 (13.3%)<br>6. Total analysed: 60<br>a. Etanercept: 30<br>b. Placebo: 30<br>7. Age, years, median (range)<br>a. Etanercept: 46 (30–70)<br>b. Placebo: 43.5 (24–63)<br>8. Gender, male% (males/total)<br>a. Etanercept: 60 (18/30)<br>b. Placebo: 53 (16/30)<br>9. C-reactive protein basal level, mg/L, median (IQR)<br>a. Etanercept: 14 (7, 28)<br>b. Placebo: 12 (8, 22)<br>10. Inclusion criteria: |

**Mease 2000** *(Continued)*

a. Age: between 18 and 70 years;
b. Sex: all;
c. Active psoriatic arthritis (defined as ≥ 3 swollen joints and ≥ 3 tender or painful joints);
d. Inadequate response to nonsteroidal anti-inflammatory drugs and were thought to be candidates for immunomodulatory therapy;
e. Patients taking methotrexate (≤ 25 mg/week) were allowed to continue methotrexate if the dose was stable for 4 weeks before the study started and remained stable throughout the study;
f. Corticosteroids were allowed if the dose was ≤ 10 mg/day of prednisone, stable for at least 2 weeks before the study started, and maintained throughout the study.

11. Exclusion criteria:
a. Evidence of skin conditions other than psoriasis (such as eczema);
b. Other disease-modifying antirheumatic drugs;
c. Hepatic transaminase concentrations greater than twice the upper limit of normal;
d. Haemoglobin less than 85 g/L or higher;
e. Platelet count less than 125,000 per mL;
f. Serum creatinine above 152 mmol/L.

| | |
|---|---|
| Interventions | 1. Intervention:<br>a. Etanercept: (Enbrel®)<br>b. Pharmaceutical laboratory: Immunex Corporation<br>c. Dose: 25 mg, twice-weekly for 12 weeks<br>d. Administration route: subcutaneous<br>2. Control:<br>a. Placebo ("... was identically supplied and formulated except that it contained no etanercept", p. 386) twice-weekly for 12 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention<br>a. Methotrexate, corticosteroids, and NSAIDs |
| Outcomes | 1. Primary (baseline to week 12)<br>a. Proportion meeting the Psoriatic Arthritis Response Criteria (PsARC)<br>b. Proportion of participants who met 75% of improvement in the PASI (PASI75)<br>2. Secondary (baseline to week 12)<br>a. Proportion meeting the ACR preliminary criteria for 20%, 50%, and 70% improvement (ACR20; designed for assessment of rheumatoid arthritis)<br>b. Other arthritis activity measurements: tender joint count, swollen joint count, quality of life (by the Health Assessment Questionnaire (HAQ)), CRP, erythrocyte sedimentation rate (ESR)<br>c. Adverse events |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: not stated<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: grant support from the Immunex Corporation<br>5. Disclosure comment: not stated<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "A block randomisation was used: within each group of four patients enroled; two were assigned at random to the placebo group and two to the etanercept group" (p. 386). |

**Mease 2000** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to judge "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Placebo was identically supplied and formulated except that it contained no etanercept" (p. 386). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 60<br>a. Etanercept: 30<br>b. Placebo: 30<br>2. Withdrawals<br>a. Etanercept: 0<br>b. Placebo: 13.33% (4/30)<br>3. Completed study:<br>a. Etanercept: 100% (30/30)<br>b. Placebo: 86.66% (26/30)<br>c. Imbalance: 13.44% |
| Selective reporting (reporting bias) | High risk | Trial reported only adverse events and quality of life. |
| Other bias | High risk | Grant support from the Immunex Corporation |

**Mease 2004**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 2 years<br>4. Follow-up period: 24 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (17)<br>9. Country: United States<br>10.Study setting: outpatient<br>11.Type trial: not stated<br>12.Type of prevention: primary |
| Participants | 1. Type of disease: psoriatic arthritis<br>2. Diagnosis criteria: ≥ 3 swollen and ≥ 3 tender joints and previous inadequate response to NSAID therapy<br>3. Severity: not stated<br>4. Total randomised: 205 participants<br>a. Etanercept: 104<br>b. Placebo: 101<br>5. Number lost to follow-up/withdrawn: 40 (19.5%) |

**Mease 2004** *(Continued)*

a. Etanercept: 8 (8%)
b. Placebo: 32 (31%)

6. Total analysed: 205
   a. Etanercept: 104
   b. Placebo: 101
7. Age, years, mean
   a. Etanercept: 47.6
   b. Placebo: 47.3
8. Gender, male% (males/total)
   a. Etanercept: 57 (58/104)
   b. Placebo: 45 (47/101)
9. C-reactive protein basal level: not stated
10. Inclusion criteria:
    a. Age: 18–70 years old;
    b. Active psoriatic arthritis, with ≥ 3 swollen and ≥ 3 tender joints;
    c. Previous inadequate response to NSAID therapy;
    d. One of the following clinical subtypes of psoriatic arthritis: distal interphalangeal (DIP) joint involvement, polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis), arthritis *mutilans*, asymmetric peripheral arthritis, or ankylosing spondylitis–like arthritis;
    e. Stable plaque psoriasis with a qualifying target lesion (≥ 2 cm in diameter);
    f. Concomitant methotrexate therapy stable for 2 months could be continued at a stable dosage of ≤ 25 mg/week.
11. Exclusion criteria:
    a. Other disease-modifying antirheumatic drugs were discontinued at least 4 weeks before the study started;
    b. Corticosteroids stable for 4 weeks could be continued at ≤ 10 mg/day of prednisone (or equivalent);
    c. Phototherapy was discontinued at least 2 weeks before the study started;
    d. Oral retinoids, topical vitamin A or D analogue preparations, and anthralin were not allowed.

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|---|---|
| Interventions | 1. Intervention:<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Immunex Corporation, a wholly-owned subsidiary of Amgen, Inc.<br>c. Dose: 25 mg, twice-weekly for 24 weeks<br>d. Administration route: subcutaneous<br>2. Control:<br>a. Placebo (composition not stated), twice-weekly for 24 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: methotrexate, corticosteroids, and NSAIDs |
| Outcomes | 1. Primary (baseline to week 24)<br>a. Proportion achieving American College of Rheumatology 20% improvement criteria (ACR20)<br>2. Secondary (baseline, week 24, and through week 72)<br>a. ACR50 and ACR70 responses<br>b. Psoriatic Arthritis Response Criteria (PsARC)<br>c. Dermatologist's static global assessment of psoriasis and the PASI 50 and PASI 75<br>d. Quality of life: Short Form 36 (SF-36) Health Survey and Health Assessment Questionnaire (HAQ)<br>e. Modified total Sharp score (TSS; joint erosion plus joint space narrowing [JSN] scores)<br>f. Adverse events<br>g. Antibody to etanercept |
| Notes | 1. Trial registration number: NCT00317499<br>2. Trial dates: March 2000-August 2002<br>3. A priori sample size estimation: yes |

**Mease 2004** *(Continued)*

4. Financial disclosure: Immunex Corporation, a wholly-owned subsidiary of Amgen Inc., supported the study.
5. Disclosure comment: "Drs Mease, Siegel, Cohen, and Ory have received consulting fees and honoraria from Amgen. Drs Mease, Kivitz, and Siegel have stock ownership or options in Amgen. Drs Ory, Salonen, Rubenstein, and Sharp were compensated for reading radiographs in this study."
6. Ethical committee approved: yes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Eligible patients were randomly assigned to receive placebo or etanercept at a dosage of 25 mg subcutaneously twice weekly in an initial 24-week blinded phase" (p. 2265).<br>Comment: insufficient information to judge as "high" or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Quote: "Eligible patients were randomly assigned to receive placebo or etanercept at a dosage of 25 mg subcutaneously twice weekly in an initial 24-week blinded phase" (p. 2265).<br>Comment: insufficient information to judge as "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: #1: "...placebo-controlled double-blind trial..." (p. 2265).<br>Quote: #2: "in syringes, each containing the contents of 1 reconstituted vial of etanercept or otherwise identically furnished placebo..." (p. 2265). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 205<br>a. Etanercept: 101<br>b. Placebo: 104<br>2. Withdrawals:<br>a. Etanercept: 7.92% (8/101)<br>b. Placebo: 30.76% (32/104)<br>c. Imbalance: 22.84%<br>d. Overall: 19.51% (40/205)<br>3. Main reasons for withdrawing (lack of efficacy):<br>a. Etanercept: 62.5% (5/8)<br>b. Placebo: 71.87% (23/32)<br>4. Completed study (24 weeks):<br>a. Etanercept: 92% (93/101)<br>b. Placebo: 69.23% (72/104)<br>c. Imbalance: 22.77%<br>d. Overall: 80.48% (165/205) |
| Selective reporting (reporting bias) | High risk | There were no reports of cardiovascular outcomes. The trial reported only information about quality of life and adverse events. |
| Other bias | Low risk | No other bias identified |

**Menter 2007**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 3 arms*<br>3. Duration: 2 years<br>4. Follow-up period: 50 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (63)<br>9. Country: Austria, Canada, France, Italy, and the United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary<br><br>*Data from participants during the induction period only (first 16 weeks), as per protocol |
| Participants | 1. Type of disease: plaque psoriasis<br>2. Diagnosis criteria: PASI score ≥ 12, 10% of body surface cover in lesions<br>3. Severity: moderate-to-severe<br>4. Total randomised: 835 participants*<br>a. Infliximab (3 mg/kg): 313<br>b. Infliximab (5 mg/kg): 314<br>c. Placebo: 208<br>5. Number lost to follow-up/withdrawn (%): 62 (7.4)*<br>a. Infliximab (3 mg/kg): 21 (6.7)<br>b. Infliximab (5 mg/kg): 17 (5.4)<br>c. Placebo: 24 (11.5)<br>6. Total analysed: 835*<br>a. Infliximab (3 mg/kg): 313<br>b. Infliximab (5 mg/kg): 314<br>c. Placebo: 208<br>7. Age, years, mean (SD)<br>a. Infliximab (3 mg/kg): 43.4 (12.6)<br>b. Infliximab (5 mg/kg): 44.5 (13.0)<br>c. Placebo: 44.4 (12.5)<br>8. Gender, male% (males/total)<br>a. Infliximab (3 mg/kg): 65.8 (206/313)<br>b. Infliximab (5 mg/kg): 65 (204/314)<br>c. Placebo: 69.2 (144/208)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. Age: 18 years or older;<br>b. Sex: all;<br>c. Plaque psoriasis with a PASI score ≥ 12 and at least 10% of total body surface involvement;<br>d. Candidates for phototherapy or systemic therapy.<br>11. Exclusion criteria:<br>a. Non-plaque forms of psoriasis;<br>b. Current drug-induced psoriasis;<br>c. Pregnancy, breastfeeding, or planning pregnancy (both men and women) within 18 months of enrolment;<br>d. Previous treatment with infliximab or any therapeutic agent targeted at reducing tumour necrosis factor; |

**Menter 2007** *(Continued)*

e. Lymphoproliferative disease, or active tuberculosis (TB);
f. Concomitant topical therapy, phototherapy, or systemic therapy for psoriasis was prohibited, except for low-potency topical corticosteroids;
g. Use of disease-modifying antirheumatic drugs;
h. Stable doses of NSAIDs were allowed..

*Data from participants during the induction period only (first 16 weeks), as per protocol

| | |
|---|---|
| Interventions | 1. Intervention*<br>a. Infliximab (Remicade®)<br>b. Pharmaceutical laboratory: Centocor Inc (Horsham, Pennsylvania, USA)<br>c. Dose: 3 mg/kg at weeks 0, 2, and 6<br>d. Administration route: intravenous<br>2. Intervention*<br>a. Infliximab (Remicade®)<br>b. Pharmaceutical laboratory: Centocor Inc (Horsham, Pennsylvania, USA)<br>c. Dose: 5 mg/kg at weeks 0, 2, and 6<br>d. Administration route: intravenous<br>3. Control*<br>a. Placebo (composition not stated) at weeks 0, 2, and 6<br>b. Administration route: intravenous<br>4. Co-intervention: low-potency topical corticosteroids<br><br>*Data from participants during the induction period only (first 16 weeks), as per protocol |
| Outcomes | 1. Primary (baseline to week 10)<br>a. Proportion of participants achieving PASI75<br>2. Secondary (baseline, weeks 10, 16, 30, and 50)<br>a. Physician's Global Assessment (PGA)<br>b. Quality of life through DLQI<br>c. PASI 75 and 90<br>d. Adverse effects<br>e. Antibodies to infliximab |
| Notes | 1. Trial registration number: NCT00106847<br>2. Trial dates: January 2003-July 2005<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Centocor, Inc (Malvern, Pennsylvania) and Schering-Plough (Kenilworth, New Jersey) funded the study.<br>5. Disclosure comment: "conflict of interest can be found in the appendix" https://www.jaad.org/article/S0190-9622(06)02083-4/fulltext#appseca1<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomizations were performed by (...), allocating patients using a minimization algorithm with a biased coin assignment by means of an interactive voice response system" (p. 31.e2). |
| Allocation concealment (selection bias) | Low risk | Quote: "Randomizations were performed by (...), allocating patients using a minimization algorithm with a biased coin assignment by means of an interactive voice response system" (p. 31.e2). |

**Menter 2007** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "Patients, investigators, and all study staff except pharmacists were blinded to treatment assignments" (p. 31.e2).<br><br>Comment: insufficient information to judge as "high" or "low" risk of bias. No information about appearance of study medication and placebo." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Randomised: 835<br>a. Infliximab (3 mg/kg): 313<br>b. Infliximab (5 mg/kg): 314<br>c. Placebo: 208<br>2. Withdrawals:<br>a. Infliximab (3 mg/kg): 6.7% (21/313)<br>b. Infliximab (5 mg/kg): 5.41% (17/314)<br>c. Placebo: 11.53% (24/208)<br>d. Overall: 7.42% (62/835)<br>3. The main reasons for withdrawing:<br>a. Adverse events in infliximab (3 mg/kg): 61.90% (13/21)<br>b. Adverse events in infliximab (5 mg/kg): 70.58% (12/17)<br>c. Lack of efficacy in the placebo group: 41.66% (10/24) |
| Selective reporting (reporting bias) | High risk | No information about cardiovascular outcomes. There were reports about quality of life and adverse events. |
| Other bias | Low risk | Centocor, Inc (Malvern, Pennsylvania) and Schering-Plough (Kenilworth, New Jersey) funded the study. |

**Meyer 2021**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 180 days<br>4. Follow-up period: 180 days (approx. 25.7 weeks)<br>5. Run-in period: no stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): no<br>9. Country: Denmark<br>10.Study setting: inpatient<br>11.Type trial: not stated<br>12.Type of prevention: secondary |
| Participants | 1. Type of disease: out-of-hospital cardiac arrest (OHCA)<br>2. Diagnosis criteria: not stated<br>3. Severity: not applicable<br>4. Total randomised: 85 participants<br>a. Tocilizumab: 42<br>b. Placebo: 43 |

**Meyer 2021** *(Continued)*

5. Number lost to follow-up/withdrawn (%): 5 (5.8)
   a. Tocilizumab: 3 (7)
   b. Placebo: 2 (4.7)
6. Total analysed: 80
   a. Tocilizumab: 39
   b. Placebo: 41
7. Age, years, median (IQR)
   a. Tocilizumab: 65 (53–73)
   b. Placebo: 60 (57–70)
8. Gender, male% (males/total)
   a. Tocilizumab: 82.1 (32/39)
   b. Placebo: 82.9 (34/41)
9. High-sensitivity C-reactive protein basal level, mg/L, median (IQR)
   a. Tocilizumab: 2 (1-10)
   b. Placebo: 2 (1-3)
10. Inclusion criteria:
    a. Age ≥ 18 years;
    b. OHCA of a presumed cardiac cause;
    c. Unconsciousness upon admission, i.e. a Glasgow Coma Scale (GCS) < 9;
    d. Sustained return of spontaneous circulation (ROSC) for more than 20 minutes.
11. Exclusion criteria:
    a. Consciousness upon admission, i.e. a GCS ≥ 9;
    b. Presumed non-cardiac cause of arrest;
    c. Unwitnessed asystole;
    d. Suspected or confirmed intracranial bleeding or stroke;
    e. Pregnancy, or females of fertile age, unless a negative serum HCG can rule out pregnancy within the inclusion window;
    f. Temperature on admission < 30 °C;
    g. Persistent cardiogenic shock that is not reversed within the inclusion window;
    h. Known disease making 180-day survival unlikely;
    i. Known limitations in therapy;
    j. Known pre-arrest Cerebral Performance Category of 3 to 4;
    k. > 240 minutes from ROSC to randomisation;
    l. Known allergies to medication, known infections, and known hepatic cirrhosis.

| | |
|---|---|
| Interventions | 1. Intervention:<br>a. Tocilizumab (RoActemra®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 8 mg/kg (max. 800 mg), single dose<br>d. Administration route: intravenous<br>2. Control:<br>a. Placebo (isotonic saline), single dose<br>b. Administration route: intravenous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to 72 hours)<br>a. Concentration of high-sensitivity CRP<br>2. Secondary(baseline, hours 24, 48 and 72, and until day 180)<br>a. Biomarkers of organ damage: neuron-specific enolase, Troponin T (TnT), CKMB levels, creatinine, ALAT, ASAT, bilirubin, INR, soluble thrombomodulin levels<br>b. Markers of inflammation: INF-γ, IL-1b, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17A, G-CSF, GM-CSF, MCP-1, MIP-1β, TNF-α, leukocyte differential count, daily Sequential Organ Failure Assessment (SOFA) scores<br>c. Markers of coagulation: fibrinogen, thrombelastography |

**Meyer 2021** *(Continued)*

d. Markers of haemodynamic function: Swan-Ganz catheter, arterial blood gases, echocardiography
e. Clinical endpoints: survival, Montreal Cognitive Assessment (MOCA), Cerebral Performance Category (CPC)
f. Safety: incidence of adverse events

| | |
|---|---|
| Notes | 1. Trial registration number: NCT03863015<br>2. Trial dates: March 2019-December 2019<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: "funding from The Danish Heart Foundation (Reference No. 19-R135-A9302-22125), “Region Hovedstadens Forskningsfond til sundhedsforskning” (Capital Region Research Foundation, Denmark; Reference No. A6030), “Hjertecenterets Forskningsudvalg” (The Heart Center Research Council, Rigshospitalet), NovoNordisk Foundation (unrestricted research grant for Dr. Kjaergaard, NNF17OC0028706), Lundbeck Foundation (Reference No. R186-2015-2132)."<br>5. Disclosure comment: "None"<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Random assignments of eligible patients were performed using a web-based secure electronic Case Report System (Zenodotus eCRF)" (p. 1843). |
| Allocation concealment (selection bias) | Low risk | Quote: "Random assignments of eligible patients were performed using a web-based secure electronic Case Report System (Zenodotus eCRF)" (p. 1843). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: #1: "Blinding to the allocation sequence was upheld for all treating physicians and study coordinators throughout the trial" (p. 1843).<br>Quote: #2: "The infusion of either IL-6RA or placebo was commenced in a blinded fashion at the earliest possible time after randomization" (p. 1843). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Randomised 85<br>a. Tocilizumab: 42<br>b. Placebo: 43<br>2. Received allocated intervention: 95.29% (81/85)<br>a. Tocilizumab: 39<br>b. Placebo: 42<br>3. Withdrawal:<br>a. Tocilizumab: (0/39)<br>b. Placebo: 2.38% (1/42)<br>4. Analysed:<br>a. Tocilizumab: 92.85% (39/42)<br>b. Placebo: 95.34% (41/43) |
| Selective reporting (reporting bias) | High risk | There was only information about all-cause mortality and adverse events. |
| Other bias | High risk | Disclosure none. NovoNordisk Foundation (unrestricted research grant for Dr. Kjaergaard) |

**Micali 2015**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 2 years<br>4. Follow-up period: 32 weeks<br>5. Run-in period: yes<br>6. Run-in period time: 6 weeks<br>7. International: yes<br>8. Multicentre (number of centres): yes (22)<br>9. Country: Germany, Greece, Italy, Malta, and Spain<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: plaque psoriasis<br>2. Diagnosis criteria: PASI score ≥ 10, lesions involving at least 10% of body surface<br>3. Severity: moderate-to-severe<br>4. Total randomised: 120 participants<br>a. Etanercept: 58<br>b. Placebo: 62<br>5. Number lost to follow-up/withdrawn (%): 63 (52.5)<br>a. Etanercept: 20 (34.5)<br>b. Placebo: 43 (69.3)<br>6. Total analysed: 120<br>a. Etanercept: 58<br>b. Placebo: 62<br>7. Age, years, mean (range)<br>a. Etanercept: 41.8 (36–48)<br>b. Placebo: 41.5 (31–58)<br>8. Gender, male% (males/total)<br>a. Etanercept: 65.5 (38/58)<br>b. Placebo: 72.6 (45/62)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. Between the ages of 18 and 70 years;<br>b. Active and stable plaque psoriasis with a Body Surface Area (BSA) ≥ 10% or PASI score ≥ 10.<br>11. Exclusion criteria:<br>a. Evidence of skin conditions other than psoriasis;<br>b. Psoralen + ultraviolet A (PUVA), cyclosporin, acitretin, alefacept, anakinra, or any other systemic anti-psoriasis therapy or disease-modifying antirheumatic drugs (DMARD) with 28 days of screening;<br>c. Ultraviolet B (UVB) therapy, topical steroids, topical vitamin A or D analogue preparations, or anthralin;<br>d. Prior exposure to any TNF inhibitor. Prior exposure to efalizumab;<br>e. Corticosteroid dose of prednisone > 10 mg/day;<br>f. Serious infection;<br>g. Receipt of any live vaccine;<br>h. Abnormal haematology or chemistry;<br>i. Body mass index (BMI) > 38;<br>j. Pregnancy or breastfeeding; |

**Micali 2015** *(Continued)*

| | |
|---|---|
| | k. Significant concurrent medical conditions. |
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 50 mg, once weekly for 24 weeks<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated), once weekly for 24 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention<br>a. Cyclosporine: 1-5 mg/kg/day (lead-in period) |
| Outcomes | 1. Primary (baseline to week 30)<br>a. Change in PASI score<br>2. Secondary (baseline, weeks 6, 12, 30)<br>a. PASI Area Under the Curve (AUC)<br>b. Change in Physician's Global Assessment<br>c. Relapse (loss of 50% improvement in PASI)<br>d. Probability of being relapse-free<br>e. Change of PASI score<br>f. Quality of life: change in DLQI<br>g. Percentage of rebound effects |
| Notes | 1. Trial registration number: NCT00581555<br>2. Trial dates: October 2007-November 2009<br>3. A priori sample size estimation: not stated<br>4. Financial disclosure: Wyeth (acquired by Pfizer Inc. in October 2009) sponsored the study.<br>5. Disclosure comment: "The writing support was provided by Stephanie Eide of Engage Scientific Solutions and was funded by Pfizer Inc. G. Micali has received financial support for performing clinical trials. D. Wilsmann-Theis has received financial support for performing clinical trials and has received speakers' honoraria and travel scholarships from Pfizer GmbH. L. Mallbris, G. Gallo, V. Marino, Y. Brault, and J-M Germain are employees of Pfizer Inc."<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "...randomised 1:1 to etanercept (50 mg/week) or placebo for 24 weeks" (p. 58). |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "...24-week double-blind treatment.." (p. 58).<br>Comment: insufficient information to judge as "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias) | High risk | 1. Randomised: 120<br>a. Etanercept: 58 |

**Micali 2015** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | b. Placebo: 62<br>2. Withdrawal: 44.16% (53/120)<br>a. Etanercept: (34.48% (20/58)<br>b. Placebo: 69.35% (43/62)<br>3. The main reason for withdrawing:<br>a. Subject request (n = 9), loss to follow-up (n = 2) in etanercept arm<br>b. Subject request (n = 18), lack of efficacy (n = 10) in placebo arm<br>4. Completed treatment:<br>a. Etanercept: 65.51% (38/58)<br>b. Placebo: 30.64% (19/62)<br>5. Analysed (for intention-to-treat):<br>a. Etanercept: 58<br>b. Placebo: 62 |
| Selective reporting (reporting bias) | High risk | The trial reported only information about quality of life and adverse events. |
| Other bias | High risk | Design bias due to lack of estimation of sample size. |

**Morton 2015**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 3 years<br>4. Follow-up period: 1 year<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: not<br>8. Multicentre (number of centres): yes (5)<br>9. Country: United Kingdom<br>10.Study setting: inpatient<br>11.Type trial: not stated<br>12.Type of prevention: secondary |
| Participants | 1. Type of disease: non-ST elevation acute coronary syndromes<br>2. Diagnosis criteria: typical cardiac chest pain, 48 hours from onset of symptoms, ECG changes of ischaemia, and an elevated troponin<br>3. Severity: not stated<br>4. Total randomised: 182 participants<br>a. Anakinra: 93<br>b. Placebo: 89<br>5. Number lost to follow-up/withdrawn (%): 27 (14.8)<br>a. Anakinra: 15 (16.1)<br>b. Placebo: 12 (13.5)<br>6. Total analysed<br>a. Anakinra: varies with each outcome<br>b. Placebo: varies with each outcome<br>7. Age, years, mean (SD)<br>a. Anakinra: 61.4 (11.7)<br>b. Placebo: 61.3 (12.3) |

**Morton 2015** *(Continued)*

8. Gender, male% (males/total)
   a. Anakinra: 67.7 (63/93)
   b. Placebo: 75.3 (67/89)
9. High-sensitive C-reactive protein basal level, mg/dL, geometrical mean (95% CI)
   a. Anakinra: 5.38 (4.12, 7.04)
   b. Placebo: 5.21 (3.75, 7.22)
10. Inclusion criteria:
    a. Aged over 18 years;
    b. Acute severe cardiac chest pain consistent with an acute coronary syndrome;
    c. Less than 48 hours from the onset of symptoms that led to hospital admissions;
    d. At least one of the following:
       i. Horizontal or down-sloping ST depression of at least 0.5 mm in at least two ECG leads
       ii. A raised troponin as defined by local parameters specified at each centre
       iii. Other ECG changes consistent with acute myocardial ischaemia (e.g. T-wave inversion of at least 3 mm, in at least two leads of the ECG, or new onset bundle branch block)
       iv. An elevated level of troponin above local laboratory values indicating myocardial damage.
11. Exclusion criteria:
    a. Persistent ST elevation on the presenting ECG;
    b. Intention-to-treat with an urgent reperfusion strategy (thrombolysis or primary percutaneous coronary intervention);
    c. Percutaneous coronary intervention within the previous three months;
    d. Previous coronary artery bypass grafting;
    e. ECG showing paced rhythm;
    f. Cardiogenic shock;
    g. Any serious comorbidity which makes it unlikely that the patient will complete trial procedures and follow-up;
    h. Treatment or under active follow-up for rheumatoid arthritis, other connective tissue diseases, or inflammatory bowel disease;
    i. End-stage renal disease or a creatinine of more than 220 µmol/L;
    j. Pregnancy or suspected pregnancy;
    k. Eosinophilia;
    l. Anti-tumour necrotising factor biologics;
    m. Active infection;
    n. Malignancy.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Anakinra (Kineret®)<br>b. Pharmaceutical laboratory: Amgen Corporation<br>c. Dose: 100 mg, once daily for 14 days<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated) once daily for 14 days<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to day 7)<br>a. Area under the curve of serum high sensitivity C-Reactive Protein (hs-CRP) over the first seven days<br>2. Secondary (baseline, days 7, 14, 30: months 3 and 12)<br>a. Mean hs-CRP<br>b. Area under the curve of troponin-I, von Willebrand Factor (vWF) and interleukin-6 (IL-6)<br>c. ST-segment depression on Holter monitor<br>d. Myocardial injury as determined by gadolinium-enhanced Cardiovascular Magnetic Resonance (CMR) scan<br>e. Forearm endothelial cell response |

**Morton 2015** *(Continued)*

f. Incidence of Major Adverse Cardiovascular Events (MACE)

| | |
|---|---|
| Notes | 1. Trial registration number: ISRCTN89369318<br>2. Trial dates: July 2007-March 2010<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: "supported by UK Medical Research Council Experimental Medicine Grant number G0502131 and a UK Medical Research Council Clinical Research Training Fellowship MR/K002406/1 (A.M.K.R.). IL-1ra (Anakinra) and matching placebo were donated by Amgen Corporation. Funding to pay the Open Access publication charges for this article was provided by the University of Sheffield."<br>5. Disclosure comment: "D.C.C. has received grant funding from Novartis"<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "...using a central 24 h telephone system, stratified by study centre ..." (p. 378) |
| Allocation concealment (selection bias) | Low risk | Quote: "using a central 24 h telephone system, stratified by study centre..." (p. 378) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "The study drug and placebo will be provided by Amgen Inc. in its commercially available recombinant form which is in clinical use for the treatment of arthritic conditions. The study drug and placebo will be relabelled by Amgen, in collaboration with CTEU according to MHRA guidelines" (p. 4 from study protocol).<br>Quote: "All personnel will be blinded to the identity of the syringe contents" (p. 5 from study protocol).<br>CTEU: Clinical Trials and Evaluation Unit of the Royal Brompton Hospital, London |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "All personnel will be blinded to the identity of the syringe contents" (p. 5 from study protocol).<br>All endpoints were objective. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 182<br>a. Anakinra: 93<br>b. Placebo: 89<br>2. Total withdrawals: 14.83% (27/182)<br>a. Anakinra: 16.12% (15/93)<br>b. Placebo: (13.48% 12/ 89)<br>3. Main reasons for withdrawing:<br>a. Withdrew (N = 6), died (N = 5) in anakinra arm<br>b. Withdrew (N = 8), died (N = 2) in placebo arm<br>4. Follow-up (at one year):<br>a. Anakinra: 83.87% (78/93)<br>b. Placebo: 86.51% (77/ 89) |
| Selective reporting (reporting bias) | Low risk | The trial reported major cardiovascular outcomes and adverse events. |
| Other bias | Low risk | Found no other bias |

**Padfield 2013**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 24 hours<br>4. Follow-up period: 24 hours<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): no<br>9. Country: United Kingdom<br>10. Study setting: inpatient<br>11. Type trial: not stated<br>12. Type of prevention: secondary |
| Participants | 1. Type of disease: non-ST elevation acute myocardial infarction<br>2. Diagnosis criteria: ischaemic electrocardiographic changes and an elevated troponin-I concentration (> 0.2 µg/L)<br>3. Severity<br>4. Total randomised: 26 participants<br>a. Etanercept: 13<br>b. Placebo: 13<br>5. Number lost to follow-up/withdrawn (%): 0<br>a. Etanercept: 0<br>b. Placebo: 0<br>6. Total analysed: 26<br>a. Etanercept: 13<br>b. Placebo: 13<br>7. Age, years, mean (SEM)<br>a. Etanercept: 61 (4)<br>b. Placebo: 63 (3)<br>8. Gender, male% (males/total)<br>a. Etanercept: 69 (9/13)<br>b. Placebo: 77 (10/13)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. Age: 18 years and older;<br>b. Sex: all;<br>c. History of myocardial ischaemia lasting more than 20 min within 24 hours of hospitalisation with ischaemic electrocardiographic changes and an elevated troponin-I concentration (> 0.2 µg/L).<br>11. Exclusion criteria:<br>a. Significant comorbidity, including active systemic inflammatory disorders, insulin-dependent diabetes mellitus, and the use of anti-inflammatory drugs other than aspirin;<br>b. History of recent or recurrent infection, tuberculosis, or any opportunistic infection within the previous six months. |
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 10 mg, single dose<br>d. Administration route: intravenous<br>2. Control<br>a. Placebo (saline), single dose |

**Padfield 2013** *(Continued)*

| | |
|---|---|
| | b. Administration route: intravenous<br>3. Co-intervention: Standard of care, substance P, sodium nitroprusside |
| Outcomes | 1. Cellular response (baseline and after 24 hours)<br>a. Neutrophils<br>b. Lymphocytes<br>c. Monocytes<br>2. Cytokines (baseline and after 24 hours)<br>a. Interleukin-6<br>b. TNF-α<br>3. Platelet activation (baseline and after 24 hours)<br>a. Platelet monocyte aggregates<br>b. Platelet surface P-selectin<br>4. Fibrinolytic function<br>a. tPA (tissue plasminogen activator) activity<br>b. PAI-1 (plasminogen activator inhibitor type 1) activity |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: not stated<br>3. A priori sample size estimation: not stated<br>4. Financial disclosure: funded through the University of Edinburgh with additional support from the British Heart Foundation (PG/2001068), which also supported Dr Padfield (SS/CH/92010 and PG/07/012) and Professor Newby (CH/09/002) to undertake the work. NHS Research Scotland supports the Wellcome Trust Clinical Research Facility through NHS Lothian.<br>5. Disclosure comment: "none"<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomisation was performed by a computer generated sequence to ensure concealment of treatment allocation and following minimisation..." (p. 1331). |
| Allocation concealment (selection bias) | Low risk | Quote: "Randomisation was performed by a computer generated sequence to ensure concealment of treatment allocation and following minimisation..." (p. 1331). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "In a randomised, double-blind, parallel group..." (p. 1331).<br>Comment: insufficient information to judge as "high" or low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Randomised 26<br>Etanercept: 13<br>Placebo: 13<br><br>The trial reported no withdrawals. |
| Selective reporting (reporting bias) | High risk | The trial reported no information about cardiovascular outcomes. |

**Padfield 2013** *(Continued)*

| | | |
|---|---|---|
| Other bias | High risk | Design bias: there was no a priori sample size estimation. |

**Papp 2005**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 3 arms<br>3. Duration: 1 year<br>4. Follow-up period: 24 weeks*<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (50)<br>9. Country: Canada, France, Germany, the Netherlands, United Kingdom, and the United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary<br><br>*Included data from the study's doubled-blinded period (first 12 weeks), as per protocol |
| Participants | 1. Type of disease: plaque psoriasis<br>2. Diagnosis criteria: lesions involving ≥ 10% of the total body surface, and a PASI score ≥ 10<br>3. Severity: not stated<br>4. Total randomised: 611 participants<br>a. Etanercept 50 mg: 203<br>b. Etanercept 25 mg: 204<br>c. Placebo: 204<br>5. Number lost to follow-up/withdrawn (%): 52 (8.5)<br>a. Etanercept 50 mg: 13 (6.4)<br>b. Etanercept 25 mg: 13 (6.4)<br>c. Placebo: 26 (12.7)<br>6. Total analysed: 583<br>a. Etanercept 50 mg: 194<br>b. Etanercept 25 mg: 196<br>c. Placebo: 193<br>7. Age, years, median (range)<br>a. Etanercept 50 mg: 44.5 (21–80)<br>b. Etanercept 25 mg: 46 (20–87)<br>c. Placebo: 44 (18–80)<br>8. Gender, male% (males/total)<br>a. Etanercept 50 mg: 67 (130/194)<br>b. Etanercept 25 mg: 65 (128/196)<br>c. Placebo: 64 (124/193)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. Age: 18 years or older;<br>b. Sex: all;<br>c. Active, but clinically stable, plaque psoriasis involving ≥10% of total body surface area, and PASI ≥10;<br>d. Received at least one previous phototherapy or systemic therapy for psoriasis or have been a candidate to do so; |

**Papp 2005** *(Continued)*

e. Adequate haematological, renal, and hepatic function.

11. Exclusion criteria:
    a. Received antibiotics within one week of study drug initiation or had a severe active infection within four weeks of study screening;
    b. Skin conditions other than psoriasis that would interfere with study evaluations;
    c. Active guttate, erythrodermic, or pustular psoriasis;
    d. Received systemic psoriasis therapy or psoralen plus ultraviolet (UV) A phototherapy for four weeks before the study; topical corticosteroids, vitamin A or D analogue preparations, dithranol or UVB phototherapy for two weeks before the study; or etanercept or an anti-TNF antibody at any time;
    e. Topical corticosteroids of moderate strength on the scalp, axilla, and groin, or tar compound or steroid-free topical emollients, were allowed.

| | |
|---|---|
| Interventions | 1. Intervention*<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Immunex-Wyeth<br>c. Dose: 50 mg, twice-weekly for 12 weeks<br>d. Administration route: subcutaneous<br>2. Intervention*<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Immunex-Wyeth<br>c. Dose: 25 mg, twice-weekly for 12 weeks<br>d. Administration route: subcutaneous<br>3. Control*<br>a. Placebo (composition not stated), twice-weekly for 12 weeks<br>b. Administration route: subcutaneous<br><br>*Included data from the study's doubled-blinded period (first 12 weeks), as per protocol |
| Outcomes | 1. Primary (baseline to week 12)<br>a. Achievement of a 75% or greater improvement from baseline in the PASI (PASI 75) after<br>2. Secondary (baseline to weeks 12 and 24)<br>a. PASI 50 and PASI 90 responses<br>b. Percentage improvement from baseline in PASI<br>c. Static physician's global assessment (sPGA)<br>d. Visual confirmation of the effect of etanercept on psoriatic lesions (photography)<br>e. Adverse events, infections and injection site reactions (ISRs); abnormalities in laboratory variables; and antibody formation to etanercept |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: May 2002-July 2003<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Immunex Corporation (Seattle, WA, U.S.A.), a wholly-owned subsidiary of Amgen Inc, funded the study.<br>5. Disclosure comment: "S.T. has received research support from Amgen; C.E.M.G. has been a paid consultant for Wyeth and Amgen; A.M.N and R.Z. are both full-time employees of Amgen."<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "patients were randomly assigned (using an Interactive Voice Response System)..." (p. 1305). |

**Papp 2005** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | Quote: "patients were randomly assigned (using an Interactive Voice Response System)..." (p. 1305). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "To maintain the treatment blind, all patients received two injections per dose of study drug, with placebo making up the balance of injections for the 25-mg regimen"(p. 1305). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Randomised: 611 (28 did not receive intervention study)<br>a. Etanercept (25 mg): 8<br>b. Etanercept (50 mg): 9<br>c. Placebo: 11<br>2. Received intervention study: 583<br>a. Etanercept (25 mg): 34.61% (196/583)<br>b. Etanercept (50 mg): 33.27% (194/583)<br>c. Placebo: 33.10% (193/583)<br>3. Total withdrawal: 4.11% (24/583)<br>a. Etanercept (25 mg): 0.85% (5/583)<br>b. Etanercept (50 mg): 0.68% (4/583)<br>c. Placebo: 2.57% (15/583)<br>4. The main reasons for withdrawing:<br>a. Adverse events (3), lack of efficacy (1) in etanercept (25 mg)<br>b. Adverse events (2), lack of efficacy (1) in etanercept (50 mg)<br>c. Adverse events (2), lack of efficacy (4), lack of efficacy (4), lost to follow-up (4) in placebo.<br>5. Completed study:<br>a. Etanercept (25 mg): 97.44% (191/196)<br>b. Etanercept (50 mg): 97.93% (190/194)<br>c. Placebo: 92.22% (178/193) |
| Selective reporting (reporting bias) | High risk | Trial reported only adverse events. |
| Other bias | High risk | 1. Financial disclosure: Immunex Corporation (Seattle, WA, U.S.A.), a wholly-owned subsidiary of Amgen Inc, funded the study.<br>2. Disclosure comment: "S.T. has received research support from Amgen; C.E.M.G. has been a paid consultant for Wyeth and Amgen; A.M.N and R.Z. are both full-time employees of Amgen." |

**Ralph 2020**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 2 years<br>4. Follow-up period: 30 days<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable |

**Ralph 2020** *(Continued)*

7. International: no
8. Multicentre (number of centres): no
9. Country: Australia
10. Study setting: outpatient
11. Type trial: not stated
12. Type of prevention: secondary

| | |
|---|---|
| Participants | 1. Type of disease: chronic stroke, post-stroke pain<br>2. Diagnosis criteria: not stated<br>3. Severity: moderate-to-severe<br>4. Total randomised: 26 participants<br>a. Etanercept: 13<br>b. Placebo: 13<br>5. Number lost to follow-up/withdrawn (%): 4 (15.4)<br>a. Etanercept: 3 (23.1)<br>b. Placebo: 1 (7.7)<br>6. Total analysed: 22<br>a. Etanercept: 10<br>b. Placebo: 12<br>7. Age, years, mean (SE)<br>a. Etanercept: 57.3 (4.95)<br>b. Placebo: 61.65 (8.66)<br>8. Gender, male% (males/total)<br>a. Etanercept: 50 (5/10)<br>b. Placebo: 58.3 (7/12)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. Sex: all;<br>b. Age: 27-80 years old;<br>c. Stroke occurring at least 6 months and not more than 15 years before screening for the study;<br>d. Ischaemic or haemorrhagic stroke in the territory of the right or left middle cerebral artery (MCA); or the basal ganglia from subarachnoid haemorrhage;<br>e. Constant daily pain post-stroke incorporating one or both contralateral limbs and experiencing intractable chronic post-stroke pain with hemiplegic post-stroke shoulder pain and central post-stroke pain. The post-stroke pain is moderate-to-severe in intensity, with a daily average intensity between 4 and 8 inclusive on an 11-point (0–10) vertical Numerical Pain Rating Scale supplemented with a Faces pain scale;<br>f. Stroke-induced cognitive impairment by the Mini-Mental State Examination (MMSE) scores 16-25, or Montreal Cognitive Assessment (MOCA) score in the range of 12-24, inclusive, performed upon assessment during enrolment.<br>11. Exclusion criteria:<br>a. Dementia diagnosis prior to the date of stroke;<br>b. Brain stem or cerebellar stroke;<br>c. More than one stroke in the past 3 years;<br>d. Parkinson's disease or Parkinsonian symptoms;<br>e. Dementia with Lewy bodies;<br>f. Multiple sclerosis in the present or in the past;<br>g. Demyelinating disease in the present or in the past;<br>h. History of tuberculosis;<br>i. Positive PPD;<br>j. For the complete list of exclusion criteria, read supplementary table 1 of the study Ralph 2020. |
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®) |

**Ralph 2020** *(Continued)*

| | |
|---|---|
| | b. Pharmaceutical laboratory: Pfizer (USA)<br>c. Dose: 25 mg on days 1 and 14<br>d. Administration route: perispinal<br>2. Control<br>a. Placebo (saline) on days 1 and 14<br>b. Administration route: perispinal<br>3. Co-intervention: standard of treatment for the condition |
| Outcomes | 1. Primary (baseline to day 30)<br>a. Vertical Numerical Pain Rating Scale<br>2. Secondary (baseline through day 30)<br>a. Average level of pain<br>b. Change in the Montreal Cognitive Assessment (MOCA)<br>c. Change in Albert's Line Bisection Test<br>d. Fatigue Assessment Scale<br>e. Change in Clock Drawing Test<br>f. Thermal detection and pain sensitivity |
| Notes | 1. Trial registration number: ACTRN12615001377527<br>2. Trial dates: November 2016-March 2019<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: A grant from the Stroke Recovery Trial Fund and public donations supported the study.<br>5. Disclosure comment: "The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed." (p. 13)<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "... randomized controlled parallel trial with 1:1". Quote: "A computer-based random number generator in blocks of five was used by the pharmacist to establish the trial unblinding code for random assignment of enrolled patients into either group" (p. 5). |
| Allocation concealment (selection bias) | Low risk | Quote: "A computer-based random number generator in blocks of five was used by the pharmacist to establish the trial unblinding code for random assignment of enrolled patients into either group" (p. 5) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "...all injections double-blinded to the principal medical investigators and participants. Assessments measuring the responses of participants to treatments were also undertaken in a blinded manner" (p. 3).<br><br>Quote: "...sterile saline (suitable for human injection) as a clear colorless solution, with the same appearance as for [the] etanercept, and prepared in the same type of syringe with the same volume of 1.8 ml as for the test drug. The control was administered using the identical perispinal injection procedure as for the active drug treatment..." (p. 4). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: information insufficient to judge a "high" or "low" risk of bias. Authors did not describe how blinding of outcome assessment was conducted. Lack of group-specific attrition data and details on handling of missing data limits assessment of potential bias. |

**Ralph 2020** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Total sample: 26<br>a. Etanercept: 13<br>b. Placebo: 13<br>2. Withdrawal: 15.38% (4/26)<br>a. Etanercept: 23% (3/13) at least one by adverse event<br>b. Placebo: 8.33% (1/12)<br>c. Imbalance: 14.5% |
| Selective reporting (reporting bias) | High risk | The trial reported no information about the Cochrane review's predefined outcomes. |
| Other bias | Low risk | No other bias identified |

**RECOVER 2000**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 3 arms<br>3. Duration: 2 years<br>4. Follow-up period: 24 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (194)<br>9. Country: Australia, Austria, Belgium, Croatia, Czechia, Denmark, Estonia, Finland, France, Germany, Hungary, Israel, Italy, Latvia, Lithuania, New Zealand, Norway, Poland, Portugal, Slovakia, Spain, Sweden, The Netherlands, and the United Kingdom<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: secondary |
| Participants | 1. Type of disease: heart failure<br>2. Diagnosis criteria: LVEF ≤ 0.30<br>3. Severity: NYHA class II to IV<br>4. Total randomised: 1,123 participants<br>a. Etanercept (once weekly): 375<br>b. Etanercept (twice-weekly): 375<br>c. Placebo: 373<br>5. Number lost to follow-up/withdrawn: 73%<br>a. Etanercept (once weekly): not stated<br>b. Etanercept (twice-weekly): not stated<br>c. Placebo: not stated<br>6. Total analysed: 1,123<br>a. Etanercept (once weekly): 375<br>b. Etanercept (twice-weekly): 375<br>c. Placebo: 373<br>7. Age, years, mean (SD)<br>a. Etanercept (once weekly): 64.8 (10.3)<br>b. Etanercept (twice-weekly): 64.1 (10.4)<br>c. Placebo: 64.6 (10.8)<br>8. Gender, male% (males/total) |

**RECOVER 2000** *(Continued)*

a. Etanercept (once weekly): 77 (289/375)
b. Etanercept (twice-weekly): 81 (304/375)
c. Placebo: 75 (280/373)

9. C-reactive protein basal level: not stated
10. Inclusion criteria:
    a. Age 18 to 85 years;
    b. NYHA class II to IV;
    c. LVEF ≤ 30;
    d. Ischaemic or not ischaemic aetiology of heart failure;
    e. Stable doses of diuretics, ACEIs, and β-blockers or spironolactone for three months;
    f. 6 minutes walk distance < 375 m or < 425 m if hospitalised due to CHF in the last six months.
11. Exclusion criteria:
    a. Severe infection within one month;
    b. Surgically correctable causes of heart failure;
    c. Other serious illness;
    d. Acute myocardial infarction or hospitalisation in 3 months;
    e. Recent (3 months) or planned surgery/coronary revascularisation.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 25 mg once weekly duration not stated<br>d. Administration route: subcutaneous<br>2. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 25 mg twice-weekly, duration not stated<br>d. Administration route: subcutaneous<br>3. Control<br>a. Placebo (composition not stated); frequency and duration not stated<br>b. Administration route: subcutaneous<br>4. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to week 24)<br>a. Change in clinical status<br>2. Secondary: not stated<br><br>RENEWAL outcomes*<br><br>1. Primary (duration not stated)<br>a. Composite of death (all causes) or hospitalisations for CHF<br>2. Secondary (baseline to week 24)<br>a. All-cause mortality<br>b. Hospitalisation and emergency room visits for CHF<br>c. Change in NYHA class<br>d. Patient's Global Assessment<br>e. Quality of life<br><br>*This study was terminated due to futility in March 2001, and the results of both RECOVER and RENAISSANCE studies were published as a single analysis named RENEWAL. |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: June 1999-March 2001<br>3. A priori sample size estimation: yes |

**RECOVER 2000** *(Continued)*

4. Financial disclosure: Amgen Inc (Amgen Corporation, Thousand Oaks, California, USA) and Wyeth Research (Collegeville, Pennsylvania, USA) funded the study.
5. Disclosure comment: not stated
6. Ethical committee approved: yes
7. Other notes: This study was terminated due to futility in March 2001, and the results of both RECOVER and RENAISSANCE studies were published as a single analysis named RENEWAL.

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "... randomized..." (p. 1595).<br>Insufficient information to judge a "high" or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Quote: "... randomized..." (p. 1595).<br>Insufficient information to judge "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "...double-blind..." (p. 1595)<br>Insufficient information to judge "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "...double-blind..." (p. 1595)<br>Comment: insufficient information to judge a "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Quote: "...37% and 73% of the patients in RECOVER and RENAISSANCE, respectively, had completed the 24-week evaluation. One percent or less of any treatment group of RECOVER or RENAISSANCE was lost to follow-up for assessment of vital status, and 0.4% and 0.9% of patients withdrew consent for evaluation of clinical status in RECOVER and RENAISSANCE, respectively." (p. 1598)<br><br>Insufficient information to judge a "high" or "low" risk of bias |
| Selective reporting (reporting bias) | Unclear risk | The trial only reported death, chronic heart failure and adverse events. |
| Other bias | Unclear risk | We lacked information to judge "high" or "low" risk of bias. |

**Reich 2017**

***Study characteristics***

Methods

1. Study design: parallel
2. Number of arms: 3 arms*
3. Duration: 2 years
4. Follow-up period: 104 weeks*
5. Run-in period: not stated
6. Run-in period time: not applicable
7. International: yes
8. Multicentre (number of centres): yes (82)
9. Country: Canada, Czechia, Estonia, Germany, Hungary, Latvia, the Netherlands, the United Kingdom, and the United States
10. Study setting: outpatient
11. Type trial: not stated

**Reich 2017** *(Continued)*

12.Type of prevention: primary

*Included data from etanercept and placebo groups during the first 16 weeks of the study, as per protocol

| | |
|---|---|
| Participants | 1. Type of disease: plaque psoriasis<br>2. Diagnosis criteria: PASI score ≥ 12, affected body surface area [BSA] ≥ 10%, static Physician Global Assessment [sPGA] score ≥ 3<br>3. Severity: moderate-to-severe<br>4. Total randomised: 250 participants<br>a. Etanercept: 83*<br>b. Placebo: 84*<br>5. Number lost to follow-up/withdrawn (%)*<br>a. Etanercept: 2 (2.4)<br>b. Placebo: 9 (10.7)<br>6. Total analysed*<br>a. Etanercept: 83<br>b. Placebo: 84<br>7. Age, years, mean (SD)*<br>a. Etanercept: 47 (14.1)<br>b. Placebo: 43.4 (14.9)<br>8. Gender, male% (males/total)*<br>a. Etanercept: 59 (49/84)<br>b. Placebo: 70.2 (59/83)<br>9. C-reactive protein basal level: not stated<br>10.Inclusion criteria:<br>a. Males or females ≥ 18 years of age;<br>b. Diagnosis of chronic, moderate to severe plaque psoriasis for at least 12 months prior to screening and a candidate for phototherapy and/or systemic (including etanercept) therapy;<br>c. Had an inadequate response, intolerance, or contraindication to at least 1 conventional systemic agent for the treatment of psoriasis;<br>d. No prior exposure to biologics for the treatment of psoriatic arthritis or psoriasis.<br>11.Exclusion criteria:<br>a. Prior failure of > 3 systemic agents for the treatment of psoriasis;<br>b. History of known demyelinating diseases such as multiple sclerosis or optic neuritis or history of or concurrent congestive heart failure, including medically controlled, asymptomatic congestive heart failure;<br>c. Other clinically significant or major uncontrolled disease; serious infection; latent, active, or history of incompletely treated tuberculosis.<br>*Included data from etanercept and placebo groups during the first 16 weeks of the study, as per protocol |
| Interventions | 1. Intervention*<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 50 mg, weekly for 16 weeks<br>d. Administration route: subcutaneous<br>2. Control*<br>a. Placebo (saline), weekly for 16 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: low-potency topical corticosteroids<br>*Included data from etanercept and placebo groups during the first 16 weeks of the study, as per protocol |

**Reich 2017** *(Continued)*

| | |
|---|---|
| Outcomes | 1. Primary (baseline to week 16)<br>a. Percentage of participants achieving a 75% improvement in the PASI score<br>2. Secondary (baseline, weeks 16 and 52)<br>a. Static Physician Global Assessment (sPGA) score<br>b. Affected Body Surface Area (BSA)<br>c. PASI-50<br>d. Dermatology Life Quality Index (DLQI)<br>e. Mental Component Summary (MCS) Score of the Medical Outcome Study Short Form 36-item (SF-36) Health Survey Version 2.0<br>f. Lattice System Physician's Global Assessment (LS-PGA)<br>g. Treatment-Emergent Adverse Events (TEAE)<br>h. Psoriasis flare/rebound |
| Notes | 1. Trial registration number: NCT01690299<br>2. Trial dates: October 2012-July 2014<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Celgene Corporation sponsored the study.<br>5. Disclosure comment: several authors of this study informed that they have worked as paid speakers, consultants, or advisors or received research funding from several privately owned companies in the health area, including the one that sponsored this study. Z. Zhang, R. M. Day, and J. Goncalves are employees of and hold stock/stock options in Celgene Corporation. K. Shah and I. Khanskaya were employees of Celgene Corporation at the time of study conduct and own stock, stock options, and restricted stock units in Celgene Corporation.<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "...via an interactive voice response system..." (p. 509). |
| Allocation concealment (selection bias) | Low risk | Quote: "...via an interactive voice response system..." (p. 509). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Per the double-dummy design, patients received oral tablets (apremilast 30 mg or placebo) BID and two subcutaneous injections (etanercept 25 mg each dose or saline placebo) QW..." ((p. 509). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Randomised: 250<br>a. Etanercept (50 mg): 83<br>b. Apremilast (30 mg): 83<br>c. Placebo: 84<br>2. Total withdrawals: 6.8% (17/250)<br>a. Etanercept (50 mg): 2.4% (2/83)<br>b. Apremilast (30 mg): 7.2% (6/83)<br>c. Placebo: 10.71% (9/84)<br>3. The main reasons for withdrawing:<br>a. Adverse events (1) in etanercept (50 mg)<br>b. Adverse events (2), and withdrew consent (3) in apremilast (30 mg) |

**Reich 2017** *(Continued)*

| | | |
|---|---|---|
| | | c. Adverse events (2), lack of efficacy (4), withdrew consent (1) in placebo.<br>4. Completed study (at 12 weeks): 93.2% (233/250)<br>a. Etanercept (50 mg): 97.59% (81/83)<br>b. Apremilast (30 mg): 92.77% (77/83)<br>c. Placebo: 89.28% (75/84) |
| Selective reporting (reporting bias) | High risk | The trial reported only adverse events. |
| Other bias | High risk | Celgene Corporation funded the study, and several authors had financial ties to the company, including employment, stock ownership, and receiving payments for various services, posing potential conflicts of interest. |

**RENAISSANCE 2001**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 3 arms<br>3. Duration: 2 years<br>4. Follow-up period: 24 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (105)<br>9. Country: Canada and the United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: heart failure<br>2. Diagnosis criteria: LVEF ≤ 0.30<br>3. Severity: NYHA class II to IV<br>4. Total randomised: 925 participants<br>a. Etanercept (twice-weekly): 308<br>b. Etanercept (three times weekly): 308<br>c. Placebo: 309<br>5. Number lost to follow-up/withdrawn: 27%<br>a. Etanercept (twice-weekly): not stated<br>b. Etanercept (three times weekly): not stated<br>c. Placebo: not stated<br>6. Total analysed: 925<br>a. Etanercept (twice-weekly): 308<br>b. Etanercept (three times weekly): 308<br>c. Placebo: 309<br>7. Age, years, mean (SD)<br>a. Etanercept (twice-weekly): 61.8 (12.1)<br>b. Etanercept (three times weekly): 62.4 (11)<br>c. Placebo: 62.6 (11.9)<br>8. Gender, male% (males/total)<br>a. Etanercept (twice-weekly): 77 (237/308)<br>b. Etanercept (three times weekly): 81 (249/308) |

**RENAISSANCE 2001** *(Continued)*

c. Placebo: 77 (238/309)
9. C-reactive protein basal level: not stated
10. Inclusion criteria:
    a. Age 18 to 85 years;
    b. NYHA class II to IV;
    c. LVEF ≤ 30;
    d. Ischaemic or not ischaemic aetiology of heart failure;
    e. Stable doses of diuretics, ACEIs, and β-blockers or spironolactone for three months;
    f. 6 minutes walk distance < 375 m or <;425 m if hospitalised due to CHF in the last six months.
11. Exclusion criteria:
    a. Severe infection within one month;
    b. Surgically correctable causes of heart failure;
    c. Other serious illness;
    d. Acute myocardial infarction or hospitalisation in 3 months;
    e. Recent (3 months) or planned surgery/coronary revascularisation.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 25 mg twice-weekly, duration not stated<br>d. Administration route: subcutaneous<br>2. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 25 mg three times weekly; duration not stated.<br>d. Administration route: subcutaneous<br>3. Control<br>a. Placebo (composition not stated); frequency and duration not stated<br>b. Administration route: subcutaneous<br>4. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to week 24)<br>a. Change in clinical status<br>2. Secondary: not stated<br><br>RENEWAL outcomes*<br><br>1. Primary (duration not stated)<br>a. Composite of death (all causes) or hospitalisations for CHF<br>2. Secondary (baseline to week 24)<br>a. All-cause mortality<br>b. Hospitalisation and emergency room visits for CHF<br>c. Change in NYHA class<br>d. Patient's Global Assessment<br>e. Quality of life<br><br>*This study was terminated due to futility in March 2001, and the results of both RECOVER and RENAISSANCE studies were published as a single analysis named RENEWAL. |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: March 1999-March 2001<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Amgen Inc (Amgen Corporation, Thousand Oaks, California, USA) and Wyeth Research (Collegeville, Pennsylvania, USA) funded the study.<br>5. Disclosure comment: not stated |

**RENAISSANCE 2001** *(Continued)*

6. Ethical committee approved: yes
7. Other notes: This study was terminated due to futility in March 2001, and the results of both RECOVER and RENAISSANCE studies were published as a single analysis named RENEWAL.

