Cochrane Library

Cochrane Database of Systematic Reviews

Antithrombotic treatment following coronary artery bypass surgery: a network meta-analysis (Protocol)

Cardiothoracic Interdisciplinary Research Network, Abbasciano RG, Gradinariu G, Kourliouros A, Lai F, Langrish J, Murphy G, Quarto C, Radhakrishnan A, Raja S, Rogers LJ, Townend J, Tyson N, Vaja R, Verdichizzo D, Wynne R

Cardiothoracic Interdisciplinary Research Network, Abbasciano RG, Gradinariu G, Kourliouros A, Lai F, Langrish J, Murphy G, Quarto C, Radhakrishnan A, Raja S, Rogers LJ, Townend J, Tyson N, Vaja R, Verdichizzo D, Wynne R.
Antithrombotic treatment following coronary artery bypass surgery: a network meta-analysis (Protocol).
Cochrane Database of Systematic Reviews 2021, Issue 12. Art. No.: CD014817.
DOI: 10.1002/14651858.CD014817.

www.cochranelibrary.com

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Protocol]

Antithrombotic treatment following coronary artery bypass surgery: a network meta-analysis

Cardiothoracic Interdisciplinary Research Network[1], Riccardo Giuseppe Abbasciano[1], George Gradinariu[2], Antonios Kourliouros[3], Florence Lai[1], Jeremy Langrish[3], Gavin Murphy[1], Cesare Quarto[4], Ashwin Radhakrishnan[5], Shahzad Raja[4], Luke J Rogers[6], Jonathan Townend[7], Nathan Tyson[8], Ricky Vaja[4], Danilo Verdichizzo[3], Rochelle Wynne[9]

[1]Department of Cardiovascular Sciences, University of Leicester, Leicester, UK. [2]Department of Cardiothoracic Surgery, Golden Jubilee National Hospital, Glasgow, UK. [3]Oxford Heart Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK. [4]Department of Cardiac Surgery, Royal Brompton and Harefield Hospital, London, UK. [5]Department of Cardiology, New Cross Hospital, Wolverhampton, UK. [6]Bristol Heart Institute, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK. [7]Department of Cardiology, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Trust, Birmingham, UK. [8]Trent Cardiac Centre, Nottingham University Hospitals NHS Trust, Nottingham, UK. [9]Western Sydney Nursing & Midwifery Research Centre, Western Sydney University, Sydney, Australia

Contact: Luke J Rogers, ljrogers@doctors.org.uk.

Editorial group: Cochrane Heart Group.
Publication status and date: New, published in Issue 12, 2021.

Citation: Cardiothoracic Interdisciplinary Research Network, Abbasciano RG, Gradinariu G, Kourliouros A, Lai F, Langrish J, Murphy G, Quarto C, Radhakrishnan A, Raja S, Rogers LJ, Townend J, Tyson N, Vaja R, Verdichizzo D, Wynne R. Antithrombotic treatment following coronary artery bypass surgery: a network meta-analysis (Protocol). *Cochrane Database of Systematic Reviews* 2021, Issue 12. Art. No.: CD014817. DOI: 10.1002/14651858.CD014817.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Objectives

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

Primary objective

- To assess the clinical effectiveness of antithrombotic agents in reducing all-cause mortality after CABG surgery.

Secondary objectives

- To evaluate the effect of antithrombotic agents on graft patency, cardiovascular morbidity and bleeding after CABG surgery.
- To present ranking probabilities of antithrombotic agents in relation to all-cause mortality and bleeding.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

BACKGROUND

Cardiovascular disease is the leading cause of death worldwide, with the vast majority of these deaths attributable to coronary heart disease (CHD) (World Health Organization 2017). CHD, ischaemic heart disease (IHD) or coronary artery disease (CAD) all describe the same condition; a situation in which the blood flow to the heart muscle is reduced as a consequence of a build-up of plaque (atherosclerosis) in the arteries of the heart. It commonly causes chest pain or discomfort (angina), which may travel to the shoulder, arm, back, neck and/or jaw, and which is not infrequently confused with indigestion. Symptoms usually occur with exercise or emotional stress, last a few minutes and improve with rest. Shortness of breath may also occur and sometimes, no symptoms may present at all. Unfortunately, in many cases the first sign of this disease is a heart attack or myocardial infarction (MI).

Treatment of CHD is multifaceted, with lifestyle changes that include regular exercise, stopping smoking and a greater emphasis on a plant-based diet (i.e. based on vegetables and fruit). Medications such as beta-blockers, statins (HMG-CoA reductase inhibitors) and nitrates are the mainstay of medical therapy.

Despite these interventions, it is sometimes necessary to unblock or bypass the narrowed arteries. This can be performed via a catheter-based intervention known as balloon angioplasty, also called percutaneous coronary intervention (PCI). PCI involves widening the narrowed artery with an inflatable balloon and then, in most cases, supporting this with the deployment of a coronary stent. An alternative approach involves surgical revascularisation or coronary artery bypass grafting (CABG) which improves the blood supply to the heart by 'bypassing' the diseased portion(s) of the arteries with grafts (conduit) taken from elsewhere in the body, most commonly the left internal mammary artery (LIMA) and one or more of the long saphenous veins (LSV) of the lower limbs. This is a well-established means of improving the blood supply to the heart and has been demonstrated not only to improve the symptoms associated with CHD, notably chest pain (angina) and shortness of breath, but also to improve survival (Head 2018). In accordance with the European Society of Cardiology (ESC) Guidelines (Neumann 2019) the operation is indicated (Class I) for the treatment of left main stem, proximal left anterior descending (LAD) artery and three-vessel CHD, respectively.

