Cochrane Database of Systematic Reviews | Protocol - Intervention

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

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Authors' declarations of interest

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Abstract

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

1. To assess the clinical benefits and harms of interleukin-receptor antagonists and tumor necrosis factor (TNF) inhibitors for the primary and secondary prevention of atherosclerotic cardiovascular diseases.
2. To determine whether interleukin-receptor antagonists or TNF inhibitors, provided to people both with and without pre-existing cardiovascular disease, are:
    1. useful in preventing adverse cardiovascular outcomes; and
    2. safe.

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 (Jagannathan 2019; 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, are continually increasing in all ethnic groups in the USA and are the major target for ACVDs' primary and secondary prevention (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 has a central role in forming unstable atherosclerotic plaques, which lead to acute coronary syndromes (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 derived from 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 also 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 through both adaptive and innate immunity (Alexander 1994; Charla 2020; Liberale 2020; Liu 2020; Martinod 2020; Masters 2015; Ross 1999; Rymer 2017). 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). 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; Norouzi 2020; van Boheemen 2020; Widdifield 2018). Recent reports suggest there is 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).

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.
- Tumor 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 (Williams 2019). Cytokines have three basic properties (O'Shea 2019; Rider 2016). First, they are pleiotropic, meaning cytokines can have more than one effect 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 among different receptor complexes (O'Shea 2019; Rider 2016). Third, they can have specific and unique functions, like the regulation of 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; Riksen 2020; Tabas 2017; Upadhye 2020; Wang 2020a).

Interleukin-1 (IL-1) is an essential cytokine for local and systemic inflammation (Cavalli 2018; Dinarello 2013; Dayer 2017). 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; Sarwar 2012; Moriya 2019). The cytokines so far 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 the prevention and treatment of 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-1Ra are monoclonal antibodies (MoAbs). The mechanism of action of MoAbs has been reviewed elsewhere (Cavalli 2018; Mitoma 2018; Varadé 2020).

There are three approved biologics for blocking IL-1: anakinra, rilonacept, and canakinumab (Abbate 2020). However, at present, none of them have 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 2018a; Chung 2003; Deswal 1999; Fichtlscherer 2001; Kleveland 2016; Mann 2004; Morton 2015; Padfield 2013; Ridker 2012; Ridker 2017; Van Tassell 2014; Van Tassell 2017a; Van Tassell 2017; Van Tassell 2016; Van Tassell 2018). Moreover, there are ongoing trials to assess the clinical benefits and harms of these drugs in ACVDs (NCT02272946; NCT03797001; Tao 2020).

Description of the intervention

This section will only describe the biological agents (IL-Ra and TNF inhibitors) that have been assessed in 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).

Interleukin-receptor antagonists

Interleukin-1 receptor antagonists

- Anakinra is a recombinant human IL-1 receptor antagonist protein that inhibits signaling 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. The most common side effect of anakinra is injection site reaction. The short half-life of anakinra allows immediate withdrawal of treatment 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 humanized monoclonal antibody directed against soluble and membrane-bound IL-6 receptors, produced by recombinant DNA technology (EMA 2020b; Carroll 2018b; Sheppard 2017; Varadé 2020).

Tumor 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 crystallizable (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 approximately of 70 hours (range: 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 of 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; Giles 2020; 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, minimizing 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, resulting in inhibition of tumor angiogenesis (NCI 2020a).

- Canakinumab is a human recombinant polypeptide that acts as a receptor antagonist to IL-1β. Canakinumab neutralizes the action of human IL-1β (Singh 2018; EMA 2020a). This event suppresses the inflammatory responses mediated by IL-1b (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 signaling cascade of IL-6 (EMA 2020b; FDA 2020a).

Tumor 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 solubilized and cell-surface TNFα, thus neutralizing 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 neutralizes the biological activity of soluble and cell-surface TNFα by inhibiting its interaction with the TNF receptor. Moreover, TNFα up-regulates IL-6 production (Moreland 2004).