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "... randomized..." (p. 1595)<br>Insufficient information to judge a "high" or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Quote: "... randomized..." (p. 1595)<br>Insufficient information to judge a "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "...double-blind..." (p. 1595)<br>Insufficient information to judge a "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "...double-blind..." (p. 1595)<br>Insufficient information to judge a "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Quote: "...37% and 73% of the patients in RECOVER and RENAISSANCE, respectively, had completed the 24-week evaluation. One per cent or less of any treatment group of RECOVER or RENAISSANCE was lost to follow-up for assessment of vital status, and 0.4% and 0.9% of patients withdrew consent for evaluation of clinical status in RECOVER and RENAISSANCE, respectively" (p. 1598).<br><br>Insufficient information to judge a "high" or "low" risk of bias |
| Selective reporting (reporting bias) | Unclear risk | The trial only reported death, chronic heart failure and adverse events. |
| Other bias | Unclear risk | We lacked information to judge "high" or "low" risk of bias. |

**Ridker 2012**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 5 arms<br>3. Duration: 1 year<br>4. Follow-up period: 4 months<br>5. Run-in period: yes<br>6. Run-in period time: 8 weeks<br>7. International: yes<br>8. Multicentre (number of centres): yes (108)<br>9. Country: Argentina, Belgium, Germany, Great Britain, Hong Kong, Hungary, India, Japan, Peru, Romania, South Africa, Korea, Türkiye, and the United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: type 2 diabetes mellitus |

**Ridker 2012** *(Continued)*

2. Diagnosis criteria: fasting plasma glucose ≥ 7.0 mmol/L or an oral glucose tolerance test 2-hour plasma glucose ≥ 11.1 mmol/L
3. Severity: "well-controlled HbA1c"
4. Total randomised: 556 participants
   a. Canakinumab 5 mg: 94
   b. Canakinumab 15 mg: 96
   c. Canakinumab 50 mg: 93
   d. Canakinumab 150 mg: 92
   e. Placebo: 181
5. Number lost to follow-up/withdrawn (%): 5 (0.89)
   a. Canakinumab 5 mg: 1 (1.06)
   b. Canakinumab 15 mg: 1 (1.04)
   c. Canakinumab 50 mg: 1 (1.07)
   d. Canakinumab 150 mg: 0 (0)
   e. Placebo: 2 (1.1)
6. Total analysed
   a. Canakinumab 5 mg: varies with each outcome
   b. Canakinumab 15 mg: varies with each outcome
   c. Canakinumab 50 mg: varies with each outcome
   d. Canakinumab 150 mg: varies with each outcome
   e. Placebo: varies with each outcome
7. Age, years, mean
   a. Canakinumab 5 mg: 53.5
   b. Canakinumab 15 mg: 55.5
   c. Canakinumab 50 mg: 53.0
   d. Canakinumab 150 mg: 53.7
   e. Placebo: 54.3
8. Gender, male% (males/total): 56.4 (311/556)
   a. Canakinumab 5 mg: 59.1 (55/93)
   b. Canakinumab 15 mg: 51.6 (49/95)
   c. Canakinumab 50 mg: 48.9 (45/92)
   d. Canakinumab 150 mg: 62 (57/92)
   e. Placebo: 58.7 (105/179)
9. High-sensitive C-reactive protein basal level, mg/L, mean:
   a. Canakinumab 5 mg: 2.0
   b. Canakinumab 15 mg: 2.4
   c. Canakinumab 50 mg: 2.8
   d. Canakinumab 150 mg: 2.5
   e. Placebo: 1.9
10. Inclusion criteria:
    a. Age: 18-74 years old;
    b. Sex: all;
    c. Type 2 diabetes confirmed by World Health Organization (WHO) criteria, either a Fasting Plasma Glucose (FPG) ≥ 7.0 mmol/L (126 mg/dL) or an oral glucose tolerance test (OGTT) test 2-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dL);
    d. Naive to anti-diabetes drug therapy (except for short-term treatment courses with insulin in connection with hospitalisation, etc.);
    e. Meet protocol-specified glycosylated haemoglobin/haemoglobin A1c (HbA1c) criteria;
    f. Eligible for metformin monotherapy or be on stable metformin monotherapy treatment for at least three months;
    g. Take metformin as their first and only treatment with anti-diabetes drug therapy or take alpha-glucosidase inhibitors (AGI) as their first and only anti-diabetes drug therapy (except for short-term treatment courses with insulin in connection with hospitalisations, etc.);

**Ridker 2012** *(Continued)*

h. Morning fasting plasma glucose result < 180 mg/dL at visit 3 (month -1) analysed by the Central Laboratory;
i. Daily dose of metformin ≥ 1000 mg (or less according to local regulations).

11. Exclusion criteria:
a. Type 1 diabetes mellitus, diabetes resulting from pancreatic injury or secondary forms of diabetes;
b. Relative contraindication for IL-1β inhibition, including risk factors for tuberculosis, active or recurrent hepatitis B or C, chronic infections associated with an immunocompromised condition;
c. Use of other immune-modulating agents;
d. History of cancer or recent cardiovascular event;
e. Requirement for live vaccinations during or immediately preceding the trial;
f. Women who were pregnant, nursing, or unable to use effective contraception.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Canakinumab (Ilaris®)<br>b. Pharmaceutical laboratory: Novartis<br>c. Dose: 5 mg, once monthly, for 4 months<br>d. Administration route: subcutaneous<br>2. Intervention<br>a. Canakinumab (Ilaris®)<br>b. Pharmaceutical laboratory: Novartis<br>c. Dose: 15 mg, once monthly, for 4 months<br>d. Administration route: subcutaneous<br>3. Intervention<br>a. Canakinumab (Ilaris®)<br>b. Pharmaceutical laboratory: Novartis<br>c. Dose: 50 mg, once monthly, for 4 months<br>d. Administration route: subcutaneous<br>4. Intervention<br>a. Canakinumab (Ilaris®)<br>b. Pharmaceutical laboratory: Novartis<br>c. Dose: 150 mg, once monthly, for 4 months<br>d. Administration route: subcutaneous<br>5. Control<br>a. Placebo (composition not stated), once monthly, for 4 months<br>b. Administration route: subcutaneous<br>6. Co-intervention: metformin |
| Outcomes | 1. Primary (baseline to month 4)<br>a. Change in HbA1c<br>2. Secondary (baseline to month 4)<br>• Change in average plasma glucose, average insulin, Homeostatic Model Assessment Insulin Resistance (HOMA2 IR), and fasting lipids profile<br>• Change in hs-CRP, IL-6, and fibrinogen<br>• Adverse events |
| Notes | 1. Trial registration number: NCT00900146<br>2. Trial dates: April 2009-November 2010<br>3. A priori sample size estimation: no<br>4. Financial disclosure: Novartis Pharma AG (Basel, Switzerland) and Novartis Pharmaceutical Corporation (East Hanover, New Jersey, USA) supported the study.<br>5. Disclosure comment: "Dr. Ridker is the principal investigator of the investigator-initiated CANTOS trial, which is being funded by Novartis. Dr. Ridker has served as a consultant to Merck, ISIS, Vascular Biogenics, and Genyzyme and is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes melli- |

**Ridker 2012** *(Continued)*

tus that have been licensed to Siemens and AstraZeneca. Drs Howard, Walter, and Thuren are employees of Novartis. Dr. Libby is an unpaid consultant or involved in clinical trials for Amgen, AstraZeneca, Genzyme, GlaxoSmithKline, Merck, Novartis, Pfizer, ProNova, and Sigma-Tau; and is a member of the Scientific Advisory Boards for Athera Biotechnologies, Carolus Therapeutics, Interleukin Genetics, and BIND Biosciences. Dr. Everett reports no conflicts."

6. Ethical committee approved: yes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "...participants were randomized to 1 of 4 active treatment groups (SC canakinumab at 5, 15, 50, or 150 mg monthly) or to SC placebo monthly" (p. 2740).<br><br>Comment: insufficient information to judge as "high" or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "We conducted a double-blind...." (p. 2739).<br>Insufficient information to judge as "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | The endpoints were objective. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Randomised: 556<br>a. Canakinumab (5 mg): 94<br>b. Canakinumab (15 mg): 96<br>c. Canakinumab (50 mg): 93<br>d. Canakinumab (150 mg): 92<br>e. Placebo: 181<br>2. Received medication study: 99.1% (551/556)<br>a. Canakinumab (5 mg): 93<br>b. Canakinumab (15 mg): 95<br>c. Canakinumab (50 mg): 92<br>d. Canakinumab (150 mg): 92<br>e. Placebo: 179<br>3. Withdrawals: 0.89% (5/556)<br>a. Canakinumab (5 mg): 1.06% (1/94)<br>b. Canakinumab (15 mg): 1.04% (1/96)<br>c. Canakinumab (50 mg): 1.07% (1/93)<br>d. Canakinumab (150 mg): 0% (0/92)<br>e. Placebo: 1.10% (2/181) |
| Selective reporting (reporting bias) | High risk | The trial reported only adverse events. |
| Other bias | High risk | Design bias: trial reported no a priori sample size estimation. |

**Ridker 2017**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 4 arms<br>3. Duration: 6 years<br>4. Follow-up period: 48 months<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (1113)<br>9. Country: Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, Colombia, Croatia, Czechia, Estonia, Germany, Greece, Guatemala, Hungary, Iceland, India, Italy, Japan, Korea (Republic of), Latvia, Lithuania, Mexico, the Netherlands, Norway, Peru, Poland, Puerto Rico, Romania, Russian Federation, Serbia, Slovakia, Slovenia, South Africa, Sweden, Taiwan, Türkiye, the United Kingdom, and the United States<br>10. Study setting: outpatient<br>11. Type trial: superiority<br>12. Type of prevention: secondary |
| Participants | 1. Type of disease: myocardial infarction<br>2. Diagnosis criteria: universal MI criteria with or without evidence of ST-segment elevation<br>3. Severity: not stated<br>4. Total randomised: 10,061 participants<br>a. Canakinumab (50 mg): 2170<br>b. Canakinumab (150 mg): 2284<br>c. Canakinumab (300 mg): 2263<br>d. Placebo: 3344<br>5. Number of lost to follow-up/withdrawn: 1859 (18.47)<br>a. Canakinumab (50 mg): 362 (16.68)<br>b. Canakinumab (150 mg): 438 (19.17)<br>c. Canakinumab (300 mg): 454 (20.06)<br>d. Placebo: 605 (18.09)<br>6. Number analysed:<br>a. Canakinumab (50 mg): 2170<br>b. Canakinumab (150 mg): 2284<br>c. Canakinumab (300 mg): 2263<br>d. Placebo: 3344<br>7. Age, years, mean (SD):<br>a. Canakinumab (50 mg): 61.1 (10.1)<br>b. Canakinumab (150 mg): 61.2 (10)<br>c. Canakinumab (300 mg): 61.1 (10.1)<br>d. Placebo: 61.1 (10)<br>8. Gender, male% (males/total)<br>a. Canakinumab (50 mg): 75.1 (1619/2170)<br>b. Canakinumab (150 mg): 74.8 (1709/2284)<br>c. Canakinumab (300 mg): 73.3 (1657/2263)<br>d. Placebo: 74.1 (2479/3344)<br>9. High-sensitive C-reactive protein basal level, mg/L, mean (IQR)<br>a. Canakinumab (50 mg): 4.25 (2.80-7.15)<br>b. Canakinumab (150 mg): 4.25 (2.85-7.05)<br>c. Canakinumab (300 mg): 4.15 (2.85-7.15)<br>d. Placebo: 4.10 (2.75-6.85)<br>10. Inclusion criteria: |

**Ridker 2017** *(Continued)*

a. Written informed consent must be obtained before any assessment is performed;
b. Male or female of non-childbearing potential;
c. Age ≥ 18 years;
d. Documented spontaneous MI (diagnosed according to the universal MI criteria with or without evidence of ST-segment elevation) at least 30 days before randomisation;
e. Have an hsCRP ≥ 2 mg/L;
f. On stable (at least 4 weeks) long-term (cardiovascular) medications.

11. Exclusion criteria:
    a. Pregnant or nursing (lactating) women;
    b. Women of childbearing potential;
    c. Any of the following concomitant diseases
        i. Planned coronary revascularisation (PCI or CABG)
        ii. Major non-cardiac surgical or endoscopic procedure within the past 6 months
        iii. Multi-vessel CABG surgery within the past 3 years
        iv. Class IV heart failure (HF) New York Heart Association (NYHA)
        v. Uncontrolled hypertension
        vi. Uncontrolled diabetes
        vii. History or evidence of active tuberculosis (TB) infection
        viii. Nephrotic syndrome or eGFR < 30 mL/min/1.73 $m^2$ per MDRD formula or kidney transplant (regardless of renal function)
        ix. Known active or recurrent hepatic disorder
        x. Prior malignancy other than basal cell skin carcinoma.

List of full inclusion and exclusion criteria available at Ridker 2017.

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Interventions

1. Intervention*
    a. Canakinumab (Ilaris®)
    b. Pharmaceutical laboratory: Novartis
    c. Dose: 50 mg every 3 months for approximately 36 months
    d. Administration route: subcutaneous
2. Intervention*
    a. Canakinumab (Ilaris®)
    b. Pharmaceutical laboratory: Novartis
    c. Dose: 150 mg every 3 months for approximately 36 months
    d. Administration route: subcutaneous
3. Intervention*
    a. Canakinumab (Ilaris®)
    b. Pharmaceutical laboratory: Novartis
    c. Dose: 300 mg every 2 weeks for the first two doses, then once every 3 months for approximately 36 months
    d. Administration route: subcutaneous
4. Control*
    a. Placebo (composition not stated), every 3 months, for approximately 36 months
    b. Administration route: subcutaneous
5. Co-intervention: standard of care for the condition

*Information from the "double-blinded phase" of the study

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Outcomes

1. Primary (from baseline, 30 days after the end of treatment, and up to 6 years)
    a. Major Adverse Cardiovascular Events (MACE)
2. Secondary (from baseline, 30 days after the end of treatment, and up to 6 years)
    a. Components of the primary outcome and hospitalisation for unstable angina that led to urgent revascularisation
    b. Incidence of new-onset type 2 diabetes in participants with prediabetes

**Ridker 2017** *(Continued)*

| | |
|---|---|
| | c. Death from any cause<br>d. Composite of nonfatal myocardial infarction, any nonfatal stroke, or death from any cause<br>e. Adverse events<br><br>A list of complete endpoints for the study and its substudies is available at Ridker 2017. |
| Notes | 1. Trial registration number: NCT01327846<br>2. Trial dates: April 2011-June 2017<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Novartis supported the study.<br>5. Disclosure comment: disclosure form available at Ridker 2017<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was performed with the use of a centralized computer system, with stratification according ..." (p. 1120). |
| Allocation concealment (selection bias) | Low risk | Quote: "Randomization was performed with the use of a centralized computer system, with stratification according ..." (p. 1120). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: #1: "Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:..." (p. 31 from clinical trial protocol).<br><br>Quote: #2: "Each study site will be supplied by Novartis with study treatment in packaging of identical appearance" (p. 31 from clinical trial protocol). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: #1: "Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:..." (p. 31 from clinical trial protocol). |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Discontinued study:<br>a. Canakinumab (50 mg): 16.88% (362/2170)<br>b. Canakinumab (150 mg): 19.48% (438/2284)<br>c. Canakinumab (300 mg): 20% (454/2263)<br>d. Placebo: 18% (605/3344)<br>e. Overall: 18.47% (1859/10061)<br>2. Unknown vital clinical status:<br>a. Canakinumab (50 mg): 0.41% (9/2170)<br>b. Canakinumab (150 mg): 0.21% (5/2284)<br>c. Canakinumab (300 mg): 0.17% (4/2263)<br>d. Placebo: 0.26% (9/3344)<br>e. Overall: 0.26% (27/10061)<br><br>Comment: from supplemental Figure S1: CANTOS Consort Diagram (p. 28) |
| Selective reporting (reporting bias) | Low risk | The trial included major clinical outcomes. |
| Other bias | High risk | Financial disclosure: Novartis supported the study. |

**Russel 2019**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 3 years<br>4. Follow-up period: 12 months<br>5. Run-in period: yes<br>6. Run-in period time: 7 days<br>7. International: yes<br>8. Multicentre (number of centres): yes (16)<br>9. Country: Germany, Jordan, and the United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: secondary |
| Participants | 1. Type of disease: peripheral arterial disease<br>2. Diagnosis criteria: ankle-brachial index between 0.4 and 0.9<br>3. Severity: not stated<br>4. Total randomised: 38 participants<br>a. Canakinumab: 18<br>b. Placebo: 20<br>5. Number lost to follow-up/withdrawn (%): 12 (31.6)<br>a. Canakinumab: 4 (22.2)<br>b. Placebo: 8 (40)<br>6. Total analysed<br>a. Canakinumab: change with the outcome<br>b. Placebo: change with the outcome<br>7. Age, years, mean (SD)<br>a. Canakinumab: 66 (8.64)<br>b. Placebo: 65.5 (7.98)<br>8. Gender, male% (males/total)<br>a. Canakinumab: 77.8 (14/18)<br>b. Placebo: 65 (13/20)<br>9. C-reactive protein basal level, mg/L, geometric mean:<br>a. Canakinumab: 2.62<br>b. Placebo: 2.54<br>10. Inclusion criteria:<br>a. Provided written informed consent;<br>b. Age of 18-85 years;<br>c. Intermittent claudications (including atypical symptoms as adjudicated by the investigator) and met the ankle-brachial index (ABI) criteria;<br>d. Stable statin and aspirin (or other antiplatelet) therapy for at least 6 weeks before screening (unless there was a documented statin or aspirin intolerance or contraindication);<br>e. Baseline acquisition of evaluable MRI images of the superficial femoral artery;<br>f. Met criteria for vital signs ranges (oral body temperature: 35–37.5 °C; systolic blood pressure (BP): 90–170 mmHg; diastolic BP: 50–100 mmHg; pulse rate 40–100 beats per min).<br>11. Exclusion criteria:<br>a. Use of other investigational drugs;<br>b. History of hypersensitivity to canakinumab or other drugs of a similar class;<br>c. Pregnant or nursing women or women of childbearing potential (unless using specified methods of contraception during the study treatment); |

**Russel 2019** *(Continued)*

d. Inability to ambulate more than 15 m;
e. Use of the following medications: chronic systemic steroids or other systemic immunosuppression, any biologics targeting the immune system, or more than one chronic opiate for pain;
f. Presence of a non-healing wound or active infection;
g. Critical limb ischaemia;
h. Recent significant illnesses, including myocardial infarction, stroke, or major surgical procedures;
i. Significant concomitant diseases;
j. History of malignancy (except localised skin basal cell carcinoma) within the past 5 years;
k. Live vaccinations planned during the study or within the past 3 months;
l. History of untreated or active tuberculosis, immunodeficiency diseases (including HIV), or viral hepatitis;
m. Contraindication to MRI (e.g. metal implants).

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Canakinumab (Ilaris®)<br>b. Pharmaceutical laboratory: Novartis<br>c. Dose: 150 mg, once weekly for 12 weeks<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated) once weekly for 12 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to month 12)<br>a. Mean vessel wall area in the superficial femoral artery<br>2. Secondary (baseline to months 3 and 12)<br>a. Safety and tolerability of canakinumab<br>b. hs-CRP and IL-6<br>c. Functional capacity |
| Notes | 1. Trial registration number: NCT01731990<br>2. Trial dates: February 2013-August 2016<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Novartis Institutes for BioMedical Research funded the study.<br>5. Disclosure comment: "Kerry S Russel, Denise Yates, Andrea Feller, Ping Mahling, Laurence Colin, Timothy Clough, Tianke Wang, and Craig T Basson are employees of Novartis. The other authors declared no potential conflicts of interest." (p. 420)<br>6. Ethical committee approved: yes<br>7. Other disclosure if noted: "This study was stopped after the third interim analysis based on futility of the primary endpoint" (p. 415). |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Randomization was performed by Novartis Drug Supply Management using a validated system that automated the random assignment of treatment arms to randomization numbers in the specified (1:1) ratio to ensure that the treatment assignment was unbiased and concealed from patients and investigator staff..." (p. S2).<br><br>Comment: insufficient information to judge "high" risk or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Quote: "Randomization was performed by Novartis Drug Supply Management using a validated system that automated the random assignment of treatment |

**Russel 2019** *(Continued)*

| | | |
|---|---|---|
| | | arms to randomization numbers in the specified (1:1) ratio to ensure that the treatment assignment was unbiased and concealed from patients and investigator staff..." (Additional Supplement p. #2).<br><br>Comment: insufficient information to judge as "high" risk or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Study drugs were administered at each study site by qualified site personnel. The identity of the treatments was concealed by using study drugs that were all identical in packaging, labeling, schedule of administration, appearance, taste and odor."<br><br>(Additional supplement p. #2) |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: insufficient information to judge as "high" risk or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Total sample: 38<br>a. Eternacept: 18<br>b. Placebo: 20<br>2. Total withdrawals (at longest follow-up: 12 months): 31.57% (12/38)<br>a. Eternacept: 22.22% (4/18): one person by death after myocardial infarction, one by removed consent, one by protocol deviations<br>b. Placebo: 40% (8/20): two people by adverse events, one by removed consent, two by protocol deviations<br>c. Imbalance: 17.78% |
| Selective reporting (reporting bias) | High risk | The trial reported no information about major clinical outcomes. |
| Other bias | High risk | The study's funding by Novartis Institute for BioMedical Research and the employment of several authors by Novartis raise concerns about potential conflicts of interest, which could influence the study design, conduct, or reporting of results. |

**Smith 2018**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 3 years<br>4. Follow-up period: 3 months<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): no<br>9. Country: United Kingdom<br>10.Study setting: inpatient<br>11.Type trial: not stated<br>12.Type of prevention: secondary |
| Participants | 1. Type of disease: ischaemic stroke<br>2. Diagnosis criteria: not stated<br>3. Severity: minor-to-severe (National Institutes of Health Stroke Scale [NIHSS] 4 to 26) |

**Smith 2018** *(Continued)*

4. Total randomised: 80 participants
   a. Anakinra: 39
   b. Placebo: 41
5. Number lost to follow-up/withdrawn (%): 23 (28.75)
   a. Anakinra: 15 (38.46)
   b. Placebo: 8 (19.51)
6. Total analysed: 63
   a. Anakinra: 28
   b. Placebo: 35
7. Age, years, mean (SD)
   a. Anakinra: 72 (12)
   b. Placebo: 72 (13)
8. Gender, male% (males/total)
   a. Anakinra: 56 (22/39)
   b. Placebo: 68 (28/41)
9. C-reactive protein basal level: not stated
10. Inclusion criteria:
    a. Confirmed ischaemic stroke in whom consent can be obtained and drug administered within 6 hours of symptom onset;
    b. Aged 18 years or over;
    c. NIHSS score between 4 and 26;
    d. Able to give informed consent; or consent available from a personal consultee or professional consultee;
    e. No concomitant health problems that, in the opinion of the chief investigator or their designee, would interfere with participation, administration of study treatment, or assessment of outcomes, including safety.
11. Exclusion criteria:
    a. Unconfirmed or uncertain diagnosis of ischaemic stroke or rapidly improving symptoms;
    b. Primary intracerebral haemorrhage;
    c. Non-English-speaking people;
    d. Abnormal renal function (previous eGFR < 32 mL/min/1.73 $m^2$ in the 3 months prior to presenting stroke);
    e. Neutrophil count < 2.0 x $10^9$/L or known neutropenia;
    f. Evidence of current severe infection or infection requiring treatment within the past 4 weeks;
    g. Known allergy to proteins made from bacterial cells (*E. coli*) as established by the patients themselves, reliable representative and clinical records;
    h. Previous or current treatment with recombinant IL-1Ra known at the time of study entry;
    i. Previous or current treatment with medication suspected of interacting with recombinant IL-1Ra, such as TNF-α inhibitors;
    j. Known to have participated in a clinical trial of an investigational agent or device in the previous 30 days;
    k. Pregnant or breastfeeding;
    l. Previous inclusion in the current study.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Anakinra (Kineret®)<br>b. Pharmaceutical laboratory: Swedish Orphan Biovitrum<br>c. Dose: 100 mg; the first dose was started within 6 hours of symptom onset. Five further doses were administered at least 6 hours after the first dose and continued every 12 hours until completion of the 6 doses.<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated), the first dose was started within 6 hours of symptom onset. Five further doses were administered at least 6 hours after the first dose and continued every 12 hours until completion of the 6 doses. |

**Smith 2018** *(Continued)*

| | |
|---|---|
| | b. Administration route: subcutaneous<br>3. Co-intervention: Alteplase |
| Outcomes | 1. Primary (baseline to day 3)<br>a. Area under the curve for the log-transformed concentration of plasma IL-6<br>2. Secondary (baseline, day 3 and month 3)<br>a. Area under the curve for plasma log-transformed concentration of CRP and vWF<br>b. Adverse events<br>c. Brain imaging<br>d. Modified Rankin Scale |
| Notes | 1. Trial registration number: ISRCTN74236229<br>2. Trial dates: March 2014-February 2017<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: the Stroke Association (TSA 2012/08) funded the study.<br>5. Disclosure comment: "none"<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization (1:1) was undertaken using an independent third-party, web-based service, stratified for stroke severity (National Institutes of Health Stroke Scale < 13 or ≥ 13) and intravenous thrombolysis" (p. 1211). |
| Allocation concealment (selection bias) | Low risk | Quote: "Randomization (1:1) was undertaken using an independent third party, web-based service, stratified for stroke severity (National Institutes of Health Stroke Scale < 13 or ≥ 13) and intravenous thrombolysis." (p. 1211). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: #1: "All brain imaging was reported by neuroradiologists independent of the study, who were blinded to test treatment allocation" (p. 1211).<br>Quote: #2: "The day 5 to 7 sample was discontinued after blinded review by the Trial Steering Committee after recruitment of the first 58 participants as it had only been obtained in 51% of participants (largely because of participant repatriation to their base hospital after day 3)" (p. 1211). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: #1: "Laboratory staff were blinded to treatment allocation" (p. 1211).<br>Quote: #2: "All brain imaging was reported by neuroradiologists independent of the study, who were blinded to test treatment allocation. Hemorrhagic transformation was classified using the European Cooperative Acute Stroke Study criteria, 11 that is, hemorrhagic infarction 1 or 2 and parenchymal hemorrhage 1 or 2. The clinical secondary outcome was the mRS at 3 months, undertaken by a single, trained rater blinded to treatment allocation, either face-to-face or by telephone" (p. 1211)." |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 80<br>a. Anakinra: 39<br>b. Placebo: 41<br>2. First withdrawals: 28.75% (23/80)<br>a. Anakinra: 38.46% (15/39)<br>b. Placebo: 19.51% (8/41)<br>3. Analysed for primary outcome: 78.75% (63/80)<br>a. Anakinra: 71.79% (28/39)<br>b. Placebo: 85.36% (35/41) |

**Smith 2018** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Other bias | High risk | Bias in the presentation of the data (see Figure 1) |

**Smolen 2008**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 3 arms<br>3. Duration: 1 year<br>4. Follow-up period: 32 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (73)<br>9. Country: Argentina, Australia, Austria, Brazil, Bulgaria, Canada, China, France, Germany, Hungary, Israel, Italy, Mexico, Singapore, Slovakia, Switzerland, and Thailand<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: rheumatoid arthritis<br>2. Diagnosis criteria: American College of Rheumatology (ACR) criteria, swollen joint count of 6 or more plus a tender joint count of 8 or more and CRP over 10 mg/L or ESR of 28 mm/h or more<br>3. Severity: moderate-to-severe<br>4. Total randomised: 623 participants<br>a. Tocilizumab 4 mg/kg: 214<br>b. Tocilizumab 8 mg/kg: 205<br>c. Placebo: 204<br>5. Number lost to follow-up/withdrawn (%): 57 (9.14)<br>a. Tocilizumab 4 mg/kg: 28 (13)<br>b. Tocilizumab 8 mg/kg: 14 (6.8)<br>c. Placebo: 15 (7.3)<br>6. Total analysed: 622<br>a. Tocilizumab 4 mg/kg: 213<br>b. Tocilizumab 8 mg/kg: 205<br>c. Placebo: 204<br>7. Age, years, mean, (SD)<br>a. Tocilizumab 4 mg/kg: 51.4 (12.8)<br>b. Tocilizumab 8 mg/kg: 50.8 (11.8)<br>c. Placebo: 50.6 (12.1)<br>8. Gender, male% (males/total)<br>a. Tocilizumab 4 mg/kg: 18 (38/213)<br>b. Tocilizumab 8 mg/kg: 15 (30/205)<br>c. Placebo: 22 (45/204)<br>9. C-reactive protein basal level, mg/L, mean (SD)<br>a. Tocilizumab 4 mg/kg: 28 (34)<br>b. Tocilizumab 8 mg/kg: 26 (26)<br>c. Placebo: 24 (28) |

**Smolen 2008** *(Continued)*

10. Inclusion criteria:
    a. At least 18 years of age;
    b. Sex: all;
    c. Moderate-to-severe active RA for at least 6 months;
    d. Inadequate response to a stable dose of methotrexate;
    e. Participants of reproductive potential must be using reliable methods of contraception.
11. Exclusion criteria:
    a. Other autoimmune diseases or significant systemic involvement secondary to rheumatoid arthritis (e.g. vasculitis, pulmonary fibrosis, or Felty's syndrome);
    b. Functional class IV rheumatoid arthritis, previous or current inflammatory joint disease other than rheumatoid arthritis;
    c. Currently, active or previous recurrent bacterial, viral, fungal, or other infections including, but not limited to, tuberculosis and atypical mycobacterial disease, clinically significant abnormalities on chest radiograph, hepatitis B and C, and recurrent herpes zoster;
    d. History of unacceptably frequent recurrent infections;
    e. Active liver disease;
    f. Previous unsuccessful treatment with an anti-TNF agent.

Note: there is an inconsistency in the completed study. Trial authors reported two categories in the three arms: the original group and "on rescue therapy." (p. 988)

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Tocilizumab (Actemra®/RoActemra®)<br>b. Pharmaceutical laboratory: F Hoffmann-La Roche<br>c. Dose: 4 mg/kg, every 4 weeks until week 24.<br>d. Administration route: intravenous<br>2. Intervention<br>a. Tocilizumab (Actemra®/RoActemra®)<br>b. Pharmaceutical laboratory: F Hoffmann-La Roche<br>c. Dose: 8 mg/kg, every 4 weeks until week 24<br>d. Administration route: intravenous<br>3. Control<br>a. Placebo (composition not stated), every 4 weeks until week 24<br>b. Administration route: intravenous<br>4. Co-intervention:<br>a. Methotrexate, intraarticular corticosteroids |
| Outcomes | 1. Primary (baseline to week 24)<br>a. Proportion with a 20% improvement in rheumatoid arthritis signs and symptoms according to ACR criteria (ACR20 response)<br>2. Secondary (baseline through week 24)<br>a. Proportion with an ACR50 and ACR70 response<br>b. Change in disease activity score using 28 joint counts (DAS28), the proportion of participants in DAS28 remission (DAS28 < 2.6), and categorical DAS28 (European League Against Rheumatoid Arthritis [EULAR]) response<br>c. Haemoglobin concentrations<br>d. Patient's pain and patient's or physician's global assessment of disease activity<br>e. The Health Assessment Questionnaire-Disability Index (HAQ-DI)<br>f. Quality of life: Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue assessment<br>g. Adverse events |
| Notes | 1. Trial registration number: NCT00106548<br>2. Trial dates: February 2005-November 2006<br>3. A priori sample size estimation: yes |

**Smolen 2008** *(Continued)*

4. Financial disclosure: F Hoffmann-La Roche and Chugai Pharmaceutical supported the study.
5. Disclosure comment: Several authors stated they had worked as paid consultants and lecturers or had received research support from several privately owned companies in the health area, including the ones that funded this study. EA and TW are employees of Roche.
6. Ethical committee approved: yes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomisation was done centrally with an interactive voice response system, stratified by site... (p. 688). |
| Allocation concealment (selection bias) | Low risk | Quote: "Randomisation was done centrally with an interactive voice response system, stratified by site... (p. 688). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | The trial did not describe the process for blinding participants and personnel. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "Swollen and tender joint counts based on 66/68 joints were done by trained assessors who had no access to patient data. A physician blinded to patient's treatment made all treatment decisions on the basis of the patient's clinical response and safety data" (pp.s 988 and 999). |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Randomised: 623<br>a. Tocilizumab 4 mg/kg: 214<br>b. Tocilizumab 8 mg/kg: 205<br>c. Placebo: 204<br>2. Withdrawals:<br>a. Tocilizumab 4 mg/kg: 11.68% (25/214)<br>b. Tocilizumab 8 mg/kg: 6.34% (13/205)<br>c. Placebo: 5.88% (12/204)<br>d. Overall: 8.02% (50/623)<br>3. Main reason for withdrawing:<br>a. Adverse events in tocilizumab 4 mg/kg: 56% (14/25)<br>b. Adverse events in tocilizumab 8 mg/kg: 93.30% (12/13)<br>c. Adverse events in placebo: 50% (6/12)<br>4. Completed study:<br>a. Tocilizumab 4 mg/kg: 73.83% (158/214)<br>b. Tocilizumab 8 mg/kg: 84.39% (173/205)<br>c. Placebo: 60.78% (124/204)<br>d. Overall: 73% (455/623) |
| Selective reporting (reporting bias) | High risk | The trial reported no cardiovascular outcomes. |
| Other bias | High risk | the rescue therapy could lead to bias. The study was funded by F Hoffmann-La Roche and Chugai Pharmaceutical. Several authors had financial ties to these companies, including employment and receiving payments for various services, potentially creating conflicts of interest. |

**Stanley 2011**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 3 years<br>4. Follow-up period: 6 months<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: not<br>8. Multicentre (number of centres): no<br>9. Country: United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: metabolic syndrome<br>2. Diagnosis criteria: modified World Health Organization (WHO) criteria for metabolic syndrome<br>3. Severity: not stated<br>4. Total randomised: 40 participants<br>a. Etanercept: 16<br>b. Placebo: 24<br>5. Number lost to follow-up/withdrawn (%): 6 (15)<br>a. Etanercept: 4 (25)<br>b. Placebo: 2 (8.3)<br>6. Total analysed: 34<br>a. Etanercept: 12<br>b. Placebo: 22<br>7. Age, years, mean (SE)[a]<br>a. Etanercept: 41 (2)<br>b. Placebo: 47 (2)<br>8. Gender, male% (males/total)[a]<br>a. Etanercept: 50 (8/16)<br>b. Placebo: 50 (12/24)<br>9. C-reactive protein basal level, mg/L, mean (SE)[a]<br>a. Etanercept: 6.8 (1.7)<br>b. Placebo: 6.0 (1.2)<br>10. Inclusion criteria:<br>a. Ages 18–60 years;<br>b. Sex: all;<br>c. Body mass index (BMI) > 30 kg/m$^2$;<br>d. Metabolic syndrome, defined using modified World Health Organization criteria (either fasting insulin ≥ 10 µU/mL or fasting glucose 110–125 mg/dL and at least one of the following: systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, triglyceride > 150 mg/dL, or high-density lipoprotein < 35 mg/dL for males or < 39 mg/dL for females)<br>11. Exclusion criteria:<br>a. Haemoglobin less than 11 g/dL;<br>b. Creatinine higher than 1.5 mg/dL;<br>c. Serious chronic or recurrent infectious disease, diabetes mellitus, inflammatory or autoimmune conditions, known cardiovascular disease, immunosuppressant use, statin use, history of malignancy or demyelinating disorder;<br>d. Pregnancy;<br>e. Initiation of niacin, antihypertensives, or fibrates within 6 weeks before baseline. |

**Stanley 2011** *(Continued)*

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 50 mg, twice per week for 3 months, followed by 50 mg once per week for three months<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated), twice per week for 3 months, followed by once per week for 3 months<br>b. Administration route: subcutaneous<br>3. Co-intervention: none |
| Outcomes | 1. Primary (baseline, months 3 and 6)<br>a. C-reactive Protein (CRP)<br>b. Interleukin-6 (IL-6)<br>c. Adiponectin<br>2. Secondary (baseline, months 3 and 6)<br>a. Glucose Tolerance<br>b. Endothelial function: Reactive Hyperaemia Index (RHI) using peripheral artery tonometry<br>c. White Blood Cell (WBC) count<br>d. Cardiac Echo Ejection Fraction (EF)<br>e. Body composition<br>f. Tumour Necrosis Factor (TNF) receptor<br>g. Other adipocytokines<br>h. Lipid levels<br>i. Adipocyte Messenger Ribonucleic Acid (mRNA) Levels of adipocytokines, including Tumour Necrosis Factor (TNF)-Alpha<br>j. TNF-α<br>k. sICAM-1<br>l. Vascular cell adhesion molecule-1 (VCAM-1) |
| Notes | 1. Trial registration number: NCT00413400*<br>2. Trial dates: December 2006-September 2009<br>3. A priori sample size estimation: not stated<br>4. Financial disclosure: "S.K.G. received funding from Amgen in the form of an investigator-initiated research grant. Funding was also provided by the National Institutes of Health (NIH) M01-RR-01066 and 1 UL1 RR025758-01, Harvard Clinical and Translational Science Center, from the National Center for Research Resources. NIH funding was also provided through F32 DK080642-02 and K23 DK089910-01 to T.L.S., K24 DK064545-06 to S.G., PO1-DK049210 to R.S.A., and F32 DK085969-01 to M.V.Z. Funding to S.J. was provided by The Danish Agency for Science, Technology, and Innovation."<br>5. Disclosure comment: "T.L.S., M.V.Z., S.R., H.M., H.L., V.K.K., and R.S.A. have nothing to disclose".<br>6. Ethical committee approved: yes<br><br>*Not stated in the publication, retrieved by the authors of this review |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "This was a randomized, ...." (p. E147).<br>Comment: insufficient information to judge "high" or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Comment: insufficient information to judge "high" or "low" risk of bias |

**Stanley 2011** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "This was a (...) placebo-controlled, double-blind, 6-month intervention" (p. E147).<br>Comment: insufficient information to judge "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Endpoints objective |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 40<br>a. Etanercept (50 mg): 16<br>b. Placebo: 24<br>2. Withdrawal: 15% (6/40)<br>a. Etanercept (50 mg): 25% (4/16)<br>b. Placebo: 8.33% (2/24)<br>3. One participant withdrew: not reported from which group<br>4. Completed study: 85% (34/40).<br><br>Trial authors did not report a flowchart as recommended by PRISMA. |
| Selective reporting (reporting bias) | High risk | No reporting about major cardiovascular outcomes and adverse events |
| Other bias | High risk | There is an inconsistency between the loss before three months and those randomised (See Results first paragraph).<br>Design bias: lack of a prior sample size estimation |

**Torii 2010**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 78 weeks<br>4. Follow-up period: 14 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (28)<br>9. Country: Japan<br>10.Study setting: outpatient<br>11.Type trial: not stated<br>12.Type of prevention: primary |
| Participants | 1. Type of disease: plaque psoriasis and psoriatic arthritis<br>2. Diagnosis criteria: a PASI score ≥ 12 and involvement of at least 10% of BSA<br>3. Severity: moderate-to-severe<br>4. Total randomised: 54 participants<br>a. Infliximab: 35<br>b. Placebo: 19<br>5. Number lost to follow-up/withdrawn (%): 7 (12.9)*<br>a. Infliximab: 3 (8.57)<br>b. Placebo: 4 (21.05) |

**Torii 2010** *(Continued)*

6. Total analysed
   a. Infliximab: varies with each outcome
   b. Placebo: varies with each outcome
7. Age, years, mean (SD)
   a. Infliximab: 46.9 (13)
   b. Placebo: 43.3 (12.3)
8. Gender, male% (males/total)
   a. Infliximab: 62.9 (22/35)
   b. Placebo: 73.7 (14/19)
9. C-reactive protein basal level: not stated
10. Inclusion criteria:
    a. Age: 18 years and over;
    b. Sex: all;
    c. Moderate-to-severe plaque psoriasis for 6 months;
    d. PASI score ≥ 12 and involvement of at least 10% of BSA;
    e. Psoriatic arthritis;
    f. Need for systematic therapy or phototherapy with plaque psoriasis.
11. Exclusion criteria:
    a. History or risk of serious infection, lymphoproliferative disease, or active tuberculosis;
    b. Use of systemic therapies was prohibited, including DMARDs (methotrexate, leflunomide, salazosulfapyridine, etc.), immunosuppressive agents (cyclosporine, tacrolimus), etretinate, and corticosteroids (oral/ injection), as well as topical therapies comprising corticosteroids (except mild or weak corticosteroids to the head, face, and inguinal regions) and active vitamin D3 derivatives, and phototherapy.

*Data from the first 14 weeks of the study, labelled as the "induction phase"

| | |
|---|---|
| Interventions | 1. Intervention*<br>a. Infliximab (Remicade®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 5 mg/kg at weeks 0, 2 and 6<br>d. Administration route: intravenous<br>2. Control*<br>a. Placebo (composition not stated) at weeks 0, 2 and 6<br>b. Administration route: intravenous<br>3. Co-intervention: low-potency corticosteroids<br><br>*Data from the first 14 weeks of the study, labelled as the "induction phase." After week 14, all participants received infliximab. |
| Outcomes | 1. Primary (baseline to week 10)<br>a. Proportion achieving PASI75<br>2. Secondary (baseline through week 78)<br>a. PASI 50, 75 and 90<br>b. Physician's Global Assessment<br>c. Nail Psoriasis Severity Index (NAPSI) change,<br>d. Dermatology Life Quality Index (DLQI)<br>e. Patient's pain assessment<br>f. Adverse events |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: not stated<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: not stated<br>5. Disclosure comment: not stated |

**Torii 2010** *(Continued)*

6. Ethical committee approved: yes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Eligible patients were randomized in a 2:1 ratio to either the infliximab or placebo group using the dynamic allocation method." (p. 42).<br><br>Comment: Insufficient information to judge as "high" or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Comment: insufficient information to judge as "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "...induction phase of the treatment (...) double-blind, placebo-controlled trial..." (p. 42).<br>Comment: insufficient information to judge as "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Randomised: 54<br>Infliximab (5 mg): 64.81% (35/54)<br>Placebo: 35/18% (19/54)<br><br>Withdrawals: 12.96% (7/54)<br>Infliximab (5 mg): 8.57% (3/35)<br>Placebo: 21.05% (4/19)<br><br>Main reasons for withdrawing:<br>Lack of therapeutic efficacy (2) and adverse events (1) in infliximab (5 mg)<br>Adverse events (1) and withdrew consent (3) in the placebo group.<br><br>These data belong before all placebo group participants received infliximab (14-week induction phase). This trial was not a crossover-design trial. |
| Selective reporting (reporting bias) | High risk | No reporting of major cardiovascular events |
| Other bias | Low risk | No other bias identified |

**Tyring 2006**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 2 years<br>4. Follow-up period: 96 weeks*<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (39)<br>9. Country: Canada and the United States |

**Tyring 2006** *(Continued)*

10. Study setting: outpatient
11. Type trial: not stated
12. Type of prevention: primary

*Data from the study's-double-blinded period (first 12 weeks), as per protocol

| | |
|---|---|
| Participants | 1. Type of disease: plaque psoriasis<br>2. Diagnosis criteria: PASI ≥ 10<br>3. Severity: moderate-to-severe<br>4. Total randomised: 620 participants<br>a. Etanercept: 311<br>b. Placebo: 309<br>5. Number lost to follow-up/withdrawn (%): 23 (3.71)*<br>a. Etanercept: 6 (1.92)<br>b. Placebo: 17 (5.50)<br>6. Total analysed*: 618<br>a. Etanercept: 312<br>b. Placebo: 306<br>7. Age, years, mean (SD)<br>a. Etanercept: 45.8 (12.8)<br>b. Placebo: 45.6 (12.1)<br>8. Gender, male% (males/total)<br>a. Etanercept: 65.3 (203/311)<br>b. Placebo: 70.4 (216/307)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. Age: 18 years or older;<br>b. Sex: all;<br>c. Active, clinically stable plaque psoriasis involving 10% or more of total body surface area;<br>d. PASI ≥ 10;<br>e. Received at least one previous phototherapy or systemic therapy (or have been a candidate to do so);<br>f. Adequate haematological, renal, and hepatic function.<br>11. Exclusion criteria:<br>a. History of psychiatric disease that would interfere with study participation or the ability to give informed consent;<br>b. Skin conditions other than psoriasis that would interfere with study evaluations;<br>c. Active guttate, erythrodermic, or pustular psoriasis;<br>d. Received systemic psoriasis therapy or psoralen ultraviolet A phototherapy for 4 weeks before the study; topical corticosteroids, vitamin A or D analogue preparations, dithranol, or ultraviolet B phototherapy for 2 weeks before the study; or etanercept or an anti-TNFα antibody at any time.<br>*Data from the study's-double-blinded period (first 12 weeks), as per protocol |
| Interventions | 1. Intervention*<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Immunex-Wyeth, Boehringer Ingelheim (Biberach, Germany)<br>c. Dose: 50 mg, twice-weekly for 12 weeks<br>d. Administration route: subcutaneous<br>2. Control*<br>a. Placebo (composition not stated), twice-weekly for 12 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: low-potency topical corticosteroids<br>*Data from the study's-double-blinded period (first 12 weeks), as per protocol |

**Tyring 2006** *(Continued)*

| | |
|---|---|
| Outcomes | 1. Primary (baseline to week 12)<br>a. Proportion achieving at least PASI 75<br>2. Secondary (baseline, week 12, and long-term therapy)<br>a. Dermatology Live Quality Index (DLQI)<br>b. Subject's assessment of itching and joint pain (visual analogue scale [VAS])<br>c. Psoriasis pain (VAS)<br>d. Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale<br>e. PASI 50, 75 and 90 response<br>f. Static physician's global assessment of psoriasis (sPGA)<br>g. Adverse events<br>h. Clinical laboratory values, vital signs and antibodies to etanercept |
| Notes | 1. Trial registration number: NCT00111449<br>2. Trial dates: June 2003-January 2004<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Amgen funded the study in collaboration with Wyeth (now a wholly-owned subsidiary of Pfizer).<br>5. Disclosure comment: several authors declared having worked as paid consultants, advisors, or speakers or have received funds for research from several private companies in the health area, including the one that sponsored this trial. R Zitnik, M Woolley, A Jahreis, and A Wang are employees of Amgen.<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "randomly assigned in a 1:1 ratio (using an interactive voice response system) to receive either placebo or etanercept ..." (p. 30) |
| Allocation concealment (selection bias) | Low risk | Quote: "randomly assigned in a 1:1 ratio (using an interactive voice response system) to receive either placebo or etanercept ..." (p. 30). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "To maintain the treatment blind, all patients received two injections per dose of investigational product. Injections were done either by the patient or by a trained caregiver" (p. 30). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Randomised: 620<br>a. Etanercept: 311<br>b. Placebo: 309<br>2. Withdrawals:<br>a. Etanercept: 1.92% (6/311)<br>b. Placebo: 5.50% (17/309)<br>c. Overall: 3.71% (23/620)<br>3. Reasons for withdrawing:<br>a. Adverse events (4) in etanercept: 66.66% (4/6)<br>b. Withdrew consent (5), adverse events (3), disease progression (4), and loss to follow-up (4) in placebo: 94.11% (16/17)<br>4. Completed study:<br>a. Etanercept: 98.08% (305/311)<br>b. Placebo: 94.5% (292/309) |

**Tyring 2006** *(Continued)*

| | | |
|---|---|---|
| | | c. Overall: 96.29% (597/620) |
| Selective reporting (reporting bias) | High risk | The trial reported no cardiovascular outcomes. |
| Other bias | High risk | Amgen and Wyeth (Pfizer) funded the study; several authors had financial ties to these companies, including employment, potentially creating conflicts of interest. |

**Van de Kerkhof 2008**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 1 year<br>4. Follow-up period: 24 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (not stated)<br>9. Country: Belgium, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, and Spain<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: primary |
| Participants | 1. Type of disease: plaque psoriasis<br>2. Diagnosis criteria: ≥ 10% of the body surface area (BSA) affected and a minimum PASI score of 10<br>3. Severity: moderate-to-severe<br>4. Total randomised: 143 participants<br>a. Etanercept: 96<br>b. Placebo: 46<br>c. Other: 1‡<br>5. Number lost to follow-up/withdrawn (%): 17 (11.88)*<br>a. Etanercept: 6 (6.25)<br>b. Placebo: 10 (21.74)<br>c. Other: 1‡<br>6. Total analysed: 142*<br>a. Etanercept: 96<br>b. Placebo: 46<br>7. Age, years, mean (SD)<br>a. Etanercept: 45.9 (12.8)<br>b. Placebo: 43.6 (12.6)<br>8. Gender, male% (males/total)<br>a. Etanercept: 61.5 (59/96)<br>b. Placebo: 54.4 (25/46)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. Age: 18 years and over;<br>b. Sex: all;<br>c. Clinically stable plaque psoriasis involving at least 10% of BSA, and a PASI score of at least 10; |

**Van de Kerkhof 2008** *(Continued)*

d. Failed to respond to, had a contraindication for, or were intolerant of at least one systemic or phototherapy at an adequate dose of sufficient duration.