Unfortunately, these grafts can sometimes fail, a complication known as graft failure or occlusion. Although this can occur in any graft, it most commonly occurs in LSV grafts. This can result in a recurrence in symptoms (angina, shortness of breath) and on occasion require additional steps to improve the blood supply to the heart. This can be performed with further surgery, but is most commonly achieved with PCI. In an effort to reduce the risk of graft failure antithrombotic agents are often commenced early in the developement of symptoms of CHD and especially after intervention whether by PCI or CABG. The focus of this review will be on the choice of antithrombotic agents administered after CABG.

Description of the condition

Although CABG is the most effective treatment for CHD, it is not a cure. Sometimes, graft failure or occlusion may develop, with the grafts becoming hardened and narrow. Ultimately, this may even result in complete blockage of the graft. The likelihood of this occurring varies, dependent on the type of graft (conduit) used for the bypass, with higher rates of failure seen with LSV grafts compared to arterial grafts (Gaudino 2018). At 10 years post-CABG, up to 40% of LSV grafts in angiographic studies were found to be occluded (Fitzgibbon 1996; Goldman 2004). Graft failure is associated with an increased risk of major adverse cardiovascular events, with Halabi 2005 showing that at 10 years post-CABG, the composite outcome of death, myocardial infarction or repeat revascularization occurred in 67.1% of patients with occluded LSV grafts, compared to 27.9% with no vein graft disease ($P < 0.0001$) (Halabi 2005). Thus, graft failure is a significant source of morbidity and mortality in patients with established CHD, treated with CABG. Interventions that reduce graft failure may therefore lead to better outcomes for patients.

Description of the intervention

An antithrombotic agent is a drug that reduces the formation of a blood clot (thrombus). Antithrombotic agents encompass medications that alter the function of platelets (antiplatelets) and those that prevent or reduce the coagulation of blood (anticoagulant), thereby increasing the time it takes for blood to clot. Oral formulations of these agents are used after CABG, in an effort to minimise graft occlusion. Antiplatelet therapy is the recommended treatment of choice after CABG (Kulik 2015; Neumann 2019), but the choice of agent, duration of treatment and dose varies significantly in clinical practice. Studies of aspirin post-CABG have shown reduced perioperative MI and improved survival, compared to placebo (Farooq 2012; Mangano 2002). In addition to aspirin, a variety of other antiplatelet agents are available, including clopidogrel, prasugrel, dipyridamole and ticagrelor.

A recent network meta-analysis of oral antiplatelet therapy post-CABG showed that the combinations of aspirin with clopidogrel or ticagrelor appeared to reduce rates of graft failure, compared to aspirin monotherapy (Solo 2019). A previous meta-analysis, however, did not show a survival benefit after CABG with the combination of aspirin and clopidogrel (de Leon 2012). The combination of aspirin with other P2Y12 inhibitors (ticagrelor or prasugrel), compared to aspirin and clopidogrel or aspirin monotherapy, appears to demonstrate a survival benefit in all-cause mortality (risk ratio (RR) 0.49. 95% confidence interval (CI) 0.33 to 0.7) (Verma 2015). However, this reduction in all-cause mortality may increased risk of bleeding (RR 1.31, 95% CI 0.81 to 2.1) (Solo 2019; Verma 2015).

Although anticoagulant therapy is not routinely recommended for graft patency post-CABG, (Kulik 2015; Neumann 2019) a minority of patients undergoing CABG have an alternative indication for anticoagulation, such as atrial fibrillation or history of venous thromboembolism (VTE). A variety of oral anticoagulant agents are in use, including vitamin K antagonists such as warfarin, or more recently, direct oral anticoagulants (DOACs). The effect of anticoagulants on graft patency and survival after CABG is not clear, either independently or in combination with antiplatelet agent(s).

How the intervention might work

Graft failure represents the total occlusion of the conduit, which stops blood flowing to the revascularised area of the heart. Graft occlusion can occur early (within the first year from surgery) or late (more than one year from surgery) (Gaudino 2017). Very early failure (within the first month from surgery) is likely due to acute thrombosis of the graft caused by endothelial injury,

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

technical factors or hypercoagulable states in the perioperative period. Platelet activation and thrombus formation are key steps in graft occlusion at this stage. Neo-intimal hyperplasia of the graft occurs in the first months after surgery and is responsible for most occlusions beyond one month. Late failure usually results from a combination of neo-intimal hyperplasia and atherosclerotic degeneration. In vascular grafts, this is an accelerated process which, unlike the atherosclerosis of native vessels, usually has a concentric and diffuse pattern, leading to a higher risk of plaque rupture that triggers platelet activation and thrombus formation; resulting eventually in vessel occlusion (Badimon 2012; Yahagi 2016). Antiplatelet agents have a role in reducing graft occlusion through their beneficial effects inn reducing platelet aggregation. Similarly, anticoagulants may play a role, by reducing fibrin aggregation. This has been demonstrated to reduce mortality after CABG, partly by reducing the incidence of graft occlusion. This Cochrane Review, however, will identify the antithrombotic agent or combination of agents that current evidence suggests may be the most likely to increase survival and minimise graft occlusion, following CABG in adult patients. In addition, it will also illustrate the potential side-effects, notably bleeding, that may be associated with these treatment regimens.

