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Pharmacological treatment of vascular risk factors for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm (Review)

Robertson L, Atallah E, Stansby G

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[Intervention Review]

Pharmacological treatment of vascular risk factors for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm

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ABSTRACT

Background

Pharmacological prophylaxis has been proven to reduce the risk of cardiovascular events in individuals with atherosclerotic occlusive arterial disease. However, the role of prophylaxis in individuals with abdominal aortic aneurysm (AAA) remains unclear. Several studies have shown that despite successful repair, those people with AAA have a poorer rate of survival than healthy controls. People with AAA have an increased prevalence of coronary heart disease and risk of cardiovascular events. Despite this association, little is known about the effectiveness of pharmacological prophylaxis in reducing cardiovascular risk in people with AAA. This is an update of a Cochrane review first published in 2014.

Objectives

To determine the long-term effectiveness of antiplatelet, antihypertensive or lipid-lowering medication in reducing mortality and cardiovascular events in people with abdominal aortic aneurysm (AAA).

Search methods

For this update the Cochrane Vascular Information Specialist (CIS) searched the Cochrane Vascular Specialised Register (14 April 2016). In addition, the CIS searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2016, Issue 3) and trials registries (14 April 2016) and We also searched the reference lists of relevant articles.

Selection criteria

Randomised controlled trials in which people with AAA were randomly allocated to one prophylactic treatment versus another, a different regimen of the same treatment, a placebo, or no treatment were eligible for inclusion in this review. Primary outcomes included all-cause mortality and cardiovascular mortality.

Data collection and analysis

Two review authors independently selected studies for inclusion, and completed quality assessment and data extraction. We resolved any disagreements by discussion. Only one study met the inclusion criteria of the review, therefore we were unable to perform meta-analysis.

Main results

No new studies met the inclusion criteria for this update. We included one randomised controlled trial in the review. A subgroup of 227 participants with AAA received either metoprolol (N = 111) or placebo (N = 116). There was no clear evidence that metoprolol reduced all-cause mortality (odds ratio (OR) 0.17, 95% confidence interval (CI) 0.02 to 1.41), cardiovascular death (OR 0.20, 95% CI 0.02 to 1.76), AAA-related death (OR 1.05, 95% CI 0.06 to 16.92) or increased nonfatal cardiovascular events (OR 1.44, 95% CI 0.58 to 3.57) 30 days postoperatively. Furthermore, at six months postoperatively, estimated effects were compatible with benefit and harm for all-cause mortality (OR 0.71, 95% CI 0.26 to 1.95), cardiovascular death (OR 0.73, 95% CI 0.23 to 2.39) and nonfatal cardiovascular events (OR 1.41, 95% CI 0.59 to 3.35). Adverse drug effects were reported for the whole study population and were not available for the subgroup of participants with AAA. We considered the study to be at a generally low risk of bias. We downgraded the quality of the evidence for all outcomes to low. We downgraded the quality of evidence for imprecision as only one study with a small number of participants was available, the number of events was small and the result was consistent with benefit and harm.

Authors' conclusions

Due to the limited number of included trials, there is insufficient evidence to draw any conclusions about the effectiveness of cardiovascular prophylaxis in reducing mortality and cardiovascular events in people with AAA. Further good-quality randomised controlled trials that examine many types of prophylaxis with long-term follow-up are required before firm conclusions can be made.

PLAIN LANGUAGE SUMMARY

Medical treatment of vascular risk factors for reducing death and cardiovascular events in people with abdominal aortic aneurysm

Background

Abdominal aortic aneurysm (AAA) is a potentially life-threatening condition where the aorta enlarges and can ultimately burst, leading to massive internal bleeding. Current guidelines recommend that AAAs of 55 mm or more should be surgically repaired because, at this size, the risk of rupture outweighs the risk of surgical repair. AAAs between 30 mm and 54 mm in size are not as high risk and are generally monitored by regular scans to check for further enlargement. Recent research has shown that even after the aneurysm is repaired, the survival rate in people with AAA is poorer than in people without AAA. In most cases, the cause of death is a cardiovascular event, such as a heart attack or a stroke. Conditions such as high blood pressure or high cholesterol increase the risk of cardiovascular death. However, both conditions can be reversed through medical treatment. Given the increased risk of mortality with AAA, it is important to determine which medical treatment is most effective in preventing cardiovascular death in people with AAA.