11. Exclusion criteria:
    a. Active guttate, erythrodermic, or pustular psoriasis;
    b. Other active skin conditions that would interfere with study evaluations;
    c. Serious infection within 1 month of study screening;
    d. Body mass index (BMI) greater than 38 kg/m$^2$;
    e. Have received etanercept, an antibody to TNF, or other TNF inhibitors at any time; alefacept, efalizumab, anti-CD4 agents, or diphtheria interleukin-2 fusion protein within the previous 6 months; ultraviolet A or B phototherapy, psoralen and ultraviolet A phototherapy, systemic psoriasis therapy (methotrexate, cyclosporin, acitretin, or fumarates), or oral or parenteral corticosteroids within the previous month; or topical corticosteroids in high strengths, topical vitamin A or D analogue preparations, dithranol, or topical calcineurin inhibitors (pimecrolimus or tacrolimus) within the previous 2 weeks;
    f. Use of topical corticosteroids of low-to-moderate strength on the scalp, axillae, and groin was permitted.

*Data from the first phase (12 weeks) of the study, as per protocol

‡: One participant was randomly assigned (arm not stated) but withdrew consent before the dose was started

| | |
|---|---|
| Interventions | 1. Intervention*<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Amgen/Wyeth<br>c. Dose: 50 mg, weekly for 12 weeks<br>d. Administration route: subcutaneous<br>2. Control*<br>a. Placebo (composition not stated), weekly for 12 weeks<br>b. Administration route: subcutaneous<br><br>*Data from the first phase (12 weeks) of the study |
| Outcomes | 1. Primary (baseline to week 12)<br>a. Proportion achieving PASI 75<br>2. Secondary (baseline, weeks 2, 4, 8, 12, 16, 20, 24)<br>a. PASI 50, 75, 90 and 100<br>b. Physician's and Patient's Global Assessment<br>c. DLQI<br>d. Adverse events<br>e. Etanercept pharmacokinetics |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: June 2006-May 2007<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Wyeth Pharmaceuticals (Collegeville, Pennsylvania, U.S.A) supported the study.<br>5. Disclosure comment: C.Z., M.P.B., L.P., and J.W. are employees of Wyeth Pharmaceuticals.<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "patients were randomly assigned (using the Clinical Operations Randomization Environment system) ..." (p. 1178).<br>Comment: insufficient information to judge as "high" or "low" risk of bias |

**Van de Kerkhof 2008** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Quote: "patients were randomly assigned (using the Clinical Operations Randomization Environment system) ..." (p. 1178).<br>Comment: insufficient information to judge as "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "...double-blind, placebo-controlled study... " (p. 1178).<br>Comment: insufficient information to judge as "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 143<br>a. Etanercept: 96<br>b. Placebo: 46<br>2. Withdrawal<br>a. Etanercept: 6.25% (6/96)<br>b. Placebo: 21.74% (10/46)<br>c. Imbalance: 15.48%<br>d. Overall: 11.18% (16/143).<br>3. Main reasons for withdrawing:<br>a. Adverse events (3) and lack of efficacy (2) in etanercept: 83.33% (5/6)<br>b. Adverse events (3) and lack of efficacy (4) in placebo: 70% (7/10)<br>4. Completed study (At 12 weeks)<br>a. Etanercept: 93.75% (90/96)<br>b. Placebo: 78.26% (36/46)<br>c. Overall: 88.11% (126/143) |
| Selective reporting (reporting bias) | High risk | The trial reported no cardiovascular outcomes. |
| Other bias | High risk | Wyeth Pharmaceuticals funded the study; C.Z., M.P.B., L.P., and J.W. are Wyeth employees, potentially creating conflicts of interest. |

**Van der Heijde 2006**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 3 arms<br>3. Duration: 12 weeks<br>4. Follow-up period: 12 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: yes<br>8. Multicentre (number of centres): yes (38)<br>9. Country: Belgium, France, Germany, Greece, Hungary, the Netherlands, Poland, Portugal, Spain, and the United Kingdom<br>10. Study setting: outpatient<br>11. Type trial: non-inferiority<br>12. Type of prevention: primary |

**Van der Heijde 2006** *(Continued)*

| | |
|---|---|
| Participants | 1. Type of disease: ankylosing spondylitis<br>2. Diagnosis criteria: modified New York criteria for ankylosing spondylitis<br>3. Severity: not stated<br>4. Total randomised: 356 participants<br>a. Etanercept (50 mg once weekly): 155<br>b. Etanercept (25 mg twice-weekly): 150<br>c. Placebo: 51<br>5. Number lost to follow-up/withdrawn (%): 35 (9.8)<br>a. Etanercept (50 mg once weekly): 14 (9)<br>b. Etanercept (25 mg twice-weekly): 14 (9.3)<br>c. Placebo: 7 (13.7)<br>6. Total analysed: 356<br>a. Etanercept (50 mg once weekly): 155<br>b. Etanercept (25 mg twice-weekly): 150<br>c. Placebo: 51<br>7. Age, years, mean (SD)<br>a. Etanercept (50 mg once weekly): 41.5 (11)<br>b. Etanercept (25 mg twice-weekly): 39.8 (10.7)<br>c. Placebo: 40.1 (10.9)<br>8. Gender, male% (males/total)<br>a. Etanercept (50 mg once weekly): 69.7 (108/155)<br>b. Etanercept (25 mg twice-weekly): 76 (114/150)<br>c. Placebo: 78.4 (40/51)<br>9. C-reactive protein basal level, mg/L, mean (SD)<br>a. Etanercept (50 mg once weekly): 21.7 (24.6)<br>b. Etanercept (25 mg twice-weekly): 19.8 (20.8)<br>c. Placebo: 22 (22.9)<br>10. Inclusion criteria:<br>a. Age: 18-70 years old;<br>b. Sex: all;<br>c. Diagnosis of ankylosing spondylitis according to modified New York criteria;<br>d. Active disease;<br>e. Concomitant oral NSAIDs and oral corticosteroids ((10 mg/day), if stable for >;2 weeks before randomisation, and DMARDs (hydroxychloroquine, sulfasalazine, and methotrexate), if stable for >;4 weeks before randomisation, were permitted.<br>11. Exclusion criteria:<br>a. Previous treatment with TNFα inhibitors, other biological agents, or other DMARDs besides the permitted ones in the 4 weeks before enrolment;<br>b. Complete ankylosis of the spine;<br>c. Concurrent medical events such as uncontrolled hypertension, unstable angina pectoris, congestive heart failure, severe pulmonary disease, cancer, demyelinating diseases of the central nervous system, and serious infections. |
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Wyeth Pharmaceuticals (Collegeville, Pennsylvania, USA)<br>c. Dose: 50 mg once weekly for 12 weeks<br>d. Administration route: not stated<br>2. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Wyeth Pharmaceuticals (Collegeville, Pennsylvania, USA)<br>c. Dose: 25 mg twice-weekly for 12 weeks<br>d. Administration route: not stated |

**Van der Heijde 2006** *(Continued)*

3. Control
   a. Placebo, composition, and intervals were not stated.
   b. Administration route: not stated
4. Co-intervention: standard of care for the condition

| | |
|---|---|
| Outcomes | 1. Primary (baseline to week 12)<br>a. Proportion achieving ASAS 20 response<br>2. Secondary (baseline to week 12)<br>a. Proportion achieving ASAS 40 response and ASAS 5/6 criteria<br>b. Patient's global assessment<br>c. Physician's global assessment<br>d. Back pain<br>e. Bath Ankylosing Spondylitis Disease Activities Index (BASDAI)<br>f. Partial remission<br>g. Time to partial remission<br>h. Spinal mobility<br>i. Joint assessment<br>j. CRP<br>k. Etanercept pharmacokinetics<br>l. Adverse events |
| Notes | 1. Trial registration number: not stated<br>2. Trial dates: not stated<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Wyeth Pharmaceutical (Collegeville, Pennsylvania, USA) supported the study.<br>5. Disclosure comment: several authors claimed they had received honoraria from several privately owned companies in the healthcare field, including the one that supported the study. Also, several authors worked for Wyeth Research.<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "The trial was a 12-week, randomised..." (p. 1572)<br>Insufficient information to judge a "high" or "low" as risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to judge a "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "double-blind, placebo controlled..." (p. 1572)<br>Insufficient information to judge a "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge a "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Total sample 356<br>2. Total withdrawals: 9.83% (35/356)<br>a. Etanercept: 9.18% (28/ 305). Fourteen people due to adverse events, seven for protocol violation, and five for lack of efficacy<br>b. Placebo: 13.72% (7/51). One for protocol violation and three for lack of efficacy |

**Van der Heijde 2006** *(Continued)*

| | | |
|---|---|---|
| | | 3. Imbalance: 4.54% |
| Selective reporting (reporting bias) | High risk | Lack of information about many clinical outcomes predefined in this Cochrane review |
| Other bias | High risk | Financial conflict of interest: Most authors have financial connections or interests with the company that makes the drug used in the study and who provided the funding for the trial. |

**Van Tassell 2016**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 1 year<br>4. Follow-up period: 14 days<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): no<br>9. Country: United States<br>10. Study setting: inpatient and outpatient<br>11. Type trial: not stated<br>12. Type of prevention: secondary |
| Participants | 1. Type of disease: heart failure<br>2. Diagnosis criteria: impaired left ventricular systolic function (ejection fraction < 40%)<br>3. Severity: moderate-to-severe<br>4. Total randomised: 30 participants<br>a. Anakinra: 15<br>b. Placebo: 15<br>5. Number lost to follow-up/withdrawn (%): 13 (43.33)<br>a. Anakinra: 6 (40)<br>b. Placebo: 7 (46.66)<br>6. Total analysed<br>a. Anakinra: varies with the outcome<br>b. Placebo: varies with the outcome<br>7. Age, years, mean (IQR)<br>a. Anakinra: 60 (49, 64)<br>b. Placebo: 54 (49, 66)<br>8. Gender, male% (males/total)<br>a. Anakinra: 67 (10/15)<br>b. Placebo: 80 (12/15)<br>9. C-reactive protein basal level, mg/L, mean (IQR)<br>a. Anakinra: 22.3 (10.8, 95.9)<br>b. Placebo: 27.4 (12.0, 47.2)<br>10. Inclusion criteria: All 5 criteria need to be met for enrolment.<br>a. Primary diagnosis of acute decompensated heart failure within the last 24 hours as evidenced by both of the following:<br>i. Dyspnoea or respiratory distress or tachypnoea at rest or with minimal exertion<br>ii. Evidence of elevated cardiac filling pressure or pulmonary congestion; |

**Van Tassell 2016** *(Continued)*

b. Left ventricular systolic dysfunction (LVEF < 40%) during the index hospitalisation or prior 12 months;
c. Age ≥ 18 years old;
d. Willing and able to provide written informed consent;
e. Screening plasma C-reactive protein levels > 5 mg/L.

11. Exclusion criteria:
a. The primary diagnosis for admission is NOT decompensated heart failure;
b. Concomitant clinically significant comorbidities that would interfere with the execution or interpretation of the study;
c. Recent (previous 3 months) or planned cardiac resynchronisation therapy (CRT), coronary artery revascularisation procedures, or heart valve surgeries;
d. Previous or planned implantation of left ventricular assist devices or heart transplant;
e. Chronic use of intravenous inotropes;
f. Recent (< 14 days) use of immunosuppressive or anti-inflammatory drugs (not including nonsteroidal anti-inflammatory drugs [NSAIDs]);
g. Chronic inflammatory disorder;
h. Active infection (of any type);
i. Chronic/recurrent infectious diseases (including hepatitis B virus [HBV], hepatitis C virus [HCV], and HIV/AIDS);
j. Prior (within the past 10 years) or current malignancy;
k. Any comorbidity limiting survival or ability to complete the study;
l. End-stage kidney disease requiring renal replacement therapy;
m. Neutropenia (< 2000/mm$^3$) or thrombocytopenia (< 50,000/mm$^3$);
n. Pregnancy;
o. Angina, arrhythmias, or electrocardiograph (ECG) changes that limit maximum exertion during cardiopulmonary exercise testing.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Anakinra (Kineret®)<br>b. Pharmaceutical laboratory: Swedish Orphan Biovitrum<br>c. Dose: 100 mg twice daily for the first 3 days, followed by 100 mg daily for days 4-14<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated) twice daily for the first 3 days, followed by once daily for days 4-14<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to 72 hours)<br>a. Area under the curve for hsCRP<br>2. Secondary (baseline to day 14)<br>a. Biomarkers: CRP, IL-6, NTproBNP, hsTnI, IL-17A, MPO, Lp-PLA2, galectin-3, leptin, adiponectin, ferritin, complete blood count.<br>b. LVEF<br>c. Clinical markers of congestion<br>d. Adverse events |
| Notes | 1. Trial registration number: NCT01936844<br>2. Trial dates: January 2014-May 2015<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: funded by an American Heart Association Beginning Grant-in-Aid to Dr. Van Tassell and the grant UL1TR000058 from the National Institutes of Health's National Center for Advancing Translational Science<br>5. Disclosure comment: not stated |

**Van Tassell 2016** *(Continued)*

6. Ethical committee approved: yes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "We designed a randomized, (...) pilot study" (p. 545).<br>Comment: insufficient information to judge as "high" or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Comment: insufficient information to judge as "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: We designed a (...) double-blinded, placebo-controlled pilot study (p. 545).<br>Comment: insufficient information to judge as "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Objective endpoints |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised 30<br>a. Anakinra: 15<br>b. Placebo: 15<br>2. Total withdrawal: 43% (13/30)<br>a. Anakinra: 40% (6/15)<br>b. Placebo: 46.66% (7/15)<br>3. Clinical visit: 56.66% (17/30)<br>a. Anakinra: 60% (9/15)<br>b. Placebo: 53.33% (8/15) |
| Selective reporting (reporting bias) | Low risk | Trial reported only information about death, heart failure and and adverse events. |
| Other bias | Low risk | No other bias identified |

**Van Tassell 2017**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 3 arms<br>3. Duration: 2 years<br>4. Follow-up period: 24 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): no<br>9. Country: United States<br>10.Study setting: inpatient and outpatient<br>11.Type trial: not stated<br>12.Type of prevention: secondary |
| Participants | 1. Type of disease: heart failure |

**Van Tassell 2017** *(Continued)*

2. Diagnosis criteria: impaired left ventricular systolic function (ejection fraction < 50%)
3. Severity: not stated
4. Total randomised: 60 participants
   a. Anakinra 2 weeks: 20
   b. Anakinra 12 weeks: 20
   c. Placebo: 20
5. Number lost to follow-up/withdrawn (%): 8 (13.33)
   a. Anakinra 2 weeks: 4 (20)
   b. Anakinra 12 weeks: 2 (10)
   c. Placebo: 2 (10)
6. Total analysed: 52
   a. Anakinra 2 weeks: 16
   b. Anakinra 12 weeks: 18
   c. Placebo: 18
7. Age, years, median (IQR)
   a. Anakinra 2 weeks: 57 (53–66)
   b. Anakinra 12 weeks: 55 (49–61)
   c. Placebo: 61 (56–68)
8. Gender, male% (males/total)
   a. Anakinra 2 weeks: 75 (12/16)
   b. Anakinra 12 weeks: 72 (13/18)
   c. Placebo: 72 (13/18)
9. C-reactive protein basal level, mg/L, median (IQR)
   a. Anakinra 2 weeks: 7.2 (3.3–12.3)
   b. Anakinra 12 weeks: 5.2 (2.6–13.4)
   c. Placebo: 5.2 (2.0–11.9)
10. Inclusion criteria: All 6 criteria need to be met for enrolment.
    a. Primary diagnosis for hospitalisation is decompensated heart failure, established as the finding at admission of all 2 conditions listed below:
       i. Dyspnoea or respiratory distress or tachypnoea at rest or with minimal exertion;
       ii. Evidence of elevated cardiac filling pressure or pulmonary congestion (at least one of the conditions must be met);
    b. Prior documentation of impaired left ventricular systolic function (ejection fraction < 50%) at the most recent assessment by any imaging modality (within 12 months);
    c. Clinically stable and meets standard criteria for hospital discharge;
    d. Age ≥ 21 years old and is willing and able to provide written informed consent;
    e. Willing and able to comply with the protocol (i.e. self-administration of the treatment and exercise protocol);
    f. Plasma C-reactive protein levels > 2 mg/L.
11. Exclusion criteria:
    a. The primary diagnosis for admission is NOT decompensated heart failure;
    b. Concomitant clinically significant comorbidities that would interfere with the execution or interpretation of the study;
    c. Recent (previous 3 months) or planned cardiac resynchronisation therapy (CRT), coronary artery revascularisation procedures, or heart valve surgeries;
    d. Previous or planned implantation of left ventricular assist devices or heart transplant;
    e. Chronic use of intravenous inotropes;
    f. Recent (< 14 days) use of immunosuppressive or anti-inflammatory drugs (not including nonsteroidal anti-inflammatory drugs [NSAIDs]).

Complete inclusion and exclusion criteria available at Van Tassell 2017

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Anakinra (Kineret®)<br>b. Pharmaceutical laboratory: Swedish Orphan Biovitrum (SOBI, Stockholm, Sweden) |

**Van Tassell 2017** *(Continued)*

| | |
|---|---|
| | c. Dose: 100 mg, once daily for 2 weeks, followed by 9 weeks of placebo<br>d. Administration route: subcutaneous<br>2. Intervention<br>a. Anakinra (Kineret®)<br>b. Pharmaceutical laboratory: Swedish Orphan Biovitrum (SOBI, Stockholm, Sweden)<br>c. Dose: 100 mg, once daily for 12 weeks<br>d. Administration route: subcutaneous<br>3. Control<br>a. Placebo ("vehicle" p. 2), once daily for 12 weeks<br>b. Administration route: subcutaneous<br>4. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to week 2)<br>a. Change in peak $Vo_2$ or the VE/$Vco_2$ slope<br>2. Secondary (baseline, weeks 4, 12 and 24)<br>a. Change in peak $Vo_2$ or the VE/$Vco_2$ slope<br>b. Structural and functional parameters at Doppler echocardiography<br>c. Quality-of-life assessment: the MLWHF and the DASI<br>d. Biomarkers<br>e. Clinical outcomes: death (cardiac and noncardiac) and rehospitalisation for HF or for other causes |
| Notes | 1. Trial registration number: NCT01936909<br>2. Trial dates: January 2014-March 2016<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: "Funded by the National Heart, Lung, and Blood Institute (1R34HL117026) to Dr Abbate and Dr Van Tassell, and a Clinical and Translational Science Award to Virginia Commonwealth University (UL1TR000058 from the National Center for Research Resources) to Dr Moeller."<br>5. Disclosure comment: "None"<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "An independent investigator (G.B.-Z.) created a randomization sheet that was then provided to the Investigational Pharmacy in Richmond, Virginia" (p. 2). |
| Allocation concealment (selection bias) | Low risk | Quote: "To further ensure concealment of group allocation, the investigators were blinded to all CRP levels throughout the study other than the screening level" (p. 2). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Anakinra or placebo (vehicle) were provided (...) in 0.67 mL syringes identifiable by lot number but otherwise indistinguishable" (p. 2). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "A dedicated committee adjudicated all clinical events" (p. 3) |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Randomised: 60<br>a. Anakinra (100 mg daily for 2 weeks): 20<br>b. Anakinra (100 mg daily for 12 weeks): 20<br>c. Placebo (12 weeks): 20 |

**Van Tassell 2017** *(Continued)*

| | | |
|---|---|---|
| | | 2. Withdrawals: 13.33% (8/60)<br>a. Anakinra (100 mg daily for two weeks): 20% (4/20)<br>b. Anakinra (100 mg daily for 12 weeks): 10% (2/20)<br>c. Placebo (12 weeks): 10% (2/20)<br>3. Reason for withdrawing:<br>a. Consent withdrew (2) unable to complete CPX (2) in anakinra (two weeks).<br>b. Consent withdrew (2) in anakinra (12 weeks).<br>c. Consent withdrew (2) in the placebo<br>4. Event adjudication:<br>a. Anakinra (100 mg daily for two weeks): 80% (16/20)<br>b. Anakinra (100 mg daily for 12 weeks): 90% (18/20)<br>c. Placebo (12 weeks): 90% (18/20) |
| Selective reporting (reporting bias) | Low risk | The trial reported all information about predefined outcomes in this Cochrane review. |
| Other bias | Low risk | No other bias identified |

**Van Tassell 2018**

| ***Study characteristics*** | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 3 years<br>4. Follow-up period: 24 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): no<br>9. Country: United States<br>10. Study setting: outpatient<br>11. Type trial: not stated<br>12. Type of prevention: secondary |
| Participants | 1. Type of disease: heart failure with preserved ejection fraction<br>2. Diagnosis criteria: diagnosis criteria from the European Society of Cardiology 2007<br>3. Severity: not stated<br>4. Total randomised: 31 participants<br>a. Anakinra: 21<br>b. Placebo: 10<br>5. Number lost to follow-up/withdrawn (%): 3 (9.67)<br>a. Anakinra: 1 (4.76)<br>b. Placebo: 2 (20)<br>6. Total analysed: 28<br>a. Anakinra: 20<br>b. Placebo: 8<br>7. Age, years, median (IQR)<br>a. Anakinra: 54 (45–61)<br>b. Placebo: 58 (51–64)<br>8. Gender, male% (males/total)<br>a. Anakinra: 35 (7/20) |

**Van Tassell 2018** *(Continued)*

b. Placebo: 37 (3/8)

9. C-reactive protein basal level, mg/L, median (IQR)
   a. Anakinra: 6.1 (3.9–18.4)
   b. Placebo: 7.6 (3.4–12.2)
10. Inclusion criteria:
   a. Age: 21 years and older;
   b. Symptoms and signs of heart failure (NYHA II-III) and prior hospitalisation for heart failure;
   c. Recent imaging study (< 12 months) showing LVEF < 50% and left ventricular end diastolic volume index (LVEDVI) < 97 mL/$m^2$;
   d. Evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness;
   e. CRP > 2.0 mg/L.
11. Exclusion criteria:
   a. Concomitant conditions or treatments which would affect the completion of the study or interpretation of the study tests;
   b. Angina, uncontrolled hypertension, or electrocardiograph (ECG) changes (i.e. ischaemia, arrhythmias) that limit maximum exertion during cardiopulmonary exercise testing;
   c. Anticipated need for cardiac resynchronisation therapy (CRT) or automated-implantable cardioverter defibrillator (AICD) or coronary revascularisation, or cardiac surgery;
   d. Active infection, including chronic infection;
   e. Active cancer (or prior diagnosis of cancer within the past 10 years);
   f. Recent (< 14 days) or active use of immunosuppressive drugs;
   g. Chronic autoimmune or auto-inflammatory disease;
   h. Neutropenia;
   i. Severe impairment in renal function;
   j. Recent or planned use of vaccination with live attenuated viruses;
   k. Allergy to rubber or latex;
   l. Allergy to products derived from *Escherichia coli;*
   m. Pregnancy or breastfeeding;
   n. Inability to give informed consent.

| | |
|---|---|
| Interventions | 1. Intervention<br>a. Anakinra (Kineret®)<br>b. Pharmaceutical laboratory: Swedish Orphan Biovitrum LLC (Stockholm, Sweden)<br>c. Dose: 100 mg. once daily for 12 weeks<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated), once daily for 12 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to week 12)<br>a. Placebo-corrected change in peak $Vo_2$ and VE/$Vco_2$ slope<br>2. Secondary (baseline, weeks 4, 12 and 24)<br>a. Interval changes in peak $Vo_2$ or the VE/$Vco_2$ slope<br>b. Structural and functional parameters at Doppler echocardiography<br>c. Quality of life<br>d. Biomarkers<br>e. Composite clinical outcomes of death and rehospitalisation for heart failure (or hospitalisation for any cause) |
| Notes | 1. Trial registration number: NCT02173548<br>2. Trial dates: August 2014-June 2017<br>3. A priori sample size estimation: yes |

**Van Tassell 2018** *(Continued)*

4. Financial disclosure: supported by a grant from the National Heart, Lung, and Blood Institute, no. R34HL118348 and a Clinical and Translational Science Award (UL1TR000058 from the National Center for Research Resources) to the Virginia Commonwealth University Center for Clinical and Translational Research
5. Disclosure comment: "Drs Abbate and Van Tassell have served as consultants and received grant support from Swedish Orphan Biovitrum."
6. Ethical committee approved: yes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The randomization log was prepared by an outside consultant and sent electronically to the director of the investigational pharmacy at Virginia Commonwealth University" (p. 628 Data Supplement). See additional reference to Van Tassell 2018. |
| Allocation concealment (selection bias) | Low risk | Quote: "The randomization log was prepared by an outside consultant and sent electronically to the director of the investigational pharmacy at Virginia Commonwealth University" (p. 628 Data Supplement). See additional reference to Van Tassell 2018. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Investigators were blinded to all CRP levels during the study. Identical anakinra or placebo syringes were dispensed by the investigational pharmacy" (p. 628 Data Supplement). See additional reference to Van Tassell 2018. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Objective endpoints |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | 1. Randomised: 31<br>a. Anakinra: 21<br>b. Placebo: 10<br>2. Total withdrawals:<br>a. Anakinra: 9.53% (2/21)<br>b. Placebo: 30% (3/10)<br>3. Imbalance: 20.47% |
| Selective reporting (reporting bias) | Low risk | The trial focused on heart failure, and reported adverse events. |
| Other bias | Low risk | No other bias identified |

**Villiger 2016**

***Study characteristics***

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 2 years<br>4. Follow-up period: 52 weeks<br>5. Run-in period: yes<br>6. Run-in period time: 10 days<br>7. International: no |

**Villiger 2016** *(Continued)*

8. Multicentre (number of centres): no
9. Country: Switzerland
10. Study setting: outpatient
11. Type trial: not stated
12. Type of prevention: primary

| | |
|---|---|
| Participants | 1. Type of disease: giant cell arteritis (GCA)<br>2. Diagnosis criteria: 1990 American College of Rheumatology criteria for giant cell arteritis<br>3. Severity: not stated<br>4. Total randomised: 30 participants<br>a. Tocilizumab: 20<br>b. Placebo: 10<br>5. Number lost to follow-up/withdrawn (%): 7 (23.3)<br>a. Tocilizumab: 2 (10)<br>b. Placebo: 5 (50)<br>6. Total analysed: 30<br>a. Tocilizumab: 20<br>b. Placebo: 10<br>7. Age, years, mean (SD)<br>a. Tocilizumab: 71.3 (8.9)<br>b. Placebo: 68.8 (16.9)<br>8. Gender, male% (males/total)<br>a. Tocilizumab: 35 (7/20)<br>b. Placebo: 20 (2/10)<br>9. C-reactive protein basal level, mg/L, median (IQR)<br>a. Tocilizumab: 25.5 (16.8–50.3)<br>b. Placebo: 39 (23.5–64.3)<br>10. Inclusion criteria:<br>a. Newly onset or relapsed GCA who fulfilled the 1990 American College of Rheumatology criteria;<br>b. > 50 years of age;<br>c. Elevated ESR > 40 mm;<br>d. CRP > 20 mg/L;<br>e. Histologically proven GCA or with large vessel vasculitis assessed by MRI.<br>11. Exclusion criteria:<br>a. Uncontrolled concomitant health problems, active infection, or any disease requiring systemic glucocorticoid treatment;<br>b. Previous treatment with tocilizumab or any other biological agent;<br>c. Prednisolone up to 1 mg/kg bodyweight for a maximum of 10 days between inclusion in the trial and the first infusion was permitted. |
| Interventions | 1. Intervention<br>a. Tocilizumab (RoActemra®/Actemra®)<br>b. Pharmaceutical laboratory: Roche<br>c. Dose: 8 mg/kg every 4 weeks until week 52<br>d. Administration route: intravenous<br>2. Control<br>a. Placebo (composition not stated) every 4 weeks until week 52<br>b. Administration route: intravenous<br>3. Co-intervention:<br>a. Prednisolone: "started at 1 mg/kg per day and tapered weekly by 0.1 mg/kg per day until week 8, then weekly by 0.05 mg/kg, reaching 0.1 mg/kg by week 12. Thereafter, the dose was reduced every month by 1 mg per day to 0 mg." (p. 2-3)<br>b. Aspirin: 100 mg daily<br>c. Pantoprazole: 40 mg daily |

**Villiger 2016** *(Continued)*

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|---|---|
| | d. Calcium: 1000 mg daily<br>e. Cholecalciferol: 800 units daily<br>f. Ibandronate: 3 mg every three months |
| Outcomes | 1. Primary (baseline to week 12)<br>a. Number achieving complete remission of the disease<br>2. Secondary (baseline through week 52)<br>a. Relapse-free survival<br>b. Time to first relapse after remission<br>c. Cumulative dose of prednisolone |
| Notes | 1. Trial registration number: NCT01450137<br>2. Trial dates: March 2012-September 2014<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Roche and the University of Bern funded the study.<br>5. Disclosure comment: "We declare no competing interests." (p. 7)<br>6. Ethical committee approved: yes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Allocation to treatment groups was done using a central computerised randomisation procedure with a permuted block design and a block size of three, and concealed using central randomisation generated by the clinical trials unit" (p. 1921). |
| Allocation concealment (selection bias) | Low risk | Quote: "... and concealed using central randomisation generated by the clinical trials unit" (p. 1921).<br><br>Quote: "...we used subsequently opened sealed, opaque, sequentially numbered envelopes containing the allocation information..." (p. 1921). |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "The responsible senior statistician was not involved in study conduct or monitoring. Patients, investigators, and study personnel were masked to treatment assignments during the study; we used subsequently opened sealed, opaque, sequentially numbered envelopes containing the allocation information. The site oncology nurse who prepared the study drug was not masked to this information but had no contact with patients or health professionals involved in their care" (p. 1921). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to judge as "high" or "low" risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 1. Total sample: 30<br>a. Tocilizumab: 20<br>b. Placebo: 10<br>2. Total withdrawals: 23.33% (7/30)<br>a. Tocilizumab: 10% (2/20)<br>b. Placebo: 50% (5/10)<br>3. Imbalance: 40% |
| Selective reporting (reporting bias) | High risk | Lack of information about the predefined outcomes of this Cochrane review, with the exception of adverse events |

**Villiger 2016** *(Continued)*

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|---|---|---|
| Other bias | Low risk | No other bias identified |

**Weisman 2007**

***Study characteristics***

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|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 4 years<br>4. Follow-up period: 20 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (48)<br>9. Country: United States<br>10. Study setting: out of hospital<br>11. Type trial: not stated<br>12. Type of prevention: secondary$^{\mathbb{P}}$<br><br>$^{\mathbb{P}}$More than eighty per cent of the participants have at least one cardiovascular disease. |
| Participants | 1. Type of disease: rheumatoid arthritis<br>2. Diagnosis criteria: American College of Rheumatology criteria for RA<br>3. Severity: not stated<br>4. Total randomised: 564 participants<br>a. Etanercept: not stated<br>b. Placebo: not stated<br>5. Number lost to follow-up/withdrawn (%): 29 (5.14)<br>a. Etanercept: unclear<br>b. Placebo: unclear<br>6. Total analysed: 535<br>a. Etanercept: 266<br>b. Placebo: 269<br>7. Age, years, mean (min-max)<br>a. Etanercept: 60.6 (19–84)<br>b. Placebo: 59.3 (23–85)<br>8. Gender, male% (males/total)<br>a. Etanercept: 27.8 (74/266)<br>b. Placebo: 21.9 (59/269)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. 18 years of age and older;<br>b. Meet the American College of Rheumatology criteria for RA;<br>c. Had at least one qualifying comorbidity: diabetes mellitus (only patients taking insulin and/or oral hypoglycaemic agents), chronic pulmonary disease (asthma or chronic obstructive pulmonary disease), or pneumonia or recurrent infections (bronchitis, sinusitis, or urinary tract infection) in the preceding year.<br>11. Exclusion criteria:<br>a. Recent myocardial infarction, uncontrolled hypertension, angina pectoris, or severe pulmonary disease requiring continuous oxygen therapy; |

**Weisman 2007** *(Continued)*

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|---|---|
| | b. Use of TNF antagonists before or during the study, but could receive corticosteroids, nonsteroidal anti-inflammatory drugs, disease-modifying anti-rheumatic drugs (except azathioprine, cyclosporine, and cyclophosphamide), and pain medications at the discretion of their physicians. |
| Interventions | 1. Intervention<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: Immunex Corporation<br>c. Dose: 25 mg, twice-weekly for 16 weeks<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated), twice-weekly for 16 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: standard of care for participants' condition |
| Outcomes | 1. Primary (baseline to end of follow-up)<br>a. Incidence of medically important infections (MII)<br>2. Secondary (baseline to end of follow-up)<br>a. Adverse events |
| Notes | 1. Trial registration number: NCT00132418<br>2. Trial dates: April 2000-February 2004<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Immunex Corporation, a wholly-owned subsidiary of Amgen Inc. and Wyeth Pharmaceuticals funded the study.<br>5. Disclosure comment: Several authors received research support and honoraries from Amgen. Mr Kerr served as a consultant for Amgen, and Dr Paulus, Dr Fierer, and Dr Weisman were members of the Data Safety Monitoring Board. Ms Dunn, Dr Tsuji, and Dr Baumgartner worked for Amgen at the time of the study.<br>6. Ethical committee approved: yes<br>7. Other disclosure if noted: the study was terminated early because of slow enrolment and lower than predicted incidence of infections. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Randomization was stratified by diagnosis of diabetes (with or without another comorbidity) and the diabetic stratum was further stratified by treatment with oral hypoglycaemic agents or insulin (or both therapies)" (p. 1122).<br>Comment: insufficient information to judge "high" or "low" risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to judge the "high" or "low" risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "...double-blind, placebo-controlled safety study" (p. 1122).<br>Comment: insufficient information to judge the "high" or "low" risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "An independent data safety monitoring board (DSMB) was established before study initiation to periodically review unblinded safety data, recommend protocol modifications and propose early study termination if persuasive evidence was observed for futility or for harm or benefit attributable to etanercept" (p. 1122). |

**Weisman 2007** *(Continued)*

| | | |
|---|---|---|
| | | Quote: "During an interim review, the DSMB found no safety issues that warranted stopping the trial, but noted that the incidence of MIIs was markedly lower than anticipated (3% overall), providing only 43% power to detect a 2-fold increase in the etanercept group over the expected 10% placebo incidence" (p. 1123). |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1. Randomised: 564<br>a. Etanercept: not stated<br>b. Placebo: not stated<br>2. Withdrawal: 5.14% (29/ 564)<br>a. Etanercept: unclear<br>b. Placebo: unclear<br>3. Analysed: 94.6% (535/564)<br>a. Etanercept: 49.71% (266/535)<br>b. Placebo: 50.28% (269/535) |
| Selective reporting (reporting bias) | Unclear risk | Inappropriate report about cardiovascular outcome incidence |
| Other bias | High risk | There was inappropriate description of the original groups post randomisation.<br><br>Immunex (Amgen) and Wyeth funded the study. Several authors had financial ties to Amgen, including employment and consultancy, potentially creating conflicts of interest. |

1. ABI: Ankle-Brachial Index
2. ACB: Aortocoronary bypass
3. ACE: Angiotensin-Converting Enzyme
4. ACEIs: Angiotensin-Converting Enzyme Inhibitors
5. ACR: American College of Rheumatology
6. ACR20/50/70: American College of Rheumatology preliminary criteria for 20%/50%/70% improvement
7. AGI: Alpha-Glucosidase Inhibitor
8. AICD: Automated Implantable Cardioverter Defibrillator
9. AIDS: Acquired Immunodeficiency Syndrome
10. ALAT: Alanine Aminotransferase
11. ANA: Anti-nuclear Antibodies
12. Anti-dsDNA: Anti-Double-Stranded DNA
13. ARBs: Angiotensin II Receptor Blockers
14. ASAS: Assessment of SpondyloArthritis International Society
15. ASAS20/50/70: Assessment of SpondyloArthritis International Society 20%/50%/70% improvement criteria
16. ASAF: Ankylosing Spondylitis Assessment Form
17. AUC: Area Under the Curve
18. BASDI: Bath Ankylosing Spondylitis Disease Activity Index
19. BASFI: Bath Ankylosing Spondylitis Functional Index
20. BASMI: Bath Ankylosing Spondylitis Metrology Index
21. BID: Twice a day
22. BMI: Body Mass Index
23. BNP: Brain-Type Natriuretic Peptide
24. BP: Blood Pressure
25. BSA: Body Surface Area
26. CABG: Coronary Artery Bypass Grafting
27. CAI: Central Augmentation Index
28. CBC: Complete Blood Count

29.CCBs: Calcium Channel Blockers
30.CD4: Cluster of Differentiation 4
31.CFR: Coronary Flow Reserve
32.CHF: Congestive Heart Failure
33.CKMB: Creatine Kinase-MB
34.CMR: Cardiac Magnetic Resonance
35.CPC: Cerebral Performance Category
36.CPR: Cardiopulmonary Resuscitation
37.CRP: C-Reactive Protein
38.CRT: Cardiac Resynchronisation Therapy
39.CSBP: Central Systolic Blood Pressure
40.CT: Computed Tomography
41.DAS28: Disease Activity Score in 28 joints
42.DASI: Duke Activity Status Index
43.DI: Damage Index
44.DIP: Distal Interphalangeal
45.DLQI: Dermatology Life Quality Index
46.DMARDs: Disease-Modifying Antirheumatic Drugs
47.DNA: Deoxyribonucleic Acid
48.dsDNA: Double-Stranded DNA
49.ECG/EKG: Electrocardiogram
50.EF: Ejection Fraction
51.eGFR: Estimated Glomerular Filtration Rate
52.ESR: Erythrocyte Sedimentation Rate
53.EULAR: European League Against Rheumatism
54.FACIT: Functional Assessment of Chronic Illness Therapy
55.FPG: Fasting Plasma Glucose
56.FSH: Follicle-Stimulating Hormone
57.FSMC: Fatigue Scale for Motor and Cognitive Functions
58.FVC: Forced Vital Capacity
59.GCA: Giant Cell Arteritis
60.GCS: Glasgow Coma Scale
61.GI: Gastrointestinal
62.GLS: Global Longitudinal Strain
63.G-CSF: Granulocyte Colony-Stimulating Factor
64.GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor
65.HAQ: Health Assessment Questionnaire
66.HbA1c: Glycated Haemoglobin
67.HBV: Hepatitis B Virus
68.HCG: Human Chorionic Gonadotropin
69.HCV: Hepatitis C Virus
70.HF: Heart Failure
71.HIV: Human Immunodeficiency Virus
72.HOMA: Homeostatic Model Assessment
73.HOMA2 IR: Homeostatic Model Assessment 2 Insulin Resistance
74.hsCPR: High-Sensitivity C-Reactive Protein
75.hsCRP: High-Sensitivity C-Reactive Protein
76.hsTnl: High-Sensitivity Troponin I
77.hsTNT: High-Sensitivity Troponin T
78.IIEF: International Index of Erectile Function
79.IL-10: Interleukin 10
80.IL-12: Interleukin 12

81. IL-17: Interleukin 17
82. IL-6: Interleukin 6
83. INF: Interferon
84. INR: International Normalised Ratio
85. IQR: Interquartile Range
86. ISR: In-Stent Restenosis
87. IV: Intravenous
88. JSN: Joint Space Narrowing
89. LH: Luteinising Hormone
90. Lp-PLA2: Lipoprotein-Associated Phospholipase A2
91. LS-PGA: Lattice System Physician's Global Assessment
92. LV: Left Ventricle
93. LVDD: Left Ventricle End-Diastolic Diameter
94. LVEF: Left Ventricle Ejection Fraction
95. LVEDVI: Left Ventricular End-Diastolic Volume Index
96. LVESVi: Left Ventricular End-Systolic Volume Index
97. LVSD: Left Ventricle End-Systolic Diameter
98. MACE: Major Adverse Cardiac Event
99. MB: Myoglobin
100. MCA: Middle Cerebral Artery
101. MCP: Metacarpophalangeal
102. MCS: Mental Component Summary
103. MDA: Malondialdehyde
104. MDRD: Modification of Diet in Renal Disease
105. MI: Myocardial Infarction
106. MII: Myocardial Infarction Index
107. MIP: Maximum Intensity Projection
108. MLWHF: Minnesota Living with Heart Failure Questionnaire
109. MMSE: Mini-Mental State Examination
110. MOS SF-36: Medical Outcomes Study Short-Form 36
111. MPO: Myeloperoxidase
112. MRI: Magnetic Resonance Imaging
113. mRNA: Messenger Ribonucleic Acid
114. MRS: Modified Rankin Scale
115. mRSS: Modified Rodnan Skin Score
116. MTX: Methotrexate
117. MVO: Mitral Valve Opening
118. N/A: Not Applicable
119. NaCl: Sodium Chloride
120. NAPSI: Nail Psoriasis Severity Index
121. NIHSS: National Institutes of Health Stroke Scale
122. NSAIDs: Nonsteroidal Anti-Inflammatory Drugs
123. NSTEMI: Non-ST Elevation Myocardial Infarction
124. NT-proBNP: N-Terminal Pro-B-Type Natriuretic Peptide
125. NYHA: New York Heart Association
126. OGTT: Oral Glucose Tolerance Test
127. OHCA: Out-of-Hospital Cardiac Arrest
128. PAI-1: Plasminogen Activator Inhibitor-1
129. PASI: Psoriasis Area and Severity Index
130. PASI50/75/90: Psoriasis Area and Severity Index 50%/75%/90% improvement
131. PCI: Percutaneous Coronary Intervention
132. PMR: Polymyalgia Rheumatica

PPD: Purified Protein Derivative
ppFVC: Percent Predicted Forced Vital Capacity
PR: Partial Response
PsARC: Psoriatic Arthritis Response Criteria
PSSI: Psoriasis Scalp Severity Index
PUVA: Psoralen and Ultraviolet A
PWV: Pulse Wave Velocity
qADAM: Quantitative Androgen Deficiency in Aging Males
QT(c): QT interval (corrected)
QW: Once a week
RA: Rheumatoid Arthritis
RHI: Reactive Hyperaemia Index
RNA: Ribonucleic Acid
ROSC: Return of Spontaneous Circulation
SD: Standard Deviation
SE: Standard Error
SF-36: Short Form 36
SEM: Standard Error of the Mean
SHBG: Sex Hormone-Binding Globulin
sICAM(-1): Soluble Intercellular Adhesion Molecule(-1)
SOFA: Sequential Organ Failure Assessment
sPGA: Static Physician Global Assessment
SSA: Sjögren's Syndrome A
ST: ST segment
STEMI: ST-Elevation Myocardial Infarction
TB: Tuberculosis
TCZ: Tocilizumab
TEAE: Treatment-Emergent Adverse Event
TNF-α: Tumour Necrosis Factor-Alpha
tPA: Tissue Plasminogen Activator
TSS: Total Sharp Score
UV(-A)(-B): Ultraviolet Light (-A)(-B)
VAS: Visual Analogue Scale
VCAM-1: Vascular Cell Adhesion Molecule-1
Vco2: Carbon Dioxide Production
VE: Minute Ventilation
VEGF: Vascular Endothelial Growth Factor
Vo2: Oxygen Uptake
vWF: von Willebrand Factor
WBC: White Blood Cells
WHO: World Health Organization
WHR: Waist-to-Hip Ratio

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Antoni 2005 | Randomised controlled trial. However, participants in the placebo group who didn't show improvement started receiving infliximab at week 16. Therefore, efficacy endpoints used an intention-to-treat analysis, but the safety endpoint used all patients who received the medication against those who didn't. This approach probably counts participants twice in the analysis. |

| Study | Reason for exclusion |
|---|---|
| Bissonnette 2011 | Randomised controlled trial, and both groups received the medication study at different timing (p. 1404). |
| Chaudhari 2001 | According to the following report, "Patients were randomly assigned placebo or infliximab 5 or 10 mg/kg at weeks 0, 2, and 6 in a 1/1/1 fashion by means of a block-of-six randomisation scheme. For every six patients enrolled, two were assigned infliximab 5 mg/kg, two were assigned infliximab 10 mg/kg, and two were assigned placebo. " (p. 1843); this trial likely was not randomised. |
| Martínez-Taboada 2008 | Randomised controlled trial conducted: "The primary outcome was the ability to withdraw the corticosteroid therapy and control the disease activity at 12 months in patients who had developed side effects secondary to corticosteroid treatment." |
| Reich 2005 | Randomised controlled trial. However, the parallel design didn't remain during the whole study nor the analysis of data.<br>• The control group (placebo) crossed to the treatment group (infliximab) at week 24, but the treatment group remained in the original allocation.<br>• Safety analysis compared the placebo group of the first 24 weeks against everybody that received medication during the whole study, which included some placebo group participants, probably counting patients twice. |

## Characteristics of studies awaiting classification *[ordered by study ID]*

### Gottlieb 2011

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 3 arms*<br>3. Duration: 1 year<br>4. Follow-up period: 12 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (33)<br>9. Country: United States<br>10. Study setting: outpatient<br>11. Type trial: superiority<br>12. Type of prevention: secondary ℙ<br><br>*Data shown are from the etanercept and placebo arms only.<br><br>ℙMore than a third of participants included had at least one cardiovascular disease. |
| Participants | 1. Type of disease: plaque psoriasis<br>2. Diagnosis criteria: affected body surface area ≥ 10%, Physician's Global Assessment (PGA) of at least moderate (≥ 3), and PASI ≥ 12<br>3. Severity: moderate-to-severe<br>4. Total randomised*: 347 participants<br>a. Etanercept: 141<br>b. Placebo: 68<br>5. Number lost to follow-up/withdrawn (%)<br>a. Etanercept: 7 (4.96)<br>b. Placebo: 5 (7.35)<br>6. Total analysed |

**Gottlieb 2011** *(Continued)*

a. Etanercept: 141
b. Placebo: 68

7. Age, years, mean (SD)
   a. Etanercept: 43.1 (12.5)
   b. Placebo: 44 (13.6)
8. Gender, male % (males/total)
   a. Etanercept: 69.5 (98/141)
   b. Placebo: 69.1 (47/68)
9. C-reactive protein basal level: not stated
10. Inclusion criteria:
    a. Age over 18 years;
    b. Sex: all;
    c. Diagnosis of plaque psoriasis for 6 months;
    d. BSA ≥ 10%;
    e. PASI 12 or above;
    f. PGA 3 or above.
11. Exclusion criteria:
    a. Previous exposure to systemic anti-IL-12/23p40 therapy;
    b. Previous exposure to etanercept or known hypersensitivity to etanercept;
    c. Inability to discontinue topical therapies, phototherapies, or systemic therapies.

*Data shown are from the etanercept and placebo arms only.

| | |
|---|---|
| Interventions | 1. Intervention*<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 50 mg, twice-weekly for 12 weeks<br>d. Administration route: subcutaneous<br>2. Control*<br>a. Placebo (composition not stated), twice-weekly for 12 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: briakinumab<br><br>*Data shown are from the etanercept and placebo arms only. |
| Outcomes | 1. Primary (baseline to week 12)<br>a. Proportion achieving PGA of "clear" or "minimal"<br>b. Proportion achieving PASI75<br>2. Secondary (baseline, weeks 2, 4, 8, and 12)<br>a. PASI75 and PGA 0/1<br>b. Median time in achieving PASI75 and PGA 0/1<br>c. PASI90 and PASI100<br>d. Dermatology Life Quality Index (DLQI)<br>e. Adverse events |
| Notes | 1. Trial registration number: NCT00691964<br>2. Trial dates: June 2008-March 2009<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Abbott Laboratories funded the study.<br>5. Disclosure comment: several authors declared they have served as speakers and advisors or received educational or investigational grants from several privately owned companies in the healthcare area, including the one that funded the study. "M.O. and D.A.W. are employees of Abbott." (p. 660)<br>6. Ethical committee approved: yes |

**Parry-Jones 2023**

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 2 arms<br>3. Duration: 2 years<br>4. Follow-up period: 3 months<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable<br>7. International: no<br>8. Multicentre (number of centres): yes (5)<br>9. Country: United Kingdom<br>10. Study setting: inpatient and outpatient<br>11. Type trial: not stated<br>12. Type of prevention: secondary |
| Participants | 1. Type of disease: intracerebral haemorrhage (ICH)<br>2. Diagnosis criteria: acute, spontaneous, nontraumatic, supratentorial intracerebral haemorrhage<br>3. Severity: mild-to-moderate<br>4. Total randomised: 25 participants<br>a. Anakinra: 14<br>b. Placebo: 11<br>5. Number lost to follow-up/withdrawn (%): 3 (12)<br>a. Anakinra: 2 (14.3)<br>b. Placebo: 1 (9.1)<br>6. Total analysed: varies by outcome<br>7. Age, years, mean (SD):<br>a. Anakinra: 70 (11.5)<br>b. Placebo: 62 (14.6)<br>8. Gender, male% (males/total)<br>a. Anakinra: 57 (8/14)<br>b. Placebo: 45 (5/11)<br>9. C-reactive protein basal level, mg/L, median (IQR)<br>a. Anakinra: 4.1 (1.3 to 6.2)<br>b. Placebo: 4.8 (2.3 to 6.9)<br>10. Inclusion criteria:<br>a. Participants with spontaneous, non-traumatic, supratentorial ICH with no underlying macrovascular or neoplastic cause who were admitted to a participating centre within 8 hours of symptom onset;<br>b. No concomitant health problems that, in the opinion of the principal Investigator (PI) or designee, would interfere with participation, study drug administration or assessment of outcomes, including safety;<br>c. Willing and able to give informed consent or consent available from a patient representative for trial inclusion, including agreement in principle to receive the study drug and undergo all study assessments;<br>d. Male or female aged 18 years or above.<br>11. Exclusion criteria:<br>a. Severe ICH, unlikely to survive to 72 hours scan, in the opinion of the treating clinician;<br>b. Confirmed or suspected structural abnormality as cause of ICH (including tumour, vascular malformation);<br>c. Confirmed or suspected haemorrhagic transformation of an arterial or venous infarct;<br>d. Acute neurosurgery planned within 72 hours of admission;<br>e. Known active tuberculosis or active hepatitis;<br>f. Known active malignancy; |

**Parry-Jones 2023** *(Continued)*

g. Neutropenia (absolute neutrophil count (ANC) < 1.5 x 10^9/L).
h. Abnormal renal function (creatinine clearance or estimated Glomerular Filtration Rate (eGFR) < 30 mLl/minute) documented in the last 3 months prior to this ICH;
i. Live vaccinations within the last 10 days prior to this ICH;
j. Previous or concurrent treatment with IL-1Ra known at the time of trial entry or previous participation in this trial;
k. *See the article for the full list.*

| | |
|---|---|
| Interventions | 1. Intervention<br>• Anakinra (Kineret®)<br>• Pharmaceutical laboratory: Swedish Orphan Biovitrum AB (Stockholm, Sweden)<br>• Dose: 100 mg, twice daily for 3 days<br>• Administration route: subcutaneous<br>2. Control<br>• Placebo (composition not stated), once daily for 14 days<br>• Administration route: subcutaneous<br>3. Co-intervention: standard of care for the condition |
| Outcomes | 1. Primary (baseline to 72 hours)<br>a. Oedema extension distance (OED) on CT scan.<br>2. Secondary (baseline, 72 hours, day 4 and 3 months)<br>• Early neurological decline (END) between baseline and Day 4<br>• Haematoma expansion (baseline to 72 h)<br>• Area under the curve for CRP and IL-6 to day 4<br>• Clinical outcomes at 3 months:<br>◦ Modified Rankin Scale (mRS)<br>◦ Stroke Impact Scale (SIS)<br>◦ Fatigue Severity Scale (FSS)<br>◦ Quality of life (EQ-5D-5L)<br>◦ Hospital Anxiety and Depression Scale (HADS) |
| Notes | 1. Trial registration number: NCT03737344<br>2. Trial dates: May 2019-February 2021<br>3. A priori sample size estimation: yes*<br>4. Financial disclosure: financial support from the National Institute for Health Research (UK) funded this study. Also, Swedish Orphan Biovitrum AB provided the intervention and placebo free of charge.<br>5. Disclosure comment: "The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article." (p. 826)<br>6. Ethical committee approved: yes<br><br>*The recruitment target was 80, aiming for 66 participants; however, due to the COVID-19 pandemic, recruitment stopped at 25 (p. 821). |

**Strober 2011**

| | |
|---|---|
| Methods | 1. Study design: parallel<br>2. Number of arms: 3 arms*<br>3. Duration: 1 year<br>4. Follow-up period: 12 weeks<br>5. Run-in period: not stated<br>6. Run-in period time: not applicable |

**Strober 2011** *(Continued)*

7. International: not
8. Multicentre (number of centres): yes (41)
9. Country: United States
10. Study setting: outpatient
11. Type trial: superiority
12. Type of prevention: secondary ℙ

*Data shown are from the etanercept and placebo arms only.