Why it is important to do this review

There are heritable and non-heritable links between atherosclerosis and inflammation that may explain residual cardiovascular risk, after accounting for traditional risk factors (Bazeley 2020; Fang 2020; Jung 2020; Sano 2018; Yura 2020). Several molecular mechanisms play an essential role in ACVDs development (Holte 2017; Kleveland 2018; Ueland 2018). The biological agents described above have been approved for non-ACVDs medical conditions, and their effects on the cardiovascular system have not been systematically reviewed. The purpose of this review is to synthesize the current knowledge on the clinical benefits and harms of the IL-receptor antagonists and TNF inhibitors in preventing ACVDs; in particular, these drugs are associated with a high risk of developing severe infections, such as the reactivation of tuberculosis (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, hyperlipidemia, 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 will be of interest to epidemiologists and healthcare decision-makers.

Objectives

1. To assess the clinical benefits and harms of interleukin-receptor antagonists and tumor necrosis factor (TNF) inhibitors for the primary and secondary prevention of atherosclerotic cardiovascular diseases.
2. To determine whether interleukin-receptor antagonists or TNF inhibitors, provided to people both with and without pre-existing cardiovascular disease, are:
    1. useful in preventing adverse cardiovascular outcomes; and
    2. safe.

Methods

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs). We will exclude non-randomized clinical trials. We will include studies reported as full-text, those published as an abstract only, and unpublished data, if available. Furthermore, we will not apply any limitations regarding language, country, or follow-up duration. We will only include studies with a parallel design. Due to the nature of the clinical condition and the intervention's pharmacodynamic properties, we consider that cross-over and cluster-randomized trials are not suitable.

The IL-receptor antagonists and TNF inhibitors must meet all of the three following conditions.

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

Types of participants

We will include adults (aged 18 years or more) with or without a history of cardiovascular disease (myocardial infarction, unstable angina, heart failure, stroke, peripheral vascular disease). We will include participants from those who have or do not have the following comorbidities: hypertension, diabetes mellitus, and chronic kidney disease.

If a trial includes at least ten participants that meet our inclusion criteria, and it has a clear subgroup analysis, it will be included in the analysis. Otherwise, we will exclude from the analysis any study that has 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 will be excluded from our analysis. Nonetheless, before making the final decision, we will try to obtain the data for the participants of interest from the trialists.

Types of interventions

We will include trials comparing IL-receptor antagonists or TNF antagonists with placebo or usual care. For the purposes of the review, and in the absence of a standard definition of usual care, we will accept the following: "it can include the routine care received by patients for prevention or treatment of diseases" (Gellman 2013). We will include interventions

given at any dosage, and via any administration route, as follows.

Interventions

- Interleukin-1 (IL-1) receptor antagonists (anakinra, canakinumab)
- Interleukin-6 (IL-6) receptor antagonists (tocilizumab)
- Tumor necrosis factor ionhibitors (etanercept, infliximab)

Comparisons

- Placebo
- Usual care

For the analysis, comparisons will be treated separately. This means there will be 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;
- TNFinhibitors (etanercept, infliximab) compared with placebo or usual care.

We will accept co-medication use (such as the use of 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 is not an inclusion criterion for the review. We will try to access the trial protocol or contact the trial authors to ascertain all measured outcomes, even if not reported. Relevant trials that measure these outcomes but do not report the data at all, or not in a usable format, will be included in the narrative. We will 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 will be interested in the number of participants with at least one event. All outcomes will be 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 will analyze adverse events both by the number of patient events that experienced at least one, and the total number of adverse events. We will report these analyses separately. We will prioritize reporting of infections.

Secondary outcomes

1. Peripheral vascular disease
2. Stroke (fatal or non-fatal). We will include either acute ischaemic stroke or acute cerebral haemorrhage. Clinical diagnosis with imaging will be 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 will be excluded as an outcome of this Cochrane Review. However, economic costs will be narratively discussed in the 'Discussion' section of the review, if data are available.

Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library.
- MEDLINE (Ovid, from 1946 to present).
- Embase (Ovid, from 1980 to present).
- Web of Science CPCI-S (Conference Proceedings Citation Index-Science) (Clarivate Analytics, from 1990 to present).
- LILACS (Latin American and Caribbean Health Science Information database) (Bireme, from 1982 to present).

The preliminary search strategy for MEDLINE (Ovid) will be adapted for use in the other databases (Appendix 5). The Cochrane sensitivity-precision maximising RCT filter (Lefebvre 2019) will be applied to MEDLINE (Ovid) and adaptations of it to the other databases, except CENTRAL. We will search all databases from their inception to the present, and we will impose no restriction on language of publication or publication status. We will also search the following ongoing trial registries.