In this review, researchers from Cochrane examined the effectiveness of medical treatment to treat vascular risk factors and reduce deaths and cardiovascular deaths and events in people with an AAA.

Study characteristics and key results

After searching for all relevant studies (until 14 April 2016), we found one study in which a subgroup of 227 people with AAA received either the beta-blocker metoprolol (medication that reduces blood pressure) or a placebo (dummy treatment). This study's results were imprecise for all causes of death and death from cardiovascular disease or nonfatal cardiovascular events at 30 days or six months after AAA repair. Side effects from the drug were reported for the whole study population and were not available for the subgroup of participants with AAA.

Quality of the evidence

We judged this study to be at a generally low risk of bias. We graded the quality of the evidence to low as we only included one small sized study in the review, there were few events reported and the result was consistent with benefit and harm.

Larger and longer studies are needed to find out which treatment is most effective. At present, people with AAA are offered a wide range of pharmacological treatment including antiplatelet drugs, antihypertensives and lipid-lowering drugs. Future trials should test available drugs to find the most effective strategy, whether that be one single drug or a combination of treatments. In addition, the acceptability of such interventions needs to be assessed and future studies should measure adverse side effects associated with these drugs and their impact on quality of life.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Metoprolol compared to placebo for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm (AAA)

Patient or population: patients of any age with AAA less than 30 mm in diameter
Setting: hospital
Intervention: metoprolol
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with metoprolol				
All-cause mortality, 30 days[1]	Study population		OR 0.17 (0.02 to 1.41)	227 (1 RCT)	⊕⊕◯◯ low[2]	-
	52 per 1000	9 per 1000 (1 to 71)				
Cardiovascular death, 30 days[3]	Study population		OR 0.20 (0.02 to 1.76)	227 (1 RCT)	⊕⊕◯◯ low[2]	-
	43 per 1000	9 per 1000 (1 to 73)				
AAA-related death, 30 days[4]	Study population		OR 1.05 (0.06 to 16.92)	227 (1 RCT)	⊕⊕◯◯ low[2]	-
	9 per 1000	9 per 1000 (1 to 128)				
Nonfatal cardiovascular event, 30 days[5]	Study population		OR 1.44 (0.58 to 3.57)	227 (1 RCT)	⊕⊕◯◯ low[2]	-
	78 per 1000	108 per 1000 (47 to 231)				
All-cause mortality, 6 months[1]	Study population		OR 0.71 (0.26 to 1.95)	227 (1 RCT)	⊕⊕◯◯ low[2]	-

	86 per 1000	63 per 1000 (24 to 155)				
Cardiovascular death, 6 months[3]	Study population		OR 0.73 (0.23 to 2.39)	227 (1 RCT)	⊕⊕◯◯ low[2]	-
	60 per 1000	45 per 1000 (15 to 133)				
AAA-related death, 6 months[4]	See comments		See comments	See comments	See comments	The incidence of AAA-related death was not measured at six months
Nonfatal cardiovascular event, 6 months[5]	Study population		OR 1.41 (0.59 to 3.35)	227 (1 RCT)	⊕⊕◯◯ low[2]	-
	86 per 1000	117 per 1000 (53 to 240)				

*The risk with placebo was the average risk in the placebo group (i.e. the number of participants with events divided by total number of participants of the placebo group included in the meta-analysis). The risk in the metoprolol group (and its 95% CI) is based on the assumed risk in the placebo group and the relative effect of the intervention (and its 95% CI).

Abbreviations: AAA: abdominal aortic aneurysm; **CI:** confidence interval; **MI:** myocardial infarction; **OR:** odds ratio; **RCT:** randomised controlled trial

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

[1]Death from all causes.
[2]Quality of evidence downgraded to low for imprecision due to low number of events, small sample size and wide CIs.
[3]Fatal MI, fatal stroke and other vascular deaths.
[4]Death due to abdominal aortic aneurysm.
[5]Nonfatal MI, nonfatal stroke, or transient ischaemic attack.