ℙMore than a third of participants included had at least one cardiovascular disease.

| | |
|---|---|
| Participants | 1. Type of disease: plaque psoriasis<br>2. Diagnosis criteria: affected body surface area ≥ 10%, Physician's Global Assessment (PGA) of at least moderate (≥ 3), and PASI ≥ 12<br>3. Severity: moderate-to-severe<br>4. Total randomised*: 350 participants<br>a. Etanercept: 139<br>b. Placebo: 72<br>5. Number lost to follow-up/withdrawn (%): 18 (5.1)<br>a. Etanercept: 12 (8.63)<br>b. Placebo: 6 (8.33)<br>6. Total analysed<br>a. Etanercept: 139<br>b. Placebo: 72<br>7. Age, years, mean (SD)<br>a. Etanercept: 45.2 (14.8)<br>b. Placebo: 45 (13.9)<br>8. Gender, male% (males/total)<br>a. Etanercept: 61.2 (85/139)<br>b. Placebo: 63.9 (46/72)<br>9. C-reactive protein basal level: not stated<br>10. Inclusion criteria:<br>a. Age over 18 years;<br>b. Sex: all;<br>c. Diagnosis of plaque psoriasis for 6 months;<br>d. BSA ≥ 10%;<br>e. PASI 12 or above;<br>f. PGA 3 or above.<br>11. Exclusion criteria:<br>a. Previous exposure to systemic anti-IL-12/23p40 therapy;<br>b. Previous exposure to etanercept or known hypersensitivity to etanercept;<br>c. Inability to discontinue topical therapies, phototherapies, or systemic therapies.<br>*Data shown are from the etanercept and placebo arms only. |
| Interventions | 1. Intervention*<br>a. Etanercept (Enbrel®)<br>b. Pharmaceutical laboratory: not stated<br>c. Dose: 50 mg, twice-weekly, for 12 weeks<br>d. Administration route: subcutaneous<br>2. Control<br>a. Placebo (composition not stated), twice-weekly for 12 weeks<br>b. Administration route: subcutaneous<br>3. Co-intervention: not reported |

**Strober 2011** *(Continued)*

| | |
|---|---|
| | *Data shown are from the etanercept and placebo arms only. |
| Outcomes | 1. Primary (baseline to week 12)<br>a. Proportion achieving PGA of "clear" or "minimal"<br>b. Proportion achieving PASI75<br>2. Secondary (baseline, weeks 2, 4, 8, and 12)<br>a. PASI75 and PGA 0/1<br>b. Median time in achieving PASI75 and PGA 0/1<br>c. PASI90 and PASI100<br>d. Dermatology Life Quality Index (DLQI)<br>e. Adverse events |
| Notes | 1. Trial registration number: NCT00710580<br>2. Trial dates: July 2008-April 2009<br>3. A priori sample size estimation: yes<br>4. Financial disclosure: Abbott Laboratories funded the study.<br>5. Disclosure comment: Several authors stated they have worked as consultants or advisors or have received research funding from several privately owned companies in the health area, including the sponsor of this trial. M.O. and D.A.W. are employees of Abbott.<br>6. Ethical committee approved: yes |

1. ANC: Absolute Neutrophil Count
2. BSA: Body Surface Area
3. COVID-19: Coronavirus Disease 2019
4. CRP: C-Reactive Protein
5. CT: Computed Tomography
6. DLQI: Dermatology Life Quality Index
7. eGFR: Estimated Glomerular Filtration Rate
8. END: Early neurological decline
9. EQ-5D-5L: EuroQol 5 Dimension 5 Level
10. FSS: Fatigue Severity Scale
11. HADS: Hospital Anxiety and Depression Scale
12. CH: Intracerebral Haemorrhage
13. IQR: Interquartile Range
14. mRS: Modified Rankin Scale
15. OED: Oedema extension distance
16. PASI: Psoriasis Area and Severity Index
17. PGA: Physician Global Assessment
18. PI: Principal Investigator
19. SIS: Stroke Impact Scale

## Characteristics of ongoing studies *[ordered by study ID]*

**ISRCTN12961797**

| | |
|---|---|
| Study name | Does interleukin-1 receptor antagonist improve outcome following aneurysmal subarachnoid haemorrhage (aSAH)? A phase III trial |
| Methods | 1. Study type: interventional study<br>2. Study design: randomised parallel controlled trial<br>3. Target sample size: 100 |

**ISRCTN12961797** *(Continued)*

| | |
|---|---|
| | 4. Phase: III<br><br>5. Country: United Kingdom |
| Participants | 1. Age: ≥ 18 years<br><br>2. Sex: both<br><br>3. Inclusion criteria:<br><br>• Patients with CT-positive spontaneous SAH admitted to a participating neurosurgical centre where written informed consent can be obtained and study drug can be administered within 72 hours of ictus;<br>• No concomitant health problems that, in the opinion of the PI or designee, would interfere with participation, administration of study drug or assessment of outcomes including safety;<br>• Willing and able to give informed consent or consent available from a patient representative for trial inclusion including agreement in principle to receive study drug and undergo all study assessments;<br>• Male or female aged 18 years or above.<br><br>4. Exclusion criteria:<br><br>• Unconfirmed or uncertain diagnosis of spontaneous SAH;<br>• Known active tuberculosis or active hepatitis;<br>• Known active malignancy;<br>• Known Still's Disease;<br>• Neutropenia (ANC < 1.5 x 109/L);<br>• Abnormal renal function (creatinine clearance or estimated Glomerular Filtration Rate (eGFR) < 30 mL/minute) documented in the last 3 months prior to this SAH;<br>• Live vaccinations within the last 10 days of this SAH;<br>• Previous or concurrent treatment with IL-1Ra known at the time of trial entry or previous participation in this trial;<br>• Current treatment with TNF antagonists;<br>• Known to have participated in a clinical trial of an investigational agent or device in the 30 days prior to ictus;<br>• Known to have participated in a clinical trial of an investigational agent or device within 5 half-lives (of the previous agent or device) prior to ictus;<br>• Known to be pregnant or breastfeeding or inability to reliably confirm that the patient is not pregnant;<br>• Clinically significant serious concurrent medical condition, pre-morbid illnesses, or concurrent serious infection, at the PI's (or designee's) discretion, which could affect the safety or tolerability of the intervention;<br>• Known allergy to IL-1Ra or any of the excipients listed in the drug SmPC;<br>• Known allergy to other products that are produced by DNA technology using the microorganism E. coli (e.g. E.coli derived protein);<br>• Current treatment with IL-6 or IL-1 inhibitors or drugs affecting the IL-1 axis. |
| Interventions | Experimental:<br><br>1. IL-1Ra (Anakinra) twice daily<br><br>Control:<br><br>1. Comparator: Placebo twice daily |
| Outcomes | • Primary:<br>1. Ordinal shift in modified Rankin Score (mRS) (time frame: 6 months post-randomisation)<br>• Secondary: |

**ISRCTN12961797** *(Continued)*

| | |
|---|---|
| | 1. Measurement of mood using HADS (time frame: 6 months post-randomisation)<br>2. Measurement of fatigue using Fatigue score (time frame: 6 months post-randomisation)<br>3. Measurement of quality of life using EQ-5D-5L score (time frame: 6 months post-randomisation) |
| Starting date | 1. Date of first enrolment: 06/11/2020<br>2. Date of registration: 14/12/2017 |
| Contact information | 1. Kayle-Anne Sands, BSc, MSc<br>2. Address:<br>3. Telephone: 0161 306 3196<br>4. Email: scil@manchester.ac.uk<br>5. Affiliation: University of Manchester |
| Notes | https://clinicaltrials.gov/ct2/show/NCT03249207?term=NCT03249207&draw=2&rank=1 |

**Kerneis 2023**

| | |
|---|---|
| Study name | Anakinra versus placebo double blind randomized controlled trial for the treatment of acute myocarditIs (ARAMIS) (NCT03018834) |
| Methods | 1. Study type: interventional study<br>2. Study design: double-blind randomised parallel group<br>3. Target sample size: 120<br>4. Phase: IIb<br>5. Country: France |
| Participants | 1. Age: 18 years to 65 years<br>2. Sex: Both<br>3. Inclusion criteria:<br>• Patients hospitalised for acute myocarditis defined as:<br>  ◦ chest pain (or modification of the ECG) AND troponin rise (*1.5 normal range) AND myocarditis proven by MRI in the first 72 h after admission;<br>• Accepting effective contraception during treatment duration (men and women of childbearing potential);<br>• Signed informed consent to normal coronary angiography or coronary CT scan (made during the previous year is acceptable) (normal is defined as stenosis < 50%) (in the case of patients under 40 with typical MRI of myocarditis, coronary angiography is not mandatory and left to the doctor's discretion).<br>4. Exclusion Criteria:<br>• Active coronary disease;<br>• Clinical suspicion or proven underlying disease: systemic lupus, antiphospholipid antibodies, Lyme disease, trypanosomiase disease, myositis, signs of sarcoidosis, giant cell myocarditis, treated chronic inflammatory disease, tuberculosis, HIV, hepatitis B virus (HBV) or hepatitis C virus (HCV), hepatitis B virus (HBV) infection;<br>• Latex allergy;<br>• Pregnancy, breastfeeding;<br>• Contraindication to ANAKINRA (known hypersensitivity to the active substance or to any of the excipients, neutropenia < 1.5.10^9/L);<br>• Renal failure, creatine clearance (CrCl) < 30 mL/min (MDRD); |

**Kerneis 2023** *(Continued)*

| | |
|---|---|
| | • Malignancy or any comorbidity limiting survival or conditions predicting inability to complete the study;<br>• History of malignancy;<br>• Nonsteroidal anti-inflammatory drug within the past 14 days;<br>• Anti-tumour necrosis factor (TNF) within the past 14 days;<br>• No affiliation to the French Health Care System "sécurité sociale";<br>• Hepatic impairment = Child-Pugh Class C;<br>• Mechanical ventilation;<br>• Circulatory assistance. |
| Interventions | Experimental:<br>1. Anakinra 100 mg/daily subcutaneously<br>Control:<br>1. Placebo 100 mg/daily subcutaneously once a day |
| Outcomes | • Primary:<br>1. Number of days alive free of any myocarditis complications (within 28 days post-hospitalisation)<br>• Secondary:<br>1. Total cost<br>2. Total quality adjusted life year (QALYs)<br>3. Incremental cost-effectiveness<br>4. Cost utility ratios<br>5. Left ventricular ejection fraction (LVEF) assessed by cardiac magnetic resonance imaging (MRI)<br>6. Left ventricular ejection fraction (LVEF) assessed by transthoracic echocardiograhy (TTE)<br>7. LVEF assessed by cardiac MRI at 1 year<br>8. LVEF assessed by cardiac TTE<br>9. All-cause death rate<br>10.Cardiovascular death<br>11.Heart failure<br>12.Ventricular tachycardia |
| Starting date | 1. Date of first enrolment: 2017/05/30<br>2. Date of registration: 2016/12/12 |
| Contact information | 1. Mathieu Kerneis, MD<br>2. Address: ACTION Study Group - Department of Cardiology - Pitié Salpétrière Hospital, 47 Bd de l'Hopital. Paris. France 75013<br>3. Telephone:<br>4. Email:<br>5. Affiliation: ACTION Study Group - Assistance Publique - Hôpitaux de Paris |
| Notes | https://clinicaltrials.gov/study/NCT03018834 |

**NCT01423591**

| | |
|---|---|
| Study name | Infliximab therapy in patients with refractory polymyalgiar rheumatica: a double blind placebo controlled trial |
| Methods | 1. Study type: interventional study<br>2. Study design: randomised parallel controlled trial |

**NCT01423591** *(Continued)*

| | |
|---|---|
| | 3. Target sample size: 23<br>4. Phase: III<br>5. Country: Spain |
| Participants | 1. Age: 18 years to 50 years<br>2. Sex: Both<br>3. Inclusion criteria:<br>• PMR patients that after 2 years of corticosteroid treatment are not able to reduce the dose of prednisone below 5 mg/day or equivalent;<br>• PMR patients that after 6 months of corticosteroid treatment are not able to reduce the dose of prednisone below 7.5 mg/day or equivalent;<br>• PMR patients should fulfil the criteria proposed by Chuang 1982:<br>○ Age ≥ 50 years;<br>○ Development of bilateral moderately/severe aching and stiffness persisting for 1 month or more, involving two of the following areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs;<br>○ ESR ≥ 40 mm/h;<br>○ Complete clinical response to low-dose steroids (prednisone or equivalent ≤ 20 mg/day).<br>4. Exclusion criteria:<br>• Patients with biopsy-proven GCA or those with cranial symptoms or signs suggestive of GCA but without biopsy-proven arteritis;<br>• Patients with clinical features suggestive of RA or other connective tissue disorders;<br>• Chronic infections such as HIV, hepatitis B or C, active mycobacterial or fungal infections, etc.;<br>• Neoplasm or a history of malignancy in the preceding 5 years;<br>• Patients with multiple sclerosis or other demilinisating disorders;<br>• Patients with cytopenias: leukopenia (leukocytes ≤ 3.5 x 109/L), thrombocytopenia (platelets ≤ 100 x 109/L) and/or anaemia (≤ 10 g/dL);<br>• Patients with cardiac failure (functional class III/IV);<br>• Any other condition that contraindicates infliximab therapy. |
| Interventions | Experimental:<br>1. Infliximab 5 mg/kg IV at weeks 0, 2, 6, 14, 22<br>Control:<br>1. Placebo: Inactive powder IV at weeks 0, 2, 6, 14, 22 |
| Outcomes | • Primary:<br>1. Proportion of responders (complete remission without corticosteroids) (time frame: at 24 weeks)<br>• Secondary:<br>1. Proportion of responders (time frame: at 48 weeks)<br>2. Time to response (time frame: 48 weeks)<br>3. Number of relapses/recurrences (time frame: 48 weeks)<br>4. Response duration (time frame: 48 weeks)<br>5. Cumulative dose and side effects of steroids (time frame: at 24 and 48 weeks)<br>6. Number of patients that should be re-treated with infliximab (time frame: 48 weeks)<br>7. Side effects of infliximab in this patient population (time frame: 48 weeks) |
| Starting date | 1. Date of first enrolment: 2007/06 |

**NCT01423591** *(Continued)*

| | |
|---|---|
| | 2. Date of registration: 2011/07/26 |
| Contact information | 1. Dr. Vicente Rodriguez Valverde, Rheumatology, MD, PhD<br>2. Address: Rheumatology Division, Hospital Universitario Marques de Valdecilla, Santander, Cantabria, Spain, 39008<br>3. Telephone: not reported<br>4. Email: not reported<br>5. Affiliation: Hospital Universitario Marqués de Valdecilla |
| Notes | https://clinicaltrials.gov/ct2/show/NCT01423591 |

**NCT02902731**

| | |
|---|---|
| Study name | Randomized, controlled, double-blind study of anakinra against placebo in addition to steroids in giant cell Arteritis |
| Methods | 1. Study type: interventional study<br>2. Study design: randomised parallel controlled trial<br>3. Target sample size: 70<br>4. Phase: III<br>5. Country: France |
| Participants | 1. Age: ≥ 51 years<br>2. Sex: Both<br>3. Inclusion criteria:<br>• Patients with temporal arteritis giant cell matching 3 of the 5 criteria of the American College of Rheumatology (ACR) that:<br>  ○ Given a temporal artery biopsy compatible with a diagnosis of GCA (not necrotising arteritis, giant cell with a granulomatous inflammatory infiltrate, usually localised to the intima-media junction, makes lymphocytes, macrophages and multinucleated giant cells; or minimum detection of a chronic inflammatory infiltrate fact lymphocytes and some neutrophils or eosinophils without giant cells).<br>• Either abdominal thoracic aortitis diagnosed by:<br>  ○ Angio CT: circumferential thickening of the aortic wall more than 3 mm, in the absence of adjacent plaque and active infection;<br>  ○ MR angiography: wall thickening of the aortic wall with hyperintense on T1 weighted and T2 weighted enhancement after gadolinium injection;<br>  ○ PET scanner: increased uptake of FDG by the aorta and its branches is not typical for GCA and may be in the atheroma. The PET scanner is probably a very sensitive technique but not specific enough to retain the diagnosis of GCA. We therefore consider the PET CT as a diagnostic method of secondary aortite the GCA if there simultaneously on the same exam fixing aortic (thoracic or abdominal) and blood of large caliber (artery(s) axillary(s), subclavian(s) and/or carotid(s) of FDG.<br>• Newly diagnosed disease and from corticosteroid started up to 14 days, the initial dose is less or equal to 1 mg/kg or;<br>• GCA recurrence of continuous therapy with corticosteroids (including hydroprednisone) and/or immunosuppression was stopped for at least 6 months. At the time of recurrence, at least 3 of 5 ACR criteria for the diagnosis of GCA must be present. Furthermore :<br>  ○ if BAT (biopsy of the temporal artery) was positive at the time of initial diagnosis, it is not necessary to make a new [one]. |

**NCT02902731** *(Continued)*

- if BAT was negative, the patient can not be included after completion of a new BAT which will be positive or if there is an aortite, evidenced by angio-CT or MR angiography or PET scanner.

- For men and women of childbearing age, effective contraception must be used by the patient or his partner for the duration of treatment with anakinra (or placebo) and for 3 months after treatment. Also, breastfeeding is allowed after 3 months of stopping anakinra. Women considered not at risk of pregnancy are defined as having menopause with no periods for at least a year or surgically sterile (tubal ligation, bilateral oophorectomy or hysterectomy);
- Patient who has given their written consent; patient affiliated with social security.

4. Exclusion criteria:

- Subjects checking one of the criteria for non-inclusion may be eligible to participate in the research. These criteria may include:
- Pathologies, habitus or other patient characteristics:
  - Pregnancy, breastfeeding women or women of childbearing potential not using contraception;
  - Dementia syndrome;
  - Patient not observing ?
  - Patients who live more than 150 km from the investigation centre;
  - Ethyl or drug intoxication history that required hospitalisation in the previous year;
  - Patient monitoring and/or treated with another autoimmune disease or known inflammatory condition;
  - Hypersensitivity to anakinra or any of its excipients (sodium citrate (E331), sodium chloride, disodium edetate (E385), polysorbate 80 (E433), sodium hydroxide (E524), water for injections, substrates of origin: escherichia coli proteins);
  - Person under judicial protection, guardianship;
  - Person deprived of liberty;
  - Person not a beneficiary of the social security system.
- Other therapeutic issues:
  - Patient has already started (or stopped there less than 6 months) in a protocol or not frame to its ACG or another disease, treatment with anti-TNF-alpha, methotrexate, cyclosporine, cyclophosphamide, dapsone or bolus corticosteroids;
    - Patients on long-term glucocorticoid for another condition;
    - Early treatment of CAG disease with a dose > 1 mg/kg whatever the duration;
    - Immunisation with live vaccines/mitigated during the 8 weeks.
- Infectious diseases:
  - Chronic viral hepatitis (acute or chronic) B or C;
  - HIV infection;
  - Persistent infection or severe infection requiring hospitalisation or treatment with IV antibiotics during the 30 days prior to inclusion;
  - Infection requiring oral antibiotic treatment in the preceding 14 days;
  - History of active tuberculosis, histoplasmosis or listeriosis;
  - Latent TB signs (based on a history of untreated contagion, an opacity of greater than 1 cm in diameter on chest x-ray, or an in vitro test (Quantiferon Gold or T-Spot TB)-positive. A history of tuberculosis disease or latent TB whose treatment is completed and has been properly conducted is not an exclusion criterion, whatever the result of Quantiferon or T-Spot TB.
- Unstable disease:
  - Uncontrolled diabetes with a history of recurrent infections;
  - Unstable ischaemic heart disease;
  - Heart failure ≥ stage III/IV NYHA;
  - Recent stroke (< 6 months); or
  - Any other severe disease resulting, in the opinion of the investigator, in a risk to the patient due to their participation in the study.
- A vascular risk, metabolic, infectious, neoplastic renal or as follows:
  - Patient at high cardiovascular risk: heart disease or vascular history of proven, type 2 diabetes at high cardiovascular risk*, vascular risk > 20% at 10 years (Framingham equation), severe dyslipidaemia with uncontrolled lipid-lowering therapy:

**NCT02902731** *(Continued)*

- Active liver disease and liver failure;
- Neutropenia (< 1500/mm$^3$) at the time of the introduction of Kineret/placebo; and a patient with initial neutropenia may be included in the study if it is corrected under Cortancyl®; and that the experimental treatment (anakinra-Kineret/placebo) may be commenced within 15 days after prednisone;

- Neoplasia for under 5 years except carcinoma in situ of the cervix and skin cancer (excluding melanoma) with complete excision whose boundaries pass in safe area;
- Severe renal impairment (clearance < 30 mL/min)
- High cardiovascular risk patients with diabetes are defined by:
  - A kidney disorder (proteinuria > 300 mg/24 h or creatinine clearance < 60 mL/min according to Cockroft);
  - Or at least two of the following risk factors:
  - Men over 50 years, women over 60 years;
- History of premature coronary disease: myocardial infarction or sudden death in the father or male relative in the first degree before age 55 and before age 65 for females;
- Current smoker or quit smoking for fewer than 3 years;
- High blood pressure regardless of treatment;
- HDL cholesterol < 0.40 g/L regardless of sex;
- Microalbuminuria (> 30 mg/24 h) NB: Moderate renal impairment (clearance ≥ 30 mL/min and < 50 mL/min) is not here a criterion for non-inclusion, but the appropriate injection of Kineret (anakinra) provided daily will be made every 2 days.

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| Interventions | Experimental:<br>1. Anakinra: subcutaneous injection of anakinra every day during 16 weeks<br>Control:<br>1. Placebo: subcutaneous injection of placebo every day during 16 weeks |
| Outcomes | • Primary:<br>1. Global relapse rate (time frame: week 26)<br>• Secondary:<br>1. Specific relapse rate (time frame: week 4 to week 16)<br>2. Specific relapse rate (time frame: week 17 to week 26)<br>3. Specific relapse rate (time frame: w27 to w52)<br>4. Speed efficiency: time of obtaining a complete remission over a follow-up of 52 weeks (time frame: baseline up to 52 weeks)<br>5. Number of first relapse (time frame: baseline up to 52 weeks)<br>6. Cumulative and the average dose of prednisone used (time frame: baseline up to 52 weeks)<br>7. Safety according CTCAE v4.0 (time frame: baseline up to 52 weeks) |
| Starting date | 1. Date of first enrolment: 2017/05/11<br>2. Date of registration: 2016/09/16 |
| Contact information | 1. Achille Aouba, MD PHD<br>2. Address: Caen, France, 14000<br>3. Telephone: +33231064579<br>4. Email: aouba-a@chu-caen.fr<br>5. Affiliation: University Hospital, Caen |
| Notes | https://clinicaltrials.gov/ct2/show/NCT02902731 |

**NCT03644667**

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|---|---|
| Study name | Targeting inflammation and alloimmunity in heart transplant recipients with tocilizumab (RTB-004) |
| Methods | 1. Study type: interventional study<br>2. Study design: randomised parallel controlled trial<br>3. Target sample size: 200<br>4. Phase: II<br>5. Country: United States of America |
| Participants | 1. Age: 18 years to 75 years<br>2. Sex: Both<br>3. Inclusion criteria:<br>Study entry:<br>Subject must be able to understand and provide informed consent;<br>1. Is a candidate for a primary heart transplant (listed as a heart transplant only);<br>2. No desensitisation therapy prior to transplant;<br>3. Agreement to use contraception: according to the FDA Office of Women's Health (http://www.fda.gov/birthcontrol), there are a number of birth control methods that are more than 80% effective. Female participants of childbearing potential must consult with their physician and determine the most suitable method(s) from the above referenced list to be used for the duration of the study. Those who choose oral contraception must agree to use a second form of contraception after administration of the study drug for a period of 1 year after the last dose of the study drug;<br>4. Mechanical support or investigational drug trials where the intervention ends at the time of transplantation are permitted;<br>5. In the absence of contraindication, vaccinations should be up-to-date for hepatitis B, influenza, pneumococcal, zoster, and Measles, Mumps, & Rubella (MMR); and<br>6. Subjects from areas of endemic coccidioidomycosis are eligible for inclusion but must be treated prophylactically with fluconazole or itraconazole.<br>Inclusion Criteria - Randomisation:<br>1. Recipient of a primary heart transplant;<br>2. Negative virtual crossmatch (according to local centre criteria);<br>3. No desensitisation therapy prior to transplant;<br>4. Female subjects of childbearing potential must have a negative pregnancy test (serum or urine) prior to randomisation; and<br>5. Agreement to use contraception: according to the FDA Office of Women's Health (http://www.fda.gov/birthcontrol), there are a number of birth control methods that are more than 80% effective. Female participants of childbearing potential must consult with their physician and determine the most suitable method(s) from the above referenced list to be used for the duration of the study. Those who choose oral contraception must agree to use a second form of contraception after administration of the study drug for a period of 1 year after the last dose of the study drug;<br>6. Negative SARS-CoV-2 real-time reverse transcription polymerase chain reaction (rRT-PCR) test result performed within 48 hours of transplant (SARS-CoV-2 is the virus that causes COVID-19).<br>4. Exclusion Criteria:<br>Study Entry:<br>1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol;<br>2. Candidate for multiple solid organ or tissue transplants; |

**NCT03644667** *(Continued)*

3. Prior history of organ or cellular transplantation requiring ongoing systemic immunosuppression;
4. Currently breastfeeding a child or planning to become pregnant during the time frame of the study follow-up period;
5. History of severe allergic and/or anaphylactic reactions to humanised or murine monoclonal antibodies;
6. Known hypersensitivity to tocilizumab (Actemra®);
7. Previous treatment with tocilizumab (Actemra®);
8. Human Immunodeficiency Virus (HIV)-positive;
9. Hepatitis B surface antigen-positive;
10. Hepatitis B core antibody-positive;
11. Hepatitis C virus antibody-positive (anti-HCV Ab+) who are either untreated or, have failed to demonstrate sustained viral remission for more than 12 months (after anti-viral treatment);
12. Recipient of a hepatitis C virus nucleic acid test (NAT)-positive donor organ;
13. Subjects must be tested for latent TB infection (LTBI) within a year prior to transplant: Subjects with a positive test for LTBI must complete appropriate therapy for LTBI. A subject is considered eligible only if they have a negative test for LTBI within one year prior to transplant OR if they have completed appropriate LTBI therapy within one year prior to transplant;
14. Subjects with a previous history of active tuberculosis (TB);
15. Subjects with a history of splenectomy;
16. Known active current viral, fungal, mycobacterial or other infections not including (left ventricular assist device [LVAD]) driveline infections;
17. History of malignancy less than 5 years in remission. Any history of adequately treated in-situ cervical carcinoma, low grade prostate carcinoma, or adequately treated basal or squamous cell carcinoma of the skin will be permitted;
18. History of haemolytic-uremic syndrome/thrombotic thrombocytopenia purpura;
19. History of demyelinating disorders such as: multiple sclerosis, chronic inflammation, demyelinating polyneuropathy;
20. History of gastrointestinal perforations, active inflammatory bowel disease or diverticulitis;
21. Any previous treatment with alkylating agents such as chlorambucil or total lymphoid irradiation;
22. Radiation therapy within 3 weeks before enrolment. Enrolment of subjects who require concurrent radiotherapy should be deferred until the radiotherapy is completed and 3 weeks have elapsed since the last date of therapy;
23. Subjects with a haemoglobin < 7.0 gm/dL (last measurement within 7 days prior to transplant);
24. Subjects with a platelet count of less than 100,000/$mm^3$ (last measurement within 7 days prior to transplant);
25. Subjects with an absolute neutrophil count (ANC) of less than 2000/$mm^3$ (last measurement within 7 days prior to transplant);
26. Subjects with Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) levels > 3 x Upper Limit of Normal (ULN);
27. Subjects who are administered or intended to be administered cytolytic or anti-cluster of differentiation 25 (CD25) monoclonal antibody agents as induction therapy in the immediate post-transplant period;
28. Intent to give the recipient a live vaccine within 30 days prior to randomisation;
29. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may: pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements, or that may impact the quality or interpretation of the data obtained from the study.

Exclusion criteria - Randomisation:

1. Recipient of multiple solid organ or tissue transplants;
2. Recipient of ex vivo preserved hearts and hearts donated after cardiac death (DCD);
3. Currently breastfeeding a child or planning to become pregnant during the time frame of the study follow-up period;
4. History of severe allergic anaphylactic reactions to humanised or murine monoclonal antibodies;

**NCT03644667** *(Continued)*

5. Known hypersensitivity to tocilizumab (Actemra®);
6. Previous treatment with tocilizumab (Actemra®);
7. HIV-positive;
8. Hepatitis B surface antigen-positive;
9. Hepatitis B core antibody-positive;
10. Hepatitis B negative transplant recipient that received a transplant from a hepatitis B core antibody-positive donor;
11. HCV+ subject(s) who are either untreated or have failed to demonstrate sustained viral remission for more than 12 months after anti-viral treatment;
12. Recipient of a hepatitis C virus nucleic acid test (NAT) positive donor organ;
13. Subject's organ donor tests positive for SARS-CoV-2 by real-time reverse transcription polymerase chain reaction (SARS-CoV-2 is the virus that causes COVID-19);
14. Subjects with a previous history of active TB;
15. Subjects must be tested for latent TB infection (LTBI) within a year prior to transplant: Subjects with a positive test for LTBI must complete appropriate therapy for LTBI. A subject is considered eligible only if they have a negative test for LTBI within one year prior to transplant OR if they have completed appropriate LTBI therapy within one year prior to transplant;
16. Subjects with a history of splenectomy;
17. Known active current viral, fungal, mycobacterial or other infections, not including (left ventricular assist device [LVAD]) driveline infections;
18. History of malignancy less than 5 years in remission. Any history of adequately treated in-situ cervical carcinoma, low grade prostate carcinoma, or adequately treated basal or squamous cell carcinoma of the skin will be permitted;
19. History of haemolytic-uremic syndrome/thrombotic thrombocytopenia purpura;
20. History of demyelinating disorders;
21. History of gastrointestinal perforations, active inflammatory bowel disease or diverticulitis;
22. Any previous treatment with alkylating agents such as chlorambucil, or with total lymphoid irradiation;
23. Radiation therapy within 3 weeks before randomisation. Enrolment of subjects who require concurrent radiotherapy should be deferred until the radiotherapy is completed and 3 weeks have elapsed since the last date of therapy;
24. Subjects with a haemoglobin < 7.0 gm/dL within 7 days prior to randomisation;
25. Subjects with a platelet count of less than 100,000/$mm^3$ within 7 days prior to randomisation;
26. Subjects with an absolute neutrophil count (ANC) of less than 2000/$mm^3$ within 7 days prior to randomisation;
27. Subjects with AST or ALT levels > 3 x ULN;
28. Subjects who are administered or intended to be administered cytolytic or anti-CD25 monoclonal antibody agents as induction therapy in the immediate post-transplant period;
29. Receipt of a live vaccine within 30 days prior to randomisation;
30. Use of investigational drugs after transplantation;
31. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study; may interfere with the participant's ability to comply with study requirements; or that may impact the quality or interpretation of the data obtained from the study;
32. Subjects with known donor-specific antibodies at the time of evaluation of antibodies for heart transplant surgery (within 6 months).

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| Interventions | Experimental:<br>1. Tocilizumab: 6 doses: 8 mg/kg (maximum of 800 mg) given once every four weeks by intravenous infusion over a 20-week period, with a minimum of 21 days between each infusion.<br>Control:<br>1. Standard of care triple IS: |

**NCT03644667** *(Continued)*

a. Standard of care triple maintenance IS includes: a calcineurin inhibitor-tacrolimus (Prograf ®) per site standards by sublingual, oral or intravenous route to attain target trough levels. Exception: Should a participant be unable to tolerate tacrolimus, the site physician investigator may choose cyclosporine treatment. An anti-proliferative treatment-mycophenolate mofetil or Myfortic® (enteric-coated mycophenolate sodium) will be administered, per protocol. Exception: Should a participant be unable to tolerate mycophenolate mofetil, the site physician investigator may choose an alternative treatment. Steroids-methylprednisolone/prednisone dosing will be given according to the local centre standard of practice early post-transplantation. After 6 months, prednisone may be withdrawn at the discretion of the site physician investigator, per protocol.

Outcomes

- Primary:

1. Proportion of participants positive for events of dnDSA, ACR, AMR, haemodynamic compromise, death or re-transplantation - by treatment group (time frame: from transplant through 12 months post-transplant surgery (12 months)):
   a. This outcome is defined by a composite 1-year post-transplant endpoint of:
      i. detection of de novo donor-specific antibodies (dnDSA) (Core Laboratory),
      ii. acute cellular rejection (ACR) ≥ ISHLT 2R rejection (Core Laboratory),
      iii. antibody-mediated rejection (AMR) ≥ ISHLT AMR 1 (Core Laboratory),
      iv. haemodynamic compromise rejection in the absence of a biopsy or histological rejection,
      v. death, or
      vi. re-transplantation.

- Secondary:

1. Freedom of detection of de novo donor-specific antibodies (dnDSA) - by treatment group (time frame: from transplant through 12 months post-transplant surgery (12 months)). A comparison by treatment group of the incidence of freedom from development of de novo donor-specific antibodies (dnDSA). dnDSA is a newly developed alloantibody that is against the donor organ.
2. Freedom from acute cellular rejection (ACR) ≥ International Society of Heart and Lung Transplantation (ISHLT) 2R rejection - by treatment group (time frame: from transplant through 12 months post-transplant surgery (12 months)). A comparison by treatment group of the incidence of freedom from development of acute cellular rejection ≥ 2R (reference: International Society of Heart and Lung Transplantation [ISHLT] acute cellular rejection-grade 2R or greater severity).
3. Freedom from antibody mediated rejection (AMR) ≥ International Society of Heart and Lung Transplantation (ISHLT) AMR 1 - by treatment group (time frame: from transplant through 12 months post-transplant surgery (12 months)). A comparison by treatment group of the incidence of freedom from development of antibody-mediated rejection defined as ISHLT grade AMR 1 or greater severity.
4. Freedom from haemodynamic compromise rejection in the absence of a biopsy or histological rejection - by treatment group (time frame: from transplant through 12 months post-transplant surgery (12 months)). A comparison by treatment group of the incidence of freedom from development of haemodynamic compromise (HDC).
5. Freedom from any-treated rejection - by treatment group (time frame: from transplant through 12 months post-transplant surgery (12 months)). A comparison by treatment group of the incidence of freedom from development of an episode of rejection requiring treatment. Reference: Acute cellular rejection as defined by the 2004 International Society of Heart and Lung Transplantation (ISHLT) grading scale.
6. Freedom from acute cellular rejection (ACR) ≥ International Society of Heart and Lung Transplantation (ISHLT) 2R per patient - by treatment group (time frame: from transplant through 12 months post-transplant surgery (12 months)). A comparison by treatment group of the incidence of freedom from acute cellular rejection (ACR) ≥ ISHLT 2R rejection. Reference: 2004 International Society of Heart and Lung Transplantation (ISHLT grading scale).
7. Freedom from antibody-mediated rejection (AMR) (≥ International Society of Heart and Lung Transplantation (ISHLT) AMR 1) per participant - by treatment group (time frame: from transplant through 12 months post-transplant surgery (12 months))
8. Freedom from haemodynamic compromise rejection in the absence of a biopsy or histological rejection per participant - by treatment group (time frame: from transplant through 12 months post-transplant surgery (12 months)). Time from transplant, free of antibody-mediated rejection, defined as ISHLT grade AMR 1 or greater will be compared between the treatment groups.

**NCT03644667** *(Continued)*

9. Occurrence of death - by treatment group (time frame: from transplant through 12 months post-transplant surgery (12 months)). Incidence of all-cause mortality will be compared between the treatment groups.
10. Occurrence of re-listed for transplantation - by treatment group (time frame: from transplant through 12 months post-transplant surgery (12 months)). Incidence of participant(s) being re-listed for transplant will be compared between the treatment groups.
11. Occurrence of re-transplantation - by treatment group (time frame: from transplant through 12 months post-transplant surgery (12 months)). Incidence of participant(s) re-transplantation will be compared between the treatment groups.
12. Number of acute cellular rejection (≥ International Society of Heart and Lung Transplantation (ISHLT) 2R) per patient - by treatment group (time frame: from transplant through 12 months post-transplant surgery (12 months)). The frequency of events will be compared between the treatment groups.
13. Number of antibody-mediated rejection (AMR) (≥ International Society of Heart and Lung Transplantation (ISHLT) AMR 1) per participant - by treatment group (time frame: 12 months post-transplantation). The frequency of events will be compared between the treatment groups.
14. Number of rejection episodes associated with haemodynamic compromise (HDC) per participant - by treatment group (time frame: from transplant through 12 months post-transplant surgery (12 months)). The frequency of events will be compared between the treatment groups.
15. Change in intravascular ultrasound (IVUS) measurements From baseline to 1-year post-transplant - by treatment group (time frame: baseline (4 to 8 weeks post-transplant), 1-year post-transplant) per protocol, per clinical research site standard of care.
16. Angiographic evidence of cardiac allograft vasculopathy (CAV) - by treatment group (time frame: 12 months post-transplantation) in accordance with the International Society of Heart and Lung Transplantation (ISHLT) Cardiac Allograft Vasculopathy (CAV) angiographic grading scale.
17. Participant loss to follow-up - by treatment group (time frame: 12 months post-transplantation). Incidence of participant loss to follow-up will be compared between the treatment groups.
18. Occurrence of serious infections requiring intravenous antimicrobial therapy and need for hospitalisation - by treatment group (time frame: through 24 months post-transplant surgery). The frequency of serious infections requiring intravenous antimicrobial therapy and need for hospitalisation will be compared between treatment groups.
19. Incidence of tuberculosis - by treatment group (time frame: through 24 months post-transplant surgery). The incidence of tuberculosis will be compared between treatment groups.
20. Incidence of cytomegalovirus (CMV) infection - by treatment group (time frame: through 24 months post-transplant surgery). The incidence of CMV infection will be compared between treatment groups.
21. Incidence of post-transplant lymphoproliferative disease (PTLD) - by treatment group (time frame: through 24 months post-transplant surgery). The incidence of PTLD will be compared between treatment groups.
22. Tolerability (discontinuation of study drug) of tocilizumab (TCZ) - by treatment group (time frame: through 24 months post-transplant surgery). The number of participants who discontinue study drug, per protocol, will be compared between treatment groups.

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| Starting date | 1. Date of first enrolment: 2018/12/20<br>2. Date of registration: 2008/08/23 |
| Contact information | 1. Jon A. Kobashigawa, MD<br>2. Address:<br>3. Telephone:<br>4. Email:<br>5. Affiliation: Cedars Sinai Medical Center: Transplantation |
| Notes | https://clinicaltrials.gov/ct2/show/NCT03644667 |

**NCT03797001**

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| Study name | Rationale and design of interleukin-1 blockade in recently decompensated heart failure (RED-HART2): a randomized, double blind, placebo controlled, single center, phase 2 study |
| Methods | 1. Study type: interventional study<br>2. Study design: randomised parallel controlled trial<br>3. Target sample size: 102<br>4. Phase: II<br>5. Country: USA |
| Participants | 1. Age: ≥ 21 years<br>2. Sex: Both<br>3. Inclusion criteria:<br>• LVEF ≤ 40% in the last 12 months with any imaging modality<br>• Primary diagnosis for hospitalisation admission is decompensated heart failure with both conditions:<br>  ○ Dyspnoea or respiratory distress or tachypnoea at rest or with minimal exertion;<br>  ○ Evidence of elevated cardiac filling pressure or pulmonary congestion (one of the following met):<br>  ■ Pulmonary congestion/oedema at physical exam OR chest xray;<br>  ■ Plasma BNP levels ≥ 200 pg/mL OR NTproBNP ≥ 600 pg/mL;<br>  ■ Invasive measurement of LVEDP > 18 mmHg OR PA occluding pressure (wedge) > 16 mmHg;<br>• Clinically stable, euvolemic, and meets standard criteria for hospital discharge as documented by all 3 of the conditions listed below:<br>  ○ Absence of dyspnoea or pulmonary congestion/distress at rest;<br>  ○ Absence of pitting oedema in the lower extremities, or in any other region;<br>  ○ Stable haemodynamic parameters (blood pressure, heart rate);<br>• Willing and able to comply with the protocol (i.e. self-administration, exercise test, screening CRP);<br>• CRP > 0.3 mg/dL or hsCRP > 2 mg/L.<br>4. Exclusion criteria:<br>• The primary diagnosis for admission is NOT decompensated heart failure (i.e. acute coronary syndromes, hypertensive urgency/emergency, tachy- or bradyarrhythmias);<br>• Concomitant comorbidities that would interfere with the execution or interpretation of the study (i.e. uncontrolled hypertension, orthostatic hypotension, tachy- or bradyarrhythmias, acute or chronic pulmonary disease, or neuromuscular disorders affecting respiration, peak respiratory exchange ratio ($VCO_2/VO_2$) < 1.0, or with angina, abnormal blood pressure or heart rate response, or ECG changes suggestive of coronary ischaemia that limit maximum exertion during CPX obtained during the baseline testing;<br>• CRT during index hospitalisation, or planned CRT or valvular heart surgery within the following 6 months;<br>• Previous or planned implantation of left ventricular assist devices or heart transplant;<br>• Chronic use of intravenous inotropes;<br>• Recent (< 14 days) use of immunosuppressive or anti-inflammatory drugs (including oral corticosteroids at a dose of prednisone equivalent of 0.5 mg/kg/day but not including inhaled or low dose oral corticosteroids or oral NSAIDs);<br>• Chronic inflammatory disorder (including but not limited to rheumatoid arthritis, systemic lupus erythematosus);<br>• Active infection (of any type), including chronic/recurrent infectious disease (i.e. HBV, HCV, and HIV/AIDS)—but excluding HCV + with undetectable plasma RNA; |

**NCT03797001** *(Continued)*

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| | • Current malignancy (excluding carcinoma in situ (any location) or localised non-melanoma skin cancer) receiving targeted therapy;<br>• Any comorbidity limiting survival or ability to complete the study;<br>• Evidence of COVID-19 within the last 60 days or recent (21 days) exposure to close personal contact;<br>• Stage V kidney disease (eGFR < 15 mL/min/1.73m$^2$) or on renal-replacement therapy;<br>• Neutropenia (< 1500/mm$^3$ or < 1000/mm$^3$ in African- American patients);<br>• Pregnancy;<br>• Hypersensitivity to Kineret (anakinra) or to *E. coli*-derived products. |
| Interventions | Experimental:<br>1. Anakinra (100 mg)<br>Control:<br>1. Placebo: dispensed in small syringes (0.67 mL) |
| Outcomes | • Primary:<br>1. Peak $VO_2$ (in $mLO_2$ $kg^{-1}$ $min^{-1}$) during CPX after 24 weeks of treatment<br>• Secondary:<br>1. Cardiac death<br>2. Re-hospitalisation for HF within the first 6 months of hospitalisation |
| Starting date | 1. Date of first enrolment: 2018<br>2. Date of registration: 2018/11/18 |
| Contact information | Contact information<br>1. Benjamin Van Tassell<br>2. Address: Pauley Heart Center, Department of Internal Medicine, Pauley Heart Center, Richmond, VA USA<br>3. Telephone:<br>4. Email: bvantassell@vcu.edu<br>5. Affiliation: Virginia Commonwealth University |
| Notes | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9198622/<br>Source(s) of Monetary Support: Clinical and Translational Science Award to Virginia Commonwealth University (UL1TR002649) from the National Center for Advancing Translational Sciences |

**NCT04017936**

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| Study name | Interleukin-1 blockade for treatment of cardiac sarcoidosis |
| Methods | 1. Study type: interventional study<br>2. Study design: randomised parallel controlled trial<br>3. Target sample size: 28<br>4. Phase: II<br>5. Country: The USA |
| Participants | 1. Age: ≥ 21 years |

**NCT04017936** *(Continued)*

2. Sex: Both

3. Inclusion criteria:

- Clinical diagnosis of cardiac sarcoidosis according to the Heart Rhythm Society or the New Japanese Cardiac Sarcoidosis Guidelines (must meet one of the diagnostic pathways);
- Heart Rhythm Society diagnostic criteria based on 2 diagnostic pathways:

1. Histological diagnosis from myocardial tissue - cardiac sarcoidosis is diagnosed in the presence of non-caseating granuloma on histologic examination of myocardial tissue with no alternative cause identified (including negative stain for microorganisms - as applicable);
2. Clinical diagnosis from invasive and/or non-invasive studies - it is probable that there is cardiac sarcoidosis if there is (a) histological diagnosis of extracardiac sarcoidosis and (b) one or more of the following: steroid +/- immunosuppressant responsive cardiomyopathy or heart block; unexplained reduction in LVEF (< 40%); unexplained sustained (spontaneous or induced) ventricular tachycardia; Mobitz type II 2nd degree or 3rd degree AV block; patchy uptake on dedicated cardiac PET (in a pattern consistent with cardiac sarcoidosis); late gadolinium enhancement on cardiac magnetic resonance (in a pattern consistent with cardiac sarcoidosis); positive gallium uptake (in a pattern consistent with cardiac sarcoidosis) and (c) other causes for the cardiac manifestation(s) have been reasonably excluded.

- Japanese Cardiac Sarcoidosis diagnostic criteria:

1. Histological diagnosis group (those with positive myocardial biopsy findings). Cardiac sarcoidosis is diagnosed histologically when endomyocardial biopsy or surgical specimens demonstrate non-caseating epithelioid granulomas;
2. Clinical diagnosis group (those with negative myocardial biopsy findings or those not undergoing myocardial biopsy).

The patient is clinically diagnosed as having sarcoidosis:

1. When epithelioid granulomas are found in organs other than the heart and clinical findings strongly suggestive of the above-mentioned cardiac involvement are present (Table 1); or
2. When the patient shows clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis; at least 2 of the 5 characteristic laboratory findings of a sarcoidosis (Table 2); and clinical findings strongly suggest the above-mentioned cardiac involvement (Table 1).

TABLE 1. Clinical findings defining cardiac involvement findings should be assessed based on the major criteria and the minor criteria. Clinical findings that satisfy the following 1) or 2) strongly suggest the presence of cardiac involvement.

1. 2 or more of the 5 major criteria (a)-(e) are satisfied.
2. 1 of the 5 major criteria (a)-(e) and 2 or more of the 3 minor criteria (f)-(h) are satisfied.

1. Major criteria:

1. High-grade AV block (including complete AV block) or fatal ventricular arrhythmia (e.g. sustained VT and VF);
2. Basal thinning of the ventricular septum or abnormal ventricular wall anatomy (ventricular aneurysm, thinning of the middle or upper ventricular septum, regional wall thickening);
3. Left ventricular contractile dysfunction (LVEF < 50%);
4. 67Ga citrate scintigraphy or 18F-FDG PET reveals abnormally high tracer accumulation in the heart;
5. Gadolinium-enhanced MRI revealed delayed contrast enhancement of the myocardium.

2. Minor criteria:

1. Abnormal ECG findings: ventricular arrhythmias (nonsustained VT, multifocal or frequent premature ventricular contractions, bundle branch block, axis deviation, or abnormal Q waves);
2. Perfusion defects on myocardial perfusion scintigraphy (SPECT);
3. Endomyocardial biopsy: monocyte infiltration and moderate or severe myocardial interstitial fibrosis.

**NCT04017936** *(Continued)*

TABLE 2. Characteristic laboratory findings of sarcoidosis

Major criteria:

6. Bilateral hilar lymphadenopathy;
7. High serum angiotensin-converting (ACE) activity or elevated serum lysozyme levels;
8. High serum soluble interleukin-2 receptor (sIL-2R) levels;
9. Significant tracer accumulation in 67Ga citrate scintigraphy or 18F-FDG PET;
10. A high percentage of lymphocytes with a CD4CD8 ration of > 3.5 in BAL fluid.

- Diagnostic guidelines for isolated cardiac sarcoidosis based on New CS Guidelines in Japan pre-requisite

1. No clinical findings characteristic of sarcoidosis are observed in any organs other than the heart (the patient should be examined in detail for respiratory, ophthalmic, and skin involvement of sarcoidosis. When the patient is symptomatic, other aetiologies that can affect the corresponding organs must be ruled out);
2. 67Ga scintigraphy or 18F-FDG PET reveals no abnormal tracer accumulation in any organs other than the heart;
3. A chest CT scan reveals no shadow along the lymphatic tracts in the lungs or no hilar and mediastinal lymphadenopathy (minor axis > 10 mm);
4. Histological diagnosis group isolated cardiac sarcoidosis is diagnosed histologically when endomyocardial biopsy or surgical specimens demonstrate non-caseating epithelioid granulomas;
5. Clinical diagnosis group isolated cardiac sarcoidosis is diagnosed clinically when criterion (d) and at least 3 other major criteria (a)-(e) are satisfied (Table 1).

- Cardiac fluoro-deoxyglucose uptake on recent PET (performed within the prior month).
- CRP high-sensitivity assay > 2 mg/l.