Why it is important to do this review

Worldwide, there is no accepted standard of care regarding the use of antithrombotic therapy following CABG. The 2018 European Society of Cardiology (ESC) guidelines include Class I recommendations for the use of dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor antagonist for up to 12 months in patients who undergo CABG after acute coronary syndrome (Neumann 2019). However, the choice of a second antiplatelet agent is not specified, and significant variation in clinical practice exists. For patients undergoing elective CABG, single antiplatelet therapy with aspirin is recommended, although DAPT may be considered (Valgimigli 2018).

Given the extensive choice of antithrombotic agents available, questions remain about the best combination of antiplatelet and/or anticoagulant agents and dose to reduce the incidence of graft occlusion and improve survival post-CABG, without a prohibitive increase in the risk of bleeding. To address this area of unmet need, we aim to use a systematic, unbiased approach to identify which antithrombotic agent(s), or combination of agents improves survival, increases graft patency and limits bleeding risk in adult patients undergoing CABG.

A network meta-analysis of the available evidence, as opposed to a conventional meta-analysis, allows the comparison of all currently available agents, including those that not been compared in head to head studies. This is particularly important in this review as many of the more recent agents are likely to have been compared with placebo or aspirin but not against each other. In addition, this approach will also provide an insight into the quantity of research that is available for each of these antithrombotic agents thereby highlighting areas in which future research can be focussed.

OBJECTIVES

Primary objective

- To assess the clinical effectiveness of antithrombotic agents in reducing all-cause mortality after CABG surgery.

Secondary objectives

- To evaluate the effect of antithrombotic agents on graft patency, cardiovascular morbidity and bleeding after CABG surgery.
- To present ranking probabilities of antithrombotic agents in relation to all-cause mortality and bleeding.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) that test antithrombotic agents following first-time isolated CABG surgery. We will also include RCTs with parallel-groups, including those of a factorial design, whether at the level of participants or clusters. We will include studies reported in full text and those published as abstract only. We will include unpublished data.

We will exclude:

- cross-over trials, due to the inability to determine the outcome of interest over the duration of follow-up post-CABG;
- prospective and retrospective cohort studies;
- cross-sectional studies;
- case-control studies;
- controlled pre- or post-intervention studies; and
- registry data.

Types of participants

We will include studies with adults (18 years of age or older) who have undergone isolated first-time CABG surgery (including either on-pump or off-pump surgery), irrespective of approach (full sternotomy or minimal-access surgery) and irrespective of the number of arterial or venous conduits used. We expect the different RCTs this identifies will on average be similar, and will therefore allow indirect comparisons.

Where studies include a population of both eligible and ineligible patients, we will contact the trial coordinators to obtain the relevant data. If we are unable to obtain such data, we will only include data if the eligible population contributes to more than 50% of the study population. This decision will be assessed in a sensitivity analysis.

Our exclusion criteria will include:

- patients requiring preoperative antithrombotic medication for an alternative medical condition, e.g. atrial fibrillation, DVT, pulmonary embolism; and
- studies whereby CABG patients are not the primary population of interest, and data relates to subgroup analysis (e.g. studies looking at antithrombotic therapy following acute coronary events and where follow-up data were acquired from those who later received CABG).

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Types of interventions

Any oral antithrombotic therapy (or placebo) initiated within one week of surgery, and continued for a minimum of three months postoperatively, will be included. We will include trials examining aspirin monotherapy, P2Y12 receptor inhibitor monotherapy, combinations of antiplatelet therapy, anticoagulant monotherapy and/or combinations of antiplatelet and anticoagulant agents. Intravenous or subcutaneous agents will be excluded. Trials simultaneously assessing concomitant medications will be excluded.

The following antiplatelet agents will be examined: aspirin, ticlodipine, dipyridamole, clopidogrel, ticagrelor and prasugrel.

The following anticoagulants will be examined: warfarin, apixaban, rivaroxaban, edoxaban and dabigatran.

Where available, different dose regimens will be considered for each drug. Each of these drugs will be treated as a node within the network; aspirin will be separated further into a 'low dose' node (≤ 100 mg) and a 'high-dose' node (> 100 mg).

We will exclude agents not licensed by the US Food and Drug Administration or the European Medicines Agency because of lack of safety or evidence of effectiveness, as they are not clinically relevant.

Types of outcome measures

Outcome measures will be assessed at the latest point of follow-up for each included trial. Where a published study does not report an outcome of interest, we will contact the study coordinators to obtain the relevant data, if available.

Primary outcomes

1. All-cause mortality

Secondary outcomes

1. Cardiovascular mortality
2. Non-fatal perioperative MI (within index admission)
3. Ischaemic or haemorrhagic stroke
4. Revascularisation (PCI or repeat surgery)
5. Graft patency - assessed either via computed tomography (CT) or invasive coronary angiography at any time during the study period
6. Bleeding, as classified by the Bleeding Academic Research Consortium criteria: type 0 - no bleeding; type 1 - bleeding that is not actionable and does not lead to intervention from a healthcare professional; type 2 - overt bleeding that requires evaluation, non-surgical or medical intervention by a healthcare professional or hospitalisation or increased level of care but does not meet criteria for types 3 to 5 bleeding; type 3a - overt bleeding with haemoglobin drop of 3 - 5 g/dL or requiring transfusion; type 3b - overt bleeding with haemoglobin drop ≥ 5 g/dL; type 4 - CABG related bleeding; type 5 - fatal bleeding (Mehran 2011).
7. Adverse events that are known side-effects of the antithrombotic agents will be included. These may include, but are not limited to the following: headache, anaphylaxis, bronchospasm, exacerbation of asthma, gastrointestinal disorders, dyspepsia, vomiting, diarrhoea, constipation. Bleeding will be reported as a separate outcome, as described above.