BACKGROUND

Description of the condition

An abdominal aortic aneurysm (AAA) is an abnormal dilatation of the aorta as it passes below the renal arteries to the point of bifurcation, where it forms the left and right common iliac arteries. The clinical definition of AAA varies, although a maximum infrarenal measurement (a measurement taken below the renal artery branches) of ≥ 30 mm is commonly used (Wanhainen 2008). The prevalence of AAA is six times greater in men than in women (Pleumeekers 1995), with one study demonstrating a prevalence of 1.3% in women and 7.6% in men (Scott 2002). Apart from male gender, other risk factors for AAA include smoking, increased age, and family history of AAA (Blanchard 2000). Conclusive evidence from several studies has shown smoking to be associated with AAA (Badger 2009; Greenhalgh 2008; Wilmink 1999). One study, Wilmink 1999, estimated that the risk of AAA is seven times higher in smokers and three times higher in ex-smokers compared with age-matched nonsmokers, and another study reported that 90% of participants with AAA were smokers (Greenhalgh 2008). Increased age has been consistently shown as a significant risk factor (Lloyd 2010; Singh 2001). One population-based study of 6386 men and women reported no AAA in participants younger than 48 years of age, but from this age onward the prevalence increased linearly in both men and women (Singh 2001). Family history is another known risk factor for AAA. One study reported that 9% to 12% of first-degree relatives of a participant with an AAA will develop an aneurysm (van Vlijmen-van Keulen 2002).

The decision to operate on an AAA is made when the risk of rupture is greater than the risk associated with the operation, and burden of co-morbidity is increasingly important (Ohrlander 2011). The UK Small Aneurysm Trial estimated that the annual rupture rate is 0.3% for AAAs that are less than 4 cm in diameter, 1.5% for 4.0 cm to 4.9 cm AAAs, and 6.5% for 5.0 cm to 5.9 cm AAAs (Brown 1999). In general, the American Heart Association and the UK Aneurysm Screening Programme recommend that patients with infrarenal AAAs measuring ≥ 55 mm should undergo repair to eliminate the risk of rupture (Hirsch 2005). AAAs can be repaired using an open or endovascular approach. Open repair with graft placement is a major procedure and may be preferred when patients are fit because complications are fewer and patients do not routinely require follow-up. Endograft repair involving stent placement (EVAR) is associated with a lower postoperative risk and is therefore considered when the patient is a high surgical risk or has coexisting medical conditions. The major risks in repairing an AAA are perioperative cardiac events, infection, and death. The 30-day mortality has been estimated at 5% in elective open surgical AAA repair compared with 1.7% with EVAR (Greenhalgh 2004; Prinssen 2004). However, a recent study showed no significant difference in survival at five years in participants who had undergone open repair compared with EVAR (Brown 2011). Patients with an infrarenal AAA of 30 mm to 54 mm are monitored by ultrasound or computed tomography (CT) scans every three, six, or 12 months for detection of possible expansion and the need for repair. These patients are considered for statin therapy to reduce vascular risk, decrease the risk of rupture and reduce aneurysm growth rates (Davis 2008). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers have also been proposed to reduce aneurysmal growth (Hackam 2006).

Studies have shown that even after successful surgical repair of an AAA, participants had a poorer survival rate than healthy controls (de Bruin 2014; De Martino 2013; Timmers 2013). A Dutch cohort study measured a survival rate of 59% 10 years after open AAA repair, and patients had a poorer health-related quality of life than age-matched controls (Timmers 2013). Another Dutch study compared statin use in patients undergoing AAA repair and found that while statins were associated with fewer cardiovascular deaths, several risk factors remained that were associated with poor survival after AAA repair including age of greater than 70 years, a history of cardiac disease, and moderate to severe tobacco use (de Bruin 2014). A further study of 2637 participants undergoing AAA repair determined that although five-year survival rates were similar between open and EVAR repair groups, advanced age ≥ 75 years, coronary artery disease, unstable angina or recent myocardial infarction (MI), oxygen-dependent chronic obstructive pulmonary disease, and an estimated glomerular filtration rate of less than 30 mL/min/1.73 m^2 were associated with poor survival at five years (De Martino 2013).

A recent study conducted in Australia demonstrated an association between AAA thrombus volume and subsequent cardiovascular events (Parr 2011). AAA thrombus products are released into the circulation where they have the potential to stimulate leukocytes and produce other changes that might promote atherosclerotic plaque activation and acute coronary and cerebrovascular events (Morange 2006; Parry 2009; Smith 2005; Takagi 2009).