4. Exclusion criteria:

- Age < 21 years;
- Pregnancy;
- Inability to obtain consent from patient or legally authorised representative;
- Contraindications to treatment with anakinra (Kineret) (i.e. prior allergic reaction to the drug or to *E. coli* derived products or severe allergy to latex);
- Severe anaemia (Hgb < 8 g/dL - due to the need for more frequent blood sampling in this study);
- Acute or chronic active infections (not including treated/cured HCV with negative viral load);
- Acute or chronic inflammatory disease or immunosuppressive therapies (excluding stable (> 1 month) oral corticosteroids at a dose of prednisone less than 0.5 mg/kg/day or methotrexate);
- Active acute or chronic psychiatric illness that, in the opinion of the investigator, may prevent the patient from complying with study instructions;
- Limited English proficiency that, in the opinion of the investigator, may prevent the patient from understanding the content of the informed consent form or safely completing the study procedures;
- Live vaccination within the prior month;
- Neutropenia (defined as absolute neutrophil count < 1500/ml or <1,000/mL if the subject is African-American);
- History of malignancy within the prior 5 years (except for basal cell skin cancer, carcinoma in-situ of the cervix or low risk prostate cancer after curative therapy);
- Participation in another concurrent intervention study within 30 days or treatment with an investigational drug within 5 half-lives prior to randomisation;
- Severe kidney disease (GFR < 30 mL/min/1.73m$^2$);
- Evidence of COVID-19 within the last 60 days or recent (21 days) exposure to close personal contact with COVID-19;
- (Chronic, moderate-to-severe kidney disease (GFR < 60 mL/min/1.73m$^2$) or acute kidney injury, or history of severe hypersensitivity reactions to gadolinium-based contrast agents) - for VCU imaging substudy

**NCT04017936** *(Continued)*

| | |
|---|---|
| Interventions | Experimental:<br>1. Anakinra: 100 mg/0.67 mL daily subcutaneous injection for 4 weeks<br>Control:<br>1. Continuing standard-of-care treatment |
| Outcomes | • Primary :<br>1. Change in inflammation marker (time frame: baseline to 28 days). Change in C-reactive protein in participant plasma samples<br>• Secondary:<br>1. Change in cardiac inflammation (time frame: baseline to 28 days). Change in heart function as measured by tracer activity using positron emission tomography (PET) scans<br>2. Change in cardiac fibrosis (time frame: baseline to 28 days). Change in late gadolinium enhancement evident on magnetic resonance imaging (MRI) scan<br>3. Number of serious cardiac events (time frame: 28 days). Sum of hospitalisations and deaths due to cardiac causes |
| Starting date | 1. Date of first enrolment: 2020/10/23<br>2. Date of registration: 2019/07/12 |
| Contact information | 1. Jordana Kron, MD<br>2. Address: Richmond, Virginia, United States, 23298<br>3. Telephone: 804-628-3981<br>4. Email: virginia.mihalick@vcuhealth.org<br>5. Affiliation: Virginia Commonwealth University |
| Notes | https://clinicaltrials.gov/ct2/show/study/NCT04017936 |

**NCT04834388**

| | |
|---|---|
| Study name | Anakinra in cerebral haemorrhage to target secondary injury resulting from neuroinflammation - a phase II clinical trial |
| Methods | 1. Study type: interventional study<br>2. Study design: randomised parallel controlled trial<br>3. Target sample size: 75<br>4. Phase: II<br>5. Country: Netherlands |
| Participants | 1. Age: ≥ 18 years<br>2. Sex: Both<br>3. Inclusion criteria:<br>• Supratentorial non-traumatic ICH confirmed by CT, without a confirmed causative lesion on admission CT-angiography (e.g. aneurysm, AVM, DAVF, cerebral venous sinus thrombosis) or other known underlying lesion (e.g. tumour, cavernoma);<br>• Minimal intracerebral haemorrhage volume of 10 mL;<br>• Intervention can be started within 8 hours from symptoms onset;<br>• Patient's or legal representative's informed consent. |

**NCT04834388** *(Continued)*

| | |
|---|---|
| | 4. Exclusion Criteria:<br>• Severe ICH, unlikely to survive the first 72 hours (defined as Glasgow Coma Scale score < 6 at time of consent);<br>• Confirmed or suspected haemorrhagic transformation of an arterial or venous infarct;<br>• Planned neurosurgical haematoma evacuation;<br>• Severe infection at admission, requiring antibiotic treatment;<br>• Known active tuberculosis or active hepatitis;<br>• Use of immunosuppressive or immune-modulating therapy at admission (see 15.1 Appendix A);<br>• Neutropenia (Absolute Neutrophil Count (ANC) < 1.5 x 109/L);<br>• Pre-stroke modified Rankin Scale score ≥ 3;<br>• Pregnancy or breastfeeding;<br>• Standard contraindications to MRI (see 15.2 Appendix B);<br>• Known prior allergic reaction to gadolinium contrast or one of the constituents of its solution for administration;<br>• Known allergy to anakinra or other products that are produced by DNA technology using the microorganism *E. coli;*<br>• Live vaccinations within the last 10 days prior to this ICH;<br>• Severe renal impairment (eGFR < 30mL/min/1.73m$^2$);<br>• Active malignancy. |
| Interventions | Experimental:<br>1. Anakinra high dose: 500 mg IV loading dose, followed by continuous IV infusion with 2 mg/kg/h over 3 days<br>2. Anakinra low dose: 100 mg SC loading dose, followed by subcutaneous administration of 100 mg twice daily for 3 days<br>Control:<br>1. Standard care group |
| Outcomes | • Primary:<br>1. Perihaematomal oedema (time frame: 7 days after ICH onset) Measured as OED/EED<br>• Secondary:<br>1. AESI and SAE (time frame: 90 days)<br>2. Blood brain barrier leakage (time frame: 7 days). Measured as Ktrans on DCE-MRI<br>3. Levels of serum inflammatory markers (time frame: 7 days) IL-1β, IL-6, hsCRP, neutrophil and total white blood cell counts<br>4. Functional outcome (time frame: 90 days) |
| Starting date | 1. Date of first enrolment: 2022/08/10<br>2. Date of registration: 2021/04/8 |
| Contact information | 1. Floris H.B.M Schreuder, MD PhD<br>2. Address:<br>3. Telephone: +31650155755<br>4. Email: floris.schreuder@radboudumc.nl<br>5. Affiliation: Radboud University Medical Center |
| Notes | https://clinicaltrials.gov/ct2/show/NCT04834388 |

**NCT05177822**

| | |
|---|---|
| Study name | Interleukin-1 blockade in acute myocardial infarction to prevent heart failure: the Virginia-Anakinra Remodeling trial 4 |
| Methods | 1. Study type: interventional study<br>2. Study design: randomised parallel controlled trial. Masking: quadruple<br>3. Target sample size: 84<br>4. Phase: II<br>5. Country: USA |
| Participants | 1. Age: ≥ 21 years<br>2. Sex: Both<br>3. Inclusion criteria:<br>• Acute ST segment elevation myocardial infarction defined as:<br>  ◦ Chest pain, consistent with angina, within the prior 12 hours (for intermittent pain lasting more than 12 hours, the time from when the pain became severe and constant);<br>  ◦ ST segment elevation on ECG > 1 mm in 2 or more anatomically contiguous leads;<br>  ◦ Reperfusion strategy planned or completed (including percutaneous coronary intervention or fibrinolysis).<br>4. Exclusion criteria:<br>• Pregnancy;<br>• Inability to obtain consent from patient;<br>• History of prior STEMI or of systolic heart failure (LVEF < 40%);<br>• Contraindications to treatment with anakinra (i.e. prior allergic reaction to Kineret® or *E. coli* derived products);<br>• Duration of chest pain > 12 hours at time of coronary artery catheterisation (continuously - see exceptions in Inclusion Criteria) or coronary artery intervention > 12 hours earlier (see exceptions in Inclusion Criteria) (max duration of chest pain 24 hours);<br>• Failed reperfusion strategy (unsuccessful percutaneous coronary intervention);<br>• Need or plan for emergent cardiac surgery;<br>• Anticipated inability to complete a CPET on a treadmill at follow-up visit at 42 days (i.e. amputee, wheelchair bound, severe non-cardiac illness limiting mobility);<br>• Active infection (such as acute, i.e. COVID-19, or chronic/recurrent infectious disease, i.e HBV, HCV, and HIV/AIDS - but excluding HCV+ patients with undetectable plasma RNA);<br>• Acute or chronic inflammatory disease or immunosuppressive therapies (including oral corticosteroids at a dose of prednisone equivalent of 0.5 mg/kg/day but not including inhaled or low dose oral corticosteroids or non-steroidal anti-inflammatory drugs);<br>• Neutropenia (< 1500/$mm^3$ or < 1000/$mm^3$ in African-American patients);<br>• Active acute or chronic psychiatric illness that, in the opinion of the investigator, may prevent patients from complying with study instructions;<br>• Stage V chronic kidney disease (estimated glomerular filtration rate 15 mL/min/1.73$m^2$ or less) or on renal-replacement therapy (a GFR ≥ 45 mL/min/1.73$m^2$ is required for the cardiac magnetic resonance portion of the study);<br>• Limited English proficiency that, in the opinion of the investigator, may prevent patients from understanding the content of the informed consent form and instructions during the tests required for the study;<br>• Any comorbidity limiting survival or ability to complete the study. |
| Interventions | Experimental:<br>1. Anakinra |

**NCT05177822** *(Continued)*

| | |
|---|---|
| | Control:<br>1. Placebo |
| Outcomes | • Primary:<br>1. Peak $VO_2$ (time frame: 6 weeks)<br>• Secondary:<br>1. none |
| Starting date | 1. Date of first enrolment: 2022/05/24<br>2. Date of registration: 2022/01/5 |
| Contact information | 1. Antonio Abbate, MD, PhD<br>2. Address: Richmond, Virginia, United States, 23298<br>3. Telephone:<br>4. Email: Antonio.abbate@virginia.edu<br>5. Affiliation: Virginia Commonwealth University |
| Notes | https://clinicaltrials.gov/ct2/show/NCT05177822 |

ACE: Angiotensin-Converting Enzyme
ACR: American College of Rheumatology
AESI: Adverse Events of Special Interest
AIDS: Acquired Immunodeficiency Syndrome
ALT: Alanine Aminotransferase
AMR: Antibody-Mediated Rejection
ANC: Absolute Neutrophil Count
AST: Aspartate Aminotransferase
AUC: Area Under the Curve
AV: Atrioventricular
AVM: Arteriovenous Malformation
BAL: Bronchoalveolar Lavage
BAT: Biopsy of the Temporal Artery
BNP: B-type Natriuretic Peptide
CAG: Coronary Angiography
CAV: Cardiac Allograft Vasculopathy
CCTA: Cardiac Computer Tomography Angiogram
CD25: Cluster of Differentiation 25
CD4: Cluster of Differentiation 4
CD8: Cluster of Differentiation 8
CMV: Cytomegalovirus
CPET: Cardiopulmonary Exercise Test
CPX: Cardiopulmonary Exercise Test
CrCl: Creatinine Clearance
CRP: C-Reactive Protein
CRT: Cardiac Resynchronisation Therapy
CT: Computed Tomography
DAVF: Dural Arteriovenous Fistula
DCD: Donation after Circulatory Death
DCE: Dynamic Contrast-Enhanced
DNA: Deoxyribonucleic Acid
dnDSA: De Novo Donor-Specific Antibodies
ECG: Electrocardiogram
eGFR: Estimated Glomerular Filtration Rate
END: Early Neurological Decline
EQ-5D-5L: EuroQol 5 Dimension 5 Level
ESR: Erythrocyte Sedimentation Rate
FDA: Food and Drug Administration
FDG: Fluorodeoxyglucose

FSS: Fatigue Severity Score
GCA: Giant Cell Arteritis
GCS: Glasgow Coma Scale
HADS: Hospital Anxiety and Depression Scale
HAQ: Health Assessment Questionnaire
HBV: Hepatitis B Virus
HCV: Hepatitis C Virus
HDC: High-Dose Chemotherapy
HF: Heart Failure
Hgb: Haemoglobin
HIV: Human Immunodeficiency Virus
HRPs: High-Risk Plaques
hsCRP: High-Sensitivity C-Reactive Protein
ICH: Intracerebral Haemorrhage
IL: Interleukin
IS: Immunosuppression
ISHLT: International Society for Heart and Lung Transplantation
IV: Intravenous
IVUS: Intravascular Ultrasound
ktrans: Transfer Constant
LTBI: Latent Tuberculosis Infection
LVAD: Left Ventricular Assist Device
LVEDP: Left Ventricular End-Diastolic Pressure
LVEF: Left Ventricular Ejection Fraction
MMR: Measles, Mumps, and Rubella
MR: Magnetic Resonance
MRI: Magnetic Resonance Imaging
MDRD: Modification of Diet in Renal Disease
mRS: Modified Rankin Scale
NAT: Nucleic Acid Testing
NCB: Non-Calcified Coronary Plaque Burden
NSAIDs: Nonsteroidal Anti-Inflammatory Drugs
NT-proBNP: N Terminal-pro B-type Natriuretic Peptide
NYHA: New York Heart Association
OED/EED: Oedema Extension Distance
PA: Pulmonary Artery
PASI: Psoriasis Area and Severity Index
Peak VO2: Peak Oxygen Consumption
PET: Positron Emission Tomography
PI: Principal Investigator
PMR: Polymyalgia Rheumatica
PTLD: Post-Transplant Lymphoproliferative Disorder
QALY: Quality-Adjusted Life Year
RA: Rheumatoid Arthritis
RNA: Ribonucleic Acid
RT-PCR: Reverse Transcription Polymerase Chain Reaction
SAE: Serious Adverse Events
SAH: Subarachnoid Haemorrhage
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
SC: Subcutaneous
SIL-2R: Soluble Interleukin-2 Receptor
SIS: Stroke Impact Scale
SmPC: Summary of Product Characteristics
SPECT: Single-Photon Emission Computed Tomography
ST: ST segment
STEMI: ST-Elevation Myocardial Infarction
TCZ: Tocilizumab
TNF: Tumour Necrosis Factor
TTE: Transthoracic Echocardiography
ULN: Upper Limit of Normal
VAS: Visual Analogue Scale
VCO2: Carbon Dioxide Production

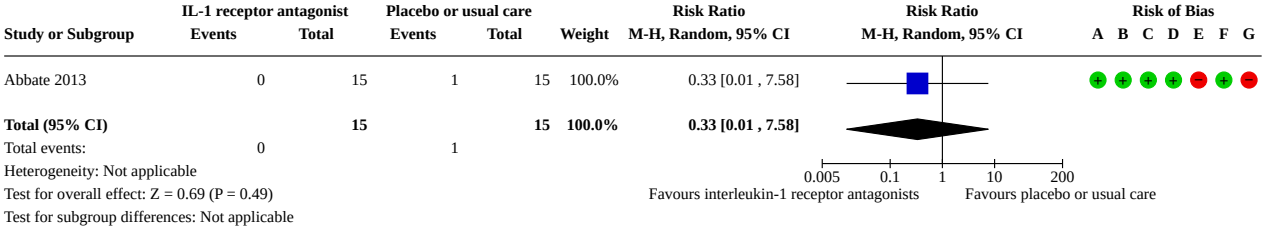
VF: Ventricular Fibrillation
VO2: Oxygen Uptake
VT: Ventricular Tachycardia

## DATA AND ANALYSES

**Comparison 1. Interleukin-1 receptor antagonists compared with placebo or usual care for primary prevention**

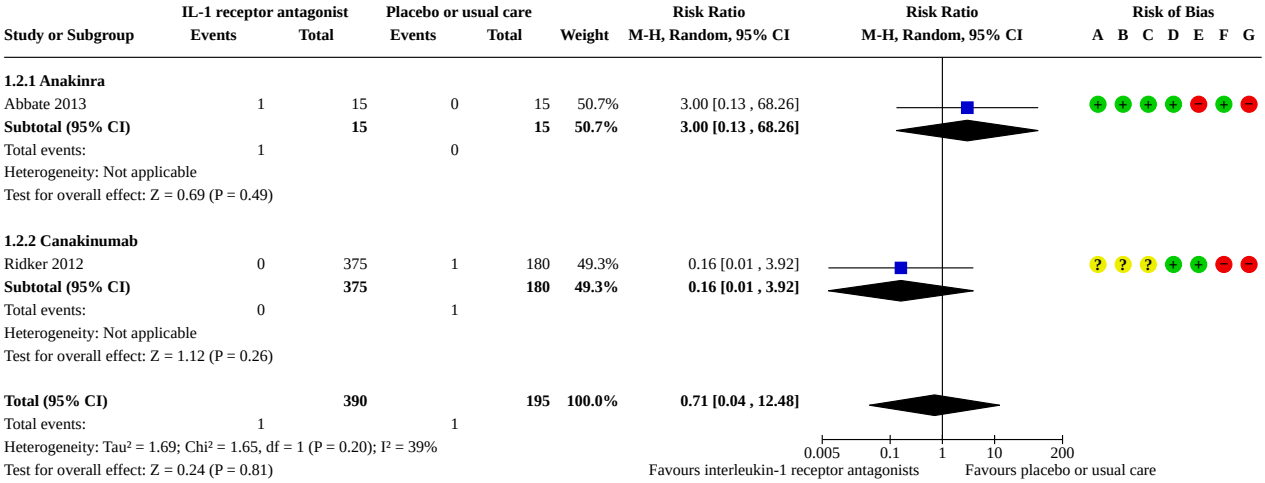
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.1 All-cause mortality | 1 | 30 | Risk Ratio (M-H, Random, 95% CI) | 0.33 [0.01, 7.58] |
| 1.2 Myocardial infarction (fatal or non-fatal) | 2 | 585 | Risk Ratio (M-H, Random, 95% CI) | 0.71 [0.04, 12.48] |
| 1.2.1 Anakinra | 1 | 30 | Risk Ratio (M-H, Random, 95% CI) | 3.00 [0.13, 68.26] |
| 1.2.2 Canakinumab | 1 | 555 | Risk Ratio (M-H, Random, 95% CI) | 0.16 [0.01, 3.92] |
| 1.3 Unstable angina | 2 | 566 | Risk Ratio (M-H, Random, 95% CI) | 0.24 [0.03, 2.11] |
| 1.3.1 Anakinra | 1 | 10 | Risk Ratio (M-H, Random, 95% CI) | 0.33 [0.02, 6.65] |
| 1.3.2 Canakinumab | 1 | 556 | Risk Ratio (M-H, Random, 95% CI) | 0.16 [0.01, 3.94] |
| 1.4 Adverse events | 3 | 596 | Risk Ratio (M-H, Random, 95% CI) | 0.85 [0.59, 1.22] |
| 1.4.1 Anakinra | 2 | 40 | Risk Ratio (M-H, Random, 95% CI) | 0.69 [0.48, 0.99] |
| 1.4.2 Canakinumab | 1 | 556 | Risk Ratio (M-H, Random, 95% CI) | 1.04 [0.85, 1.28] |
| 1.5 Adverse events (by patients) | 4 | 666 | Rate Ratio (IV, Random, 95% CI) | 1.06 [0.52, 2.16] |
| 1.5.1 Anakinra | 3 | 110 | Rate Ratio (IV, Random, 95% CI) | 1.17 [0.38, 3.67] |
| 1.5.2 Canakinumab | 1 | 556 | Rate Ratio (IV, Random, 95% CI) | 0.83 [0.56, 1.22] |
| 1.6 Adverse events (any infections) | 4 | 666 | Rate Ratio (IV, Random, 95% CI) | 0.84 [0.55, 1.29] |
| 1.6.1 Anakinra | 3 | 110 | Rate Ratio (IV, Random, 95% CI) | 1.46 [0.50, 4.30] |
| 1.6.2 Canakinumab | 1 | 556 | Rate Ratio (IV, Random, 95% CI) | 0.76 [0.47, 1.21] |
| 1.7 Stroke (fatal or non-fatal) | 1 | 556 | Risk Ratio (M-H, Fixed, 95% CI) | 2.42 [0.12, 50.15] |
| 1.8 Heart failure | 3 | 596 | Risk Ratio (M-H, Random, 95% CI) | 0.21 [0.05, 0.94] |
| 1.8.1 Anakinra | 2 | 40 | Risk Ratio (M-H, Random, 95% CI) | 0.23 [0.04, 1.23] |
| 1.8.2 Canakinumab | 1 | 556 | Risk Ratio (M-H, Random, 95% CI) | 0.16 [0.01, 3.94] |

## Analysis 1.1. Comparison 1: Interleukin-1 receptor antagonists compared with placebo or usual care for primary prevention, Outcome 1: All-cause mortality



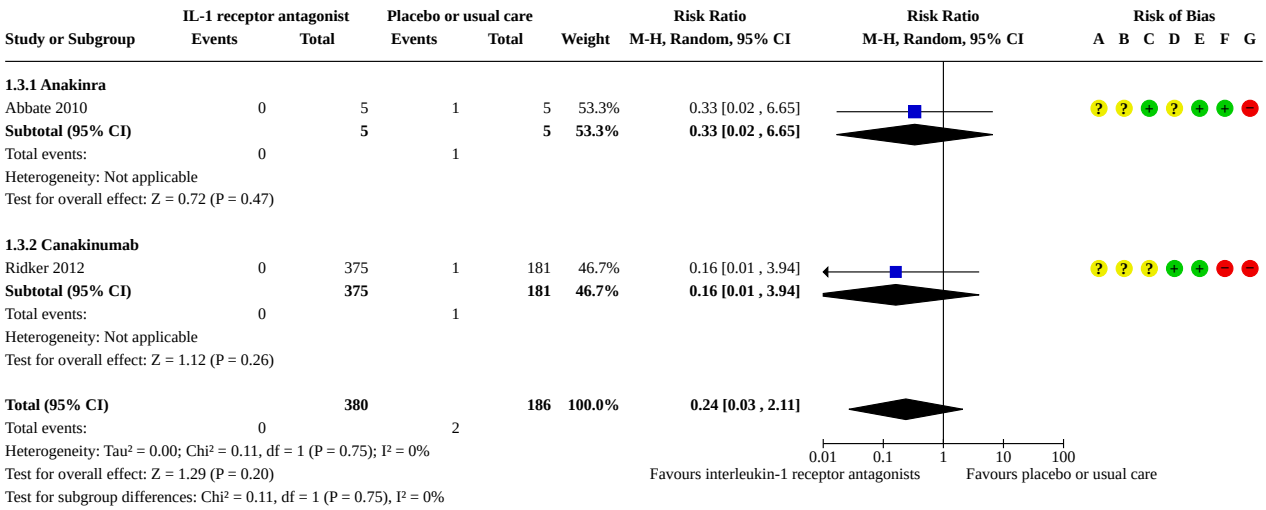

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 1.2. Comparison 1: Interleukin-1 receptor antagonists compared with placebo or usual care for primary prevention, Outcome 2: Myocardial infarction (fatal or non-fatal)



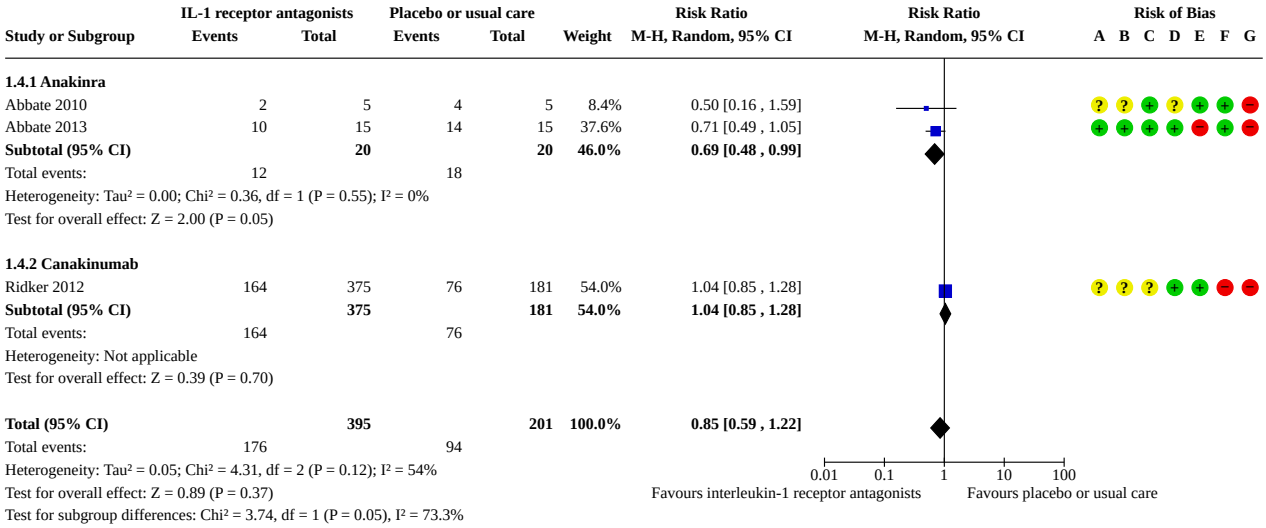

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 1.3. Comparison 1: Interleukin-1 receptor antagonists compared with placebo or usual care for primary prevention, Outcome 3: Unstable angina




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

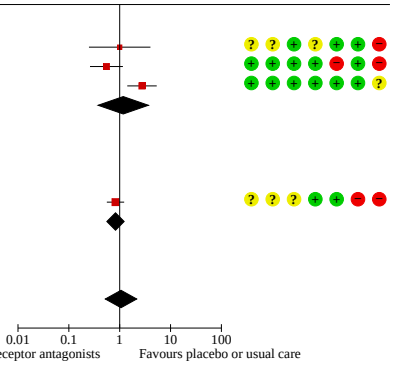
## Analysis 1.4. Comparison 1: Interleukin-1 receptor antagonists compared with placebo or usual care for primary prevention, Outcome 4: Adverse events




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 1.5. Comparison 1: Interleukin-1 receptor antagonists compared with placebo or usual care for primary prevention, Outcome 5: Adverse events (by patients)

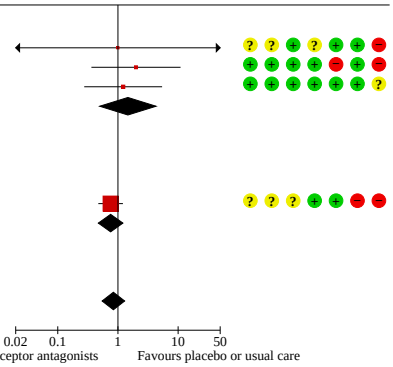
| Study or Subgroup | log[Rate Ratio] | SE | Interleukin-1 receptor antagonists Total | Placebo or usual care Total | Weight | Rate Ratio IV, Random, 95% CI | Rate Ratio IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| **1.5.1 Anakinra** | | | | | | | | |
| Abbate 2010 | 0 | 0.71 | 5 | 5 | 15.1% | 1.00 [0.25 , 4.02] | | ? ? + ? + + - |
| Abbate 2013 | -0.6 | 0.38 | 15 | 15 | 25.6% | 0.55 [0.26 , 1.16] | | + + + + - + - |
| Ebrahimi 2018 | 1.01 | 0.34 | 35 | 35 | 27.1% | 2.75 [1.41 , 5.35] | | + + + + + + ? |
| **Subtotal (95% CI)** | | | **55** | **55** | **67.9%** | **1.17 [0.38 , 3.67]** | | |
| Heterogeneity: Tau² = 0.79; Chi² = 10.12, df = 2 (P = 0.006); I² = 80% | | | | | | | | |
| Test for overall effect: Z = 0.28 (P = 0.78) | | | | | | | | |
| **1.5.2 Canakinumab** | | | | | | | | |
| Ridker 2012 | -0.19 | 0.2 | 375 | 181 | 32.1% | 0.83 [0.56 , 1.22] | | ? ? ? + + - - |
| **Subtotal (95% CI)** | | | **375** | **181** | **32.1%** | **0.83 [0.56 , 1.22]** | | |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.95 (P = 0.34) | | | | | | | | |
| **Total (95% CI)** | | | **430** | **236** | **100.0%** | **1.06 [0.52 , 2.16]** | | |
| Heterogeneity: Tau² = 0.37; Chi² = 12.22, df = 3 (P = 0.007); I² = 75% | | | | | | | | |
| Test for overall effect: Z = 0.16 (P = 0.87) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.57), I² = 0% | | | | | | | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 1.6. Comparison 1: Interleukin-1 receptor antagonists compared with placebo or usual care for primary prevention, Outcome 6: Adverse events (any infections)

| Study or Subgroup | log[Rate Ratio] | SE | Interleukin-1 receptor antagonists Total | Placebo or usual care Total | Weight | Rate Ratio IV, Random, 95% CI | Rate Ratio IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| **1.6.1 Anakinra** | | | | | | | | |
| Abbate 2010 | 0 | 2 | 5 | 5 | 1.2% | 1.00 [0.02 , 50.40] | | ? ? + ? + + - |
| Abbate 2013 | 0.69 | 0.87 | 15 | 15 | 6.4% | 1.99 [0.36 , 10.97] | | + + + + - + - |
| Ebrahimi 2018 | 0.2 | 0.76 | 35 | 35 | 8.4% | 1.22 [0.28 , 5.42] | | + + + + + + ? |
| **Subtotal (95% CI)** | | | **55** | **55** | **16.0%** | **1.46 [0.50 , 4.30]** | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 2 (P = 0.90); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 0.69 (P = 0.49) | | | | | | | | |
| **1.6.2 Canakinumab** | | | | | | | | |
| Ridker 2012 | -0.28 | 0.24 | 375 | 181 | 84.0% | 0.76 [0.47 , 1.21] | | ? ? ? + + - - |
| **Subtotal (95% CI)** | | | **375** | **181** | **84.0%** | **0.76 [0.47 , 1.21]** | | |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.17 (P = 0.24) | | | | | | | | |
| **Total (95% CI)** | | | **430** | **236** | **100.0%** | **0.84 [0.55 , 1.29]** | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 3 (P = 0.70); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 0.79 (P = 0.43) | | | | | | | | |
| Test for subgroup differences: Chi² = 1.21, df = 1 (P = 0.27), I² = 17.5% | | | | | | | | |

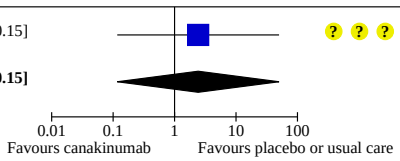



**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 1.7. Comparison 1: Interleukin-1 receptor antagonists compared with placebo or usual care for primary prevention, Outcome 7: Stroke (fatal or non-fatal)

| Study or Subgroup | IL-1 receptor antagonist Events | Total | Placebo or usual care Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Ridker 2012 | 2 | 375 | 0 | 181 | 100.0% | 2.42 [0.12 , 50.15] |
| **Total (95% CI)** | | **375** | | **181** | **100.0%** | **2.42 [0.12 , 50.15]** |
| Total events: | 2 | | 0 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)
Test for subgroup differences: Not applicable




**Risk of bias legend**
(A) Random sequence generation (selection bias)
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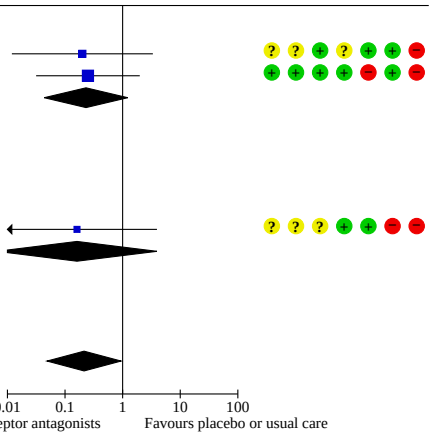
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 1.8. Comparison 1: Interleukin-1 receptor antagonists compared with placebo or usual care for primary prevention, Outcome 8: Heart failure

| Study or Subgroup | Interleukin-receptor antagonist Events | Total | Placebo or usual care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.8.1 Anakinra** | | | | | | |
| Abbate 2010 | 0 | 5 | 2 | 5 | 27.6% | 0.20 [0.01 , 3.35] |
| Abbate 2013 | 1 | 15 | 4 | 15 | 51.0% | 0.25 [0.03 , 1.98] |
| **Subtotal (95% CI)** | | **20** | | **20** | **78.6%** | **0.23 [0.04 , 1.23]** |
| Total events: | 1 | | 6 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.72 (P = 0.09) | | | | | | |
| **1.8.2 Canakinumab** | | | | | | |
| Ridker 2012 | 0 | 375 | 1 | 181 | 21.4% | 0.16 [0.01 , 3.94] |
| **Subtotal (95% CI)** | | **375** | | **181** | **21.4%** | **0.16 [0.01 , 3.94]** |
| Total events: | 0 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.12 (P = 0.26) | | | | | | |
| **Total (95% CI)** | | **395** | | **201** | **100.0%** | **0.21 [0.05 , 0.94]** |
| Total events: | 1 | | 7 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 2.04 (P = 0.04)
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
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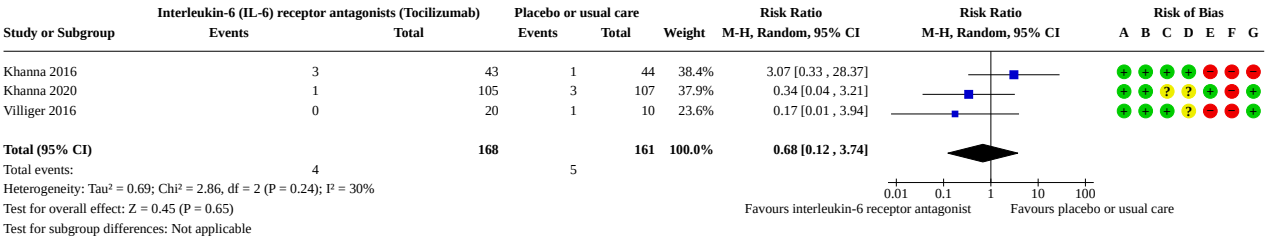
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Comparison 2. Interleukin-6 receptor antagonist compared with placebo or usual care for primary prevention

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.1 All-cause mortality | 3 | 329 | Risk Ratio (M-H, Random, 95% CI) | 0.68 [0.12, 3.74] |
| 2.2 Myocardial Infarction (fatal or non-fatal) | 3 | 329 | Risk Ratio (M-H, Random, 95% CI) | 0.27 [0.04, 1.68] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.3 Adverse events | 5 | 1051 | Risk Ratio (M-H, Random, 95% CI) | 1.13 [1.04, 1.23] |
| 2.4 Adverse events (incidence rate) | 4 | 621 | Rate Ratio (IV, Random, 95% CI) | 27.89 [19.58, 39.73] |
| 2.4.1 Tocilizumab | 4 | 621 | Rate Ratio (IV, Random, 95% CI) | 27.89 [19.58, 39.73] |
| 2.5 Adverse event: any infection (incidence rate) | 5 | 1048 | Rate Ratio (IV, Fixed, 95% CI) | 1.10 [0.88, 1.37] |
| 2.5.1 Tocilizumab | 5 | 1048 | Rate Ratio (IV, Fixed, 95% CI) | 1.10 [0.88, 1.37] |
| 2.6 Peripheral vascular disease | 1 | 212 | Risk Ratio (M-H, Random, 95% CI) | 2.94 [0.12, 71.47] |
| 2.7 Stroke (fatal or non-fatal) | 1 | 87 | Risk Ratio (M-H, Random, 95% CI) | 0.34 [0.01, 8.14] |
| 2.8 Heart failure | 2 | 299 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.11, 9.63] |

**Analysis 2.1. Comparison 2: Interleukin-6 receptor antagonist compared with placebo or usual care for primary prevention, Outcome 1: All-cause mortality**




**Risk of bias legend**
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(D) Blinding of outcome assessment (detection bias)
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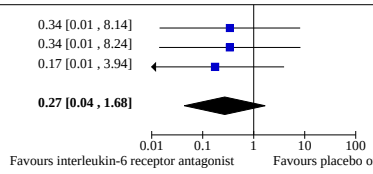
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 2.2. Comparison 2: Interleukin-6 receptor antagonist compared with placebo or usual care for primary prevention, Outcome 2: Myocardial Infarction (fatal or non-fatal)

| Study or Subgroup | Interleukin-6 (IL-6) receptor antagonists (Tocilizumab) Events | Total | Placebo or usual care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| Khanna 2016 | 0 | 43 | 1 | 44 | 33.0% | 0.34 [0.01 , 8.14] | + + + + − − − |
| Khanna 2020 | 0 | 105 | 1 | 107 | 32.7% | 0.34 [0.01 , 8.24] | + + ? ? + − + |
| Villiger 2016 | 0 | 20 | 1 | 10 | 34.3% | 0.17 [0.01 , 3.94] | + + + ? − − + |
| **Total (95% CI)** | | **168** | | **161** | **100.0%** | **0.27 [0.04 , 1.68]** | |
| Total events: | 0 | | 3 | | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable




**Risk of bias legend**
(A) Random sequence generation (selection bias)
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(C) Blinding of participants and personnel (performance bias)
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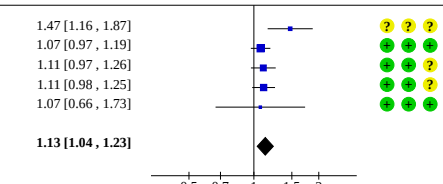
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 2.3. Comparison 2: Interleukin-6 receptor antagonist compared with placebo or usual care for primary prevention, Outcome 3: Adverse events

| Study or Subgroup | Interleukin-6 (IL-6) receptor antagonists (Tocilizumab) Events | Total | Placebo or usual care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| Baek 2019 | 43 | 48 | 31 | 51 | 10.6% | 1.47 [1.16 , 1.87] | ? ? ? ? − ? + |
| Khanna 2016 | 42 | 43 | 40 | 44 | 32.9% | 1.07 [0.97 , 1.19] | + + + + − − − |
| Khanna 2020 | 89 | 105 | 82 | 107 | 25.4% | 1.11 [0.97 , 1.26] | + + ? ? + − + |
| Smolen 2008 | 294 | 419 | 129 | 204 | 28.0% | 1.11 [0.98 , 1.25] | + + ? + + − − |
| Villiger 2016 | 15 | 20 | 7 | 10 | 3.1% | 1.07 [0.66 , 1.73] | + + + ? − − + |
| **Total (95% CI)** | | **635** | | **416** | **100.0%** | **1.13 [1.04 , 1.23]** | |
| Total events: | 483 | | 289 | | | | |

Heterogeneity: Tau² = 0.00; Chi² = 5.96, df = 4 (P = 0.20); I² = 33%
Test for overall effect: Z = 2.77 (P = 0.006)
Test for subgroup differences: Not applicable




**Risk of bias legend**
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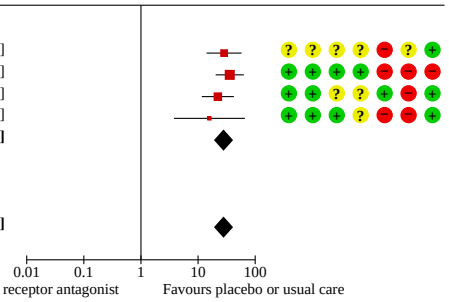
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 2.4. Comparison 2: Interleukin-6 receptor antagonist compared with placebo or usual care for primary prevention, Outcome 4: Adverse events (incidence rate)

| Study or Subgroup | log[Rate Ratio] | SE | Tocilizumab Total | Placebo or usual care Total | Weight | Rate Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **2.4.1 Tocilizumab** | | | | | | |
| Baek 2019 | 3.35 | 0.36 | 48 | 66 | 25.2% | 28.50 [14.08 , 57.72] |
| Khanna 2016 | 3.58 | 0.29 | 43 | 136 | 38.8% | 35.87 [20.32 , 63.33] |
| Khanna 2020 | 3.1 | 0.33 | 105 | 173 | 29.9% | 22.20 [11.63 , 42.38] |
| Villiger 2016 | 2.76 | 0.73 | 26 | 24 | 6.1% | 15.80 [3.78 , 66.07] |
| **Subtotal (95% CI)** | | | **222** | **399** | **100.0%** | **27.89 [19.58 , 39.73]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.84, df = 3 (P = 0.61); I² = 0% | | | | | | |
| Test for overall effect: Z = 18.43 (P < 0.00001) | | | | | | |
| **Total (95% CI)** | | | **222** | **399** | **100.0%** | **27.89 [19.58 , 39.73]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.84, df = 3 (P = 0.61); I² = 0% | | | | | | |
| Test for overall effect: Z = 18.43 (P < 0.00001) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
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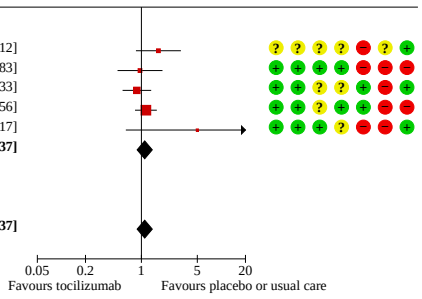
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 2.5. Comparison 2: Interleukin-6 receptor antagonist compared with placebo or usual care for primary prevention, Outcome 5: Adverse event: any infection (incidence rate)

| Study or Subgroup | log[Rate Ratio] | SE | Interleukin-6 receptor antagonist Total | Placebo or usual care Total | Weight | Rate Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **2.5.1 Tocilizumab** | | | | | | |
| Baek 2019 | 0.49 | 0.33 | 48 | 51 | 11.3% | 1.63 [0.85 , 3.12] |
| Khanna 2016 | -0.04 | 0.33 | 43 | 43 | 11.3% | 0.96 [0.50 , 1.83] |
| Khanna 2020 | -0.13 | 0.21 | 105 | 105 | 28.0% | 0.88 [0.58 , 1.33] |
| Smolen 2008 | 0.13 | 0.16 | 419 | 204 | 48.2% | 1.14 [0.83 , 1.56] |
| Villiger 2016 | 1.61 | 1.05 | 20 | 10 | 1.1% | 5.00 [0.64 , 39.17] |
| **Subtotal (95% CI)** | | | **635** | **413** | **100.0%** | **1.10 [0.88 , 1.37]** |
| Heterogeneity: Chi² = 4.88, df = 4 (P = 0.30); I² = 18% | | | | | | |
| Test for overall effect: Z = 0.86 (P = 0.39) | | | | | | |
| **Total (95% CI)** | | | **635** | **413** | **100.0%** | **1.10 [0.88 , 1.37]** |
| Heterogeneity: Chi² = 4.88, df = 4 (P = 0.30); I² = 18% | | | | | | |
| Test for overall effect: Z = 0.86 (P = 0.39) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |




**Risk of bias legend**
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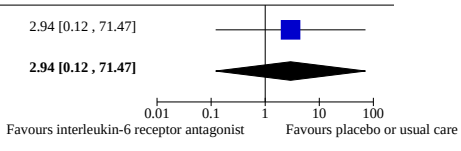
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 2.6. Comparison 2: Interleukin-6 receptor antagonist compared with placebo or usual care for primary prevention, Outcome 6: Peripheral vascular disease

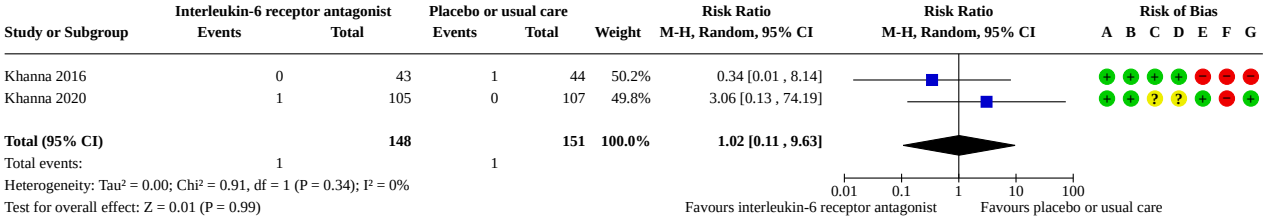
| Study or Subgroup | Interleukin-6 (IL-6) receptor antagonists (Tocilizumab) Events | Total | Placebo or usual care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Khanna 2020 | 1 | 107 | 0 | 105 | 100.0% | 2.94 [0.12 , 71.47] |
| **Total (95% CI)** | | **107** | | **105** | **100.0%** | **2.94 [0.12 , 71.47]** |
| Total events: | 1 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.66 (P = 0.51) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



## Analysis 2.7. Comparison 2: Interleukin-6 receptor antagonist compared with placebo or usual care for primary prevention, Outcome 7: Stroke (fatal or non-fatal)


**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 2.8. Comparison 2: Interleukin-6 receptor antagonist compared with placebo or usual care for primary prevention, Outcome 8: Heart failure




**Risk of bias legend**
(A) Random sequence generation (selection bias)
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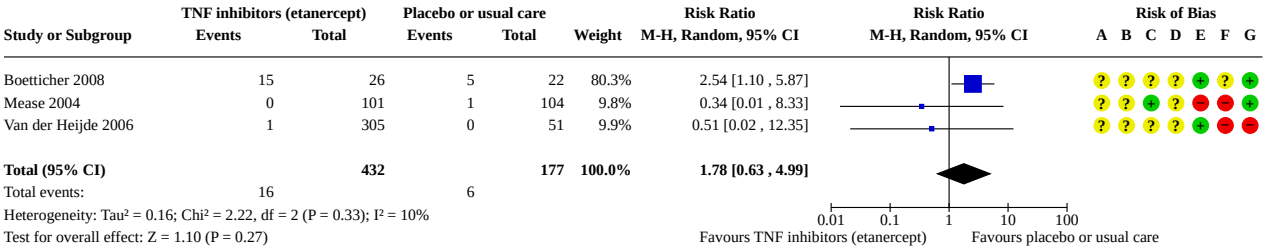
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Comparison 3. TNF inhibitors compared with placebo or usual care for primary prevention

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.1 All-cause mortality | 3 | 609 | Risk Ratio (M-H, Random, 95% CI) | 1.78 [0.63, 4.99] |
| 3.2 Myocardial infarction (fatal or non-fatal) | 1 | 84 | Risk Ratio (M-H, Fixed, 95% CI) | 2.61 [0.11, 62.26] |
| 3.3 Adverse events | 13 | 2654 | Risk Ratio (M-H, Random, 95% CI) | 1.13 [1.01, 1.25] |
| 3.3.1 Etanercept | 10 | 1516 | Risk Ratio (M-H, Random, 95% CI) | 1.06 [0.94, 1.19] |
| 3.3.2 Infliximab | 3 | 1138 | Risk Ratio (M-H, Random, 95% CI) | 1.25 [1.08, 1.46] |
| 3.4 Adverse events any infection (incidence rate) | 22 | 4998 | Rate Ratio (IV, Random, 95% CI) | 1.32 [1.16, 1.49] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.4.1 Etanercept | 20 | 4115 | Rate Ratio (IV, Random, 95% CI) | 1.30 [1.13, 1.50] |
| 3.4.2 Infliximab | 2 | 883 | Rate Ratio (IV, Random, 95% CI) | 1.40 [1.03, 1.91] |
| 3.5 Adverse events (serious infections) | 22 | 5039 | Rate Ratio (IV, Random, 95% CI) | 1.14 [0.98, 1.32] |
| 3.5.1 Etanercept | 19 | 3901 | Rate Ratio (IV, Random, 95% CI) | 1.07 [0.92, 1.26] |
| 3.5.2 Infliximab | 3 | 1138 | Rate Ratio (IV, Random, 95% CI) | 1.80 [0.78, 4.16] |
| 3.6 Stroke (fatal or non-fatal) | 3 | 566 | Risk Ratio (M-H, Random, 95% CI) | 0.46 [0.08, 2.80] |
| 3.7 Heart failure | 1 | 48 | Risk Ratio (M-H, Random, 95% CI) | 0.85 [0.06, 12.76] |

## Analysis 3.1. Comparison 3: TNF inhibitors compared with placebo or usual care for primary prevention, Outcome 1: All-cause mortality

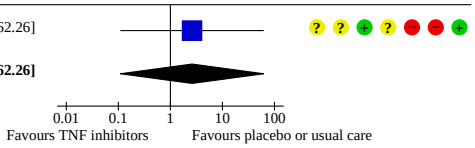



**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.2. Comparison 3: TNF inhibitors compared with placebo or usual care for primary prevention, Outcome 2: Myocardial infarction (fatal or non-fatal)

| Study or Subgroup | TNF inhibitors (etanercept, infliximab) Events | Total | Placebo or usual care Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Calin 2004 | 1 | 45 | 0 | 39 | 100.0% | 2.61 [0.11 , 62.26] |
| **Total (95% CI)** | | **45** | | **39** | **100.0%** | **2.61 [0.11 , 62.26]** |
| Total events: | 1 | | 0 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.55)
Test for subgroup differences: Not applicable




**Risk of bias legend**
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(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.3. Comparison 3: TNF inhibitors compared with placebo or usual care for primary prevention, Outcome 3: Adverse events

| Study or Subgroup | TNF inhibitors Events | Total | Placebo or usual care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **3.3.1 Etanercept** | | | | | | |
| Bachelez 2015 | 195 | 336 | 55 | 108 | 11.8% | 1.14 [0.93 , 1.40] |
| Bagel 2012 | 32 | 62 | 34 | 62 | 7.0% | 0.94 [0.68 , 1.31] |
| Bernstein 2006 | 3 | 28 | 0 | 28 | 0.1% | 7.00 [0.38 , 129.55] |
| Boetticher 2008 | 18 | 26 | 9 | 22 | 3.1% | 1.69 [0.96 , 2.97] |
| Brandt 2003 | 8 | 16 | 6 | 17 | 1.6% | 1.42 [0.63 , 3.18] |
| Butchart 2015 | 20 | 20 | 21 | 21 | 18.2% | 1.00 [0.91 , 1.10] |
| Don 2010 | 0 | 5 | 3 | 5 | 0.2% | 0.14 [0.01 , 2.21] |
| Kreiner 2010 | 2 | 10 | 0 | 12 | 0.1% | 5.91 [0.32 , 110.47] |
| Micali 2015 | 43 | 58 | 48 | 62 | 11.9% | 0.96 [0.78 , 1.17] |
| Tyring 2006 | 153 | 312 | 137 | 306 | 13.8% | 1.10 [0.93 , 1.30] |
| **Subtotal (95% CI)** | | **873** | | **643** | **67.7%** | **1.06 [0.94 , 1.19]** |
| Total events: | 474 | | 313 | | | |

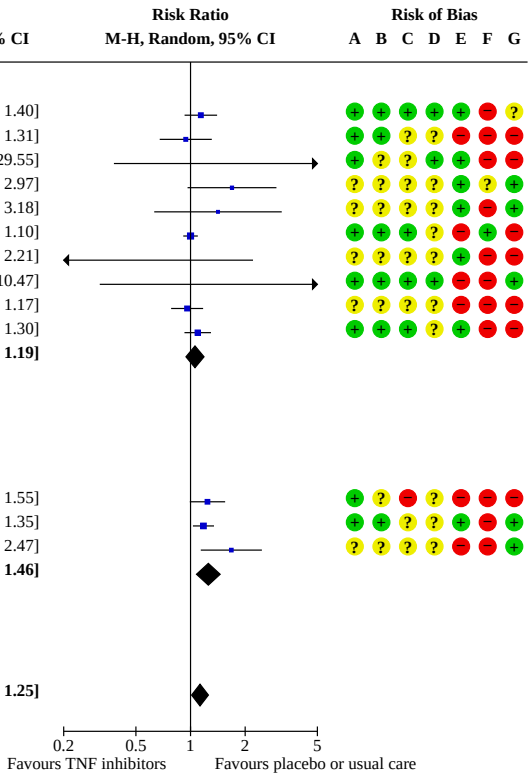
Heterogeneity: Tau² = 0.01; Chi² = 13.89, df = 9 (P = 0.13); I² = 35%
Test for overall effect: Z = 0.97 (P = 0.33)

| | | | | | | |
|---|---|---|---|---|---|---|
| **3.3.2 Infliximab** | | | | | | |
| Gottlieb 2004 | 154 | 198 | 32 | 51 | 10.9% | 1.24 [0.99 , 1.55] |
| Menter 2007 | 412 | 627 | 116 | 208 | 15.8% | 1.18 [1.03 , 1.35] |
| Torii 2010 | 34 | 35 | 11 | 19 | 5.6% | 1.68 [1.14 , 2.47] |
| **Subtotal (95% CI)** | | **860** | | **278** | **32.3%** | **1.25 [1.08 , 1.46]** |
| Total events: | 600 | | 159 | | | |

Heterogeneity: Tau² = 0.01; Chi² = 2.87, df = 2 (P = 0.24); I² = 30%
Test for overall effect: Z = 2.95 (P = 0.003)

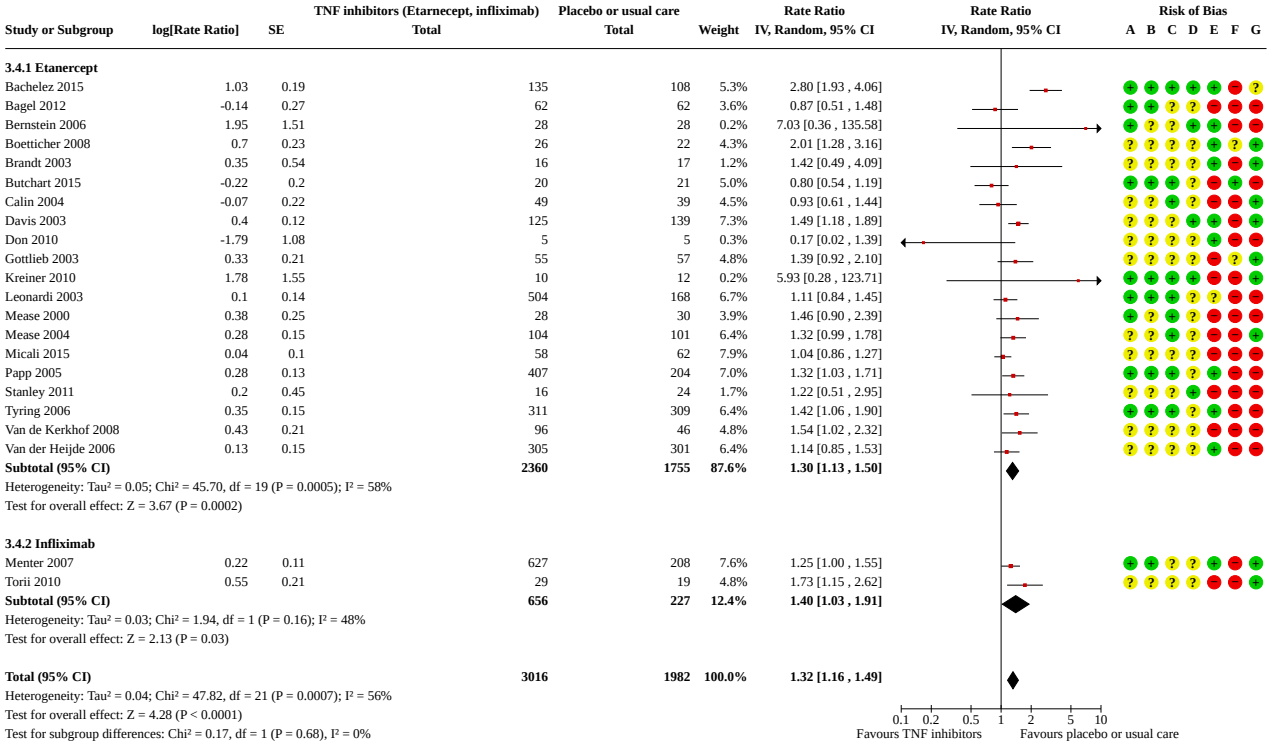
| | | | | | | |
|---|---|---|---|---|---|---|
| **Total (95% CI)** | | **1733** | | **921** | **100.0%** | **1.13 [1.01 , 1.25]** |
| Total events: | 1074 | | 472 | | | |

Heterogeneity: Tau² = 0.01; Chi² = 24.41, df = 12 (P = 0.02); I² = 51%
Test for overall effect: Z = 2.21 (P = 0.03)
Test for subgroup differences: Chi² = 3.09, df = 1 (P = 0.08), I² = 67.7%