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 onwards)
- Embase (Ovid, from 1980 onwards)
- Web of Science Core Collection (Clarivate Analytics, from 1900 onwards)

The preliminary search strategy for MEDLINE (Ovid) will be adapted for use in the other databases. We will apply the Cochrane sensitivity and precision maximising RCT filter (Lefebvre 2019) to MEDLINE (Ovid) and will apply adaptations of it to Embase (Ovid) and Web of Science.

We will also conduct searches for ongoing or unpublished trials in the ClinicalTrials.gov trials registry at the US National Institutes of Health (www.ClinicalTrials.gov) and in the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch).

We will search all databases from their inception to the present, and we will impose no restriction on language of publication or publication status.

Since adverse events will be one of our secondary outcomes, we will not perform a separate search for adverse effects of interventions used and will only consider adverse effects described in included studies.

Searching other resources

For additional references to trials, we will check the reference lists of all included studies and those of any relevant systematic reviews identified. We will also examine any relevant retraction statements and errata for included studies.

Data collection and analysis

Selection of studies

The titles and abstracts of articles from the electronic searches will be independently appraised for suitability by two review authors (any two of RV, LR, RA, DV, AR, NT, RW, or GG) in Covidence. Duplicate results will be removed prior to title and abstract screening. Eligible papers or those whose eligibility is unclear will be marked for retrieval; those papers not meeting eligibility criteria will not be retrieved. Screening results from both reviewers will be compared, and where conflicts arise, disputes will be settled by discussion with the lead authors (RV and LR).

Full-text publications will be retrieved for studies deemed to be suitable. Multiple reports of the same study will be collated so that each study, as opposed to each report, is the unit of interest in this review. Each full text will be independently screened by two review authors from the authorship group (any two of RV, LR, RA, DV, AR, NT, RW, or GG). Authors will appraise each manuscript

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

against inclusion/exclusion criteria, and any disagreements will be resolved by consensus with the lead review authors (RV and LR). Reasons for exclusion will be documented.

The selection process will be fully documented according to the PRISMA flow diagram (Liberati 2009), and in tables reporting characteristics of both included and excluded studies.

Data extraction and management

Data will be independently extracted from included studies by a minimum of two review authors from the review group (RV, LR, RA, DV, AR, NT, RW, GG). Conflicts in data extraction will be resolved by consensus between review authors and one of the lead review authors (RV or LR). Data will be extracted onto an online form using Covidence in order to maintain consistency between review authors.

To meet the intended outcomes of the review, we will record these characteristics from each study.

- **Methods:** study design, total duration of study, recruitment period, number of study centres and location, study setting, and date of study, maximum length of follow up
- **Participants:** number randomized, number lost to follow up or withdrawn, number analyzed, mean age, gender, body mass index (BMI), airway disease, diabetes, smoking status, ejection fraction, recent MI (within 30 days), previous stroke, chronic kidney disease, peripheral vascular disease, on-pump versus off-pump surgery, number of arterial grafts, bilateral internal mammary arteries, method of conduit harvest e.g. open or endoscopic. We will also document the inclusion and exclusion criteria of each study.
- **Interventions:** interventions, comparisons including placebo, timing, frequency, duration and dose, concomitant medications. Aspirin dose will be categorised as 'low dose' ≤ 100mg/day or 'high dose' > 100mg/day.
- **Outcomes:** primary and secondary outcomes (as listed above) will be extracted from the included studies at the longest period of follow up in each study.

Data will be manually transferred into RevMan Web (RevMan Web 2020) from Covidence. Accuracy of entered data will be ensured by comparison between the RevMan Web entry and the data extraction form.

Potential effect modifiers include an individual's pre-operative risk stratification, usually expressed as their EUROScore (Nashef 2012; O'Brien 2018; Roques 2003). These scores provide an indication of the risk of mortality to which adult cardiac surgery patients are exposed, based on a number of pre-operative factors such as age, urgency of procedure and pertinent comorbidities. The review authors believe that utilising these risk prediction tools will provide a more comprehensive assessment of the trial populations, compared to individual risk factors for mortality alone. We will collect summary distribution data (mean and standard deviation (SD), or median and first and third quartiles (Q1 and Q3)) for continuous data. We will compare the distribution across the direct comparisons in the network.

Assessment of risk of bias in included studies

Two review authors from among eight review authors (AR, GG, NT, RA, DV, FL, RV, LR) will independently assess the risk of bias for all outcomes. We will follow the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We will assess quantitative studies with the second version of Cochrane's 'Risk of bias' tool (RoB 2) (Sterne 2019). Disparity in bias assessments will be resolved by discussion with a third review author (RV, LR). Bias will be assessed across the following domains using signalling questions:

- bias arising from the randomization process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in outcome domains outlined and measurement;
- bias in selection of the reported result.