AAA size and growth are associated with local generation of inflammation markers such as interleukin-6, matrix metalliproteinase-2 (MMP-2), and MMP-9 (Schouten 2006). Inflammation also seems to be important in perioperative adverse cardiac events. Larger AAA size is independently associated with an increased incidence of perioperative cardiovascular complications after elective infrarenal AAA repair (Schouten 2006).

Description of the intervention

Pharmacological therapy to reduce cardiovascular risk factors such as hypertension and hypercholesterolaemia. Examples of pharmacological therapy are antiplatelet therapy (e.g. aspirin, clopidogrel, ticlopidine, cilostazol, or any other antiplatelet drugs), antihypertensive drugs (e.g. calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers (β-blockers), or any other antihypertensive drugs) and lipid-lowering therapy (e.g. statins).

How the intervention might work

As people with AAA have increased cardiovascular risks, pharmacological therapy may reduce cardiovascular mortality and nonfatal cardiovascular events.

Why it is important to do this review

Three Cochrane systematic reviews on the effectiveness of surgical treatment of AAA have been conducted. Badger 2014 and Paravastu 2014 both compared endovascular versus open surgical repair for AAA, while Filardo 2015 examined immediate repair versus routine ultrasound surveillance. Another published Cochrane review, Rughani 2012, examined the effectiveness of medical treatments in terms of the expansion rate of small abdominal aortic aneurysms. However, these reviews have focused on treatment of AAA and ruptured AAA rather than on treatment of vascular risk factors associated with cardiovascular mortality in participants with AAA.

Acquired risk factors such as hypertension and hypercholesterolaemia are often reversible through pharmacological therapy. Given the increased risk of mortality with AAA, it is important to determine which prophylaxis is most effective in preventing cardiovascular death in people with AAA. To date, no systematic review has been conducted to study the effectiveness of medical treatments in reducing cardiovascular mortality in people with AAA. This review sought to provide evidence on the most effective medical treatment for this important problem.

This is an update of a Cochrane review first published in 2014.

OBJECTIVES

To determine the long-term effectiveness of antiplatelet, antihypertensive or lipid-lowering medication in reducing mortality and cardiovascular events in people with abdominal aortic aneurysm (AAA).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials in which participants with abdominal aortic aneurysm (AAA) were randomly allocated to one prophylactic treatment versus another, a different regimen of the same treatment, a placebo, or no treatment. We planned to include published studies and studies in progress, if preliminary results were available. Non-English studies were eligible and we sought translations, where appropriate, for inclusion in the review.

Types of participants

Men and women of any age with AAA of less than 30 mm in diameter as measured by standardised techniques such as ultrasound examination or CT. We also included participants who had undergone endovascular or open surgical repair for AAA. In participants who had an AAA repair, the time period included in this review was the postoperative rather than the surveillance phase. We only included mixed population studies where data on the subset of participants with AAA were available.

Types of interventions

- Antiplatelet therapy (e.g. aspirin, clopidogrel, ticlopidine, cilostazol, or any other antiplatelet drugs).
- Antihypertensive drugs (e.g. calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers (β-blockers), or any other antihypertensive drugs).
- Lipid-lowering therapy (e.g. statins).
- Combination treatment (e.g. antiplatelet drug plus antihypertensive or statin) versus single treatment.
- Combination treatment versus no treatment.

Where possible, we planned to compare one intervention with another treatment, a different regimen of the same treatment, placebo, or no treatment. We included any type, method, duration, timing, mode of delivery, and dose of medical treatment. We excluded studies in which participants were not treated with a specific regimen but were given numerous medications as it would not be possible to attribute outcomes or side effects to one particular regimen.

This review concerns medical interventions in which the principal actions are to modify cardiovascular risk factors. Therefore, we did not include any alternative treatments for which the primary purpose was to treat the aneurysm itself, for example to reduce growth rates or prevent rupture, or both.

Types of outcome measures

Primary outcomes

- All-cause mortality.
- Cardiovascular mortality (fatal myocardial infarction (MI), fatal stroke, other vascular deaths).

Secondary outcomes

- AAA-related death.
- Nonfatal cardiovascular events (nonfatal MI, nonfatal stroke, or transient ischaemic attack).