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

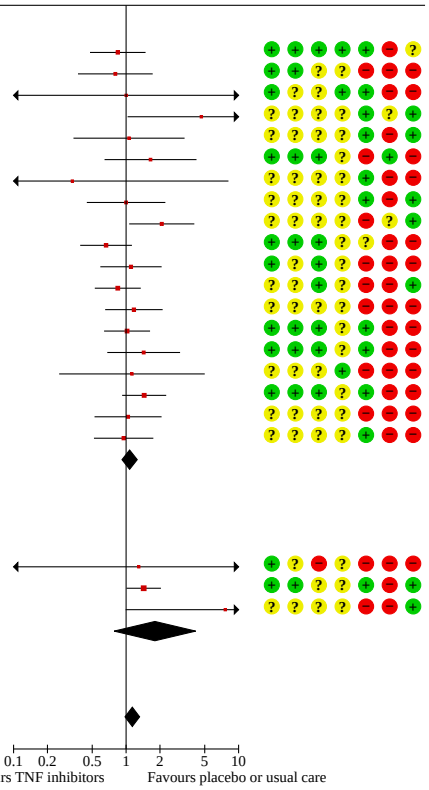
## Analysis 3.4. Comparison 3: TNF inhibitors compared with placebo or usual care for primary prevention, Outcome 4: Adverse events any infection (incidence rate)




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.5. Comparison 3: TNF inhibitors compared with placebo or usual care for primary prevention, Outcome 5: Adverse events (serious infections)

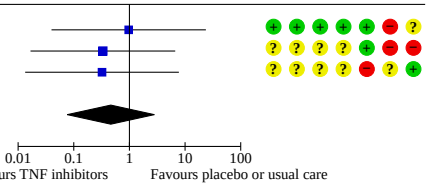
| Study or Subgroup | log[Rate Ratio] | SE | TNF inhibitors Total | Placebo or usual care Total | Weight | Rate Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **3.5.1 Etanercept** | | | | | | |
| Bachelez 2015 | -0.17 | 0.29 | 336 | 108 | 6.4% | 0.84 [0.48 , 1.49] |
| Bagel 2012 | -0.22 | 0.39 | 62 | 62 | 3.6% | 0.80 [0.37 , 1.72] |
| Bernstein 2006 | 0 | 2 | 28 | 28 | 0.1% | 1.00 [0.02 , 50.40] |
| Boetticher 2008 | 1.54 | 0.77 | 26 | 22 | 1.0% | 4.66 [1.03 , 21.10] |
| Brandt 2003 | 0.06 | 0.58 | 16 | 17 | 1.7% | 1.06 [0.34 , 3.31] |
| Butchart 2015 | 0.5 | 0.48 | 20 | 21 | 2.4% | 1.65 [0.64 , 4.22] |
| Don 2010 | -1.1 | 1.63 | 5 | 5 | 0.2% | 0.33 [0.01 , 8.12] |
| Gorman 2002 | 0 | 0.41 | 20 | 20 | 3.3% | 1.00 [0.45 , 2.23] |
| Gottlieb 2003 | 0.73 | 0.34 | 57 | 55 | 4.7% | 2.08 [1.07 , 4.04] |
| Leonardi 2003 | -0.41 | 0.27 | 504 | 168 | 7.3% | 0.66 [0.39 , 1.13] |
| Mease 2000 | 0.1 | 0.32 | 30 | 30 | 5.3% | 1.11 [0.59 , 2.07] |
| Mease 2004 | -0.17 | 0.24 | 104 | 101 | 9.0% | 0.84 [0.53 , 1.35] |
| Micali 2015 | 0.16 | 0.3 | 58 | 62 | 6.0% | 1.17 [0.65 , 2.11] |
| Papp 2005 | 0.02 | 0.24 | 407 | 204 | 9.0% | 1.02 [0.64 , 1.63] |
| Reich 2017 | 0.36 | 0.38 | 83 | 84 | 3.8% | 1.43 [0.68 , 3.02] |
| Stanley 2011 | 0.12 | 0.76 | 16 | 24 | 1.0% | 1.13 [0.25 , 5.00] |
| Tyring 2006 | 0.37 | 0.23 | 311 | 309 | 9.7% | 1.45 [0.92 , 2.27] |
| Van de Kerkhof 2008 | 0.04 | 0.35 | 96 | 46 | 4.5% | 1.04 [0.52 , 2.07] |
| Van der Heijde 2006 | -0.05 | 0.31 | 305 | 51 | 5.6% | 0.95 [0.52 , 1.75] |
| **Subtotal (95% CI)** | | | **2484** | **1417** | **84.5%** | **1.07 [0.92 , 1.26]** |
| Heterogeneity: Tau² = 0.00; Chi² = 16.75, df = 18 (P = 0.54); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.91 (P = 0.36) | | | | | | |
| **3.5.2 Infliximab** | | | | | | |
| Gottlieb 2004 | 0.26 | 1.55 | 198 | 51 | 0.2% | 1.30 [0.06 , 27.06] |
| Menter 2007 | 0.36 | 0.18 | 627 | 208 | 14.7% | 1.43 [1.01 , 2.04] |
| Torii 2010 | 2.03 | 1.04 | 35 | 19 | 0.5% | 7.61 [0.99 , 58.46] |
| **Subtotal (95% CI)** | | | **860** | **278** | **15.5%** | **1.80 [0.78 , 4.16]** |
| Heterogeneity: Tau² = 0.20; Chi² = 2.51, df = 2 (P = 0.28); I² = 20% | | | | | | |
| Test for overall effect: Z = 1.38 (P = 0.17) | | | | | | |
| **Total (95% CI)** | | | **3344** | **1695** | **100.0%** | **1.14 [0.98 , 1.32]** |
| Heterogeneity: Tau² = 0.01; Chi² = 22.25, df = 21 (P = 0.39); I² = 6% | | | | | | |
| Test for overall effect: Z = 1.67 (P = 0.10) | | | | | | |
| Test for subgroup differences: Chi² = 1.43, df = 1 (P = 0.23), I² = 30.0% | | | | | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

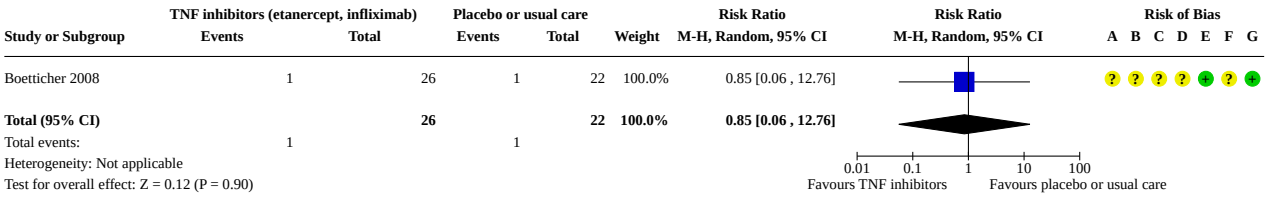
## Analysis 3.6. Comparison 3: TNF inhibitors compared with placebo or usual care for primary prevention, Outcome 6: Stroke (fatal or non-fatal)

| Study or Subgroup | TNF inhibitors (etanercept, infliximab) Events | Total | Placebo or usual care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Bachelez 2015 | 1 | 336 | 0 | 108 | 31.8% | 0.97 [0.04 , 23.65] |
| Don 2010 | 0 | 5 | 1 | 5 | 36.2% | 0.33 [0.02 , 6.65] |
| Gottlieb 2003 | 0 | 57 | 1 | 55 | 32.1% | 0.32 [0.01 , 7.74] |
| **Total (95% CI)** | | **398** | | **168** | **100.0%** | **0.46 [0.08 , 2.80]** |
| Total events: | 1 | | 2 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 2 (P = 0.86); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.84 (P = 0.40) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

### Analysis 3.7. Comparison 3: TNF inhibitors compared with placebo or usual care for primary prevention, Outcome 7: Heart failure



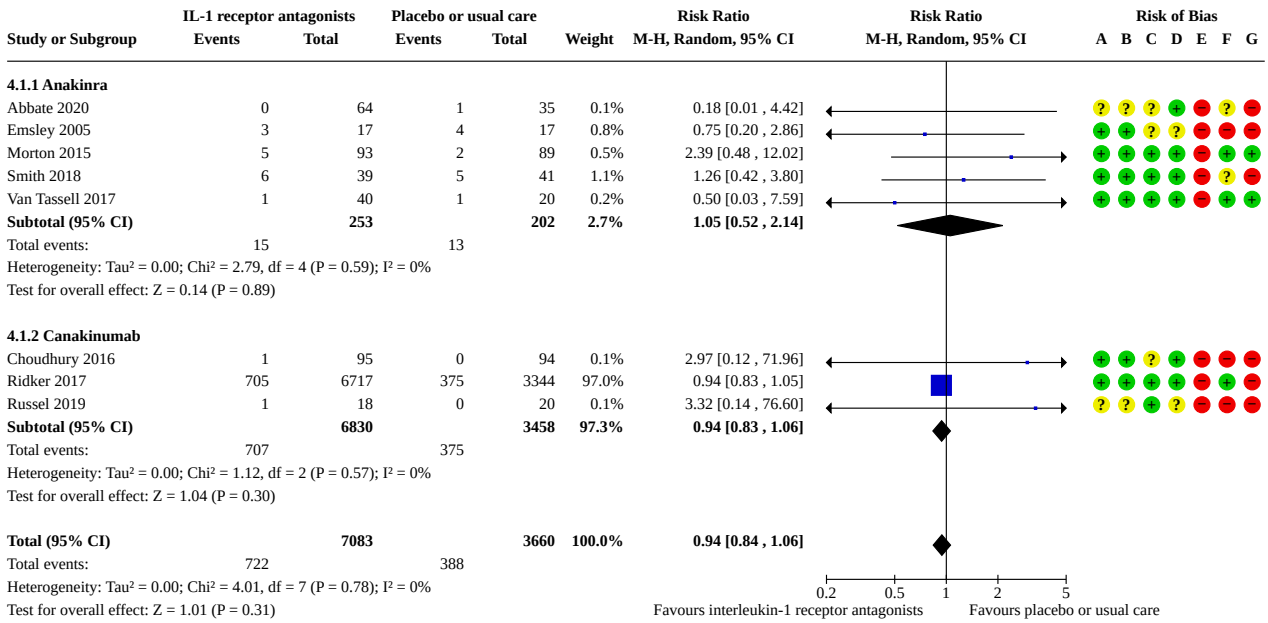

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Comparison 4. Interleukin-1 receptor antagonists compared with placebo or usual care for secondary prevention

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.1 All-cause mortality | 8 | 10743 | Risk Ratio (M-H, Random, 95% CI) | 0.94 [0.84, 1.06] |
| 4.1.1 Anakinra | 5 | 455 | Risk Ratio (M-H, Random, 95% CI) | 1.05 [0.52, 2.14] |
| 4.1.2 Canakinumab | 3 | 10288 | Risk Ratio (M-H, Random, 95% CI) | 0.94 [0.83, 1.06] |
| 4.2 Myocardial infarction (fatal or non-fatal) | 6 | 10629 | Risk Ratio (M-H, Random, 95% CI) | 0.88 [0.75, 1.04] |
| 4.2.1 Anakinra | 3 | 341 | Risk Ratio (M-H, Random, 95% CI) | 2.46 [0.75, 8.04] |
| 4.2.2 Canakinumab | 3 | 10288 | Risk Ratio (M-H, Random, 95% CI) | 0.86 [0.75, 0.99] |
| 4.3 Unstable angina | 3 | 10403 | Risk Ratio (M-H, Random, 95% CI) | 0.88 [0.65, 1.19] |
| 4.3.1 Anakinra | 1 | 99 | Risk Ratio (M-H, Random, 95% CI) | 1.66 [0.07, 39.74] |
| 4.3.2 Canakinumab | 2 | 10304 | Risk Ratio (M-H, Random, 95% CI) | 0.87 [0.64, 1.18] |
| 4.4 Adverse events | 4 | 264 | Risk Ratio (M-H, Random, 95% CI) | 0.92 [0.78, 1.09] |
| 4.4.1 Anakinra | 2 | 51 | Risk Ratio (M-H, Random, 95% CI) | 0.62 [0.33, 1.19] |
| 4.4.2 Canakinumab | 2 | 213 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.84, 1.08] |
| 4.5 Adverse events by incidence rate | 12 | 10849 | Rate Ratio (IV, Random, 95% CI) | 0.98 [0.85, 1.14] |
| 4.5.1 Anakinra | 8 | 537 | Rate Ratio (IV, Random, 95% CI) | 0.93 [0.70, 1.23] |
| 4.5.2 Canakinumab | 4 | 10312 | Rate Ratio (IV, Random, 95% CI) | 0.99 [0.81, 1.20] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.6 Adverse events: serious infections by incidence rate | 12 | 10849 | Rate Ratio (IV, Fixed, 95% CI) | 1.11 [1.05, 1.18] |
| 4.6.1 Anakinra | 8 | 537 | Rate Ratio (IV, Fixed, 95% CI) | 1.05 [0.64, 1.74] |
| 4.6.2 Canakinumab | 4 | 10312 | Rate Ratio (IV, Fixed, 95% CI) | 1.11 [1.05, 1.18] |
| 4.7 Peripheral vascular disease | 3 | 10288 | Risk Ratio (IV, Random, 95% CI) | 0.85 [0.19, 3.73] |
| 4.8 Stroke (fatal or non-fatal) | 7 | 10705 | Risk Ratio (M-H, Random, 95% CI) | 0.94 [0.74, 1.20] |
| 4.8.1 Anakinra | 5 | 455 | Risk Ratio (M-H, Random, 95% CI) | 1.10 [0.37, 3.29] |
| 4.8.2 Canakinumab | 2 | 10250 | Risk Ratio (M-H, Random, 95% CI) | 0.93 [0.73, 1.20] |
| 4.9 Heart failure | 7 | 10509 | Risk Ratio (M-H, Random, 95% CI) | 0.91 [0.50, 1.65] |
| 4.9.1 Anakinra | 4 | 220 | Risk Ratio (M-H, Random, 95% CI) | 0.65 [0.30, 1.40] |
| 4.9.2 Canakinumab | 3 | 10289 | Risk Ratio (M-H, Random, 95% CI) | 1.56 [0.59, 4.10] |

## Analysis 4.1. Comparison 4: Interleukin-1 receptor antagonists compared with placebo or usual care for secondary prevention, Outcome 1: All-cause mortality



| Study or Subgroup | IL-1 receptor antagonists Events | Total | Placebo or usual care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| **4.1.1 Anakinra** | | | | | | | |
| Abbate 2020 | 0 | 64 | 1 | 35 | 0.1% | 0.18 [0.01 , 4.42] | ? ? ? + − ? − |
| Emsley 2005 | 3 | 17 | 4 | 17 | 0.8% | 0.75 [0.20 , 2.86] | + + ? ? − − − |
| Morton 2015 | 5 | 93 | 2 | 89 | 0.5% | 2.39 [0.48 , 12.02] | + + + + − + + |
| Smith 2018 | 6 | 39 | 5 | 41 | 1.1% | 1.26 [0.42 , 3.80] | + + + + − ? − |
| Van Tassell 2017 | 1 | 40 | 1 | 20 | 0.2% | 0.50 [0.03 , 7.59] | + + + + − + + |
| **Subtotal (95% CI)** | | **253** | | **202** | **2.7%** | **1.05 [0.52 , 2.14]** | |
| Total events: | 15 | | 13 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 2.79, df = 4 (P = 0.59); I² = 0% | | | | | | | |
| Test for overall effect: Z = 0.14 (P = 0.89) | | | | | | | |
| **4.1.2 Canakinumab** | | | | | | | |
| Choudhury 2016 | 1 | 95 | 0 | 94 | 0.1% | 2.97 [0.12 , 71.96] | + + ? + − − − |
| Ridker 2017 | 705 | 6717 | 375 | 3344 | 97.0% | 0.94 [0.83 , 1.05] | + + + + − + − |
| Russel 2019 | 1 | 18 | 0 | 20 | 0.1% | 3.32 [0.14 , 76.60] | ? ? + ? − − − |
| **Subtotal (95% CI)** | | **6830** | | **3458** | **97.3%** | **0.94 [0.83 , 1.06]** | |
| Total events: | 707 | | 375 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 2 (P = 0.57); I² = 0% | | | | | | | |
| Test for overall effect: Z = 1.04 (P = 0.30) | | | | | | | |
| **Total (95% CI)** | | **7083** | | **3660** | **100.0%** | **0.94 [0.84 , 1.06]** | |
| Total events: | 722 | | 388 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 4.01, df = 7 (P = 0.78); I² = 0% | | | | | | | |
| Test for overall effect: Z = 1.01 (P = 0.31) | | | | | | | |
| Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0% | | | | | | | |

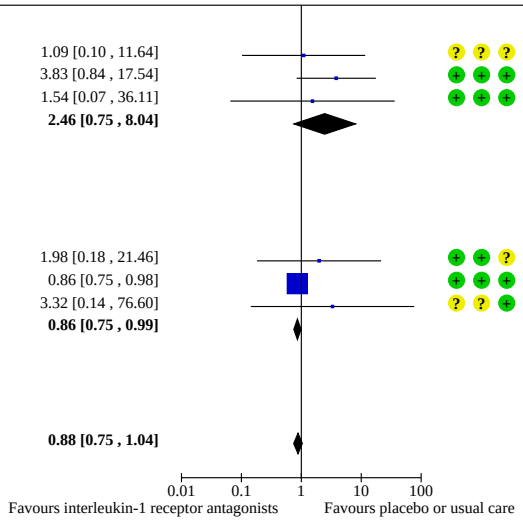


**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

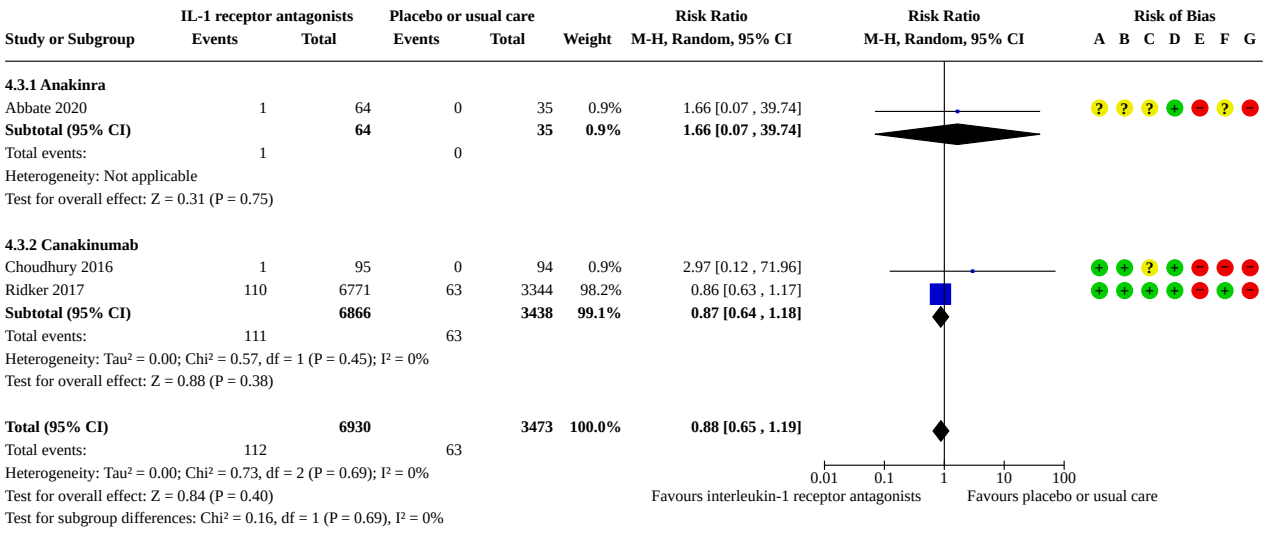
## Analysis 4.2. Comparison 4: Interleukin-1 receptor antagonists compared with placebo or usual care for secondary prevention, Outcome 2: Myocardial infarction (fatal or non-fatal)

| Study or Subgroup | IL-1 receptor antagonists Events | Total | Placebo or usual care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| **4.2.1 Anakinra** | | | | | | | |
| Abbate 2020 | 2 | 64 | 1 | 35 | 0.5% | 1.09 [0.10 , 11.64] | ? ? ? + − ? − |
| Morton 2015 | 8 | 93 | 2 | 89 | 1.2% | 3.83 [0.84 , 17.54] | + + + + − + + |
| Van Tassell 2017 | 1 | 40 | 0 | 20 | 0.3% | 1.54 [0.07 , 36.11] | + + + + − + + |
| **Subtotal (95% CI)** | | **197** | | **144** | **2.0%** | **2.46 [0.75 , 8.04]** | |
| Total events: | 11 | | 3 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 2 (P = 0.65); I² = 0% | | | | | | | |
| Test for overall effect: Z = 1.48 (P = 0.14) | | | | | | | |
| **4.2.2 Canakinumab** | | | | | | | |
| Choudhury 2016 | 2 | 95 | 1 | 94 | 0.5% | 1.98 [0.18 , 21.46] | + + ? + − − − |
| Ridker 2017 | 502 | 6717 | 292 | 3344 | 97.3% | 0.86 [0.75 , 0.98] | + + + + − + − |
| Russel 2019 | 1 | 18 | 0 | 20 | 0.3% | 3.32 [0.14 , 76.60] | ? ? + ? − − − |
| **Subtotal (95% CI)** | | **6830** | | **3458** | **98.0%** | **0.86 [0.75 , 0.99]** | |
| Total events: | 505 | | 293 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 2 (P = 0.55); I² = 0% | | | | | | | |
| Test for overall effect: Z = 2.14 (P = 0.03) | | | | | | | |
| **Total (95% CI)** | | **7027** | | **3602** | **100.0%** | **0.88 [0.75 , 1.04]** | |
| Total events: | 516 | | 296 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 5.02, df = 5 (P = 0.41); I² = 0% | | | | | | | |
| Test for overall effect: Z = 1.50 (P = 0.13) | | | | | | | |
| Test for subgroup differences: Chi² = 2.96, df = 1 (P = 0.09), I² = 66.2% | | | | | | | |



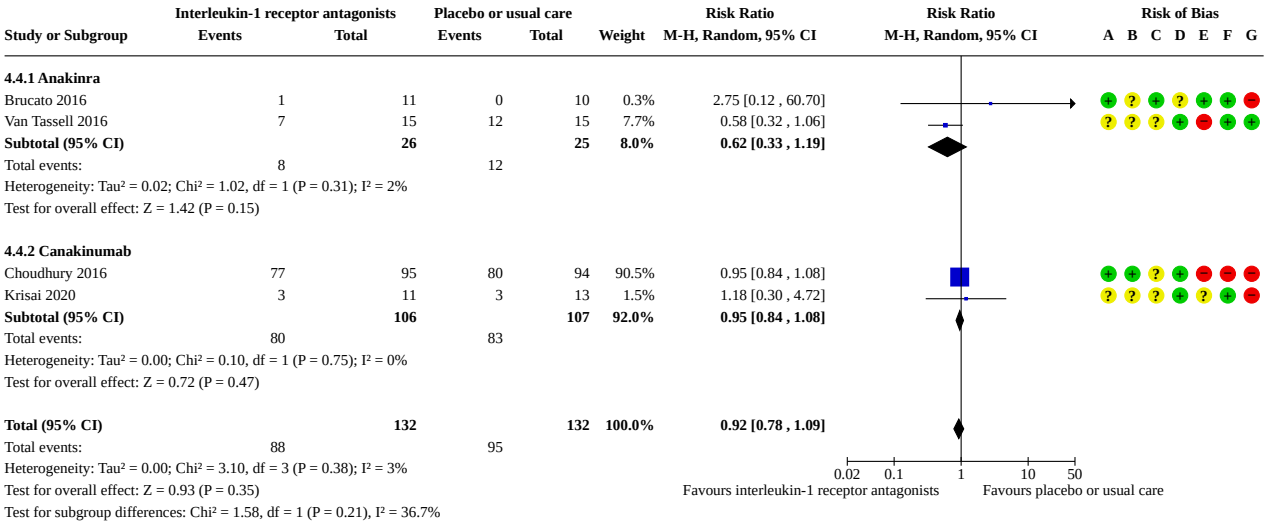

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 4.3. Comparison 4: Interleukin-1 receptor antagonists compared with placebo or usual care for secondary prevention, Outcome 3: Unstable angina



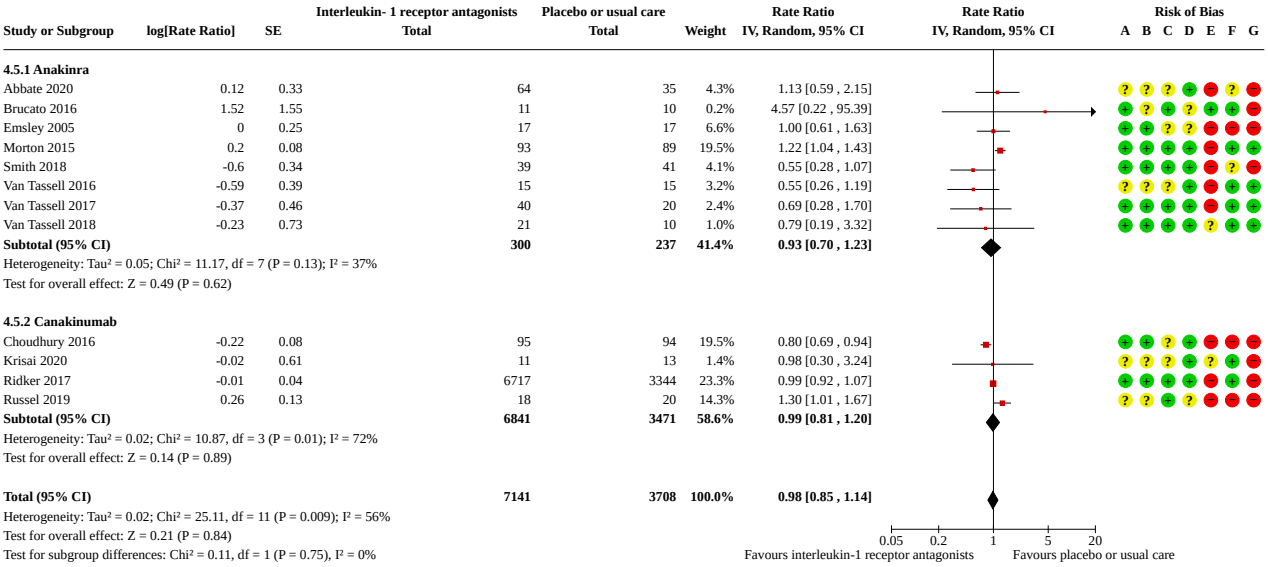

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 4.4. Comparison 4: Interleukin-1 receptor antagonists compared with placebo or usual care for secondary prevention, Outcome 4: Adverse events



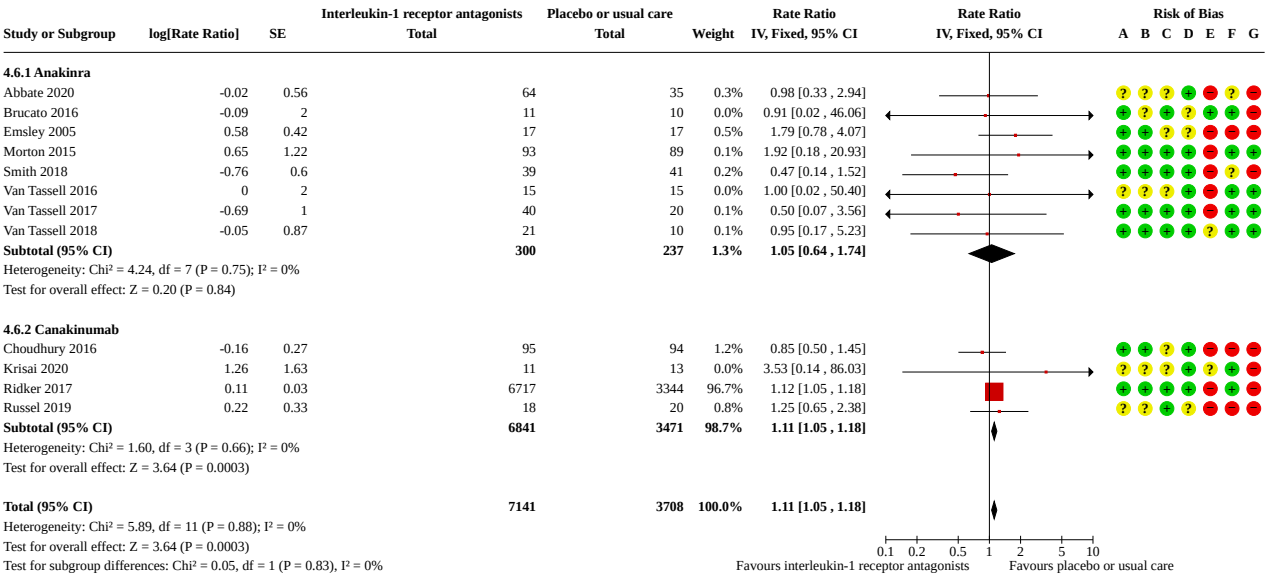

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 4.5. Comparison 4: Interleukin-1 receptor antagonists compared with placebo or usual care for secondary prevention, Outcome 5: Adverse events by incidence rate




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 4.6. Comparison 4: Interleukin-1 receptor antagonists compared with placebo or usual care for secondary prevention, Outcome 6: Adverse events: serious infections by incidence rate

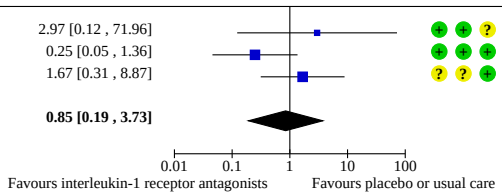


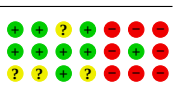

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 4.7. Comparison 4: Interleukin-1 receptor antagonists compared with placebo or usual care for secondary prevention, Outcome 7: Peripheral vascular disease

| Study or Subgroup | Interleukin-1 receptor antagonists Events | Total | Placebo or usual care Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Choudhury 2016 | 1 | 95 | 0 | 94 | 17.4% | 2.97 [0.12 , 71.96] |
| Ridker 2017 | 2 | 6717 | 4 | 3344 | 41.0% | 0.25 [0.05 , 1.36] |
| Russel 2019 | 3 | 18 | 2 | 20 | 41.6% | 1.67 [0.31 , 8.87] |
| **Total (95% CI)** | | **6830** | | **3458** | **100.0%** | **0.85 [0.19 , 3.73]** |
| Total events: | 6 | | 6 | | | |

Heterogeneity: Tau² = 0.65; Chi² = 3.21, df = 2 (P = 0.20); I² = 38%
Test for overall effect: Z = 0.22 (P = 0.82)
Test for subgroup differences: Not applicable



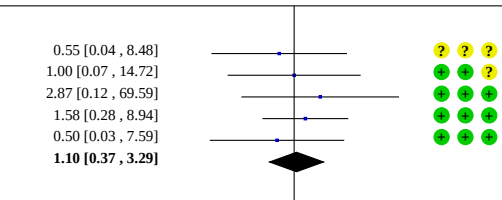




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 4.8. Comparison 4: Interleukin-1 receptor antagonists compared with placebo or usual care for secondary prevention, Outcome 8: Stroke (fatal or non-fatal)

| Study or Subgroup | Interleukin-1 receptor antagonists Events | Total | Placebo or usual care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **4.8.1 Anakinra** | | | | | | |
| Abbate 2020 | 1 | 64 | 1 | 35 | 0.8% | 0.55 [0.04 , 8.48] |
| Emsley 2005 | 1 | 17 | 1 | 17 | 0.8% | 1.00 [0.07 , 14.72] |
| Morton 2015 | 1 | 93 | 0 | 89 | 0.6% | 2.87 [0.12 , 69.59] |
| Smith 2018 | 3 | 39 | 2 | 41 | 2.0% | 1.58 [0.28 , 8.94] |
| Van Tassell 2017 | 1 | 40 | 1 | 20 | 0.8% | 0.50 [0.03 , 7.59] |
| **Subtotal (95% CI)** | | **253** | | **202** | **4.9%** | **1.10 [0.37 , 3.29]** |
| Total events: | 7 | | 5 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.09, df = 4 (P = 0.90); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.17 (P = 0.86) | | | | | | |
| **4.8.2 Canakinumab** | | | | | | |
| Choudhury 2016 | 1 | 95 | 0 | 94 | 0.6% | 2.97 [0.12 , 71.96] |
| Ridker 2017 | 171 | 6717 | 92 | 3344 | 94.5% | 0.93 [0.72 , 1.19] |
| **Subtotal (95% CI)** | | **6812** | | **3438** | **95.1%** | **0.93 [0.73 , 1.20]** |
| Total events: | 172 | | 92 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.47); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.55 (P = 0.58) | | | | | | |
| **Total (95% CI)** | | **7065** | | **3640** | **100.0%** | **0.94 [0.74 , 1.20]** |
| Total events: | 179 | | 97 | | | |

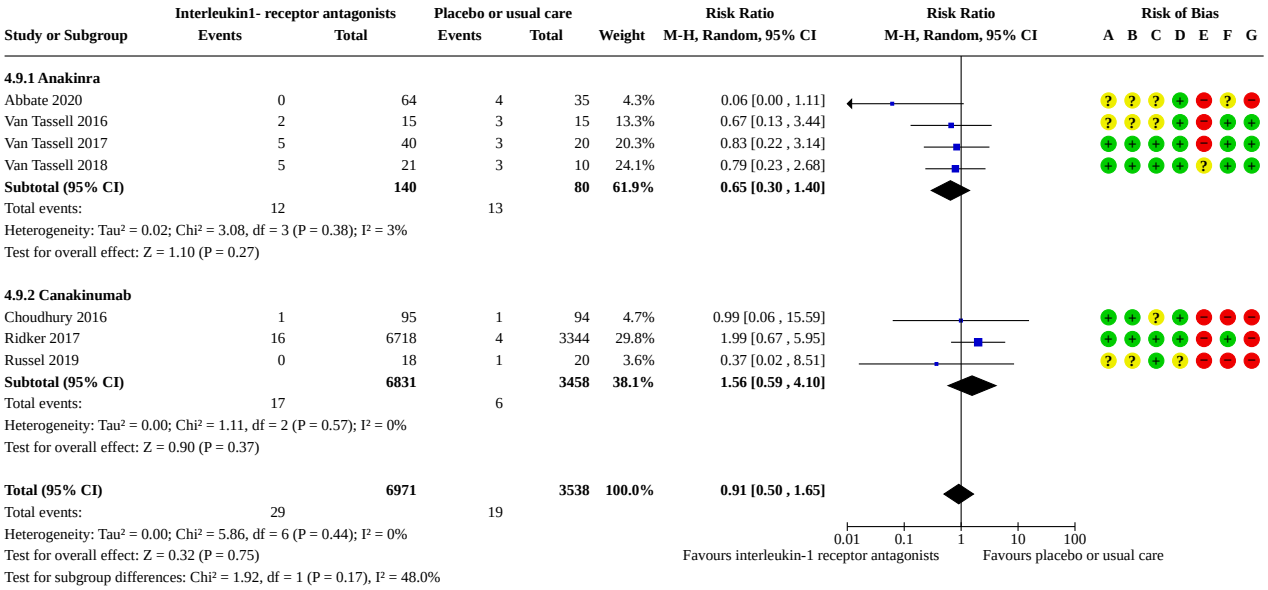
Heterogeneity: Tau² = 0.00; Chi² = 1.69, df = 6 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%





**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 4.9. Comparison 4: Interleukin-1 receptor antagonists compared with placebo or usual care for secondary prevention, Outcome 9: Heart failure



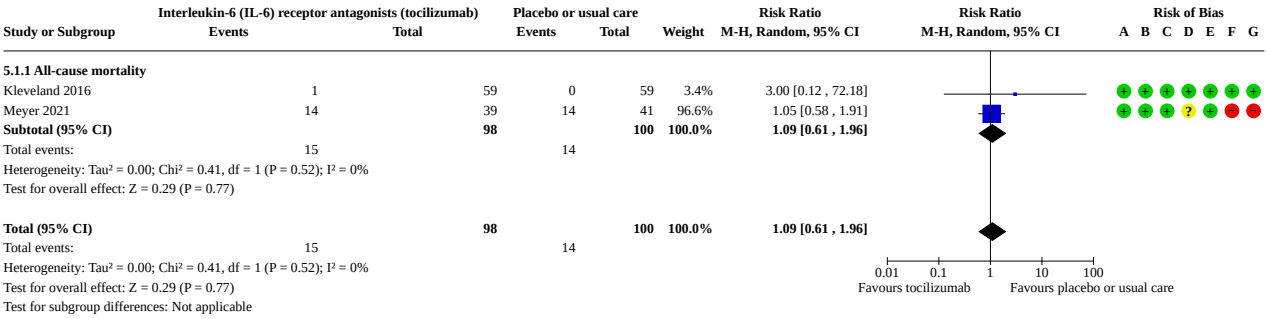

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Comparison 5. Interleukin-6 receptor antagonist compared with placebo or usual care for secondary prevention

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 5.1 All-cause mortality | 2 | 198 | Risk Ratio (M-H, Random, 95% CI) | 1.09 [0.61, 1.96] |
| 5.1.1 All-cause mortality | 2 | 198 | Risk Ratio (M-H, Random, 95% CI) | 1.09 [0.61, 1.96] |
| 5.2 Myocardial Infarction (fatal or non-fatal) | 3 | 345 | Risk Ratio (M-H, Random, 95% CI) | 0.46 [0.07, 3.04] |
| 5.2.1 Tocilizumab | 3 | 345 | Risk Ratio (M-H, Random, 95% CI) | 0.46 [0.07, 3.04] |
| 5.3 Unstable angina | 1 | 118 | Risk Ratio (M-H, Random, 95% CI) | 0.33 [0.01, 8.02] |
| 5.3.1 Tocilizumab | 1 | 118 | Risk Ratio (M-H, Random, 95% CI) | 0.33 [0.01, 8.02] |
| 5.4 Adverse events | 2 | 113 | Risk Ratio (M-H, Random, 95% CI) | 0.89 [0.76, 1.05] |
| 5.5 Adverse events (incidence rate) | 3 | 348 | Rate Ratio (IV, Random, 95% CI) | 0.81 [0.45, 1.44] |
| 5.5.1 Tocilizumab | 3 | 348 | Rate Ratio (IV, Random, 95% CI) | 0.81 [0.45, 1.44] |
| 5.6 Adverse events (any infection) incidence rate | 4 | 433 | Rate Ratio (IV, Random, 95% CI) | 0.66 [0.32, 1.36] |

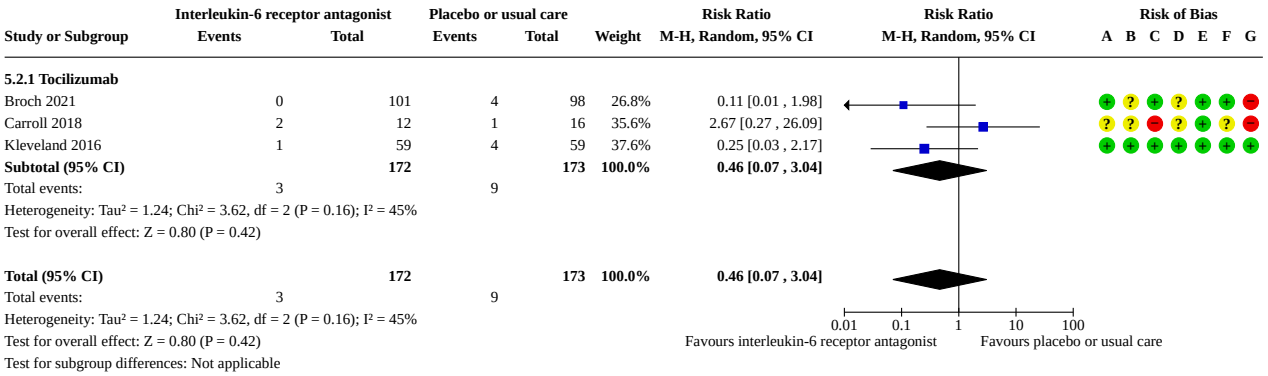
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 5.6.1 Tocilizumab | 4 | 433 | Rate Ratio (IV, Random, 95% CI) | 0.66 [0.32, 1.36] |
| 5.7 Stroke (fatal or non-fatal) | 1 | 195 | Risk Ratio (M-H, Random, 95% CI) | 1.03 [0.07, 16.25] |
| 5.7.1 Tocilizumab | 1 | 195 | Risk Ratio (M-H, Random, 95% CI) | 1.03 [0.07, 16.25] |

## Analysis 5.1. Comparison 5: Interleukin-6 receptor antagonist compared with placebo or usual care for secondary prevention, Outcome 1: All-cause mortality




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

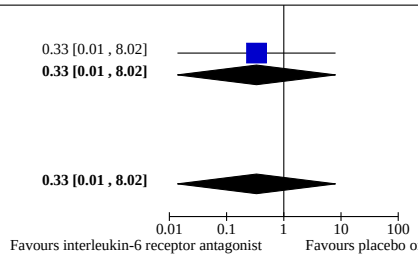
## Analysis 5.2. Comparison 5: Interleukin-6 receptor antagonist compared with placebo or usual care for secondary prevention, Outcome 2: Myocardial Infarction (fatal or non-fatal)




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 5.3. Comparison 5: Interleukin-6 receptor antagonist compared with placebo or usual care for secondary prevention, Outcome 3: Unstable angina

| Study or Subgroup | Interleukin-6 receptor antagonist Events | Total | Placebo or usual care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| **5.3.1 Tocilizumab** | | | | | | | | |
| Kleveland 2016 | 0 | 59 | 1 | 59 | 100.0% | 0.33 [0.01 , 8.02] | | + + + + + + + |
| **Subtotal (95% CI)** | | **59** | | **59** | **100.0%** | **0.33 [0.01 , 8.02]** | | |
| Total events: | 0 | | 1 | | | | | |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.68 (P = 0.50) | | | | | | | | |
| **Total (95% CI)** | | **59** | | **59** | **100.0%** | **0.33 [0.01 , 8.02]** | | |
| Total events: | 0 | | 1 | | | | | |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.68 (P = 0.50) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
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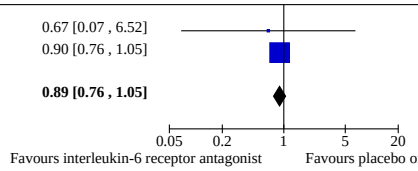
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 5.4. Comparison 5: Interleukin-6 receptor antagonist compared with placebo or usual care for secondary prevention, Outcome 4: Adverse events

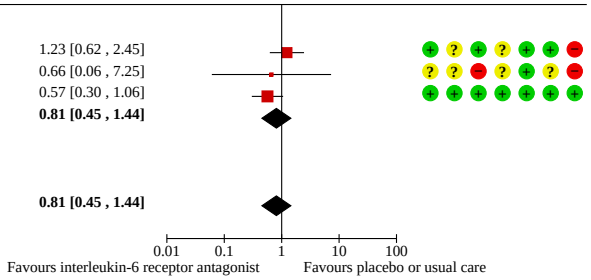
| Study or Subgroup | Interleukin-6 receptor antagonist Events | Total | Placebo or usual care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| Carroll 2018 | 1 | 12 | 2 | 16 | 0.5% | 0.67 [0.07 , 6.52] | | ? ? − ? + ? − |
| Meyer 2021 | 35 | 42 | 40 | 43 | 99.5% | 0.90 [0.76 , 1.05] | | + + + ? + − − |
| **Total (95% CI)** | | **54** | | **59** | **100.0%** | **0.89 [0.76 , 1.05]** | | |
| Total events: | 36 | | 42 | | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 1.38 (P = 0.17) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 5.5. Comparison 5: Interleukin-6 receptor antagonist compared with placebo or usual care for secondary prevention, Outcome 5: Adverse events (incidence rate)

| Study or Subgroup | log[Rate Ratio] | SE | Tocilizumab Total | Placebo or usual care Total | Weight | Rate Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **5.5.1 Tocilizumab** | | | | | | |
| Broch 2021 | 0.21 | 0.35 | 101 | 98 | 44.6% | 1.23 [0.62 , 2.45] |
| Carroll 2018 | -0.41 | 1.22 | 12 | 16 | 5.6% | 0.66 [0.06 , 7.25] |
| Kleveland 2016 | -0.57 | 0.32 | 60 | 61 | 49.7% | 0.57 [0.30 , 1.06] |
| **Subtotal (95% CI)** | | | **173** | **175** | **100.0%** | **0.81 [0.45 , 1.44]** |
| Heterogeneity: Tau² = 0.07; Chi² = 2.73, df = 2 (P = 0.26); I² = 27% | | | | | | |
| Test for overall effect: Z = 0.72 (P = 0.47) | | | | | | |
| **Total (95% CI)** | | | **173** | **175** | **100.0%** | **0.81 [0.45 , 1.44]** |
| Heterogeneity: Tau² = 0.07; Chi² = 2.73, df = 2 (P = 0.26); I² = 27% | | | | | | |
| Test for overall effect: Z = 0.72 (P = 0.47) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |




**Risk of bias legend**
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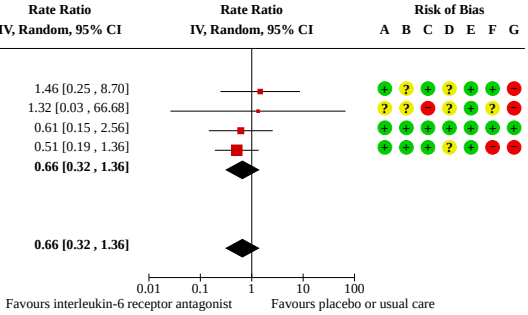
(F) Selective reporting (reporting bias)
(G) Other bias

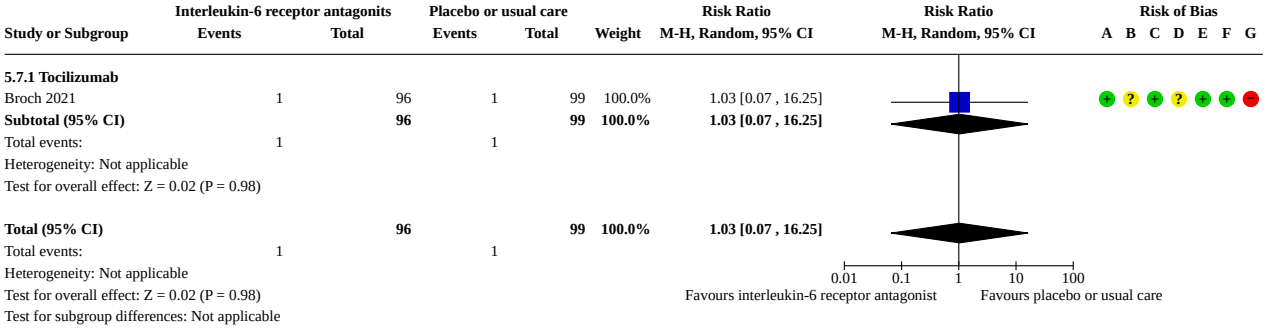
## Analysis 5.6. Comparison 5: Interleukin-6 receptor antagonist compared with placebo or usual care for secondary prevention, Outcome 6: Adverse events (any infection) incidence rate

| Study or Subgroup | log[Rate Ratio] | SE | Interleukin-6 receptor antagonist Total | Placebo or usual care Total | Weight | Rate Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **5.6.1 Tocilizumab** | | | | | | |
| Broch 2021 | 0.38 | 0.91 | 101 | 98 | 16.5% | 1.46 [0.25 , 8.70] |
| Carroll 2018 | 0.28 | 2 | 12 | 16 | 3.4% | 1.32 [0.03 , 66.68] |
| Kleveland 2016 | -0.49 | 0.73 | 60 | 61 | 25.6% | 0.61 [0.15 , 2.56] |
| Meyer 2021 | -0.67 | 0.5 | 42 | 43 | 54.5% | 0.51 [0.19 , 1.36] |
| **Subtotal (95% CI)** | | | **215** | **218** | **100.0%** | **0.66 [0.32 , 1.36]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.15, df = 3 (P = 0.76); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.13 (P = 0.26) | | | | | | |
| **Total (95% CI)** | | | **215** | **218** | **100.0%** | **0.66 [0.32 , 1.36]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.15, df = 3 (P = 0.76); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.13 (P = 0.26) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

### Analysis 5.7. Comparison 5: Interleukin-6 receptor antagonist compared with placebo or usual care for secondary prevention, Outcome 7: Stroke (fatal or non-fatal)



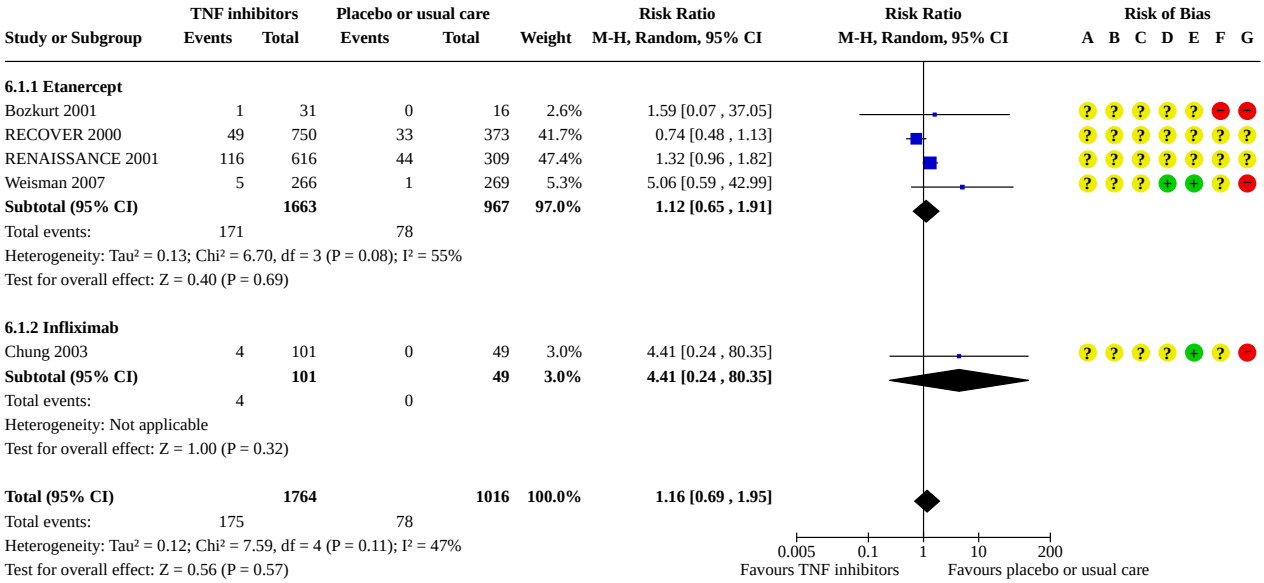

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Comparison 6. TNF inhibitors compared with placebo or usual care for secondary prevention

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 6.1 All-cause mortality | 5 | 2780 | Risk Ratio (M-H, Random, 95% CI) | 1.16 [0.69, 1.95] |
| 6.1.1 Etanercept | 4 | 2630 | Risk Ratio (M-H, Random, 95% CI) | 1.12 [0.65, 1.91] |
| 6.1.2 Infliximab | 1 | 150 | Risk Ratio (M-H, Random, 95% CI) | 4.41 [0.24, 80.35] |
| 6.2 Adverse events | 2 | 685 | Risk Ratio (M-H, Random, 95% CI) | 1.15 [0.84, 1.56] |
| 6.2.1 Etanercept | 1 | 535 | Risk Ratio (M-H, Random, 95% CI) | 1.45 [0.79, 2.69] |
| 6.2.2 Infliximab | 1 | 150 | Risk Ratio (M-H, Random, 95% CI) | 1.08 [0.93, 1.26] |
| 6.3 Adverse events by incidence rate | 6 | 2283 | Rate Ratio (IV, Fixed, 95% CI) | 1.17 [1.08, 1.28] |
| 6.3.1 Etanercept | 5 | 2133 | Rate Ratio (IV, Fixed, 95% CI) | 1.18 [1.07, 1.29] |
| 6.3.2 Infliximab | 1 | 150 | Rate Ratio (IV, Fixed, 95% CI) | 1.16 [0.88, 1.53] |
| 6.4 Adverse events: incidence rate for serious infection | 7 | 2821 | Rate Ratio (IV, Fixed, 95% CI) | 1.23 [1.04, 1.45] |
| 6.4.1 Etanercept | 6 | 2671 | Rate Ratio (IV, Fixed, 95% CI) | 1.24 [1.05, 1.47] |
| 6.4.2 Infliximab | 1 | 150 | Rate Ratio (IV, Fixed, 95% CI) | 0.97 [0.42, 2.25] |
| 6.5 Quality of life | 1 | 18 | Mean Difference (IV, Random, 95% CI) | 18.93 [-7.10, 44.96] |
| 6.6 Heart failure | 4 | 2245 | Risk Ratio (M-H, Random, 95% CI) | 0.92 [0.75, 1.14] |

| Outcome or subgroup title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 6.6.1 Etanercept | 3 | 2095 | Risk Ratio (M-H, Random, 95% CI) | 0.96 [0.76, 1.20] |
| 6.6.2 Infliximab | 1 | 150 | Risk Ratio (M-H, Random, 95% CI) | 0.69 [0.36, 1.32] |