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

We will also search 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 will check reference lists of all included studies and any relevant systematic reviews identified for additional references to trials. We will also examine any relevant retraction statements and errata for included studies. We will contact study authors for missing data and ongoing trials.

We plan to search relevant manufacturers' websites for trial information on the interventions, as follows.

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

Data collection and analysis

We will follow the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a).

Selection of studies

Two pairs of review authors (AMC/SN; MAEA/ACP) will independently, and in duplicate, screen titles and abstracts of all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, two authors will be asked to arbitrate (MD, EA). We will retrieve the full-text study reports/publications and three review authors (CMA, DM, JMPV) will independently screen the full-text and identify studies for inclusion, and identify and record reasons for excluding the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (JBDS). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record 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 will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. Three review authors (DM, CMA, SN) will independently, and in duplicate, extract study characteristics from the included studies. One author (AMC) will check this information. We will extract 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 centers and location, study setting, type of trial (superiority, equivalence, or non-inferiority trial), and date of the study.
2. Participants: number (N) randomized, N lost to follow-up/withdrawn, N analyzed, 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 was stroke 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, dyslipidemia), 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 to recollect 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.

Two review authors (AMC, MAEA) will independently extract outcome data from the included studies. We will resolve disagreements by consensus or by involving two authors (CMA, JMPV). One review author (AMC) will transfer data into Review Manager software (RevMan Web 2019). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the data extraction form. A second review author (MAEA) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two pairs of review authors (AMC/DM; ACP/CMA) will independently, and in duplicate, assess the risk of bias for each study using version two of the Cochrane 'Risk of bias' tool (RoB 2), outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Boutron 2019; Higgins 2019b). We will resolve any disagreements by discussion or by involving another author (JMPV). We will assess the risk of bias for the outcomes of the included trials that will be included in our 'Summary of findings' table (Schünemann 2019).

We will perform analysis based on the intention-to-treat principle, which includes all randomized participants irrespective of the interventions that participants actually received. We will use the following domains to assess the risk of bias in the individually randomized trials:

- bias arising from the randomization process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in the measurement of the outcome; and
- bias in the selection of the reported result (Higgins 2019b; Higgins 2021).

We will use the signalling questions in the RoB 2 tool to facilitate rating each domain as 'low risk of bias', 'some concerns', or 'high risk of bias'. The response options for the signalling questions will be:

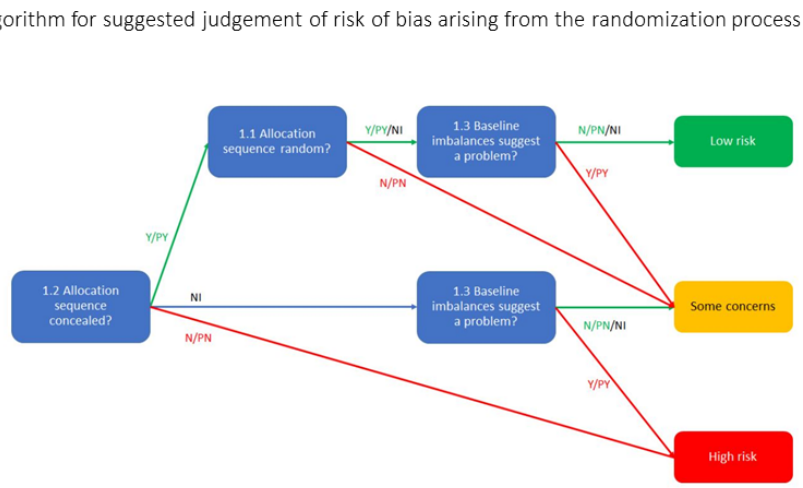
- yes;
- probably yes;
- probably no;
- no; or
- no information.

We will use algorithms to map our answers to the signalling questions per outcome and will propose a risk of bias for each domain (Higgins 2021). The following figures show the algorithms used as examples for judgement of risk of bias from each one of the domains:

- randomization process (Figure 1);