- Major amputation.
- Quality of life.
- Drug-related morbidity.
- Drug-related mortality.

We excluded outcomes that were specific to the aneurysm itself (for example, change in size or rupture rates).

Search methods for identification of studies

We sought translations of any trials that were not in the English language.

Electronic searches

For this update the Cochrane Vascular Information Specialist (CIS) searched the following databases for relevant trials.

- The Cochrane Vascular Specialised Register (14 April 2016).
- The Cochrane Central Register of Controlled Trials (CENTRAL (2016, Issue 3)) via the Cochrane Register of Studies Online.

See Appendix 1 for details of the search strategy the CIS used to search CENTRAL.

The Cochrane Vascular Specialised Register is maintained by the CIS and is constructed from weekly electronic searches of MEDLINE Ovid, Embase Ovid, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used, are described in the Specialised Register section of the Cochrane Vascular module in the Cochrane Library (www.cochranelibrary.com).

The CIS searched the following trial databases for details of ongoing and unpublished studies using the terms abdominal aneurysm (14 April 2016):

- World Health Organization International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/).
- ClinicalTrials.gov (http://clinicaltrials.gov/).
- ISRCTN Register (www.isrctn.com/).

See Appendix 2 for details of the search strategies.

Searching other resources

We reviewed the reference lists of relevant studies.

Data collection and analysis

Selection of studies

One review author (LR) used the selection criteria to identify trials for inclusion and assessed the titles and abstracts of all identified studies for relevance and design. The second review author (EA) independently confirmed this selection, and we resolved any disagreements through discussion. We obtained the full-text articles of any potentially relevant studies. Two review authors independently assessed the full-text articles. We resolved any disagreements by discussion. We listed all studies excluded after full-text assessment in a 'Characteristics of excluded studies' table. We planned to include any studies that were published in duplicate only once in the review. We constructed a PRISMA diagram to illustrate the study selection process.

Data extraction and management

Two review authors (LR, EA) independently extracted the data. We recorded information about the trial design; AAA definition and measurement methods; baseline characteristics of participants; treatment type, method, duration, timing, mode of delivery, and dose. We reported all-cause mortality and cardiovascular mortality data as the primary outcome measures. Also, we collected information on non-cardiovascular events and adverse events in accordance with the secondary outcome measures. We planned to contact the study authors for further information if we required clarification. We resolved any disagreements in data extraction and management by discussion.

Assessment of risk of bias in included studies

Two review authors (LR, EA) independently used the Cochrane 'Risk of bias' assessment tool, Higgins 2011, to assess the risk of bias in the included study). This tool provides a protocol for judgements on sequence generation, allocation methods, blinding, incomplete outcome data, selective outcome reporting, and any other relevant biases. We resolved any disagreements by discussion.

Measures of treatment effect

We planned to base the analysis on intention-to-treat data from the individual clinical trials. As the primary and secondary outcomes are all binary measures, we computed odds ratios (ORs) using a fixed-effect model. We calculated the 95% confidence intervals (CIs) of the effect sizes.

Unit of analysis issues

The unit of analysis was the individual participant. However, as the trial involved repeat measurements on participants at different points in time, it was prone to unit of analysis errors (Deeks 2011). Therefore, for the purpose of this review, we chose cardiovascular mortality at five years as the primary endpoint. We planned to include outcomes at longer follow-up periods as secondary outcomes if reported.

Dealing with missing data

We sought information about dropouts, withdrawals, and other missing data. If not reported, we attempted to contact the study authors.

Assessment of heterogeneity

The inclusion of studies on a wide range of medical treatments was likely to result in a high degree of heterogeneity. We therefore planned to assess the heterogeneity between pooled studies by using the Chi^2 test regarding the characteristics and quality of included studies (Deeks 2011).

We planned to perform the Chi^2 test to assess heterogeneity in identified subgroups, and we planned to use the I^2 statistic to measure the degree of inconsistency between studies. An I^2 statistic result of greater than 50% may represent moderate to substantial heterogeneity (Deeks 2011). Only one study met the inclusion criteria for the review and therefore it was not necessary to measure the heterogeneity between studies.

Assessment of reporting biases

We planned to assess reporting biases such as publication bias using funnel plots (Sterne 2011). As only one study met the inclusion criteria of this review, which was at a low risk of reporting bias, we did not perform this.