The RoB 2 assessment will be presented independently as a 'Risk of bias' table. We will judge each the risk of bias for each domain to be 'high', 'some concerns' or 'low', and will provide a justification of our judgement in the 'Risk of bias' table. We will use the RoB 2 Excel tool to manage assessment of bias (Sterne 2019). Consensus decisions for the signalling questions will be reported in a supplemental appendix to the review. We will summarise risk of bias judgements across different studies for each of the domains listed. All sources of bias will be considered in studies relating to treatment effect, and we will evaluate them for their contribution to the study outcome both in terms of effect of assignment and effect of adherence. As differences in these two effects may elicit important differences, this will be performed according to RoB 2 methods. The risk of bias will be assessed in cluster RCTs with the RoB 2 tool for cluster-randomised trials (Sterne 2019).

Measures of treatment effect

All outcomes are dichotomous variables. We will analyze dichotomous data in terms of RRs with their 95% CIs.

Unit of analysis issues

In RCTs with a parallel design, we will take multiple treatment arms and time points into account, where relevant, to avoid double-counting.

For graft patency, the unit of analysis will be the number of participants and not the number of grafts occluded.

For re-intervention, stroke, MI and bleeding, the unit of analysis will be a binary outcome per participant ('yes' or 'no'), and not the total number of complications.

For cluster-RCTs, we will assess if the trial analysis adequately accounted for the cluster design (using methods based on multi-level model, variance components analysis, generalised estimating equations etc.). Effect estimates and the standard errors may be meta-analysed using the generic inverse-variance method. For cluster-RCTs that have not been properly analyzed, we will attempt to obtain an estimate of the intra-cluster correlation coefficient (ICC) from similar studies. If this is feasible, we will calculate the design effect for the trial and an inflated standard error for the effect estimates, using the formulae described in the Cochrane Handbook (Higgins 2021). The effect estimates and the inflated standard error will be meta-analysed using the generic inverse-variance method.

If a reliable ICC cannot be obtained, we may extract estimates using the cluster, rather than the patient, as the unit of analysis.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified only as an abstract). Where possible, we will use the RevMan Web calculator to calculate missing SDs using other trial data, such as CIs, based on methods outlined in the *Cochrane Handbook* (Higgins 2019). Where this is not possible, and the missing data are thought to introduce serious bias, we will conduct a sensitivity analysis to explore the impact of including such studies in the overall assessment of results.

Assessment of heterogeneity

For the pairwise meta-analyses, we will assume heterogeneity will be different for each comparison. In network meta-analyses (NMAs) we will assume a common estimate for heterogeneity across the different comparisons.

We will assess clinical heterogeneity by summarising participant population characteristics and interventions across studies. Methodological heterogeneity will be assessed by looking at differences in outcome assessment and risk of bias. Global heterogeneity from the NMA models and pairwise heterogeneity measures will be reported. For pairwise meta-analyses, we will estimate the heterogeneity for each comparison. We will inspect forest plots visually to consider the direction and magnitude of effects and the degree of overlap between and among CIs. We will use the I^2 statistic to measure heterogeneity among the trials in each analysis, but will acknowledge that there is substantial uncertainty in the value of I^2 when there is only a small number of studies. We will also consider the P value from the Chi^2 test. If substantial heterogeneity (I^2 > 50%) is identified we will report it and explore possible causes. We will assess statistical heterogeneity in the entire network based on the magnitude of heterogeneity variance parameter, estimated from the NMA model (Schwarzer 2015).

Assessment of reporting biases

If we are able to pool data from 10 or more trials, we will assess publication bias, using a funnel plot and Egger's test (Egger 1997). We will assess small study effects using a funnel plot.

Data synthesis

We will include all studies in the primary analysis. Sensitivity analysis excluding studies of high risk of bias will be conducted.

Pairwise meta-analysis

Pairwise traditional meta-analyses will be conducted using a random-effects model. Pooled data will be presented as risk ratio (RR) for binary outcomes with 95% confidence interval. Heterogeneity across trials will be assessed using Q statistics and I^2 measure. We would define substantial heterogeneity as a I^2 > 50%.

Network meta-analysis (NMA)

We will perform NMA in a Bayesian framework to compare various antithrombotic treatments after cardiac surgery. Separate random-effects NMAs will be conducted for each in-hospital outcome involving three or more interventions. A random-effects model with a common heterogeneity parameter will be fitted. We will use a vague uniform prior distribution for the between-trial heterogeneity. We will run Markov Chain Monte Carlo (MCMC) sampling, where the first 10,000 posterior samples are discarded (Gamerman 2006). Following this, another 100,000 iterations will be run, with a thinning of 10 (storing every tenth iteration). Model convergence will be checked by visual inspection of the time-series plots, using the Brooks-Gelman-Rubin method (Brooks 1998).

A network-diagram will be produced for each analysis. Treatments that are not connected to the network will be excluded from the analysis. Network diagram will use nodes to represent antithrombotic treatments and edges to represent the head-to-head comparisons between treatments. The edge thickness corresponds to the numbers of included trials. We will report pairwise comparisons between all treatments. Treatments will be ranked using the surface under the cumulative ranking curve (SUCRA; Salanti 2011).