## Analysis 6.1. Comparison 6: TNF inhibitors compared with placebo or usual care for secondary prevention, Outcome 1: All-cause mortality

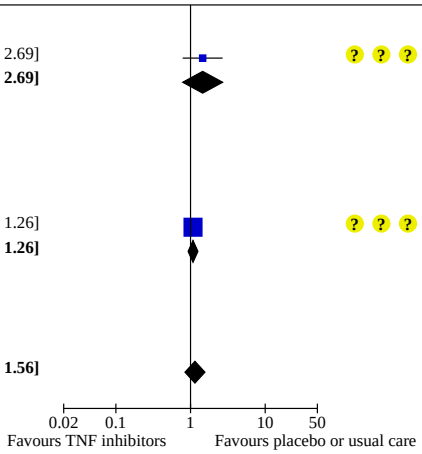



**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 6.2. Comparison 6: TNF inhibitors compared with placebo or usual care for secondary prevention, Outcome 2: Adverse events

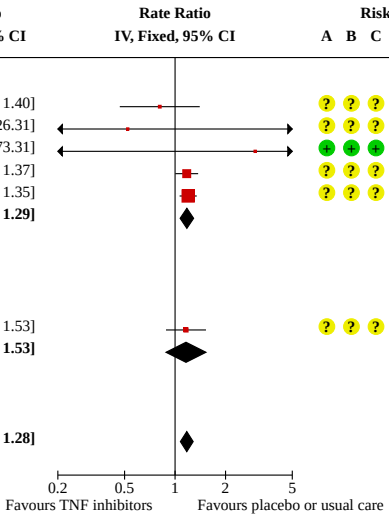
| Study or Subgroup | TNF inhibitors Events | TNF inhibitors Total | Placebo or usual care Events | Placebo or usual care Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| **6.2.1 Etanercept** | | | | | | | |
| Weisman 2007 | 23 | 266 | 16 | 269 | 20.0% | 1.45 [0.79 , 2.69] | ? ? ? + + ? − |
| **Subtotal (95% CI)** | | **266** | | **269** | **20.0%** | **1.45 [0.79 , 2.69]** | |
| Total events: | 23 | | 16 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 1.19 (P = 0.23) | | | | | | | |
| **6.2.2 Infliximab** | | | | | | | |
| Chung 2003 | 89 | 101 | 40 | 49 | 80.0% | 1.08 [0.93 , 1.26] | ? ? ? ? + ? − |
| **Subtotal (95% CI)** | | **101** | | **49** | **80.0%** | **1.08 [0.93 , 1.26]** | |
| Total events: | 89 | | 40 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 0.99 (P = 0.32) | | | | | | | |
| **Total (95% CI)** | | **367** | | **318** | **100.0%** | **1.15 [0.84 , 1.56]** | |
| Total events: | 112 | | 56 | | | | |
| Heterogeneity: Tau² = 0.02; Chi² = 1.48, df = 1 (P = 0.22); I² = 32% | | | | | | | |
| Test for overall effect: Z = 0.87 (P = 0.39) | | | | | | | |
| Test for subgroup differences: Chi² = 0.85, df = 1 (P = 0.36), I² = 0% | | | | | | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 6.3. Comparison 6: TNF inhibitors compared with placebo or usual care for secondary prevention, Outcome 3: Adverse events by incidence rate

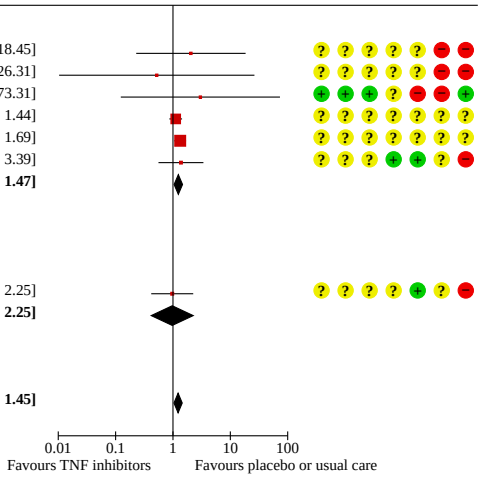
| Study or Subgroup | log[Rate Ratio] | SE | TNF inhibitors Total | Placebo or control Total | Weight | Rate Ratio IV, Fixed, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| **6.3.1 Etanercept** | | | | | | | |
| Bozkurt 2001 | -0.21 | 0.28 | 31 | 16 | 2.6% | 0.81 [0.47 , 1.40] | ? ? ? ? ? − − |
| Deswal 1999 | -0.65 | 2 | 12 | 6 | 0.1% | 0.52 [0.01 , 26.31] | ? ? ? ? ? − − |
| Ralph 2020 | 1.1 | 1.63 | 13 | 13 | 0.1% | 3.00 [0.12 , 73.31] | + + + ? − − + |
| RECOVER 2000 | 0.16 | 0.08 | 750 | 373 | 31.3% | 1.17 [1.00 , 1.37] | ? ? ? ? ? ? ? |
| RENAISSANCE 2001 | 0.18 | 0.06 | 612 | 307 | 55.7% | 1.20 [1.06 , 1.35] | ? ? ? ? ? ? ? |
| **Subtotal (95% CI)** | | | **1418** | **715** | **89.8%** | **1.18 [1.07 , 1.29]** | |
| Heterogeneity: Chi² = 2.35, df = 4 (P = 0.67); I² = 0% | | | | | | | |
| Test for overall effect: Z = 3.43 (P = 0.0006) | | | | | | | |
| **6.3.2 Infliximab** | | | | | | | |
| Chung 2003 | 0.15 | 0.14 | 101 | 49 | 10.2% | 1.16 [0.88 , 1.53] | ? ? ? ? + ? − |
| **Subtotal (95% CI)** | | | **101** | **49** | **10.2%** | **1.16 [0.88 , 1.53]** | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 1.07 (P = 0.28) | | | | | | | |
| **Total (95% CI)** | | | **1519** | **764** | **100.0%** | **1.17 [1.08 , 1.28]** | |
| Heterogeneity: Chi² = 2.36, df = 5 (P = 0.80); I² = 0% | | | | | | | |
| Test for overall effect: Z = 3.59 (P = 0.0003) | | | | | | | |
| Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0% | | | | | | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 6.4. Comparison 6: TNF inhibitors compared with placebo or usual care for secondary prevention, Outcome 4: Adverse events: incidence rate for serious infection

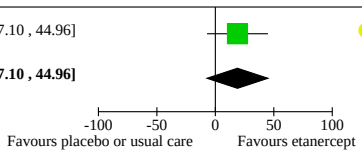
| Study or Subgroup | log[Rate Ratio] | SE | TNF inhibitors Total | Placebo or usual care Total | Weight | Rate Ratio IV, Fixed, 95% CI | Rate Ratio IV, Fixed, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| **6.4.1 Etanercept** | | | | | | | | |
| Bozkurt 2001 | 0.72 | 1.12 | 31 | 16 | 0.6% | 2.05 [0.23 , 18.45] | | ? ? ? ? ? - - |
| Deswal 1999 | -0.65 | 2 | 12 | 6 | 0.2% | 0.52 [0.01 , 26.31] | | ? ? ? ? ? - - |
| Ralph 2020 | 1.1 | 1.63 | 13 | 13 | 0.3% | 3.00 [0.12 , 73.31] | | + + + ? - - + |
| RECOVER 2000 | 0.11 | 0.13 | 750 | 373 | 42.2% | 1.12 [0.87 , 1.44] | | ? ? ? ? ? ? ? |
| RENAISSANCE 2001 | 0.29 | 0.12 | 616 | 309 | 49.5% | 1.34 [1.06 , 1.69] | | ? ? ? ? ? ? ? |
| Weisman 2007 | 0.32 | 0.46 | 266 | 266 | 3.4% | 1.38 [0.56 , 3.39] | | ? ? ? + + ? - |
| **Subtotal (95% CI)** | | | **1688** | **983** | **96.1%** | **1.24 [1.05 , 1.47]** | | |
| Heterogeneity: Chi² = 1.78, df = 5 (P = 0.88); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 2.50 (P = 0.01) | | | | | | | | |
| **6.4.2 Infliximab** | | | | | | | | |
| Chung 2003 | -0.03 | 0.43 | 101 | 49 | 3.9% | 0.97 [0.42 , 2.25] | | ? ? ? ? + ? - |
| **Subtotal (95% CI)** | | | **101** | **49** | **3.9%** | **0.97 [0.42 , 2.25]** | | |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.07 (P = 0.94) | | | | | | | | |
| **Total (95% CI)** | | | **1789** | **1032** | **100.0%** | **1.23 [1.04 , 1.45]** | | |
| Heterogeneity: Chi² = 2.09, df = 6 (P = 0.91); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 2.43 (P = 0.01) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0% | | | | | | | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

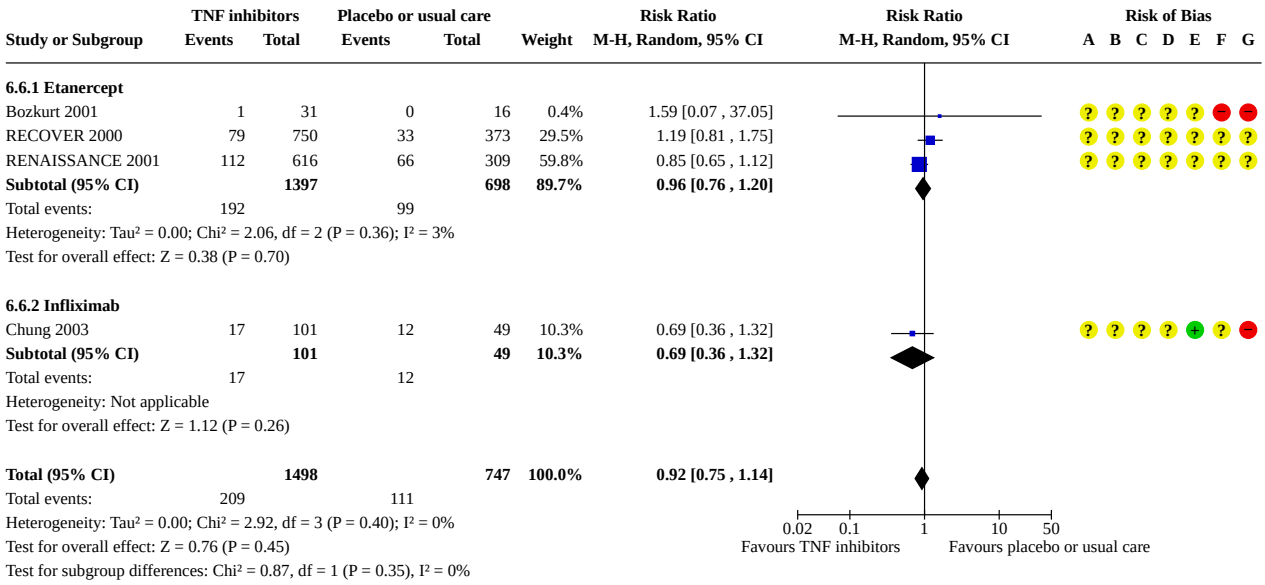
## Analysis 6.5. Comparison 6: TNF inhibitors compared with placebo or usual care for secondary prevention, Outcome 5: Quality of life

| Study or Subgroup | TNF inhibitors (Etanercept) Mean | SD | Total | Placebo or usual care Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|---|
| Deswal 1999 | 43.33 | 41.22 | 12 | 24.4 | 14.45 | 6 | 100.0% | 18.93 [-7.10 , 44.96] | | ? ? ? ? ? - - |
| **Total (95% CI)** | | | **12** | | | **6** | **100.0%** | **18.93 [-7.10 , 44.96]** | | |
| Heterogeneity: Not applicable | | | | | | | | | | |
| Test for overall effect: Z = 1.43 (P = 0.15) | | | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 6.6. Comparison 6: TNF inhibitors compared with placebo or usual care for secondary prevention, Outcome 6: Heart failure




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

# ADDITIONAL TABLES

## Table 1. Number of trials by country

| Country | Number of studies | Trials |
|---|---|---|
| Argentina | 5 | Bachelez 2015; Khanna 2020; Ridker 2012; Ridker 2017; Smolen 2008 |
| Australia | 4 | Ralph 2020; RECOVER 2000; Ridker 2017; Smolen 2008 |
| Austria | 5 | Bachelez 2015; Menter 2007; RECOVER 2000; Ridker 2017; Smolen 2008 |
| Belgium | 8 | Bachelez 2015; Calin 2004; Khanna 2020; RECOVER 2000; Ridker 2012; Ridker 2017; Van de Kerkhof 2008; Van der Heijde 2006 |
| Bosnia and Herzegovina | 1 | Bachelez 2015 |
| Brazil | 2 | Ridker 2017; Smolen 2008 |
| Bulgaria | 4 | Bachelez 2015; Khanna 2020; Ridker 2017; Smolen 2008 |
| Canada | 12 | Bagel 2012; Choudhury 2016; Davis 2003; Khanna 2016; Khanna 2020; Menter 2007; Papp 2005; Reich 2017; RENAISSANCE 2001; Ridker 2017; Smolen 2008; Tyring 2006 |
| Chile | 1 | Bachelez 2015 |

**Table 1. Number of trials by country** *(Continued)*

| | | |
|---|---|---|
| China | 2 | Ridker 2017; Smolen 2008 |
| Colombia | 2 | Bachelez 2015; Ridker 2017 |
| Croatia | 3 | Bachelez 2015; RECOVER 2000; Ridker 2017 |
| Czechia | 4 | Bachelez 2015; RECOVER 2000; Reich 2017; Ridker 2017 |
| Denmark | 5 | Bachelez 2015; Khanna 2020; Kreiner 2010; Meyer 2021; RECOVER 2000 |
| Estonia | 3 | RECOVER 2000; Reich 2017; Ridker 2017 |
| Finland | 2 | Calin 2004; RECOVER 2000 |
| France | 11 | Bachelez 2015; Calin 2004; Davis 2003; Khanna 2016; Khanna 2020; Menter 2007; Papp 2005; RECOVER 2000; Smolen 2008; Van de Kerkhof 2008; Van der Heijde 2006 |
| Germany | 18 | Bachelez 2015; Brandt 2003; Calin 2004; Choudhury 2016; Davis 2003; Khanna 2016; Khanna 2020; Krisai 2020; Micali 2015; Papp 2005; RECOVER 2000; Reich 2017; Ridker 2012; Ridker 2017; Russel 2019; Smolen 2008; Van de Kerkhof 2008; Van der Heijde 2006 |
| Greece | 4 | Khanna 2020; Micali 2015; Ridker 2017; Van der Heijde 2006 |
| Guatemala | 1 | Ridker 2017 |
| Hong Kong | 2 | Bachelez 2015; Ridker 2012 |
| Hungary | 9 | Bachelez 2015; Khanna 2020; RECOVER 2000; Reich 2017; Ridker 2012; Ridker 2017; Smolen 2008; Van de Kerkhof 2008; Van der Heijde 2006 |
| Iceland | 1 | Ridker 2017 |
| India | 2 | Ridker 2012; Ridker 2017 |
| Israel | 4 | Bachelez 2015; Choudhury 2016; RECOVER 2000; Smolen 2008 |
| Italy | 9 | Calin 2004; Khanna 2020; Menter 2007; Micali 2015; RECOVER 2000; Ridker 2017; Smolen 2008; Van de Kerkhof 2008 |
| Japan | 4 | Khanna 2020; Ridker 2012; Ridker 2017; Torii 2010 |
| Jordan | 1 | Russel 2019 |
| Korea (Republic of) | 4 | Bachelez 2015; Baek 2019; Ridker 2012; Ridker 2017 |
| Latvia | 3 | RECOVER 2000; Reich 2017; Ridker 2017 |
| Lithuania | 3 | Khanna 2020; RECOVER 2000; Ridker 2017 |
| Malta | 1 | Russel 2019 |
| Mexico | 3 | Khanna 2020; Ridker 2017; Smolen 2008 |

**Table 1. Number of trials by country** *(Continued)*

| | | |
|---|---|---|
| The Netherlands | 10 | Bachelez 2015; Calin 2004; Davis 2003; Khanna 2020; Papp 2005; RECOVER 2000; Reich 2017; Ridker 2017; Van de Kerkhof 2008; Van der Heijde 2006 |
| New Zealand | 1 | RECOVER 2000 |
| Norway | 4 | Broch 2021; Kleveland 2016; RECOVER 2000; Ridker 2017 |
| Peru | 2 | Ridker 2012; Ridker 2017 |
| Poland | 6 | Bachelez 2015; Khanna 2020; RECOVER 2000; Ridker 2017; Van de Kerkhof 2008; Van der Heijde 2006 |
| Portugal | 3 | Khanna 2020; RECOVER 2000; Van der Heijde 2006 |
| Puerto Rico | 2 | Khanna 2020; Ridker 2017 |
| Romania | 4 | Khanna 2020; Ridker 2012; Ridker 2017; Van de Kerkhof 2008 |
| Russian Federation | 2 | Bachelez 2015; Ridker 2017 |
| Serbia | 1 | Ridker 2017 |
| Singapore | 2 | Bachelez 2015; Smolen 2008 |
| Slovakia | 4 | Bachelez 2015; RECOVER 2000; Ridker 2017; Smolen 2008 |
| Slovenia | 1 | Ridker 2017 |
| South Africa | 2 | Ridker 2012; Ridker 2017 |
| Spain | 7 | Bachelez 2015; Bachelez 2015; Calin 2004; Khanna 2020; Micali 2015; RECOVER 2000; Van de Kerkhof 2008; Van der Heijde 2006 |
| Sweden | 3 | Bachelez 2015; RECOVER 2000; Ridker 2017 |
| Switzerland | 6 | Bachelez 2015; Ebrahimi 2018; Khanna 2020; Krisai 2020; Smolen 2008; Villiger 2016 |
| Taiwan | 1 | Ridker 2017 |
| Thailand | 1 | Smolen 2008 |
| Türkiye | 3 | Bachelez 2015; Ridker 2012; Ridker 2017 |
| United Kingdom | 16 | Bachelez 2015; Butchart 2015; Calin 2004; Choudhury 2016; Emsley 2005; Khanna 2016; Khanna 2020; Morton 2015; Padfield 2013; Papp 2005; RECOVER 2000; Reich 2017; Ridker 2012; Ridker 2017; Smith 2018; Van der Heijde 2006 |
| The United States of America | 34 | Abbate 2010; Abbate 2013; Abbate 2020; Bagel 2012; Bernstein 2006; Boettcher 2008; Bozkurt 2001; Carroll 2018; Choudhury 2016; Chung 2003; Davis 2003; Deswal 1999; Don 2010; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Papp 2005; Reich 2017; RENAISSANCE 2001; Ridker 2012; Ridker 2017; Russel 2019; Stanley 2011; Tyring 2006; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Weisman 2007 |

**Table 2. Trials and countries where they were conducted**

| Study | International | Number of countries | Country |
|---|---|---|---|
| Abbate 2010 | No | 1 | United States of America |
| Abbate 2013 | No | 1 | United States of America |
| Abbate 2020 | No | 1 | United States of America |
| Bachelez 2015 | Yes | 26 | Argentina, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Chile, Colombia, Croatia, Czechia, Denmark, France, Germany, Hong Kong, Hungary, Israel, Korea (Republic of), the Netherlands, Poland, Russian Federation, Singapore, Slovakia, Spain, Sweden, Switzerland, Türkiye, United Kingdom |
| Baek 2019 | No | 1 | Korea (Republic of) |
| Bagel 2012 | Yes | 2 | Canada, United States of America |
| Bernstein 2006 | No | 1 | United States of America |
| Boetticher 2008 | No | 1 | United States of America |
| Bozkurt 2001 | No | 1 | United States of America |
| Brandt 2003 | No | 1 | Germany |
| Broch 2021 | No | 1 | Norway |
| Brucato 2016 | No | 1 | Italy |
| Butchart 2015 | No | 1 | United Kingdom |
| Calin 2004 | Yes | 8 | Belgium, Finland, France, Germany, Italy, The Netherlands, Spain, United Kingdom. |
| Carroll 2018 | No | 1 | United States of America |
| Choudhury 2016 | Yes | 5 | Canada, Germany, Israel, United Kingdom, United States |
| Chung 2003 | No | 1 | United States of America |
| Davis 2003 | Yes | 5 | Canada, France, Germany, The Netherlands, United States of America |
| Deswal 1999 | No | 1 | United States of America |
| Don 2010 | No | 1 | United States of America |
| Ebrahimi 2018 | No | 1 | Switzerland |
| Emsley 2005 | No | 1 | United Kingdom |
| Gorman 2002 | No | 1 | United States of America |

**Table 2. Trials and countries where they were conducted** *(Continued)*

| | | | |
|---|---|---|---|
| Gottlieb 2003 | No | 1 | United States of America |
| Gottlieb 2004 | No | 1 | United States of America |
| Khanna 2016 | Yes | 5 | Canada, France, Germany, United Kingdom, United States of America |
| Khanna 2020 | Yes | 22 | Argentina, Belgium, Bulgaria, Canada, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Lithuania, Mexico, the Netherlands, Poland, Portugal, Puerto Rico, Romania, Spain, Switzerland, United Kingdom, United States of America |
| Kleveland 2016 | No | 1 | Norway |
| Kreiner 2010 | No | 1 | Denmark |
| Krisai 2020 | Yes | 2 | Germany, Switzerland |
| Leonardi 2003 | No | 1 | United States of America |
| Mease 2000 | No | 1 | United States of America |
| Mease 2004 | No | 1 | United States of America |
| Menter 2007 | Yes | 5 | Austria, Canada, France, Italy, United States of America |
| Meyer 2021 | No | 1 | Denmark |
| Micali 2015 | Yes | 5 | Germany, Greece, Italy, Malta, Spain |
| Morton 2015 | No | 1 | United Kingdom |
| Padfield 2013 | No | 1 | United Kingdom |
| Papp 2005 | Yes | 6 | Canada, France, Germany, Netherlands, United Kingdom, United States of America |
| Ralph 2020 | No | 1 | Australia |
| RECOVER 2000 | Yes | 24 | Australia, Austria, Belgium, Croatia, Czechia, Denmark, Estonia, Finland, France, Germany, Hungary, Israel, Italy, Latvia, Lithuania, New Zealand, Norway, Poland, Portugal, Slovakia, Spain, Sweden, The Netherlands, United Kingdom |
| Reich 2017 | Yes | 9 | Canada, Czechia, Estonia, Germany, Hungary, Latvia, Netherlands, United Kingdom, United States of America |
| RENAISSANCE 2001 | Yes | 2 | Canada, United States of America |
| Ridker 2012 | Yes | 14 | Argentina, Belgium, Germany, Hong Kong, Hungary, India, Japan, Peru, Romania, South Africa, Korea, Türkiye, United Kingdom, United States of America |
| Ridker 2017 | Yes | 40 | Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, Colombia, Croatia, Czechia, Estonia, Germany, Greece, Guatemala, Hungary, Iceland, India, Italy, Japan, Korea (Republic of), Latvia, Lithuania, Mexico, Netherlands, Norway, Peru, |

**Table 2. Trials and countries where they were conducted** *(Continued)*

| | | | |
|---|---|---|---|
| | | | Poland, Puerto Rico, Romania, Russian Federation, Serbia, Slovakia, Slovenia, South Africa, Sweden, Taiwan, Türkiye, United Kingdom, United States of America |
| Russel 2019 | Yes | 3 | Germany, Jordan, United States of America |
| Smith 2018 | No | 1 | United Kingdom |
| Smolen 2008 | Yes | 17 | Argentina, Australia, Austria, Brazil, Bulgaria, Canada, China, France, Germany, Hungary, Israel, Italy, Mexico, Singapore, Slovakia, Switzerland, Thailand |
| Stanley 2011 | No | 1 | United States of America |
| Torii 2010 | No | 1 | Japan |
| Tyring 2006 | Yes | 2 | Canada, United States of America |
| Van de Kerkhof 2008 | Yes | 9 | Belgium, France, Germany, Hungary, Italy, Netherlands, Poland, Romania, Spain |
| Van der Heijde 2006 | Yes | 10 | Belgium, France, Germany, Greece, Hungary, the Netherlands, Poland, Portugal, Spain, United Kingdom |
| Van Tassell 2016 | No | 1 | United States of America |
| Van Tassell 2017 | No | 1 | United States of America |
| Van Tassell 2018 | No | 1 | United States of America |
| Villiger 2016 | No | 1 | Switzerland |
| Weisman 2007 | No | 1 | United States of America |

**Table 3. Study drug dosage and frequency of administration**

| Study medication (number of trials) | Doses | Frequency of administration | Studies |
|---|---|---|---|
| **Interleukin-receptor antagonists** | | | |
| **Interleukin-1 receptor antagonists** | | | |
| **Anakinra (N = 11)** | 100 mg | Once a day | Abbate 2010; Abbate 2013; Abbate 2020; Brucato 2016; Morton 2015; Van Tassell 2017; Van Tassell 2018 |
| | | Twice a day | Abbate 2020; Ebrahimi 2018 |
| | | Others | Smith 2018; Van Tassell 2016 |
| | Others | Others | Emsley 2005 |
| **Canakinumab (N = 5)** | 5 mg | Once a month | Ridker 2012 |

**Table 3. Study drug dosage and frequency of administration** *(Continued)*

| | | | |
|---|---|---|---|
| | 15 mg | Once a month | Ridker 2012 |
| | 50 mg | Once a month | Ridker 2012 |
| | | Once every 3 months | Ridker 2017 |
| | 150 mg | Single dose | Krisai 2020 |
| | | Once a week | Russel 2019 |
| | | Once a month | Choudhury 2016; Ridker 2012 |
| | | Once every 3 months | Ridker 2017 |
| | 300 mg | Once a month | Ridker 2012 |
| **Interleukin-6 receptor antagonists** | | | |
| **Tocilizumab (N = 9)** | 4 mg/kg | Once a month | Smolen 2008 |
| | 8 mg/kg | Single dose | Meyer 2021 |
| | | Once a month | Baek 2019; Smolen 2008; Villiger 2016 |
| | 162 mg | Single dose | Carroll 2018 |
| | | Once a week | Khanna 2016; Khanna 2020 |
| | 280 mg | Single dose | Broch 2021; Kleveland 2016 |
| **Tumour necrosis factor inhibitors** | | | |
| **Etanercept (N = 29)** | 5 mg/m$^2$ | Twice a week | Bozkurt 2001 |
| | 12 mg/m$^2$ | Twice a week | Bozkurt 2001 |
| | 10 mg | Single dose | Padfield 2013 |
| | 25 mg | Once a week | Leonardi 2003; RECOVER 2000 |
| | | Twice a week | Brandt 2003; Calin 2004; Davis 2003; Don 2010; Gorman 2002; Gottlieb 2003; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Papp 2005; RECOVER 2000; RENAISSANCE 2001; Van der Heijde 2006; Weisman 2007 |
| | | Three times a week | RENAISSANCE 2001 |
| | | Once every 2 weeks | Ralph 2020 |
| | | Other | Boetticher 2008 |
| | 50 mg | Once a week | Bernstein 2006; Butchart 2015; Micali 2015; Reich 2017; Van de Kerkhof 2008; Van der Heijde 2006 |

**Table 3. Study drug dosage and frequency of administration** *(Continued)*

| | | | |
|---|---|---|---|
| | | Twice a week | Bachelez 2015; Bagel 2012; Leonardi 2003; Papp 2005; Tyring 2006 |
| | | Other | Stanley 2011 |
| | Others | Single dose | Deswal 1999 |
| **Infliximab** | 3 mg/kg | Once every 2 weeks | Gottlieb 2004 |
| **(N = 4)** | | At weeks 0, 2, 6 | Menter 2007 |
| | 5 mg/kg | Once every 2 weeks | Gottlieb 2004 |
| | | At weeks 0, 2, 6 | Chung 2003; Menter 2007; Torii 2010 |
| | 10 mg/kg | At weeks 0, 2, 6 | Chung 2003 |

"Others": see Characteristics of included studies of each study for more information

**Table 4. Composition of placebo/control**

| Comparison composition (as reported) | Study |
|---|---|
| Saline | Abbate 2010; Abbate 2013; Broch 2021; Carroll 2018; Don 2010; Ebrahimi 2018; Kleveland 2016; Kreiner 2010; Meyer 2021; Padfield 2013; Ralph 2020; Reich 2017 |
| "40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine, 1 mL bacteriostatic water" (p. 386) | Mease 2000 |
| "Bacteriostatic water" (p. 1669) | Brandt 2003 |
| "Water for injection" (p. 2163) | Butchart 2015 |
| Composition not specified | Abbate 2020; Bachelez 2015; Baek 2019; Bagel 2012; Bernstein 2006; Boetticher 2008; Bozkurt 2001; Brucato 2016; Calin 2004; Choudhury 2016; Chung 2003; Davis 2003; Deswal 1999; Emsley 2005; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Khanna 2020; Krisai 2020; Leonardi 2003; Mease 2004; Menter 2007; Micali 2015; Morton 2015; Papp 2005; RECOVER 2000; RENAISSANCE 2001; Ridker 2012; Ridker 2017; Russel 2019; Smith 2018; Smolen 2008; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018; Villiger 2016; Weisman 2007 |

**Table 5. Co-intervention types**

| Co-intervention types | Study |
|---|---|
| Low-potency topical corticosteroids | Bachelez 2015; Bagel 2012; Gottlieb 2003; Leonardi 2003; Menter 2007; Papp 2005; Reich 2017; Torii 2010; Tyring 2006; Van de Kerkhof 2008 |

**Table 5. Co-intervention types** *(Continued)*

| | |
|---|---|
| Immunomodulatory therapy | Khanna 2020 |
| Antihypertensives and statins | Bernstein 2006 |
| Cyclosporin | Micali 2015 |
| Metformin, alphaglucosidase inhibitor | Ridker 2012 |
| Methotrexate, nonsteroidal anti-inflammatory drugs, oral corticosteroids | Mease 2000; Mease 2004 |
| Methotrexate, intra-articular corticosteroids | Smolen 2008 |
| Nonsteroidal anti-inflammatory drugs | Brandt 2003 |
| Nonsteroidal anti-inflammatory drugs, corticosteroids, colchicine | Brucato 2016 |
| Prednisolone, aspirin, pantoprazole, calcium, vitamin D, ibandronate | Villiger 2016 |
| Tramadol | Kreiner 2010 |
| Cholinesterase inhibitor, memantine, antidepressant medication | Butchart 2015 |
| Methotrexate, hydroxychloroquine, or mycophenolate mofetil | Khanna 2016 |

**Table 6. Study approaches for reporting adverse events**

| **Type of intervention** | **Any adverse events (studies)** | |
|---|---|---|
| | **Primary prevention** | **Secondary prevention** |
| **Interleukin-1 receptor antagonist (anakinra, canakinumab)** | Abbate 2010; Abbate 2013; Ebrahimi 2018; Ridker 2012 | Abbate 2020; Brucato 2016; Choudhury 2016; Emsley 2005; Krisai 2020; Morton 2015; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018 |
| **Interleukin-6 receptor antagonist (tocilizumab)** | Baek 2019 ; Khanna 2016; Khanna 2020; Smolen 2008; Villiger 2016 | Broch 2021; Carroll 2018; Kleveland 2016; Meyer 2021 |
| **Tumour necrosis factor inhibitor (etanercept, infliximab)** | Bachelez 2015; Baek 2019; Bagel 2012; Bernstein 2006; Boetticher 2008; Brandt 2003; Butchart 2015; Calin 2004; Davis 2003; Don 2010; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; Reich 2017; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006 | Bozkurt 2001; Chung 2003; Deswal 1999; Ralph 2020; RECOVER 2000; RENAISSANCE 2001; Weisman 2007 |
| **Type of intervention** | **Serious adverse events (studies)** | |
| | **Primary prevention** | **Secondary prevention** |
| **Interleukin-1 receptor antagonist (anakinra, canakinumab)** | Abbate 2013; Ridker 2012 | Choudhury 2016; Emsley 2005; Krisai 2020; Morton 2015; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018 |

**Table 6. Study approaches for reporting adverse events** *(Continued)*

| | | |
|---|---|---|
| **Interleukin-6 receptor antagonist (tocilizumab)** | Baek 2019; Khanna 2016; Khanna 2020; Smolen 2008; Villiger 2016 | Broch 2021; Carroll 2018; Kleveland 2016; Meyer 2021 |
| **Tumour necrosis factor inhibitor (etanercept, infliximab)** | Bachelez 2015; Baek 2019; Bagel 2012; Boetticher 2008; Brandt 2003; Butchart 2015; Don 2010; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Kreiner 2010; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Reich 2017; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008 | Ralph 2020; Weisman 2007 |
| **Type of intervention** | **Non-serious adverse events (studies)** | |
| | **Primary prevention** | **Secondary prevention** |
| **Interleukin-1 receptor antagonist (anakinra, canakinumab)** | Abbate 2013; Ridker 2012 | Choudhury 2016; Emsley 2005; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018 |
| **Interleukin-6 receptor antagonist (tocilizumab)** | Baek 2019; Khanna 2016; Khanna 2020; Villiger 2016 | Broch 2021; Carroll 2018; Meyer 2021 |
| **Tumour necrosis factor inhibitor (etanercept, infliximab)** | Bachelez 2015; Baek 2019; Bagel 2012; Brandt 2003; Butchart 2015; Don 2010; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Kreiner 2010; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Reich 2017; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006 | Ralph 2020; RECOVER 2000; RENAISSANCE 2001 |

**Table 7. Study approaches for reporting infections**

| | | |
|---|---|---|
| **Type of intervention** | **Any infection (studies)** | |
| | **Primary prevention** | **Secondary prevention** |
| **Interleukin-1 receptor antagonist (anakinra, canakinumab)** | Abbate 2013; Ebrahimi 2018; Ridker 2012 | Abbate 2020; Brucato 2016; Choudhury 2016; Emsley 2005; Krisai 2020; Morton 2015; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018 |
| **Interleukin-6 receptor antagonist (tocilizumab)** | Baek 2019; Khanna 2016; Khanna 2020; Smolen 2008; Villiger 2016 | Broch 2021; Carroll 2018; Kleveland 2016; Meyer 2021 |
| **Tumour necrosis factor receptor antagonists (etanercept, infliximab)** | Bachelez 2015; Bagel 2012; Boetticher 2008; Brandt 2003; Butchart 2015; Davis 2003; Don 2010; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; Reich 2017; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006 | Bozkurt 2001; Chung 2003; Ralph 2020; RECOVER 2000; RENAISSANCE 2001; Weisman 2007 |
| **Type of intervention** | **Serious infections (studies)** | |
| | **Primary prevention** | **Secondary prevention** |

**Table 7. Study approaches for reporting infections** *(Continued)*

| | | |
|---|---|---|
| **Interleukin-1 receptor antagonist (anakinra, canakinumab)** | Abbate 2013; Ridker 2012 | Abbate 2020; Choudhury 2016; Emsley 2005; Krisai 2020; Morton 2015; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2016; Van Tassell 2017 |
| **Interleukin-6 receptor antagonist (tocilizumab)** | Baek 2019; Khanna 2016; Khanna 2020; Smolen 2008; Villiger 2016 | Broch 2021; Kleveland 2016; Meyer 2021 |
| **Tumour necrosis factor receptor antagonists (etanercept, infliximab)** | Bachelez 2015; Boetticher 2008; Brandt 2003; Butchart 2015; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Mease 2000; Mease 2004; Micali 2015; Reich 2017; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006 | Ralph 2020; RECOVER 2000; RENAISSANCE 2001; Weisman 2007 |

| **Type of intervention** | **Non-serious infections (studies)** | |
|---|---|---|
| | **Primary prevention** | **Secondary prevention** |
| **Interleukin-1 receptor antagonist (anakinra, canakinumab)** | Abbate 2013; Ridker 2012 | Choudhury 2016; Emsley 2005; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2018 |
| **Interleukin-6 receptor antagonist (tocilizumab)** | Baek 2019; Khanna 2016; Khanna 2020; Villiger 2016 | Broch 2021; Meyer 2021 |
| **Tumour necrosis factor receptor antagonists (etanercept, infliximab)** | Bachelez 2015; Bagel 2012; Brandt 2003; Butchart 2015; Gorman 2002; Gottlieb 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Reich 2017; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006 | Ralph 2020; RECOVER 2000; RENAISSANCE 2001 |

**Table 8. Approaches for reporting quality of life in primary prevention**

| Study | Intervention | Scale used | Approaches |
|---|---|---|---|
| Bachelez 2015 | Etanercept | Dermatology Life Quality Index (DLQI) | Quote: "At week 12, a clinically meaningful improvement in DLQI score (a reduction by five points or more) was achieved by 191 (66.3%) of 288 patients in the tofacitinib 10 mg group, 226 (78.2%) of 289 in the tofacitinib 5 mg group, 218 (74.7%) of 292 in the etanercept group, and 28 (31.8%) of 88 in the placebo group, in patients with a baseline score of 5 or higher (P < 0.0001 for each active treatment vs placebo; table 2)." p. 5<br><br>Comment: the trial reported the mean and range at the beginning of the trial for each group, but only reported the proportion of participants achieving clinical improvement at the end of the follow-up period. |
| Baek 2019 | Tocilizumab | Health Assessment Questionnaire Disability Index (HAQ-DI) | HAQ-DI at baseline (mean ± SD): placebo group 1.4 ± 0.6; tocilizumab group 1.3 ± 0.7 (p. 921, table1)<br><br>Change in HAQ-DI at week 24 (mean ± SD): placebo group –0.1 ± 1.2; tocilizumab group 0.9 ± 1.0; P = 0.0002 (p. 922, table 2) |
| Brandt 2003 | Etanercept | Medical Outcomes Study Short-Form Health Survey (MOS SF-36) | Quote: "Between baseline and week 6, the physical component score assessed with the SF-36 improved in the etanercept group but not in the placebo group. The difference between the scores in the 2 groups at week 6 reached statistical significance |

**Table 8. Approaches for reporting quality of life in primary prevention** *(Continued)*

| | | | |
|---|---|---|---|
| | | | (P = 0.026). No improvement was seen in the mental component score in either group during the first 6 weeks." (p. 1672)<br><br>Comment: the trial provided the statistical comparison of the scores at the end of the 6-week follow-up. However, it didn't report the scores at the beginning and end of the trial for each group. |
| Don 2010 | Etanercept | Medical Outcomes Study Short-Form Health Survey (MOS SF-36) | Quote: "The characteristics of the general health profile at the beginning and the end of the study are shown in Table 11; mean ± SD are given. The profile scores did not change after the trial in both the groups (P > 0.05) with the exception of energy (P = 0.0105) in the etanercept group." (p. 436)<br><br>Comment: see Table 11 on p. 436 of the study's manuscript for the full report. |
| Gorman 2002 | Etanercept | Medical Outcomes Study Short-Form Health Survey (MOS SF-36) | Quote: "…The etanercept group also had significantly greater improvement in quality-of-life measures, particularly those related to physical functioning and health (Fig. 2)." (pp. 1351 and 1354, figure 2)<br><br>Comment: the authors didn't report the scores at baseline or end of follow-up, only the median change at the end of the double-blind period. |
| Gottlieb 2003 | Etanercept | Dermatology Life Quality Index (DLQI) | Composite DLQI as% improvement, mean (SE) from baseline to week 24<br><br>Placebo group: 7 (8)<br><br>Etanercept group: 64 (5)<br><br>Quote: "…patients treated with etanercept had statistically significant improvement in quality of life as measured by the DLQI starting at week 4 (time of first assessment) compared with patients given placebo." (p. 1630, table 3)<br><br>Comment: authors reported the mean percentage of improvement and standard error; they did not report the mean scores at baseline or the end of the follow-up period. |
| Gottlieb 2004 | Infliximab | Dermatology Life Quality Index (DLQI) | Quote: "Infliximab treatment also resulted in substantial improvement in quality of life as measured by DLQI. The median change from baseline to week 10 in the<br><br>infliximab (3 and 5 mg/kg) groups were -8 and -10, respectively, compared with a median change of 0 in the placebo group (P < 0.001). At week 10, the median<br><br>DLQI scores in the infliximab groups were near normal (2 and 1 for the 3- and 5-mg/kg groups, respectively) compared with 10 in the placebo group." (p. 538)<br><br>Comment: the authors reported median and interquartile range at baseline, and mean change at the end without a measure for the dispersion of the data. |
| Khanna 2016 | Tocilizumab | European Quality of Life 5 Dimen- | Need Appendix |

**Table 8. Approaches for reporting quality of life in primary prevention** *(Continued)*

| | | | |
|---|---|---|---|
| | | sions 3 Level Version (EQ-5D-3L) | |
| Khanna 2020 | Tocilizumab | European Quality of Life 5 Dimensions 3 Level Version (EQ-5D-3L) | Need Appendix |
| Leonardi 2003 | Etanercept | Dermatology Life Quality Index (DLQI) | Quote: "The mean percentage improvement from baseline in the Dermatology Life Quality Index was significant in all the etanercept groups at week 2; by week 12, the mean improvement was 47.2 percent in the low-dose group, 50.8 percent in the medium-dose group, and 61.0 percent in the high-dose group, as compared with 10.9 percent in the placebo group (P < 0.001 for all three comparisons with the placebo group)." (p. 2020)<br><br>Comment: the trial reported the mean and standard error at baseline, and the percentage of patients reaching improvement at the end of the double-blind period (12 weeks). |
| Mease 2004 | Etanercept | Health Assessment Questionnaire Disability Index (HAQ-DI) | Quote: "Disability, as measured by the HAQ, decreased statistically significantly in the etanercept group, compared with the placebo group. At 24 weeks, mean improvement from baseline in the etanercept group was 54%, compared with 6% in the placebo group (P < 0.0001) (data not shown)." (p. 2268)<br><br>Comment: the trial only reported each group's mean change in scores. They didn't show the data from the scores at baseline and at the end of the follow-up period. |
| Menter 2007 | Infliximab | Dermatology Life Quality Index (DLQI) | Quote: "39.0% in the 5 mg/kg group and 28.3% in the 3 mg/kg group (compared with 1.0% in the placebo group) achieved a total DLQI score of 0 (P < 0.001 for both infliximab groups vs placebo, for both indices)." (p. 31.e5)<br><br>Comment: the study reported the mean and standard deviation at baseline and the percentage of participants achieving a DLQI of 0 at the end of the double-blind period (14 weeks). |
| Micali 2015 | Etanercept | Dermatology Life Quality Index (DLQI) | Quote: "At baseline, patients in both the etanercept and placebo groups had a severely affected QoL due to their psoriasis. At week 12, mean (SE) DLQI was similar in the etanercept group compared with placebo [1.0 (0.7) vs. 2.0 (0.7); P = 0.511], indicating a small effect on QoL in both groups. Mean (SE) DLQI scores at week 30 in the etanercept and placebo arms were 4.5 (0.7) and 7.3 (0.7) for a significant difference of −2.8 (95% CI: −4.7, −0.9; P = 0.004). The difference in mean change of DLQI scores was −2.8 but did not reach statistical significance (95% CI: −5.8, 0.2; P = 0.069; Table I)." |
| Reich 2017 | Etanercept | Dermatology Life Quality Index (DLQI) | Comment: the study reported the means and standard deviation at baseline, the mean change from baseline to week 16, and the percentage of participants achieving scores of 0 and 1 (pp. 512-513, table 2 and figure 4). |
| Smolen 2008 | Tocilizumab | Medical Outcomes Study Short-Form Health Survey (MOS SF-36) | Quote: "There were greater improvements in physical function, as judged by mean difference in HAQ-DI score from baseline, with both doses of tocilizumab than with placebo (table 3). A clear difference between the two tocilizumab groups from |

**Table 8. Approaches for reporting quality of life in primary prevention** *(Continued)*

| | | | |
|---|---|---|---|
| | | | placebo was noted by week 4 (Figure 2). An increase from baseline in HAQ-DI of 0.3 points or more was achieved by 77 (61%) patients in the 4 mg/kg group, 83 (59%) in the 8 mg/kg group, and 47 (47%) in the placebo group at week 24." (p. 992)<br><br>Comment: trial's authors reported the mean and standard deviation at baseline, the mean difference and the percentage achieving scores of zero to three at the end of the follow-up. |
| Torii 2010 | Infliximab | Dermatology Life Quality Index (DLQI) | Quote: "The DLQI score at Week 0 was 12.7 ± 6.8 in the infliximab group and 10.5 ± 6.8 in the placebo group. The change in DLQI at Week 10 was - 9.9 ± 7.1 in the infliximab group, compared with -0.4 ± 6.2 in the placebo group; a significant improvement in DLQI score was observed in the infliximab group (P < 0.001), and the effect persisted until Week 14 (Fig. 5)." (p. 44)<br><br>Comment: the study reported the mean and standard deviation at baseline and the mean change at the end of the double-blind period. |
| Tyring 2006 | Etanercept | Dermatology Life Quality Index (DLQI) | Quote: "At week 12, mean percentage improvement of DLQI was 69.1% in patients receiving etanercept compared with 22.1% in the placebo group (P < 0.0001; difference 47%, 95% CI 40–54)." (p. 32)<br><br>Comment: the trial reported mean and standard deviation at baseline and the percentage of participants achieving improvement at the end of the follow-up period. |
| Van de Kerkhof 2008 | Etanercept | Dermatology Life Quality Index (DLQI) | Quote: "Mean improvements in DLQI from baseline in the etanercept group were 20% and 54% at weeks 2 and 12, respectively, compared with –6.6% and 5.2% in the placebo group (Fig. 5)." (p. 1181)<br><br>Comment: the trial reported the mean and standard deviation at the beginning and the percentage of improvement at the end of the follow-up. |

- DLQI: Dermatology Life Quality Index
- EQ-5D-3L: EuroQol 5-Dimension 3-Level
- HAQ-DI: Health Assessment Questionnaire Disability Index
- MOS SF-36: Medical Outcomes Study Short Form 36
- QoL: quality of life
- SD: standard deviation
- SE: standard error

**Table 11. Type of disease and trials**

| Disease's name | Study | Number of trials |
|---|---|---|
| **Cardiovascular diseases** | | |
| Myocardial Infarction (any type) | Abbate 2010; Abbate 2013; Abbate 2020; Broch 2021; Carroll 2018; Kleveland 2016; Padfield 2013; Ridker 2017 | 8 |

**Table 11. Type of disease and trials** *(Continued)*

| | | |
|---|---|---|
| Non-ST-elevation acute coronary syndrome | Morton 2015 | 1 |
| Heart failure | Bozkurt 2001; Chung 2003; Deswal 1999; RECOVER 2000; RENAISSANCE 2001; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018 | 8 |
| Stroke (any type) | Emsley 2005; Ralph 2020; Smith 2018 | 3 |
| Out-of-hospital cardiac arrest | Meyer 2021 | 1 |
| Peripheral arterial disease | Russel 2019 | 1 |
| Recurrent pericarditis | Brucato 2016 | 1 |
| Atrial fibrillation | Krisai 2020 | 1 |
| End-stage renal disease | Don 2010 | 1 |
| Metabolic syndrome and type 2 diabetes mellitus | Bernstein 2006; Ebrahimi 2018; Ridker 2012; Stanley 2011 | 4 |
| **Non-cardiovascular diseases** | | |
| Psoriasis in any stage | Bachelez 2015; Bagel 2012; Gottlieb 2003; Gottlieb 2004; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; Reich 2017; Torii 2010; Tyring 2006; Van de Kerkhof 2008 | 16 |
| Rheumatoid arthritis | Baek 2019; Smolen 2008; Weisman 2007 | 3 |
| Liver disease (any) | Boetticher 2008 | 1 |
| Ankylosing spondylitis | Brandt 2003; Calin 2004; Davis 2003; Gorman 2002; Van der Heijde 2006 | 5 |
| Polymyalgia rheumatica | Kreiner 2010 | 1 |
| Alzheimer's disease | Butchart 2015 | 1 |
| Giant cell arteritis | Villiger 2016 | 1 |
| Systemic sclerosis | Khanna 2016; Khanna 2020 | 2 |

ST: the ST segment begins at the end of the S wave (the J point) and continues until the beginning of the T wave on an electrocardiogram.