Data synthesis

Two review authors (LR, EA) independently extracted the data. One review author (LR) entered the data into Review Manager 5 (RevMan 5) (RevMan 2014). The second review author (EA) cross-checked data entry, and we resolved any discrepancies by consulting the source publication.

We used a fixed-effect model to meta-analyse the data.

Subgroup analysis and investigation of heterogeneity

Where possible, we planned to analyse clinically relevant subgroups based on drug and participant groupings including the following.

- Diameter of aneurysm.
- Type of repair (e.g. endovascular versus surgical).
- Type of repair (e.g. endovascular or surgical) versus no repair.
- Diabetes.
- Year of publication.

However, as only one study with 227 participants met the inclusion criteria, it was not possible to perform subgroup analyses.

Sensitivity analysis

We planned to conduct a sensitivity analysis by excluding studies at a high risk of bias to measure the effect on the results. However, as there was only one included study we were unable to conduct a sensitivity analysis.

'Summary of findings' table

We presented the main findings of the review results concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data for all-cause mortality, cardiovascular mortality, AAA-related death, and nonfatal cardiovascular events in a 'Summary of findings' table, according to the GRADE principles as described by Higgins 2011 and Atkins 2004. We used the GRADEprofiler Guideline Development Tool (GRADEpro GDT) software to assist in the preparation of the 'Summary of findings' table (GRADEpro GDT 2014).