The transitivity assumption underlying network meta-analysis will be assessed by comparing the distributions of patient and clinical characteristics that could act as effect-modifiers across trials. Potential effect-modifiers include an individual's pre-operative risk stratification, usually expressed as their EUROScore (EUROScore II, logistic EUROScore or STS Score). Global heterogeneity from the NMA models and pairwise heterogeneity measures will be reported. We will assess statistical heterogeneity in the entire network, based on the magnitude of heterogeneity variance parameter, estimated from the NMA model. Consistency (or agreement between direct and indirect evidence) will be assessed based on the node-splitting method. The Bayesian NMA will be carried out using the R software package 'gemtc'.

Network meta-regression

We do not plan to conduct network meta-regression.

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analyses for all outcomes in pairwise meta-analysis, if the subgroups involved include at least 10 studies. No subgroup analyses will be conducted for NMA. We plan to carry out the following subgroup analyses for any outcomes with substantial heterogeneity.

- Monotherapy versus dual therapy ± triple therapy

We will use the formal test for subgroup differences in RevMan Web 2020, and will base our interpretation on this.

Sensitivity analysis

We plan sensitivity analysis to examine whether the methodological design affects the main results. Sensitivity analysis will be conducted for all outcomes in pairwise and network analyses; this will include only studies with an overall low risk of bias, as determined by the RoB 2 tool. It will be conducted for pairwise meta-analysis if there are three or more studies available for any outcome and for NMA if the included studies allow forming a connected network with three or more antithrombotic treatments.

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where possible, we will use the RevMan Web calculator to calculate missing SDs using other trial data, such as CIs, based on methods outlined in the *Cochrane Handbook* (Higgins 2019). Where this is not possible, and the missing data are thought to introduce serious

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

bias, we will conduct sensitivity analysis to explore the impact of including such studies in the overall assessment of results.

Summary of findings and assessment of the certainty of the evidence

We will create a GRADE 'Summary of findings' table, using the NMA-SoF table structure set out by Yepes-Nunes 2019, for the following outcomes.

1. All-cause mortality
2. Cardiovascular mortality
3. Non-fatal peri-operative MI (within index admission)
4. Ischaemic or haemorrhagic stroke
5. Revascularisation (PCI or repeat surgery)
6. Graft patency - assessed either via CT or invasive coronary angiography at any time during the study period
7. Bleeding, as classified by the Bleeding Academic Research Consortium criteria: type 0 - no bleeding; type 1 - bleeding that is not actionable and does not lead to intervention from a healthcare professional; type 2 - overt bleeding that requires evaluation, non-surgical or medical intervention by a healthcare professional or hospitalisation or increased level of care but does not meet criteria for types 3 to 5 bleeding; type 3a - overt bleeding with haemoglobin drop of 3 - 5g/dL or requiring transfusion; type 3b - overt bleeding with haemoglobin drop ≥ 5 g/dL; type 4 - CABG related bleeding; type 5 - fatal bleeding (Mehran 2011).
8. Adverse events that are known side effects of the antithrombotic agents will be included. These may include, but are not limited to the following; headache, anaphylaxis, bronchospasm, exacerbation of asthma, gastrointestinal disorders, dyspepsia, vomiting, diarrhoea, constipation.

We will use methods and recommendations described in Chapter 14 of the *Cochrane Handbook* (Schünemann 2019) and in Yepes-Nunes 2019, using GRADEpro software (GRADEpro GDT 2015). The GRADE analyses for each comparison will be presented in separate 'Summary of findings' tables. The 'Summary of findings' tables' will present our overall GRADE judgement of the certainty of evidence across studies for each pertinent outcome.

We will justify all decisions to downgrade the quality of studies using footnotes, and where necessary, we will make comments to aid readers' understanding of the review.

Judgements about evidence certainty will be made by two review authors (RV, LR) working independently, with disagreements resolved by discussion or by involving a third review author (RA). Judgements will be justified, documented and incorporated into reporting of results for each outcome. The overall RoB 2 judgement for each study will be used to feed into GRADE assessments of relevant outcomes.

Confidence in the NMA will be presented as per the Confidence in Network Meta-Analysis (CINeMA) web-based application (Nikolakopoulou 2020).

ACKNOWLEDGEMENTS

We are grateful for the support from Alberto San Roman (Contact Editor, Cochrane Heart, Clinic University Hospital, Valladolid, Spain), Rodrigo Bagur (peer review) and Gabriela Azevedo Sansoni (consumer review).

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

REFERENCES

Additional references

Badimon 2012

Badimon L, Padró T, Vilahur G. Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. *European Heart Journal. Acute Cardiovascular Care* 2012;**1**(1):60-74.

Brooks 1998

Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations . *American Statistical Association* 1998;**7**(4):434-55.

Covidence [Computer program]

Veritas Health Innovation Covidence. Version accessed 10 November 2021. Melbourne, Australia: Veritas Health Innovation. Available at covidence.org.

de Leon 2012

de Leon N, Jackevicius CA. Use of aspirin and clopidogrel after coronary artery bypass graft surgery. *Annals of Pharmacotherapy* 2012;**46**(5):678-87.

Egger 1997

Egger M, Smith GD, Schneider M, Christoph M. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629.

Farooq 2012

Farooq V, Serruys PW, Bourantas C, Vranckx P, Diletti RD, Garcia Garcia HM, et al. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial. *European Heart Journal* 2012;**33**:3105–13.