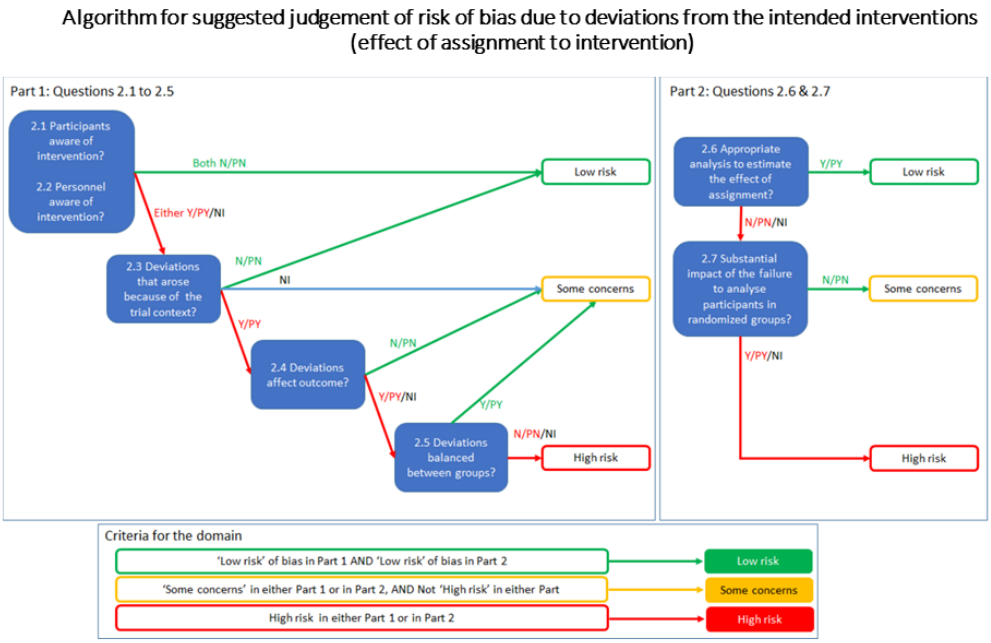
- due to deviations from the intended interventions (effect of assignment to intervention) (Figure 2);
- due to missing outcome data (Figure 3);
- in the measurement of the outcome (Figure 4);
- in the selection of the reported result (Figure 5) (Higgins 2021).

Figure 1 **Open in figure viewer**



Algorithm for suggested judgement of risk of bias arising from the randomization process

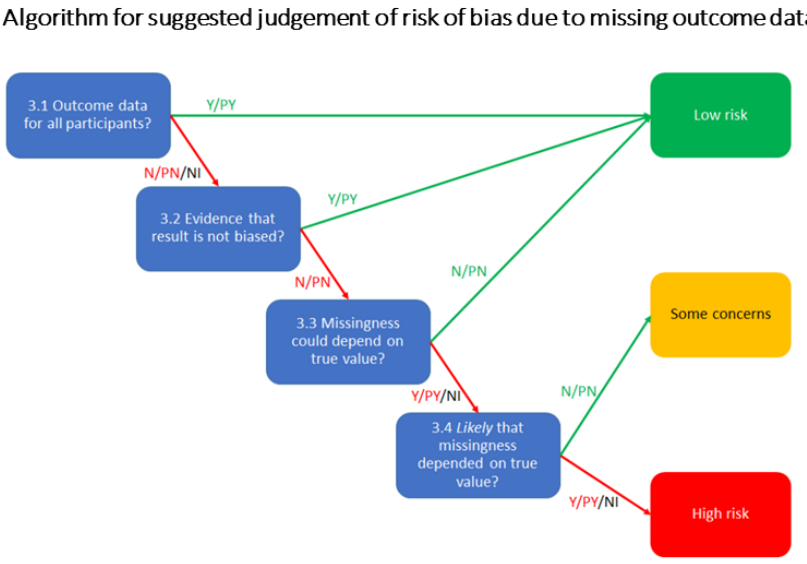
Figure 2 **Open in figure viewer**



Algorithm for suggested judgement of risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Figure 3