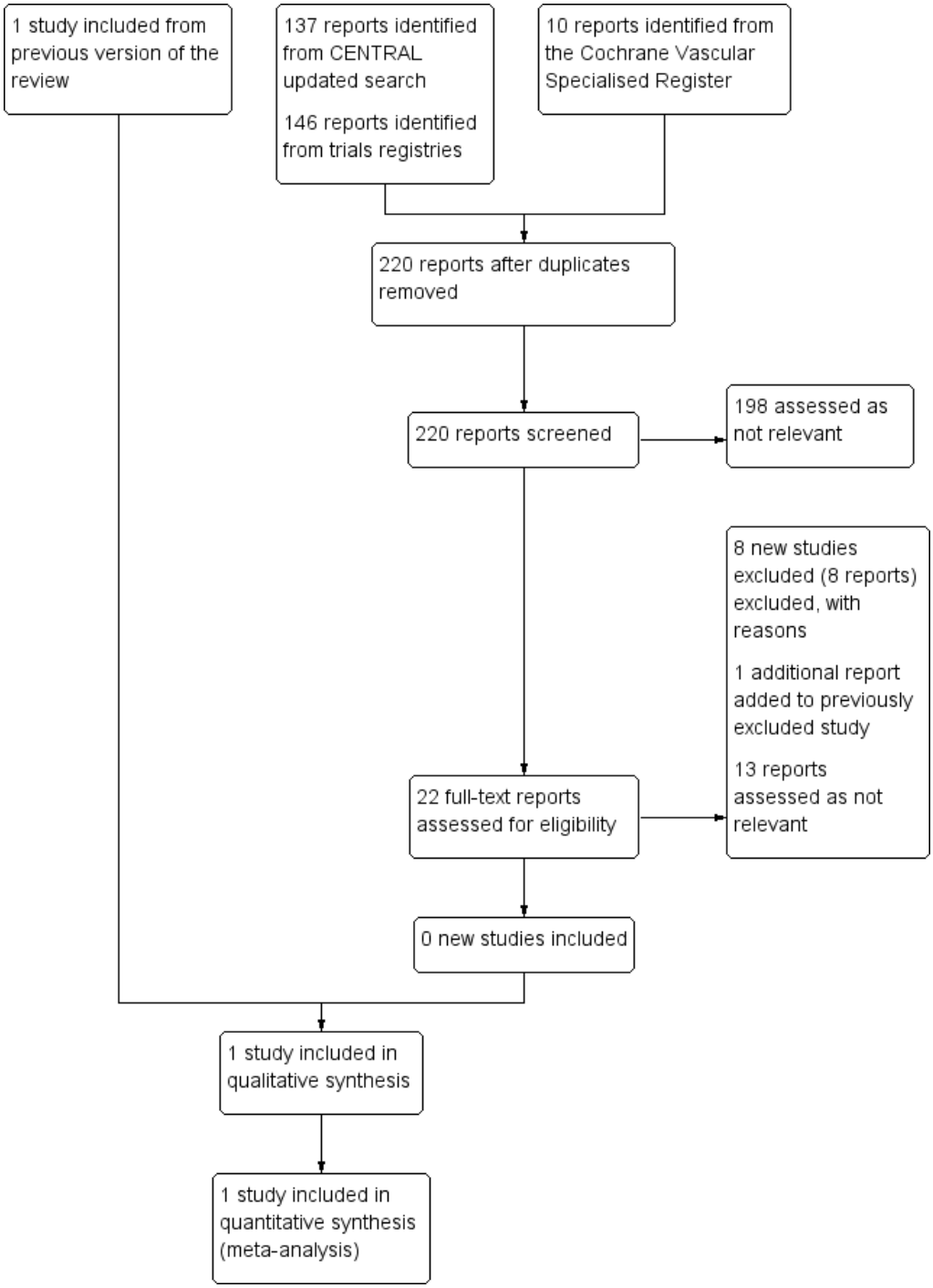
RESULTS

Description of studies

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



Included studies

See the 'Characteristics of included studies' table.
No new studies met the inclusion criteria for this update.
The review includes one study (Yang 2006). Yang 2006 is a double-blind, randomised, placebo-controlled trial that measured the effects of metoprolol on the incidence of cardiac complications at 30 days and six months after vascular surgery. The study included 496 participants who underwent procedures including abdominal aortic repair and infrainguinal or axillofemoral revascularisation. A subgroup of 227 participant had an abdominal aortic repair. Although the trial authors did not present outcome data for the abdominal aortic aneurysm (AAA) subgroup in the full report, we obtained these data through personal communication with the study author and statistician. Of the 227 AAA participants, 111 were randomised to metoprolol and 116 were randomised to a placebo. The doses of metoprolol were as follows: 100 mg in participants weighing $\geq$ 75 kg, 50 mg for participants weighing between 40 mg and 75 kg, and 25 mg for those weighing $\leq$ 40 kg. Beta-blocker therapy was commenced preoperatively on the day of surgery and continued for the duration of the hospital stay. Within two hours postsurgery, the study drug was administered orally or intravenously for 15 minutes (metoprolol 1 mg/mL or saline at 0.2 mL/kg, diluted with 20 mL of saline). Study medication was continued intravenously every six hours or orally twice a day for five days or until hospital discharge, whichever occurred sooner. Intravenous study drug was converted to oral as soon as the participant tolerated oral intake. The trial performed 30-day and six-month follow-ups by telephone for discharged participants. Yang 2006 defined the primary outcome as a composite of cardiac complications at 30 days postoperation including: cardiac death, non-fatal myocardial infarction (MI), congestive heart failure (CHF), unstable angina, and dysrhythmia requiring treatment, defined as atrial fibrillation or ventricular dysrhythmias. In the presence of more than one outcome, the first outcome was recorded. Secondary study outcomes included study drug discontinuation (due to bronchospasm, hypotension, or bradycardia), amputation, and intraoperative hypotension or bradycardia.