Fitzgibbon 1996

Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: Angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *Journal of the American College of Cardiology* 1996;**28**(3):616-26.

Gamerman 2006

Gamerman D, Lopes HF. Markov Chain Monte Carlo. Florida: Chapman & Hall/CRC, 2006.

Gaudino 2017

Gaudino M, Antoniades C, Benedetto U, Deb S, Di Franco A, Di Giammarco G, et al. Mechanisms, consequences, and prevention of coronary graft failure. *Circulation* 2017;**136**:1749-64.

Gaudino 2018

Gaudino M, Benedetto U, Fremes S, Biondi-Zoccai G, Sedrakyan A, Puskas JD, et al. Radial-artery or saphenous-vein grafts in coronary-artery bypass surgery. *New England Journal of Medicine* 2018/05/;**378**(22):2069-77.

gemtc [Computer program]

Network meta-analysis using bayesian methods. Version 1.01. Gert van Valkenhoef, Joel Kuiper, 2021. Available at: gemtc.pdf (r-project.org).

Goldman 2004

Goldman S, Zadina K, Moritz T, Ovitt T, Sethi G, Copeland JG, et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. *Journal of the American College of Cardiology* 2004;**44**(11):2149-56.

GRADEpro GDT 2015 [Computer program]

Hamilton (ON): McMaster University (developed by Evidence Prime) GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015. Available at gradepro.org.

Halabi 2005

Halabi AR, Alexander JH, Shaw LK, Lorenz TJ, Liao L, Kong DF, et al. Relation of early saphenous vein graft failure to outcomes following coronary artery bypass surgery. *American Journal of Cardiology* 2005/11;**96**(9):1254-9.

Head 2018

Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet* 2018;**391**(10124):939-48. [DOI: 10.1016/S0140-6736(18)30423-9] [PMID: 29478841]

Higgins 2019

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). In: Available from www.training.cochrane.org/handbook. The Cochrane Collaboration, 2020.

Higgins 2021

Higgins JP, Eldridge S, Li T. Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook .

Kulik 2015

Kulik A, Ruel M, Jneid H, Ferguson TB, Hiratzka LF, Ikonomidis JS, et al. Secondary prevention after coronary artery bypass graft surgery: a scientific statement from the American Heart Association. *Circulation* 2015;**131**(10):927-64.

Lefebvre 2019

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s), Cochrane Handbook for Systematic Reviews of Interventions. Version 6.0 (updated October

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

2019). The Cochrane Collaboration, 2019. Available from www.cochrane-handbook.org.

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**(7):e1000100.

Mangano 2002

Mangano DT. Aspirin and mortality from coronary bypass surgery. *New England Journal of Medicine* 2002;**347**(17):1309-17.

Mehran 2011

Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the bleeding academic research consortium. *Circulation* 2011;**123**(23):2736-47.

Nashef 2012

Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. *European Journal of Cardiothoracic Surgery* 2012;**41**(4):734–45.

Neumann 2019

Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *European Heart Journal* 2019;**40**(2):87-165.

Nikolakopoulou 2020

Nikolakopoulou A, Higgins JP, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, et al. CINeMA: an approach for assessing confidence in the results of a network meta-analysis. *PLOS Medicine* 2020;**Apr 3;17(4)**:e1003082.

O'Brien 2018

O'Brien SM, Feng L, He X, Xian Y, Jacobs JP, Badhwar V, et al. The Society of Thoracic Surgeons 2018 Adult cardiac surgery risk models: part 2 - statistical methods and results. *Annals of Thoracic Surgery* 2018;**105**(5):1419-28.

R [Computer program]

R Foundation for Statistical Computing R: A language and environment for statistical computing. Version 3.4.2. Vienna, Austria: R Foundation for Statistical Computing, 2017. Available at www.R-project.org.

RevMan Web 2020 [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). Version 1.22.0. Available at revman.cochrane.org: The Cochrane Collaboration, 2020.

Roques 2003

Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. *European Heart Journal* 2003;**24**(9):882-3.

Salanti 2011

Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. . *Journal of Clinical Epidemiology* 2011;**64**(2):163-71.

Schünemann 2019

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, et al, editor(s), Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated October 2019). The Cochrane Collaboration, 2019. Available from www.training.cochrane.org/handbook.

Schwarzer 2015

Schwarzer G, Carpenter JR, Rücker G. Meta-analysis with R. Springer, 2015.

Solo 2019

Solo K, Lavi S, Kabali C, Levine GN, Kulik A, John-Baptiste AA, et al. Antithrombotic treatment after coronary artery bypass graft surgery: Systematic review and network meta-analysis. *BMJ* 2019;**367**:l5476.

Sterne 2019

Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

Valgimigli 2018

Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *European Heart Journal* 2018;**39**(3):213-54.

Verma 2015

Verma S, Goodman SG, Mehta SR, Latter DA, Ruel M, Gupta M, et al. Should dual antiplatelet therapy be used in patients following coronary artery bypass surgery? A meta-analysis of randomized controlled trials. Vascular and thoracic surgery. *BMC Surgery* 2015;**15**(1):112.

World Health Organization 2017

World Health Organization. Cardiovascular diseases (CVDs). www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (accessed prior to 12 October 2021).

Yahagi 2016

Yahagi K, Kolodgie FD, Otsuka F, Finn AV, Davis HR, Joner M, et al. Pathophysiology of native coronary, vein graft, and in-stent atherosclerosis. *Nature Reviews Cardiology* 2016;**13**(2):79-98.