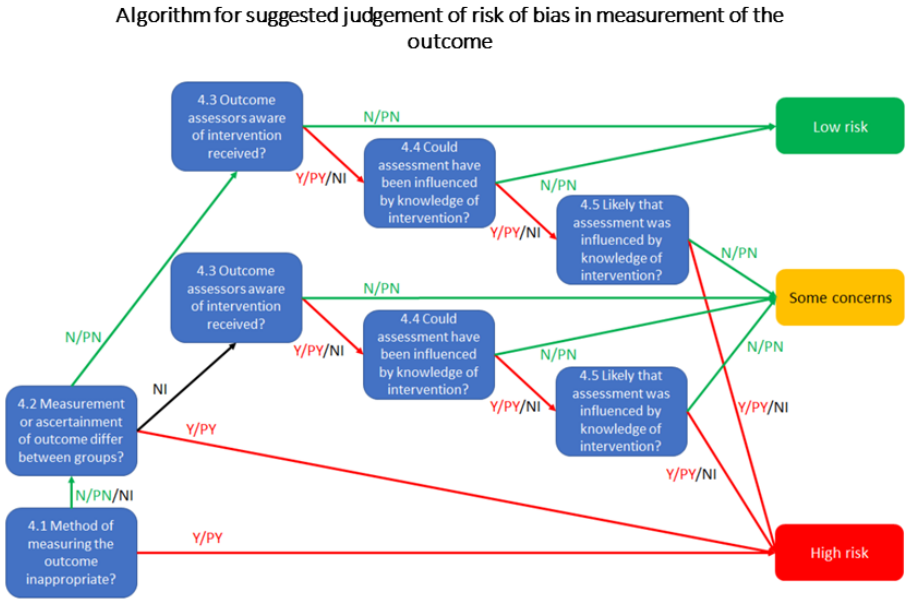
Open in figure viewer



Algorithm for suggested judgement of risk of bias due to missing outcome data

Figure 4

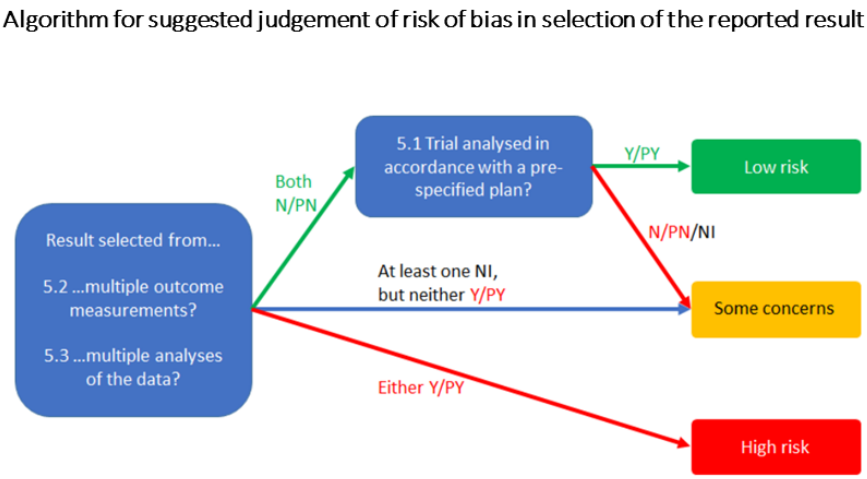
Open in figure viewer



Algorithm for suggested judgement of risk of bias in measurement of the outcome

Figure 5

Open in figure viewer



Algorithm for suggested judgement of risk of bias in selection of the reported result

When we judge a result to be at a particular level of risk of bias for an individual domain, it implies that the overall result has a risk of bias that is at least this severe. Therefore, a judgement of ‘high risk of bias' within any domain will have a similar implication for the result as a whole, irrespective of which domain is being assessed. ‘Some concerns’ in multiple domains may lead the review authors to decide on an overall judgement of ‘high risk of bias' for that outcome or group of outcomes (Higgins 2019a; Higgins 2021).

The overall risk of bias for the result will be the least favourable assessment across the domains of bias (Figure 6). 'Low risk of bias' will denote that the study was judged to be at low risk of bias for all domains for this result. 'Some concerns' will denote that the study was judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain. 'High risk of bias' will denote that the study was judged to be at high risk of bias in at least one domain for this result, or the study was judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result (Higgins 2019a; Higgins 2021). We will store the data on a server that can be accessed by other researchers.

Figure 6 **Open in figure viewer**

The overall risk of bias

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall Risk
Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Low risk	Some concerns	Some concerns	Low risk	Some concerns	High risk
Low risk	Low risk	Low risk	High risk	Low risk	High risk

The overall risk of bias

Measures of treatment effect

We will analyse dichotomous data (all-cause mortality, myocardial infarction, unstable angina, adverse events, heart failure, and stroke) with risk ratios (RiRs) and 95% confidence intervals (CIs). With the exception of all-cause mortality, if any of these outcomes is reported as incidence rate (count data), we will report the rate ratio (RR) and 95% CI.