**Table 9. Approaches for reporting quality of life in secondary prevention**

| Study | Intervention | Scale used | Approaches |
|---|---|---|---|
| Chung 2003 | Infliximab | Minnesota Living with Heart Failure Questionnaire (MLWHFQ) | Quote "….There were no significant changes in quality of life scores among the 3 treatment groups either at 14 weeks ([1] 4.0, [1] 6.5, and [1] 4.0 for placebo, 5 mg/kg, and 10 mg/kg [P0.829]) or at 28 weeks (0.0, [1] 3.0, and [1] 6.0 for placebo, 5 mg/kg, and 10 mg/kg, respectively [P0.811])." p. 3136 |

**Table 9. Approaches for reporting quality of life in secondary prevention** *(Continued)*

| | | | |
|---|---|---|---|
| Van Tassell 2017 | Anakinra | Duke Activity Status Index (DASI) and Minnesota Living with Heart Failure Questionnaire (MLWHFQ) | Quote "Patients treated with anakinra for 12 weeks reported a significant improvement in the DASI over time, reflecting an improved perceived functional capacity, while those treated with placebo or with anakinra for 2 weeks did not (Figure 5). The improvement in DASI at 12 weeks showed a modest correlation with the improvement in peak VO2 (R = +0.30, P = 0.034), reduction in CRP levels (R = −0.29, P = 0.039), as well as improved $E_a$/$E_{es}$ (R = +0.33, P = 0.023) and stroke work efficiency (R = +0.30, P = 0.043). HF symptoms burden measured with as MLWHF scores significantly improved in all 3 treatment groups, although the improvement was numerically greatest in the anakinra groups, and the improvement in MLWHF at 12 weeks also showed a correlation with peak VO2 (R = −0.33 and P = 0.018)." p. 8<br><br>Comment: trial authors reported no information to make an intervention effect estimation. |
| Van Tassell 2018 | Anakinra | Duke Activity Status Index (DASI) and Minnesota Living with Heart Failure Questionnaire (MLWHFQ) | Quote "There were no significant differences in baseline Duke Activity Status Index score or MLWHFQ score and physical domain scores between the groups, and there were no significant between-groups differences on the effects of treatments on any of the outcomes of interest (Figure 6). Patients randomized to treatment with anakinra reported a significant improvement in perceived functional capacity, as assessed by the Duke Activity Status Index questionnaire (+11 [95% from +2 to +20], P = 0.044 for within-group), and of the MLWHFQ questionnaire score as a whole as well as the physical domain (−21% [95% CI from +17% to −136% of the mean value] and −66% [95% CI from −16% to −76% of the mean value], P = 0.031 and P = 0.001 at within-group analysis, respectively, at 12 weeks), whereas no significant changes were seen in the placebo group (all P values > 0.05 for within-group in placebo), and none of the differences in anakinra versus placebo changes reached statistical significance for any of the changes in questionnaires over time (all P > 0.05 for time × group interaction; Figure 6)." p. 6<br><br>Comment: there was no information about the placebo group, and authors only reported data as anakinra within-group. |

CI: confidence interval
DASI: Duke Activity Status Index
$E_a$/$E_{es}$: ventriculo-arterial coupling
HF: heart failure
MLWHFQ: Minnesota Living with Heart Failure Questionnaire
VO2: volume of oxygen consumed

**Table 10. Summary of percentage of missing data reported for any adverse events by intervention type and prevention type**

| **Primary prevention** | | |
|---|---|---|
| **Intervention** | **Mean % (95% CI)** | **Trials** |
| Interleukin-1 receptor antagonists | 7.28 (-13.33 to 27.90) | (Abbate 2013; Ebrahimi 2018; Ridker 2012) |

**Table 10. Summary of percentage of missing data reported for any adverse events by intervention type and prevention type** *(Continued)*

| | | |
|---|---|---|
| Interleukin-6 receptor antagonists | 15.74 (5.17 to 26.32) | (Baek 2019; Khanna 2020; Smolen 2008; Villiger 2016) |
| Tumour necrosis factor inhibitors | 17.41 (11.35 to 23.46) | (Bachelez 2015; Bagel 2012; Bernstein 2006; Boetticher 2008; Brandt 2003; Butchart 2015; Calin 2004; Davis 2003; Don 2010; Gorman 2002; Gottlieb 2003; Gottlieb 2004; Khanna 2016; Kreiner 2010; Leonardi 2003; Mease 2000; Mease 2004; Menter 2007; Micali 2015; Papp 2005; Reich 2017; Ridker 2012; Stanley 2011; Torii 2010; Tyring 2006; Van de Kerkhof 2008; Van der Heijde 2006) |
| **Secondary prevention** | | |
| Interleukin-1 receptor antagonists | 23.46 (16.31 to 30.60) | (Abbate 2020; Choudhury 2016; Emsley 2005; Morton 2015; Ridker 2017; Russel 2019; Smith 2018; Van Tassell 2016; Van Tassell 2017; Van Tassell 2018) |
| Interleukin-6 receptor antagonists | 4.80 (1.91 to 7.69) | (Carroll 2018; Kleveland 2016; Meyer 2021) |
| Tumour necrosis factor inhibitors | 11.57 (-1.19 to 24.33) | (Bozkurt 2001; Broch 2021; Chung 2003; Ralph 2020) |

CI: confidence interval

# APPENDICES

## Appendix 1. Medical glossary

| Medical Term | Definition |
|---|---|
| Adaptive immunity | Adaptive immunity is slower to react and relies largely on somatic rearrangement of genes and prior exposure for maximal protection (for example, by immunisation to induce antibody formation) (Moreland 2004).<br><br>The adaptive immune response, although integrated into the process of inflammation, becomes active at later stages. Its key properties are (1) specificity: each B and T lymphocyte recognises a single specific peptide sequence; and (2) memory: when an invading pathogen has been recognised once, a small number of specific cells remain dormant within the lymph tissue for many years (Thornton 2019).<br><br>The two types of adaptive immunity, called humoral immunity (antibodies) and cell-mediated immunity (T lymphocytes), are mediated by different cells and molecules and provide defence against extracellular microbes and intracellular microbes (Abbas 2020). |
| Atherosclerosis | A condition caused by the deposition of lipid in the wall of arteries in atheromatous plaques. Migration of smooth muscle cells from media to intima, smooth muscle cell proliferation, the formation of foam cells and extensive deposition of extracellular matrix all contribute to the formation of the lesions that may ultimately occlude the vessel or, following loss of the endothelium, trigger the formation of thrombi. Should be distinguished from arteriosclerosis, which is a more general term usually applied to arterial hardening through other causes. Atherosclerosis is a major medical problem in most of the developed world (Lackie 2007). |
| Atheroma | A lipid-containing deposit in the arteries undergoing hardening (Juo 2001). |

(Continued)

| | |
|---|---|
| Biological Product | Biological products include a wide range of products, such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, are often at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available (FDA 2020d). |
| Chimeric monoclonal antibodies | These are therapeutic biological agents developed as structural chimeras containing murine variable regions, which target the antigen of interest, and human Fc Ig components, which reduce the immunogenicity of the antibody (Moreland 2004). |
| Disease-modifying antirheumatic drugs | These drugs reduce the progression and tissue destruction of the inflammatory disease process, especially rheumatoid arthritis, by inhibiting tumour necrosis factor (Visovsky 2019). |
| Genetic pleiotropy | A phenomenon in which multiple and diverse phenotypic outcomes are influenced by a single gene (or single gene product). |
| Humanised monoclonal antibodies | Therapeutic monoclonal antibodies are constructed by grafting the complementarity determining regions of murine monoclonal antibody directed against the biological target of choice onto the framework of human light and heavy chain variable regions (Moreland 2004).<br><br>A type of antibody made in the laboratory by combining a human antibody with a small part of a mouse or rat monoclonal antibody. The mouse or rat part of the antibody binds to the target antigen, and the human part makes it less likely to be destroyed by the body's immune system (NCI 2020). |
| Inflammation | A process or state characterised by the accumulation of activated leukocytes (Moreland 2004)<br><br>It is appropriate as a response to physical damage, microbial infection or malignancy (Thornton 2019). |
| Immune response | The co-ordinated response of these cells and molecules (immune system) to pathogens and other substances (Abbas 2020) |
| Immune system | A composite of tissues, cells, and molecules involved in the host defence system against foreign pathogens; bacteria, viruses, fungi, and parasites. Autoimmune disease results when the multiple cellular, molecular and tissue interactions leading to host defences malfunctions (Moreland 2004).<br><br>The collection of cells, tissues, and molecules that mediate these reactions to some non-infectious substances including harmless environmental molecules, tumours, and even unaltered host components are also considered forms of immunity (allergy, tumour immunity, and autoimmunity, respectively) (Abbas 2020). |
| Immunomodulatory drugs | They are used both to control symptoms and to retard or arrest the progression of chronic inflammatory diseases. They act to inhibit inflammation in a variety of ways, and reduce the proliferation and activation of lymphocytes (Thornton 2019). |
| Innate immunity | An inherited means of defence against infection. It is synonymous with natural immunity (Moreland 2004).<br><br>Innate immunity, also called natural immunity or native immunity, is always present in healthy individuals (hence the term innate), prepared to block the entry of microbes and to rapidly eliminate microbes that do succeed in entering host tissues (Abbas 2020). |
| Monoclonal antibodies | Monoclonal antibodies are produced from the fusion of two cells to generate a hybrid cell or hybridoma with two characteristics: the production of one specific antibody and immortality (Varadé 2020). |

*(Continued)*

| | |
|---|---|
| Proinflammatory cytokines | Potent mediators of numerous biological processes and are tightly regulated in the body. Chronic uncontrolled levels of such cytokines can initiate and derive many pathologies, including incidences of autoimmunity and cancer (Rider 2016). |
| QTc | "The QT interval is measured from the beginning of the QRS complex to the end of the T wave. The corrected QT interval (QTc) takes into account the heart rate, because the QT interval increases at slower heart rates" (Levine 2018). |

## Appendix 2. Interleukin family assessed in randomized clinical trials to prevent cardiovascular events

| Cytokine families | Source | Function | Role in heart diseases |
|---|---|---|---|
| **Interleukin 1 family** | | | |
| IL-1β | Blood monocytes, tissue macrophages, and dendritic cells (Klimov 2019).<br>It is a product of activated macrophages (Moreland 2004). | IL-1β is mainly produced by inflammatory cells of the myeloid compartment. This self-sustained induction of IL-1 is a key mechanism of autoinflammation (Cavalli 2018).<br>It is one of two forms of IL-1, which are products of separate genes. The two forms of IL-1 act as cytokine hormones and have similar effects on cells. Il-1 was first described as an endogenous pyrogen and is one of the most proinflammatory molecules known (Moreland 2004). | 1. Tissue levels IL-1β in ischaemia-reperfusion<br>2. Increased tissue IL-1β mRNA in dilated cardiomyopathy<br>3. Increased circulating IL-1β in dilated cardiomyopathy<br>4. Increased circulating IL-1β in acute myocarditis<br>5. Increased tissue IL-1β mRNA in acute myocarditis<br>6. IL-1Ra provides cardioprotection in ischaemia-reperfusion.<br>7. Increased serum IL-1β predicts a high risk of mortality in idiopathic dilated cardiomyopathy.<br>Source: Bartekova 2018 reports several references. |
| IL-1 | IL-1β is an inducible cytokine primarily produced not only by monocytes and macrophages but also by neutrophils (Abbate 2020). | IL-1 is a family of cytokines, including IL-1 and IL-1β.These macrophage products have profound proinflammatory effects (Moreland 2004).<br>The IL-1 family has 11 cytokine members and 10 receptors (Abbate 2020). IL-1–mediated inflammation is initiated when IL-1 binds to its receptors. There are two receptors for IL-1; IL-1R1 (IL-1 receptor type 1) is the ligand-binding chain, and IL-1R3 is the coreceptor (Abbate 2020). | |
| IL-1α | Although IL-1α is also inducible in myeloid cells, the IL-1α precursor is present constitutively in all mesenchymal cells in health, including the myocardium (Abbate 2020). | It is synthesised by a wide variety of cells, may function in the same manner as IL-1β, but also plays an essential role in the maintenance of the skin barrier. It is a member of the IL-1 family of cytokines (Klimov 2019). | |
| IL-6 | Macrophages, endothelial cells, T cells | IL-6 is a cytokine that exerts both local and distant effects in the human body. It is classified as an endogenous pyrogen as it can increase body temperatures via the | 1. Increased circulating IL-6 post-acute myocardial infarction |

(Continued)

| | | | |
|---|---|---|---|
| | | hypothalamus. Within an elevated body temperature, pathogens are less likely to thrive, the adaptive immune responses are more reactive, and host cells are more resistant to TNF-α side effects. IL-6 has an important direct role in our immune system. It unleashes the acute-phase response that produces opsonins, along with increased opsonization IL-6 recruits neutrophils from the bone marrow increasing opsonin identified foreign body phagocytosis (Moreland 2004). | 2. Increased tissue IL-6 mRNA post-acute myocardial infarction<br>3. Increased levels of sIL-6R post-acute myocardial infarction<br>4. Recombinant IL-6 induced cardioprotection in ischaemia-reperfusion<br>5. Increased plasma IL-6 in chronic heart failure<br>6. Increased plasma IL-6 predicts adverse cardiovascular events following acute coronary syndrome and coronary heart disease.<br>7. IL-6 silencing abrogated cardioprotection by explant-derived stem cells<br>8. Increased circulating IL-6 in dilated cardiomyopathy and hypertrophic cardiomyopathy<br>9. IL-6 polymorphism is associated with risk of dilated cardiomyopathy.<br><br>Source: Bartekova 2018 reports several references. |
| **Tumour necrosis factors** | | | |
| TNFα | Macrophages, T cells,<br>mast cells | Endothelial cells: activation (inflammation, coagulation). Neutrophils: activation. Hypothalamus: fever. Liver: synthesis of acute-phase proteins. Muscle, fat: catabolism (cachexia). Many cell types: apoptosis | 1. Toxic or protective in acute myocardial infarction<br>2. Increased in plasma TNFα in heart failure<br>3. Positive correlation between TNFα gene expression and level, severity, and aetiology of heart failure<br>4. Cardiac-restricted overexpression of membrane-bound TNFα—ventricular hypertrophy and consequent dysfunction<br>5. Cardiac-restricted overexpression of secreted TNFα—ventricular dilation and consequent dysfunction<br><br>Source: Bartekova 2018 reports several references. |
| TNFβ (lymphotoxin) | Lymphocytes | It is secreted by lymphocytes. Its effects are similar to those of TNFα, but TNFβ is more critical for the development of lymphoid tissue (Klimov 2019). | 1. Involvement in cardiac remodelling<br>2. Cardiac fibrosis<br>3. Positive correlation between TGF-β1 and left ventricular mass<br>4. Increased TGF-β1 gene expression after transition from stable hypertrophy to heart failure<br>5. Increased TGF-β1 level—in hypertrophic cardiomyopathy<br>6. Involvement in formation of border zone around the infarcted area<br>7. Biomarker revealing aortic dilation |

*(Continued)*

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| | Source: Bartekova 2018 reports several references. |

**Sources**: Abbas 2020, Klimov 2019; O'Shea 2019, Morton 2015, Cavalli 2018

**Abbreviations:**
IL-1β: interleukin-1 beta
IL-1: interleukin-1
IL-1α: interleukin- 1 alpha
IL-6: interleukin-6
TNFα: tumour necrosis factor alfa
TNFβ: tumour necrosis factor beta

## Appendix 3. Pharmacological summary and primary clinical application of interleukin-receptor antagonist therapy in preventing cardiovascular outcomes

| Interleukin-receptor antagonist | Total Drug Content | Concentration | Dosage | Route | Presentation | Anatomical therapeutic chemical code | Approval date by Food and Drugs Administration (FDA 2020) | Approval date year of European Medicines Agency | Primary clinical application |
|---|---|---|---|---|---|---|---|---|---|
| **Monoclonal antibodies against interleukin-1 receptors** | | | | | | | | | |
| Anakinra | 100 mg/0.67 mL | 100 mg/0.67 mL | Solution | Subcutaneous | Prefilled syringe | L04AC03 (EMA 2020). | 11 April 2001 | 08 March 2002 (EMA 2020) | Rheumatoid arthritis, cryopyrin-associated periodic syndromes, hereditary systemic inflammatory diseases, and systemic and local inflammatory diseases (Cavalli 2018) |
| Canakinumab | 150 mg/mL | 150 mg/mL | Solution | Subcutaneous | Single-dose vial | L04AC08 (EMA 2020a) | 22 December 2016 | 23 October 2009 (EMA 2020a) | Cryopyrin-associated periodic syndromes, autoinflammatory syndromes (Varadé 2020).<br>TNF- receptor associated periodic syndrome, hyperimmunoglobulin D syndrome, familial Mediterranean syndrome (ACTIP 2017; Singh 2018) |
| **Monoclonal antibodies against interleukin-6 receptors** | | | | | | | | | |
| Tocilizumab | 80 mg/4 mL | 20 mg/mL | Solution | Intravenous | Single-dose vial | L04AC07 (EMA 2020b). | 08 January 2010 | 15 January 2009 (EMA 2020b)<br>Available only<br>Each vial contains 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL).<br>Each vial contains | • Rheumatoid arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis, cytokine release syndrome (Singh 2018; Varadé 2020)<br>• Castleman's disease (Sheppard 2017)<br>• Crohn's disease, systemic lupus erythematosus, Takayasu arteritis, giant cell arteritis<br>• Polymyalgia rheumatica, and refractory adult-onset Still disease, has not yet received licences in these indications (Sheppard 2017). |
| Tocilizumab | 200 mg/10 mL | 20 mg/mL | Solution | Intravenous | Single-dose vial | | 08 January 2010 | | |
| Tocilizumab | 400 mg/20 mL | 20 mg/mL | Solution | Intravenous | Single-dose vial | | 08 January 2010 | | |
| Tocilizumab | 162 mg/0.9 mL | 179 mg/mL | Solution | Subcutaneous | Prefilled syringe | | 21 October 2013 | | |

*(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Tocilizumab | 162 mg/0.9 mL | 179 mg/mL | Solution | Subcutaneous | Autoinjector | | 19 November 2018 | 20 mg/mL) (EMA 2020b). | |
| **Tumour necrosis factor inhibitors** | | | | | | | | | |
| Etanercept | 25 mg | 25 mg/vial | Powder | Subcutaneous | Multi-dose vial | L04AB01 (EMA 2020c) | 02 November 1998 | 23 June 2017 (EMA 2020c) | Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis, and paediatric plaque psoriasis (EMA 2020c) |
| Etanercept | 50 mg/mL | 50 mg/mL | Solution | Subcutaneous | Prefilled syringe | | 27 September 2004 | | |
| Etanercept | 50 mg/mL | 50 mg/mL | Solution | Subcutaneous | Autoinjector | | 27 September 2004 | | |
| Etanercept | 25 mg/0.5 mL | 50 mg/mL | Solution | Subcutaneous | Single-dose vial and prefilled syringe | | 27 September 2004 | | |
| Etanercept | 50 mg/mL | 50 mg/mL | Solution | Subcutaneous | Autoinjector | | 09 September 2017 | | |
| Infliximab | 100 mg | 100 mg/vial | Powder | Intravenous | Single-dose vial | L04AB02 (EMA 2020d) | 24 August 1998 | 10 September 2013 (EMA 2020d) | Psoriasis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis and ulcerative colitis (Singh 2018; Varadé 2020) |

## Appendix 4. Interleukin-receptor antagonist therapy: warnings and precautions for use

| Drug | Warnings | Comments/Recommendations | Source |
|---|---|---|---|
| Anakinra | 1. Allergic reactions<br>2. Hepatic events<br>3. Serious infections<br>4. Renal impairment<br>5. Neutropenia<br>6. Pulmonary events<br>7. Immunosuppression | 1. Allergic reactions, including anaphylactic reactions and angioedema have been reported uncommonly. The majority of these reactions were maculopapular or urticarial rashes. If a severe allergic reaction occurs, administration of anakinra should be discontinued and appropriate treatment initiated.<br>2. In clinical studies, transient elevations of liver enzymes have been seen. These elevations have not been associated with signs or symptoms of hepatocellular damage. The efficacy and safety of anakinra in patients with AST/ALT ≥ 1.5 x upper level of normal have not been evaluated.<br>3. The safety and efficacy of anakinra treatment in patients with chronic and serious infections have not been evaluated. Treatment should not be initiated in patients with active infections. The safety of Kineret in individuals with latent tuberculosis is unknown.<br>4. Anakinra is eliminated by glomerular filtration and subsequent tubular metabolism. Consequently, plasma clearance of anakinra decreases with decreasing renal function. No dose adjustment is needed for patients with mild renal impairment. In patients with severe renal impairment or end-stage renal disease, including dialysis, administration of the prescribed dose of Kineret every other day should be considered.<br>5. It is commonly associated with neutropenia. Anakinra treatment should not be initiated in patients with neutropenia. The safety and efficacy of Kineret in patients with neutropenia have not been evaluated.<br>6. Interstitial lung disease, pulmonary alveolar proteinosis and pulmonary hypertension have been reported mainly in paediatric patients with Still's disease treated with IL-6 and IL-1 inhibitors, including anakinra.<br>7. The impact of treatment with Kineret on pre-existing malignancy has not been studied. Therefore, the use of Kineret in patients with pre-existing malignancy is not recommended. | EMA 2020 |
| Canakinumab | 1. Infections and tuberculosis screening<br>2. Neutropenia and leukopenia<br>3. Malignancies<br>4. Hypersensitivity reactions<br>5. Hepatic function | 1. Canakinumab is associated with an increased incidence of serious infections.<br>2. Neutropenia count and leukopenia have been observed with medicinal products that inhibit IL-1, including canakinumab. Treatment with canakinumab should not be initiated in patients with neutropenia or leukopenia.<br>3. Malignancy events have been reported in patients treated with canakinumab. The risk for the development of malignancies with anti-interleukin (IL)-1 therapy is unknown.<br>4. Hypersensitivity reactions with canakinumab therapy have been reported. The majority of these events were mild in severity.<br>5. Transient and asymptomatic cases of elevations of serum transaminases or bilirubin have been reported in clinical trials. | EMA 2020a |
| Tocilizumab | 1. Low absolute neutrophil count | 1. It is not recommended in patients with an absolute neutrophil count below 2 x 109/L. | EMA 2020b |

(Continued)

| | | | |
|---|---|---|---|
| | 2. Elderly<br>3. Renal impairment<br>4. Hepatic impairment<br>5. Infections<br>6. Tuberculosis<br>7. Complications of diverticulitis<br>8. Hepatotoxicity<br>9. Cardiovascular risk | 2. No dose adjustment is required in elderly patients > 65 years of age.<br>3. No dose adjustment is required in patients with mild renal impairment. RoActemra has not been studied in patients with moderate-to-severe renal impairment (see section 5.2). Renal function should be monitored closely in these patients.<br>4. RoActemra has not been studied in patients with hepatic impairment. Therefore, no dose recommendations can be made.<br>5. Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab. Therefore, tocilizumab treatment must not be initiated in patients with active infections.<br>6. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating tocilizumab. Prescribers are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised. Patients should be instructed to seek medical advice if signs/symptoms (e.g. persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur during or after therapy with tocilizumab.<br>7. Events of diverticular perforations as complications of diverticulitis have been reported uncommonly with tocilizumab in rheumatoid arthritis. That drug should be used with caution in patients with previous history of intestinal ulceration or diverticulitis.<br>8. Transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with tocilizumab treatment. Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with tocilizumab. Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of tocilizumab. Cases of liver failure resulting in liver transplantation have been reported. Patients should be advised to immediately seek medical help if they experience signs and symptoms of hepatic injury.<br>9. Rheumatoid arthritis people have an increased risk for cardiovascular disorders and should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care. | |
| Etanercept | 1. Infections<br>2. Tuberculosis<br>3. Hepatitis B reactivation<br>4. Worsening of hepatitis C<br>5. Concurrent treatment with anakinra<br>6. Allergic reactions | 1. Serious infections, sepsis, tuberculosis, and opportunistic infections, including invasive fungal infections, listeriosis and legionellosis, have been reported with the use of etanercept. Patients who develop a new infection while undergoing treatment with Erelzi should be monitored closely. Administration of this drug should be discontinued if a patient develops a serious infection.<br>2. Cases of active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary location, have been reported in patients treated with etanercept. Before starting treatment with etanercept, all patients must be evaluated for both active and inactive ('latent') tuberculosis. If active tuberculosis is diagnosed, etanercept therapy must not be initiated. All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g. persistent cough, wasting/weight loss, low-grade fever) appear during or after etanercept treatment. | EMA 2020c |

(Continued)

| | | | |
|---|---|---|---|
| | | 3. In patients who develop HBV infection, etanercept should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.<br>4. Etanercept should be used with caution in patients with a history of hepatitis C.<br>5. Concurrent administration of etanercept and anakinra has been associated with an increased risk of serious infections and neutropenia compared to etanercept alone. Thus, the combined use of etanercept and anakinra is not recommended.<br>6. Allergic reactions associated with etanercept administration have been reported commonly. If any serious allergic or anaphylactic reaction occurs, etanercept therapy should be discontinued immediately and appropriate therapy initiated. | |
| Infliximab | 1. Infusion reactions and hypersensitivity<br>2. Infections<br>3. Tuberculosis<br>4. Hepatitis B reactivation<br>5. Hepatobiliary events<br>6. Neurological events<br>7. Heart failure | 1. If serious reactions occur, symptomatic treatment must be given and further infliximab infusions must not be administered.<br>2. Clinical experience shows that host defence against infection is compromised in some patients treated with infliximab. Patients taking TNF-blockers are more susceptible to serious infections. Administration of infliximab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.<br>3. There have been reports of active tuberculosis in patients receiving infliximab. It should be noted that, in the majority of these reports, tuberculosis was extrapulmonary, presenting as either local or disseminated disease. Before starting treatment with infliximab, all patients must be evaluated for both active and inactive ('latent') tuberculosis.<br>4. Reactivation of hepatitis B has occurred in patients receiving TNF-inhibitors, including infliximab, who are chronic carriers of this virus. Some cases have had fatal outcomes. Patients should be tested for HBV infection before initiating treatment with infliximab.<br>5. If jaundice and/or alanine transaminase elevations ≥ 5 times the upper limit of normal develop(s), infliximab should be discontinued, and a thorough investigation of the abnormality should be undertaken.<br>6. Use of TNF-inhibitors, including infliximab, has been associated with cases of new-onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and peripheral demyelinating disorders, including Guillain-Barré syndrome.<br>7. Heart failure: Infliximab should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and infliximab must not be continued in patients who develop new or worsening symptoms of heart failure. | EMA 2020d |

## Appendix 5. Search strategies and results

| Database | Date searched | Number of results | Search strategy |
|---|---|---|---|
| **CENTRAL (Cochrane Library)**<br><br>2 of 12, 2022 | 01/02/2022 | 620 | ([mh Atherosclerosis] or [mh "Peripheral Arterial Disease"] or [mh "Chronic Limb-Threatening Ischemia"] or [mh "Plaque, Atherosclerotic"] or [mh "Coronary Artery Disease"] or [mh "Carotid Artery Diseases"] or [mh "Carotid Stenosis"] or [mh "Intracranial Thrombosis"] or [mh "Sinus Thrombosis, Intracranial"] or [mh "Cavernous Sinus Thrombosis"] or [mh "Lateral Sinus Thrombosis"] or [mh "Sagittal Sinus Thrombosis"] or [mh "Coronary Occlusion"] or [mh "Intracranial Arterial Diseases"] or [mh "Cerebral Arterial Diseases"] or [mh "Intracranial Arteriosclerosis"] or [mh "Renal Artery Obstruction"] or [mh Stroke] or [mh "Thrombotic Stroke"] or [mh "Ischemic Stroke"] or [mh "Stroke, Lacunar"] or [mh "Brain Infarction"] or [mh "Cerebral Infarction"] or [mh "Brain Stem Infarctions"] or [mh "Heart Failure"] or (Atherosclerosis or Atherosclerosis or Atherogenesis or Atherosclerotic or Peripheral Arterial Disease* or Peripheral Artery Disease* or Chronic Limb Threatening Ischemi* or Critical Limb Ischemi* or Chronic Limb Threatening Ischaemi* or Critical Limb Ischaemi* or Arterial Fatty Streak or Fibroatheroma* or Atheroma* or Coronary Artery Disease* or Left Main Disease* or Left Main Coronary Disease or Carotid Artery Disease* or Carotid Artery Disorder* or Carotid Arterial Disease* or Carotid Stenosis or Carotid Stenoses or Carotid Artery Narrowing* or Carotid Artery Stenosis or Carotid Artery Plaque* or Carotid Ulcer* or Carotid Artery Ulcerating Plaque* or Intracranial Thrombosis or Intracranial Thromboses or Intracranial Thrombus or Cerebral Thrombus or Cerebral Thrombosis or Cerebral Thromboses or Brain Thrombosis or Brain Thromboses or Brain Thrombus or Sinus Thrombosis or Sinus Thrombophlebitis or Sinus Thrombophlebitides or Sinus Septic Phlebitis or Coronary Occlusion* or Intracranial Arterial Disease* or Intracranial Arterial Disorder* or Arterial Brain Disease* or Arterial Brain Disorder* or Cerebral Arterial Disease* or Cerebral Artery Disease* or Intracranial Arteriosclerosis or Intracranial Arterioscleroses or Cerebral Arteriosclerosis or Cerebral Arterioscleroses or Renal Artery Obstruction* or Renal Artery Stenosis or Renal Artery Stenoses or Cerebrovascular Accident* or CVA or CVAs or Brain Vascular Accident* or Stroke or Strokes or Apoplexy or Brain Infarct* or Brain Venous Infarct* or Venous Brain Infarct* or Anterior Cerebral Circulation Infarct* or Cerebral Infarct* or Subcortical Infarct* or Choroidal Artery Infarct* or Brain Stem Infarct* or Brainstem Infarct* or Cardiac Failure* or Heart Decompensation or Heart Failure* or Myocardial Failure*):ti,ab,kw) AND ([mh "Interleukin 1 Receptor Antagonist Protein"] or [mh "Tumor Necrosis Factor Inhibitors"] or [mh Etanercept] or [mh Infliximab] or (((interleukin-1 or IL-1) NEAR/2 receptor antagonist*) or IL-1RA or il-1 inhibitor or Anakinra or Canakinumab or ((Interleukin-6 or IL-6) NEAR/2 receptor antagonist*) or Tocilizumab or Atlizumab or ((Tumor necrosis factor or TNF) NEAR/1 (blocker* or inhibitor*)) or Etanercept or Infliximab):ti,ab,kw) in Trials |
| **CENTRAL**<br><br>**(Cochrane Library)**<br><br>2 of 12, 2024 | 20/02/2024 | 65 | #1 [mh Atherosclerosis] or [mh "Peripheral Arterial Disease"] or [mh "Chronic Limb-<br>Threatening Ischemia"] or [mh "Plaque, Atherosclerotic"] or [mh "Coronary Artery<br>Disease"] or [mh "Carotid Artery Diseases"] or [mh "Carotid Stenosis"] or [mh "Intracranial |

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Thrombosis"] or [mh "Sinus Thrombosis, Intracranial"] or [mh "Cavernous Sinus

Thrombosis"] or [mh "Lateral Sinus Thrombosis"] or [mh "Sagittal Sinus Thrombosis"] or
[mh "Coronary Occlusion"] or [mh "Intracranial Arterial Diseases"] or [mh "Cerebral Arterial
Diseases"] or [mh "Intracranial Arteriosclerosis"] or [mh "Renal Artery Obstruction"] or [mh
Stroke] or [mh "Thrombotic Stroke"] or [mh "Ischemic Stroke"] or [mh "Stroke, Lacunar"] or
[mh "Brain Infarction"] or [mh "Cerebral Infarction"] or [mh "Brain Stem Infarctions"] or [mh
"Heart Failure"] 46891
#2 ((Atherosclerosis or Atherosclerоses or Atherogenesis or Atherosclerotic or
Peripheral Arterial Disease* or Peripheral Artery Disease* or Chronic Limb Threatening
Ischemi* or Critical Limb Ischemi* or Chronic Limb Threatening Ischaemi* or Critical Limb
Ischaemi* or Arterial Fatty Streak or Fibroatheroma* or Atheroma* or Coronary Artery
Disease* or Left Main Disease* or Left Main Coronary Disease or Carotid Artery Disease*
or Carotid Artery Disorder* or Carotid Arterial Disease* or Carotid Stenosis or Carotid
Stenoses or Carotid Artery Narrowing* or Carotid Artery Stenosis or Carotid Artery
Plaque* or Carotid Ulcer* or Carotid Artery Ulcerating Plaque* or Intracranial Thrombosis
or Intracranial Thromboses or Intracranial Thrombus or Cerebral Thrombus or Cerebral
Thrombosis or Cerebral Thromboses or Brain Thrombosis or Brain Thromboses or Brain
Thrombus or Sinus Thrombosis or Sinus Thrombophlebitis or Sinus Thrombophlebitides
or Sinus Septic Phlebitis or Coronary Occlusion* or Intracranial Arterial Disease* or
Intracranial Arterial Disorder* or Arterial Brain Disease* or Arterial Brain Disorder* or
Cerebral Arterial Disease* or Cerebral Artery Disease* or Intracranial Arteriosclerosis or
Intracranial Arterioscleroses or Cerebral Arteriosclerosis or Cerebral Arterioscleroses or
Renal Artery Obstruction* or Renal Artery Stenosis or Renal Artery Stenoses or
Cerebrovascular Accident* or CVA or CVAs or Brain Vascular Accident* or Stroke or
Strokes or Apoplexy or Brain Infarct* or Brain Venous Infarct* or Venous Brain Infarct* or
Anterior Cerebral Circulation Infarct* or Cerebral Infarct* or Subcortical Infarct* or
Choroidal Artery Infarct* or Brain Stem Infarct* or Brainstem Infarct* or Cardiac Failure* or
Heart Decompensation or Heart Failure* or Myocardial Failure*)):ti,ab,kw 158569
#3 #1 OR #2 160033
#4 [mh "Interleukin 1 Receptor Antagonist Protein"] or [mh "Tumor Necrosis Factor
Inhibitors"] or [mh Etanercept] or [mh Infliximab] 2513

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| | | | |
|---|---|---|---|
| | | | #5 ((interleukin-1 or IL-1) NEAR/2 "receptor antagonist*"):ti,ab,kw 827<br>#6 (IL-1RA or il-1 inhibitor or Anakinra or Canakinumab):ti,ab,kw 1615<br>#7 ((Interleukin-6 or IL-6) NEAR/2 "receptor antagonist*"):ti,ab,kw 57<br>#8 (Tocilizumab or Atlizumab):ti,ab,kw 1639<br>#9 ((("Tumor necrosis factor" or TNF) NEAR/1 (blocker* or inhibitor*))):ti,ab,kw<br>1000<br>#10 (Etanercept or Infliximab):ti,ab,kw 4633<br>#11 #4 or #5 or #6 or #7 or #8 or #9 or #10 8612<br>#12 #3 AND #11 with Cochrane Library publication date Between Feb 2022 and Feb<br>2024, in Trials 65 |
| **Ovid MEDLINE(R)**<br><br>**ALL** 1946 to January 31, 2022 | 01/02/2022 | 705 | 1 exp Atherosclerosis/ or exp Peripheral Arterial Disease/ or Chronic Limb-Threatening Ischemia/ or Plaque, Atherosclerotic/ or Coronary Artery Disease/ or Carotid Artery Diseases/ or Carotid Stenosis/ or exp Intracranial Thrombosis/ or exp Sinus Thrombosis, Intracranial/ or Cavernous Sinus Thrombosis/ or Lateral Sinus Thrombosis/ or Sagittal Sinus Thrombosis/ or Coronary Occlusion/ or Intracranial Arterial Diseases/ or Cerebral Arterial Diseases/ or Intracranial Arteriosclerosis/ or Renal Artery Obstruction/ or exp Stroke/ or exp Thrombotic Stroke/ or Ischemic Stroke/ or Stroke, Lacunar/ or exp Brain Infarction/ or exp Cerebral Infarction/ or exp Brain Stem Infarctions/ or exp Heart Failure/ or (Atherosclerosis or Atherosclerоses or Atherogenesis or Atherosclerotic or Peripheral Arterial Disease* or Peripheral Artery Disease* or Chronic Limb Threatening Ischemi* or Critical Limb Ischemi* or Chronic Limb Threatening Ischaemi* or Critical Limb Ischaemi* or Arterial Fatty Streak or Fibroatheroma* or Atheroma* or Coronary Artery Disease* or Left Main Disease* or Left Main Coronary Disease or Carotid Artery Disease* or Carotid Artery Disorder* or Carotid Arterial Disease* or Carotid Stenosis or Carotid Stenoses or Carotid Artery Narrowing* or Carotid Artery Stenosis or Carotid Artery Plaque* or Carotid Ulcer* or Carotid Artery Ulcerating Plaque* or Intracranial Thrombosis or Intracranial Thromboses or Intracranial Thrombus or Cerebral Thrombus or Cerebral Thrombosis or Cerebral Thromboses or Brain Thrombosis or Brain Thromboses or Brain Thrombus or Sinus Thrombosis or Sinus Thrombophlebitis or Sinus Thrombophlebitides or Sinus Septic Phlebitis or Coronary Occlusion* or Intracranial Arterial Disease* or Intracranial Arterial Disorder* or Arterial Brain Disease* or Arterial Brain Disorder* or Cerebral Arterial Disease* or Cerebral Artery Disease* or Intracranial Arteriosclerosis or Intracranial Arterioscleroses or Cerebral Arteriosclerosis or Cerebral Arterioscleroses or Renal Artery Obstruction* or Renal Artery Stenosis or Renal Artery Stenoses or Cerebrovascular Accident* or CVA or CVAs or Brain Vascular Accident* or Stroke or Strokes or Apoplexy or Brain Infarct* or Brain Venous Infarct* or Venous Brain Infarct* or Anterior Cerebral Circulation Infarct* or Cerebral Infarct* or Subcortical Infarct* or Choroidal Artery Infarct* or Brain Stem Infarct* or Brainstem Infarct* or Cardiac Failure* or Heart Decompensation or Heart Failure* or Myocardial Failure*).tw. (863316)<br><br>2 Interleukin 1 Receptor Antagonist Protein/ or Tumor Necrosis Factor Inhibitors/ or Etanercept/ or Infliximab/ or (((interleukin-1 or IL-1) adj2 receptor antagonist*) or IL-1RA or il-1 in- |

(Continued)

| | | | |
|---|---|---|---|
| | | | hibitor or Anakinra or Canakinumab or ((Interleukin-6 or IL-6) adj2 receptor antagonist*) or Tocilizumab or Atlizumab or ((Tumor necrosis factor or TNF) adj1 (blocker* or inhibitor*)) or Etanercept or Infliximab).tw. (40188)<br><br>3 ((Randomized Controlled Trial or Controlled Clinical Trial).pt. or (Randomi?ed or Placebo or Randomly or Trial or Groups).ab. or Drug Therapy.fs.) not (exp Animals/ not Humans.sh.) (4583690)<br><br>4 1 and 2 and 3 (705) |
| **Ovid MEDLINE(R)**<br><br>**ALL** 2022 to February 20, 2024 | 20/02/2024 | 87 | With the same search strategy |
| **Embase**<br><br>(Ovid, 1980 to 2022 week 04) | 01/02/2022 | 1153 | 1 exp Atherosclerosis/ or exp Peripheral Occlusive Artery Disease/ or Critical Limb Ischemia/ or Atherosclerotic Plaque/ or exp Coronary Artery Disease/ or exp Carotid Artery Disease/ or exp Carotid Artery Obstruction/ or exp Occlusive Cerebrovascular Disease/ or exp Cerebral Sinus Thrombosis/ or Cavernous Sinus Thrombosis/ or Lateral Sinus Thrombosis/ or Sagittal Sinus Thrombosis/ or exp Coronary Artery Occlusion/ or Cerebral Arterial Disease/ or Brain Atherosclerosis/ or Kidney Artery Stenosis/ or exp Cerebrovascular Accident/ or exp Ischemic Stroke/ or Lacunar Stroke/ or exp Brain Infarction/ or Brain Stem Infarction/ or exp Heart Failure/ or (Atherosclerosis or Atheroscleroses or Atherogenesis or Atherosclerotic or Peripheral Arterial Disease* or Peripheral Artery Disease* or Chronic Limb Threatening Ischemi* or Critical Limb Ischemi* or Chronic Limb Threatening Ischaemi* or Critical Limb Ischaemi* or Arterial Fatty Streak or Fibroatheroma* or Atheroma* or Coronary Artery Disease* or Left Main Disease* or Left Main Coronary Disease or Carotid Artery Disease* or Carotid Artery Disorder* or Carotid Arterial Disease* or Carotid Stenosis or Carotid Stenoses or Carotid Artery Narrowing* or Carotid Artery Stenosis or Carotid Artery Plaque* or Carotid Ulcer* or Carotid Artery Ulcerating Plaque* or Intracranial Thrombosis or Intracranial Thromboses or Intracranial Thrombus or Cerebral Thrombus or Cerebral Thrombosis or Cerebral Thromboses or Brain Thrombosis or Brain Thromboses or Brain Thrombus or Sinus Thrombosis or Sinus Thrombophlebitis or Sinus Thrombophlebitides or Sinus Septic Phlebitis or Coronary Occlusion* or Intracranial Arterial Disease* or Intracranial Arterial Disorder* or Arterial Brain Disease* or Arterial Brain Disorder* or Cerebral Arterial Disease* or Cerebral Artery Disease* or Intracranial Arteriosclerosis or Intracranial Arterioscleroses or Cerebral Arteriosclerosis or Cerebral Arterioscleroses or Renal Artery Obstruction* or Renal Artery Stenosis or Renal Artery Stenoses or Cerebrovascular Accident* or CVA or CVAs or Brain Vascular Accident* or Stroke or Strokes or Apoplexy or Brain Infarct* or Brain Venous Infarct* or Venous Brain Infarct* or Anterior Cerebral Circulation Infarct* or Cerebral Infarct* or Subcortical Infarct* or Choroidal Artery Infarct* or Brain Stem Infarct* or Brainstem Infarct* or Cardiac Failure* or Heart Decompensation or Heart Failure* or Myocardial Failure*).tw. (1728574)<br><br>2 Interleukin 1 Receptor Blocking Agent/ or Anakinra/ or Canakinumab/ or exp Tumor Necrosis Factor Inhibitor/ or Tocilizumab/ or Etanercept/ or Infliximab/ or (((interleukin-1 |

(Continued)

| | | | |
|---|---|---|---|
| | | | or IL-1) adj2 receptor antagonist*) or IL-1RA or il-1 inhibitor or Anakinra or Canakinumab or ((Interleukin-6 or IL-6) adj2 receptor antagonist*) or Tocilizumab or Atlizumab or ((Tumor necrosis factor or TNF) adj1 (blocker* or inhibitor*)) or Etanercept or Infliximab).tw. (141607)<br><br>3 (crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw.) not ((animal/ or nonhuman/) not human/) (2285844)<br><br>4 1 and 2 and 3 (1173)<br><br>5 limit 4 to (conference abstracts or embase) (1153) |
| **Embase (Elsevier)** | 20/02/224 | 228 | (('atherosclerosis'/exp OR 'peripheral arterial disease'/exp) AND 'critical limb ischemia'/de<br>OR 'atherosclerotic plaque'/de OR 'coronary artery disease'/exp OR 'carotid artery<br>disease'/exp OR 'carotid artery occlusion'/exp OR 'occlusive cerebrovascular disease'/exp<br>OR 'cerebral sinus thrombosis'/exp OR 'coronary occlusion'/exp OR 'cerebral artery<br>disease'/de OR 'cerebral atherosclerosis'/de OR 'renal artery stenosis'/de OR<br>'cerebrovascular accident'/exp OR 'brain infarction'/exp OR 'heart failure'/exp OR<br>atherosclerosis OR atheroscleroses OR atherogenesis OR atherosclerotic OR 'peripheral<br>arterial disease*' OR 'peripheral artery disease*' OR 'chronic limb threatening ischemi*'<br>OR 'critical limb ischemi*' OR 'chronic limb threatening ischaemi*' OR 'critical limb<br>ischaemi*' OR 'arterial fatty streak' OR fibroatheroma* OR atheroma* OR 'coronary artery<br>disease*' OR 'left main disease*' OR 'left main coronary disease' OR 'carotid artery<br>disease*' OR 'carotid artery disorder*' OR 'carotid arterial disease*' OR 'carotid stenosis'<br>OR 'carotid stenoses' OR 'carotid artery narrowing*' OR 'carotid artery stenosis' OR<br>'carotid artery plaque*' OR 'carotid ulcer*' OR 'carotid artery ulcerating plaque*' OR<br>'intracranial thrombosis' OR 'intracranial thromboses' OR 'intracranial thrombus' OR<br>'cerebral thrombus' OR 'cerebral thrombosis' OR 'cerebral thromboses' OR 'brain<br>thrombosis' OR 'brain thromboses' OR 'brain thrombus' OR 'sinus thrombosis' OR 'sinus<br>thrombophlebitis' OR 'sinus thrombophlebitides' OR 'sinus septic phlebitis' OR 'coronary<br>occlusion*' OR 'intracranial arterial disease*' OR 'intracranial arterial disorder*' OR 'arterial<br>brain disease*' OR 'arterial brain disorder*' OR 'cerebral arterial disease*' OR 'cerebral<br>artery disease*' OR 'intracranial arteriosclerosis' OR 'intracranial arterioscleroses' OR<br>'cerebral arteriosclerosis' OR 'cerebral arterioscleroses' OR 'renal artery obstruction*' OR |

(Continued)

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|---|---|---|---|
| | | | 'renal artery stenosis' OR 'renal artery stenoses' OR 'cerebrovascular accident*' OR cva OR cvas OR 'brain vascular accident*' OR stroke OR strokes OR apoplexy OR 'brain infarct*' OR 'brain venous infarct*' OR 'venous brain infarct*' OR 'anterior cerebral circulation infarct*' OR 'cerebral infarct*' OR 'subcortical infarct*' OR 'choroidal artery infarct*' OR 'brain stem infarct*' OR 'brainstem infarct*' OR 'cardiac failure*' OR 'heart decompensation' OR 'heart failure*' OR 'myocardial failure*') AND ('interleukin 1 receptor blocking agent'/de OR 'anakinra'/de OR 'canakinumab'/de OR 'tumor necrosis factor inhibitor'/de OR 'etanercept'/de OR 'infliximab'/de OR 'tocilizumab'/de OR ((('interleukin 1' OR 'il 1') NEXT/2 'receptor antagonist*'):ab,ti) OR (('il 1ra' OR 'il 1') AND inhibitor) OR anakinra OR canakinumab:ab,ti OR ((('interleukin 6' OR 'il 6') NEXT/2 'receptor antagonist*'):ab,ti) OR tocilizumab OR atlizumab:ab,ti OR ((('tumor necrosis factor' OR tnf) NEXT/1 (blocker* OR inhibitor*)):ab,ti) OR etanercept OR infliximab:ab,ti) AND ('crossover procedure'/de OR 'double blind procedure'/de OR 'randomized controlled trial'/de OR 'single blind procedure'/de OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over*':ab,ti OR placebo*:ab,ti OR ((doubl* NEXT/1 blind*):ab,ti) OR ((singl* NEXT/1 blind*):ab,ti) OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti) NOT (('animal'/de OR 'nonhuman'/de) NOT 'human'/de) AND [embase]/lim AND [01-02-2022]/sd NOT [22-03-2024]/sd |
| **WHO ICTRP**<br><br>Advanced Search | 01/02/2022 | 90 | Arteriosclerosis OR Artery OR Atherosclerosis OR Atherosclerotic OR Brain OR Cardiac Failure OR Carotid OR Cerebral OR Coronary OR Infarct OR Ischemia OR Myocardial Failure OR Obstruction OR Occlusion OR Plaque OR Stenosis OR Stroke OR Thrombosis in the Condition<br><br>Anakinra OR Canakinumab OR Etanercept OR Infliximab OR Tocilizumab OR Il-1 Inhibitor OR Il-6 Receptor Antagonist OR Interleukin-1 Receptor Antagonist OR Tumor Necrosis Factor Blocker OR Tumor Necrosis Factor Inhibitor in the Intervention<br><br>Recruitment status is ALL<br><br>251 records for 90 trials found |
| **ClinicalTrials.gov** | 01/02/2022 | 149 | Advanced Search<br><br>Condition or disease: Arteriosclerosis OR Artery OR Atherosclerosis OR Atherosclerotic OR Brain OR Cardiac Failure OR Carotid OR Cerebral OR Coronary OR Infarct OR Ischemia OR Myocardial Failure OR Obstruction OR Occlusion OR Plaque OR Stenosis OR Stroke OR Thrombosis<br>Study type: Interventional Studies (Clinical Trials) |

*(Continued)*

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| | | | Intervention/treatment: Anakinra OR Canakinumab OR Etanercept OR Infliximab OR Tocilizumab OR Il-1 Inhibitor OR Il-6 Receptor Antagonist OR Interleukin-1 Receptor Antagonist OR Tumor Necrosis Factor Blocker OR Tumor Necrosis Factor Inhibitor |
| **Web of Science** | 01/02/2022 | 846 | (Atherosclerosis OR Atherosclerosis OR Atherogenesis OR Atherosclerotic OR Peripheral Arterial Disease* OR Peripheral Artery Disease* OR Chronic Limb Threatening Ischemi* OR Critical Limb Ischemi* OR Chronic Limb Threatening Ischaemi* OR Critical Limb Ischaemi* OR Arterial Fatty Streak OR Fibroatheroma* OR Atheroma* OR Coronary Artery Disease* OR Left Main Disease* OR Left Main Coronary Disease OR Carotid Artery Disease* OR Carotid Artery Disorder* OR Carotid Arterial Disease* OR Carotid Stenosis OR Carotid Stenoses OR Carotid Artery Narrowing* OR Carotid Artery Stenosis OR Carotid Artery Plaque* OR Carotid Ulcer* OR Carotid Artery Ulcerating Plaque* OR Intracranial Thrombosis OR Intracranial Thromboses OR Intracranial Thrombus OR Cerebral Thrombus OR Cerebral Thrombosis OR Cerebral Thromboses OR Brain Thrombosis OR Brain Thromboses OR Brain Thrombus OR Sinus Thrombosis OR Sinus Thrombophlebitis OR Sinus Thrombophlebitides OR Sinus Septic Phlebitis OR Coronary Occlusion* OR Intracranial Arterial Disease* OR Intracranial Arterial Disorder* OR Arterial Brain Disease* OR Arterial Brain Disorder* OR Cerebral Arterial Disease* OR Cerebral Artery Disease* OR Intracranial Arteriosclerosis OR Intracranial Arterioscleroses OR Cerebral Arteriosclerosis OR Cerebral Arterioscleroses OR Renal Artery Obstruction* OR Renal Artery Stenosis OR Renal Artery Stenoses OR Cerebrovascular Accident* OR CVA OR CVAs OR Brain Vascular Accident* OR Stroke OR Strokes OR Apoplexy OR Brain Infarct* OR Brain Venous Infarct* OR Venous Brain Infarct* OR Anterior Cerebral Circulation Infarct* OR Cerebral Infarct* OR Subcortical Infarct* OR Choroidal Artery Infarct* OR Brain Stem Infarct* OR Brainstem Infarct* OR Cardiac Failure* OR Heart Decompensation OR Heart Failure* OR Myocardial Failure*) AND ((interleukin-1 NEAR/2 receptor antagonist*) OR (IL-1 NEAR/2 receptor antagonist*) OR IL-1RA OR il-1 inhibitor OR Anakinra OR Canakinumab OR (Interleukin-6 NEAR/2 receptor antagonist*) OR (IL-6 NEAR/2 receptor antagonist*) OR Tocilizumab OR Atlizumab OR (Tumor necrosis factor NEAR/1 Inhibitor*) OR (TNF NEAR/1 Inhibitor*) OR (Tumor necrosis factor NEAR/1 Blocker*) OR (TNF NEAR/1 Blocker) OR Etanercept OR Infliximab) AND (Random* OR Blind* OR Allocat* OR Assign* OR Trial* OR Placebo* OR Crossover* OR Cross-Over*) (Topic)<br><br>Web of Science Core Collection, Editions = CPCI-S, SCI-EXPANDED 846 |
| **Web of Science** | 20/02/2024 | 134 | With the same search strategy |
| **Other sources** | 01/02/2022 | 31 | |
| **Total (February 2022)** | | 3594 | |
| **After de-duplication (February 2022)** | | 899 | |
| **Total (February 2024)** | | 514 | |

(Continued)

| | |
|---|---|
| **After de-duplication (February 2024)** | 1 |
| **Overall** | 4108 |
| **Total duplicates** | 3208 |
| **Overall after de-duplication** | 900 |

## Appendix 6. Intervention description and replication

1. Brief name: provide the name or a phrase that describes the intervention.
2. Why: describe any rationale, theory, or goal of the elements essential to the intervention.
3. What (materials): describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (for example, online appendix, URL).
4. What (procedures): describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.
5. Who provided: for each category of intervention provider (for example, psychologist, nursing assistant), describe their expertise, background and any specific training given.
6. How: describe the modes of delivery (such as face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.
7. Where: describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.
8. When and how much: describe the number of times the intervention was delivered and over what period of time, including the number of sessions, their schedule, and their duration, intensity or dose.
9. Tailoring: if the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.
10. Modifications: if the intervention was modified during the course of the study, describe the changes (what, why, when, and how).
11. How well (planned): if intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.
12. How well (actual): if intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.

Source: Hoffmann 2014

## Appendix 7. Adverse events information domains

1. Name of the adverse events (e.g. dizziness)
2. The reported intensity of the adverse event (e.g. mild, moderate, severe)
3. Whether the trial investigators categorised the adverse event as ‘serious’
4. Whether the trial investigators identified the adverse event as being related to the intervention
5. Time point (most commonly measured as a count over the duration of the study)
6. Any reported methods for how adverse events were selected for inclusion in the publication (e.g. ‘We reported all adverse events that occurred in at least 5% of participants’)

Source: Li 2019

# HISTORY

Protocol first published: Issue 9, 2021

# CONTRIBUTIONS OF AUTHORS

Conceiving the review: AMC
Designing the review: AMC, MD, DM, EA, RRL
Coordinating the review: AMC
Designing electronic search strategy: the Cochrane Heart Group's Information Specialist and Arturo Martí-Carvajal
Screening search results: AMC, DM, ACP, MGV
Obtaining copies of trials: AMC, MGV, DM

Appraising quality of papers: AMC, MD, MGV, SN, EA
Abstracting data from papers: AMC, MGV, DM,
Data management for the review: AMC, MGV
Entering data into Review Manager: AMC
Analysis of data: AMC, MGV
Summary of findings: AMC, JMVP, DM, EA, MGV
Interpretation of data: all authors
Writing the review: AMC, MGV, MD, DM, CMA
Draft the final review: all authors
Guarantor for the review: AMC

## DECLARATIONS OF INTEREST

Eduardo Alegría: none known
Andrea Correa-Pérez: none known
Juan Bautista De Sanctis: none known
Mark Dayer: my department has received support for participating in commercial trials run by Novartis, including the CANTOS study, in which I recruited patients. I have received no fees personally. I have undertaken talks and chaired events for Biotronik in the past three years.
Cristina Martí-Amarista: none known
Arturo Martí-Carvajal: none known
Diana Monge: none known
Juan Marcos Parise Vasco: none known
Susana Nicola: none known
Mario Gemmato-Valecillos: none known
Ricardo Riera- Lizardo: none known

## SOURCES OF SUPPORT

### Internal sources

- Facultad de Ciencias de la Salud Eugenio Espejo, Universidad UTE (Cochrane Ecuador), Quito, Ecuador

  Financial and academic
- Facultad de Medicina, Universidad Francisco de Vitoria (Cochrane Madrid), Madrid, Spain

  Financial and academic
- Cátedra Rectoral de Medicina Basada en la Evidencia, Universidad de Carabobo, Venezuela

  Financial and academic

### External sources

- NIHR, UK

  This project was supported by the NIHR via Cochrane Incentive funding to the Heart Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health and Social Care.
- Iberoamerican Cochrane Network, Spain

  Academic

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We added in characteristics of the included studies:

- 'Methods' section: Primary prevention or secondary prevention.
- 'Participants' section: C-reactive protein levels (> 2 mg/L).

2. We requested permission from the Cochrane Heart Group to use RoB1 instead of RoB2 for bias assessment in accordance with the protocol.

3. We followed the recommendations of the Cochrane Collaboration and used a fixed-effect model for meta-analyses with more than five studies. See below (# 4).

4. To clarify, we did not conduct separate sensitivity analyses comparing random-effects and fixed-effect models for the meta-analyses of primary outcomes with more than five trials. Instead, we reported the results using both random-effects and fixed-effect models within the text of the review for these meta-analyses. This approach allowed us to assess the robustness of the findings and determine if the choice of model had a substantial impact on the results. We have now updated the relevant sections of the review to clearly state that we reported the results using both models simultaneously in the text rather than conducting separate sensitivity analyses with graphs. For the specific analyses mentioned (Analyses 3.3, 3.4, 3.5, 4.1, 4.2, 4.5, 4.6, 6.3, 6.4), we have ensured that the results using both random-effects and fixed-effect models are accurately reported within the text of the review.