Yepes-Nunes 2019

Yepes-Nuñez JJ, Li SA, Guyatt G, Jack SM, Brozek JL, Beyene J, et al. Development of the summary of findings table for network meta-analysis. *Journal of Clinical Epidemiology* 2019;**115**:1-13.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

APPENDICES

Appendix 1. Preliminary MEDLINE (Ovid) search strategy

1. exp Coronary Artery Bypass/
2. Coronary artery bypass.tw.
3. CABG.tw.
4. aortocoronary bypass.tw.
5. 1 or 2 or 3 or 4
6. (Antithrombotic adj3 (drug* or treatment or agent* or therapy)).tw.
7. Anticoagulants/
8. anticoagulant*.tw.
9. Warfarin/
10. Warfarin.tw.
11. ((direct* adj3 oral anticoagulant*) or DOAC or DOACs).tw.
12. Dabigatran/
13. Rivaroxaban/
14. (apixaban or betrixaban or dabigatran or edoxaban or rivaroxaban).tw.
15. Platelet Aggregation Inhibitors/
16. (antiplatelet* or antiaggregant* or platelet agglutination inhibitor* or platelet aggregation inhibitor*).tw.
17. DAPT.tw.
18. Aspirin/
19. (aspirin or acetylsalicylic acid or acetyl?salicylic acid).tw.
20. Clopidogrel/
21. Clopidogrel.tw.
22. Ticlopidine/
23. ticlopidine.tw.
24. Dipyridamole/
25. Dipyridamole.tw.
26. Prasugrel Hydrochloride/
27. Prasugrel.tw.
28. Ticagrelor/
29. Ticagrelor.tw.
30. exp Purinergic P2Y Receptor Antagonists/
31. P2Y12 receptor*.tw.
32. P2Y2.tw.
33. or/6-32
34. 5 and 33
35. randomized controlled trial.pt.
36. controlled clinical trial.pt.
37. randomized.ab.
38. placebo.ab.
39. clinical trials as topic.sh.
40. randomly.ab.
41. trial.ti.
42. 35 or 36 or 37 or 38 or 39 or 40 or 41
43. exp animals/ not humans.sh.
44. 42 not 43
45. 34 and 44

CONTRIBUTIONS OF AUTHORS

Cardiothoracic Interdisciplinary Research Network

Riccardo Giuseppe Abbasciano: reviewed and provided editorial changes to protocol

George Gradinariu: main author and editor of protocol throughout its conception, development and revision

Antonios Kourliouros: reviewed and provided editorial changes to protocol

Florence Lai: NMA expert, reviewed protocol and final articles statistical design, particularly data collection and analysis

Jeremy Langrish: reviewed and provided editorial changes to protocol

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Gavin Murphy: reviewed and provided editorial changes to protocol from its conception, developement and revision

Cesare Quarto: reviewed and provided editorial changes to protocol

Ashwin Radhakrishnan: main author and editor of protocol throughout its conception, development and revision

Shahzad Raja: reviewed and provided editorial changes to protocol

Luke J. Rogers: co-primary author and editor of protocol throughout its conception, development and revision

Jonathan Townend: reviewed and provided editorial changes to protocol

Nathan Tyson: main author and editor of protocol throughout its conception, development and revision

Ricky Vaja: co-primary author and editor of protocol throughout its conception, development and revision

Danilo Verdichizzo: reviewed and provided editorial changes to protocol

Rochelle Wynne: reviewed and provided editorial changes to protocol

DECLARATIONS OF INTEREST

Cardiothoracic Interdisciplinary Research Network: none to declare.

Riccardo Giuseppe Abbasciano: none to declare.

George Gradinariu: none to declare.

Antonios Kourliouros: none to declare.

Florence Lai: none to declare.

Jeremy Langrish: declares honorarium from Bayer.

Gavin Murphy: declares research funding from Zimmer Biomet, support for travel to educational meetings from Terumo and Baxter and support for educational activities from Vascutek.

Cesare Quarto: declares that he is a consultant/proctor for Abbott, with extensive worldwide experience in Tendyne transcatheter mitral valve implantation.

Ashwin Radhakrishnan: none to declare.

Shahzad Raja: none to declare.

Luke Rogers: declares support for travel to meetings from the Royal College of Surgeons Surgical Trials Initiative.

Jonathan Townend: declares a consultancy role with Cytosorbents Inc.

Nathan Tyson: none to declare.

Ricky Vaja: declares support for travel to meetings from the Royal College of Surgeons Surgical Trials Initiative, a grant from the British Heart Foundation for a Clinical Research Fellowship and an educational grant from Liva Nova for travel to a scientific conference.

Danilo Verdichizzo: none to declare.

Rochelle Wynne: none to declare.

SOURCES OF SUPPORT

Internal sources

- Leicester Clinical Trials Unit, UK

  Researcher expertise and statistical assistance.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

External sources

- National Institute for Health Research (NIHR), UK

  This project was supported by the NIHR via Cochrane Infrastructure 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, the UK National Health Service (NHS) or the UK Department of Health and Social Care.
- British Heart Foundation Clinical Research Collaborative Development Fund, UK

  A £5000 grant was provided to support expert statistical review of analysis through Leicester Clinical Trials Unit

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.