For continuous data (quality of life), we will estimate mean differences (MDs) with 95% CIs. If different scales are used for measuring 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 2019c).

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 clinical usefulness of the consequences of treatment (Laupacis 1988). We will estimate the NNTB with GraphPad software and with the Cochrane Stroke Group NNT calculator.

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a), if necessary we will multiply the mean values from one set of studies by −1 to ensure that all the scales point in the same direction (Higgins 2019c). We will narratively describe skewed data reported as medians and interquartile ranges. If statistical information is missing (such as standard deviations), we will try to extract them 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 will be the participant. The time of the analysis will be the longest established in each trial. In the case of multiple-armed trials, we plan to combine the groups to yield a single pairwise comparison (Higgins 2019f). For continuous outcomes, we will divide the control group denominator by two in order to have two pairwise comparisons. This approach will avoid double-counting participants.

Dealing with missing data

We will assess the percentage of dropouts for each included trial, and for each intervention group, and will evaluate whether an intention-to-treat (ITT) analysis had been performed or could have been performed from the available published information. We will try to contact the study authors to resolve any questions arising from this issue if is possible.

In order 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 or not they were later thought to be ineligible, otherwise excluded from treatment, or lost to follow-up. If this information is not forthcoming, we will perform a 'per protocol' analysis of those who completed the study, being 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-worse' case scenario): none of the dropouts/participants lost from the experimental arm, but all of the dropouts/participants lost from the control arm, experienced the outcome, including all randomized 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, experienced the outcome, including all randomized participants in the denominator (Hollis 1999).
- Gamble-Hollis analysis, which takes account of the uncertainty and generates uncertainty intervals for a trial incorporating both sampling error and the potential impact of missing data (Gamble 2005). This method increases the uncertainty of the trials using the results from the best-case and worst-case analyses (Chaimani 2014).

Assessment of heterogeneity

We will quantify statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across trials that is due to heterogeneity rather than sampling error (Higgins 2003). We will assume a range of 50% to 90% may represent substantial heterogeneity (Deeks 2019). For a proper interpretation of the I^2, we will follow the following 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 will consider statistical heterogeneity to be present if I^2 is 70% or above (Deeks 2019). We will quantify the 95% CI or uncertainty interval of I^2 with STATA statistical software (Kontopantelis 2010).

If there is both statistical heterogeneity and three or more RCTs, we will determine the 95% prediction interval, which takes into account the whole distribution of the effects (Riley 2011). Prediction intervals in meta-analysis show the expected range of true effects in similar studies (IntHout 2016). We will estimate the 95% prediction interval with STATA. If there are 10 or more RCTs and the I^2 value is 70% or greater, we will conduct a meta-regression with STATA. The

outcome variable will be predicted for the following explanatory variables (the potential effect modifiers): diabetes mellitus, chronic kidney disease, type of receptor antagonist. We plan to conduct the potential meta-regression analyses by prevention level.

Assessment of reporting biases

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 will perform meta-analyses with 95% CIs, using a random-effects model. In case of statistical heterogeneity (I^2 value of 70% or greater), we will report the prediction interval (Deeks 2019; IntHout 2016; Riley 2011). We will conduct the meta-analysis using RevMan Web (RevMan Web 2019).

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analyses either 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 to develop 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 to develop 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 to develop a cardiovascular outcome.)
5. Trials with 200 participants or less by group versus trials with more than 200 participants by a group; 200 is an arbitrary threshold or cut-off point. (Hypothesis: trials with a small sample size show 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

We will conduct sensitivity analyses in which we will do the following and compare the results with the original analyses.

- Trials with a low risk of bias compared to trials with some concerns and a high risk of bias.
- A fixed-effect model meta-analysis compared to random-effects model meta-analysis.
- Trials without missing data compared to trials without missing data.

We will use the overall risk of bias judgement for studies, rather than specific domains. We will judge whether there is a difference between the primary analysis and sensitivity analysis by comparing changes in P values.

We will only conduct these analyses for the primary outcomes.

Summary of findings and assessment of the certainty of the evidence

We will create a 'Summary of findings' table using the following outcomes: all-cause mortality, myocardial infarction, unstable angina, adverse events, peripheral vascular disease, stroke, and heart failure. We will use 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 relates to the studies which contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004; Guyatt 2008). We will use the methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019), using GRADEpro GDT software (GRADEpro GDT 2020). Each comparison (as listed in Types of interventions) will get a separate 'Summary of findings' table (Appendix 8). We will justify all decisions to downgrade the quality of the evidence using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Judgements about evidence quality will be made by two review authors (AMC, JMPV) working independently, with disagreements resolved by discussion or involving a third author (CEMA). Judgements will be justified, documented, and incorporated into reporting of results for each outcome. We will communicate the findings of interventions following the GRADE Working Group's recommendations (Santesso 2020).

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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). 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). 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).
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 drug	These drugs reduce the progression and tissue destruction of the inflammatory disease process, especially rheumatoid arthritis, by inhibiting tumor 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).
Humanized monoclonal antibodies	Therapeutic monoclonal antibodies 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). 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). 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). The collection of cells, tissues, and molecules that mediate these reactions to some noninfectious 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 of natural immunity (Moreland 2004). 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).
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). 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) IL-1B 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 ischemia-reperfusion. 2. Increased tissue IL-1β mRNA in dilated cardiomyopathy. 3. Increased circulating IL-1β in dilated cardiomyopathy. 4. Increased circulating IL-1β in acute myocarditis. 5. Increased tissue IL-1β mRNA in acute myocarditis. 6. IL-1Ra provides cardioprotection in ischemia-reperfusion.

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-1 β.These macrophage products have profound proinflammatory effects (Moreland 2004). 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).	7. Increased serum IL-1β predict a high risk of mortality in idiopathic dilated cardiomyopathy. Source: Bartekova 2018 reports several references.
IL-1α	Although IL-1α is also inducible in myeloid cells, the IL-1α precursor in 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 IL1 β, but also plays an essential role in the maintenance of the skin barrier. It is a member of the IL1 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 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).	1. Increased circulating IL-6 post-acute myocardial infarction. 2. Increased tissue IL-6 mRNA post-acute myocardial infarction. 3. Increased levels of sIL-6R post-acute myocardial infarction. 4. Recombinant IL-6 induced cardioprotection in ischemia-reperfusion.

5. Increased plasma IL-6 in chronic heart failure.
6. Increased plasma IL-6 predict adverse cardiovascular events following acute coronary syndrome and coronary heart disease.
7. IL-6 silencing abrogated cardioprotection by explant-derived stem cells.
8. Increased circulating IL-6 in dilated cardiomyopathy and hypertrophic cardiomyopathy.
9. IL-6 polymorphism is associated with risk of dilated cardiomyopathy.

Source: Bartekova 2018 reports several references.

Tumor necrosis factors

TNFα	Macrophages, T cells, 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. 2. Increased in plasma TNFα in heart failure. 3. Positive correlation between TNFα gene expression and level, severity, and aetiology of heart failure. 4. Cardiac-restricted overexpression of membrane-bound TNFα—ventricular hypertrophy and consequent dysfunction. 5. Cardiac-restricted overexpression of secreted TNFα—ventricular dilation and consequent dysfunction. 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. 2. Cardiac fibrosis. 3. Positive correlation between TGF-β1 and left ventricular mass. 4. Increased TGF-β1 gene expression after transition from stable hypertrophy to heart failure. 5. Increased TGF-β1 level—in hypertrophic cardiomyopathy. 6. Involvement in formation of border zone around the infarcted area. 7. Biomarker revealing aortic dilation. 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 alfa
IL-6: interleukin-6
TNFα: tumor necrosis factor alfa
TNFβ: tumor necrosis factor beta

Appendix 3. Pharmacological summary and primary clinical application of the 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)
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
Canakinumab	150 mg/mL	150 mg/mL	Solution	Subcutaneous	Single-dose vial	L04AC08 (EMA 2020a)	22 December 2016
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
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
Tocilizumab	162 mg/0.9 mL	179 mg/mL	Solution	Subcutaneous	Autoinjector		19 November 2018
Tumor necrosis factor inhibitors							
Etanercept	25 mg	25 mg/vial	Powder	Subcutaneous	Multi-dose vial	L04AB01 (EMA 2020c)	02 November 1998
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

Appendix 4. Interleukin-receptor antagonist therapy: warnings and precautions for use

Drug	Warnings	Comments/Recommendations	Source

Anakinra	1. Allergic reactions 2. Hepatic events 3. Serious infections 4. Renal impairment 5. Neutropenia 6. Pulmonary events 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. 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. 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. 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. 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. 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. 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 2. Neutropenia and leukopenia 3. Malignancies 4. Hypersensitivity reactions 5. Hepatic function	1. Canakinumab is associated with an increased incidence of serious infections. 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. 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. 4. Hypersensitivity reactions with canakinumab therapy have been reported. The majority of these events were mild in severity. 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 2. Elderly 3. Renal impairment 4. Hepatic impairment 5. Infections 6. Tuberculosis 7. Complications of diverticulitis 8. Hepatotoxicity 9. Cardiovascular risk	1. It is not recommended in patients with an absolute neutrophil count below 2 x 109/l. 2. No dose adjustment is required in elderly patients > 65 years of age. 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. 4. RoActemra has not been studied in patients with hepatic impairment. Therefore, no dose recommendations can be made. 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. 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. 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. 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. 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.	EMA 2020b

Etanercept	1. Infections 2. Tuberculosis 3. Hepatitis B reactivation 4. Worsening of hepatitis C 5. Concurrent treatment with anakinra 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. 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. 3. In patients who develop HBV infection, etanercept should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated. 4. Etanercept should be used with caution in patients with a history of hepatitis C. 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. 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.	EMA 2020c

Infliximab	1. Infusion reactions and hypersensitivity 2. Infections 3. Tuberculosis 4. Hepatitis B reactivation 5. Hepatobiliary events 6. Neurological events 7. Heart failure	1. If serious reactions occur, symptomatic treatment must be given and further infliximab infusions must not be administered. 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. 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. 4. Reactivation of hepatitis B has occurred in patients receiving a TNF-inhibitors including infliximab, who are chronic carriers of this virus. Some cases have had fatal outcome. Patients should be tested for HBV infection before initiating treatment with infliximab. 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. 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. 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. Preliminary MEDLINE (Ovid) search strategy

1 Interleukin 1 Receptor Antagonist Protein/ (5267)

2 ((interleukin-1 or IL-1) adj2 receptor antagonist*).tw. (6591)

3 IL-1RA.tw. (5548)

4 il-1 inhibitor.tw. (153)

5 Anakinra.tw. (1880)

6 Canakinumab.tw. (632)

7 ((Interleukin-6 or IL-6) adj2 receptor antagonist*).tw. (281)

8 Tocilizumab.tw. (3747)

9 Atlizumab.tw. (18)

10 Tumor Necrosis Factor Inhibitors/ (732)

11 ((Tumor necrosis factor or TNF) adj1 (blocker* or inhibitor*)).tw. (3413)

12 Etanercept/ (5945)

13 Etanercept.tw. (7054)

14 Infliximab/ (10488)

15 Infliximab.tw. (12601)

16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (36922)

17 randomized controlled trial.pt. (522452)

18 controlled clinical trial.pt. (94057)

19 randomized.ab. (510873)

20 placebo.ab. (215697)

21 clinical trials as topic.sh. (194604)

22 randomly.ab. (351797)

23 trial.ti. (235577)

24 17 or 18 or 19 or 20 or 21 or 22 or 23 (1348821)

25 exp animals/ not humans.sh. (4785606)

26 24 not 25 (1242209)

27 16 and 26 (4753)

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.

Appendix 8. GRADE and 'Summary of findings' table

1 Interleukin-receptor antagonist therapy for prevention cardiovascular outcomes

Interleukin-receptor antagonist therapy for prevention cardiovascular outcomes

Patient or population: prevention cardiovascular outcomes
Settings: in-hospital or community
Intervention: interleukin-receptor antagonist therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Interleukin-receptor antagonist therapy				
All-cause mortality	See comment[1]	See comment	Not estimable	0 (0)	See comment	
Myocardial infarction (fatal or non-fatal)	See comment	See comment	Not estimable	0 (0)	See comment	
Unstable angina	See comment	See comment	Not estimable	0 (0)	See comment	
Adverse events	See comment	See comment	Not estimable	0 (0)	See comment	
Peripheral Vascular Disease	See comment	See comment	Not estimable	0 (0)	See comment	
Stroke (fatal or non-fatal)	See comment	See comment	Not estimable	0 (0)	See comment	
Heart Failure	See comment[2]	See comment		0 (0)	See comment	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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 quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[1] Assumed risk will be based on median control group risks in the meta-analysis if it is available.

[2] Assumed risk for mean difference or standard mean difference with 95% confidence interval.