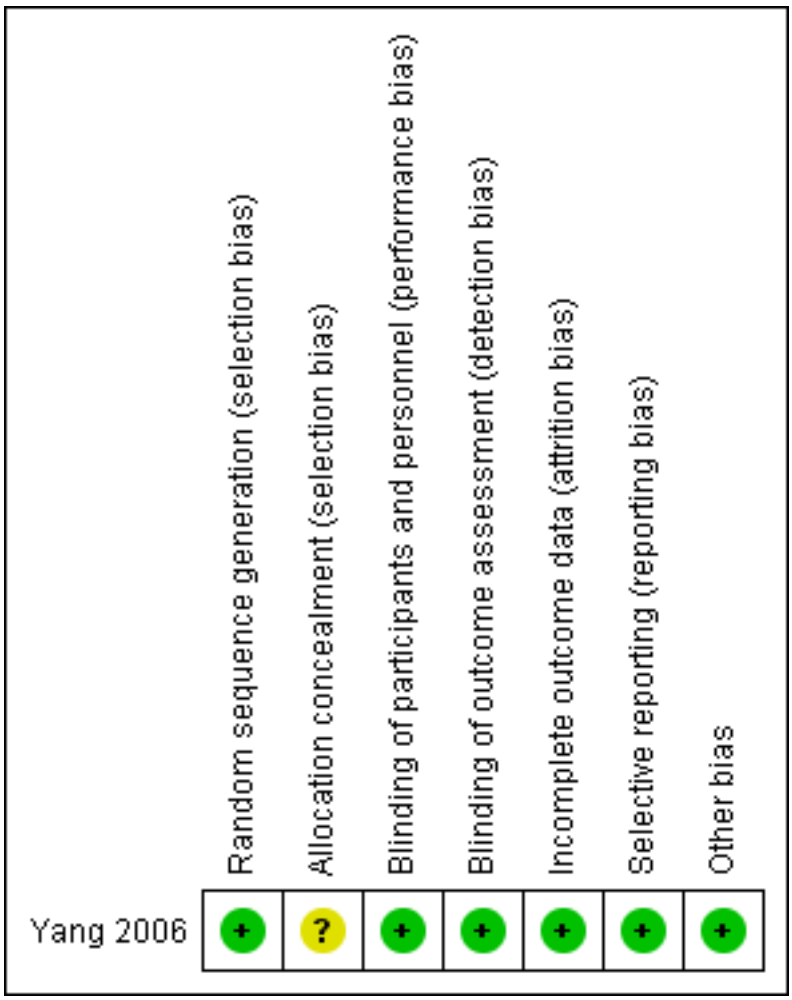
Excluded studies

See the 'Characteristics of excluded studies' table.
For this update we excluded seven completed studies (Ashes 2013; Berwanger 2015; Kouvelos 2011; Qu 2014; Schouten 2011; Xia 2014; Xia 2015), and one ongoing study (NCT01225094).
In total, we excluded 17 studies from the review (Ashes 2013; Berwanger 2015; Cesanek 2008; DECREASE Study; Durazzo 2004; Kouvelos 2011; Kouvelos 2013; Mackey 2006; Mangano 1996; NCT01225094; Neilipovitz 2012; POBBLE Trial; POISE Study; Qu 2014; Schouten 2011; Xia 2014; Xia 2015). Two studies, Durazzo 2004 and POBBLE Trial, had AAA subgroups but did not present specific outcome data for these participant. The author of one study, Durazzo 2004, confirmed through personal communication that these data were not available. We were unable to contact the authors of the POBBLE Trial. Ten studies did not report AAA subgroups (Ashes 2013; Berwanger 2015; Cesanek 2008; Kouvelos 2011; Mangano 1996; POISE Study; Qu 2014; Schouten 2011; Xia 2014; Xia 2015). Authors of the POISE Study confirmed that outcome data for AAA participants were not available, but the other nine study authors did not respond (Ashes 2013; Berwanger 2015; Cesanek 2008; Kouvelos 2011; Mangano 1996; Qu 2014; Schouten 2011; Xia 2014; Xia 2015). One study, Mackey 2006, was not a randomised controlled trial but a prospective study that measured the incidence of myocardial injury in vascular surgery patients. In two studies participants were taking co-medications and therefore we could not attribute the results to one particular drug (Kouvelos 2013; Neilipovitz 2012). We excluded the DECREASE Study as the integrity of the data was questionable. In a report released by Erasmus MC Follow-Up Committee in 2012, the principal investigator admitted that written informed consent was not obtained for every participant and that the data were collected in a negligent manner (Erasmus MC Follow-Up Committee 2012). Finally, one ongoing study tested the effects of curcumin, a natural health product (NCT01225094).

Risk of bias in included studies

See the 'Risk of bias' table in the 'Characteristics of included studies' section, and Figure 2.

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.



Allocation

A study statistician performed random sequence generation in blocks of four and therefore we judged the study to be at a low risk of selection bias. However, the study authors did not report the methods used to conceal allocation of treatment and therefore the risk of selection bias was unclear.

Blinding

All study participants, investigators, caretakers and data outcome evaluators of Yang 2006 were blinded to treatment. Furthermore, blinding was maintained throughout the study, even if study medication was discontinued.

Incomplete outcome data

The two treatment groups in Yang 2006 were well-balanced with respect to baseline characteristics, completion of the study protocol, and discontinuation of treatment. Furthermore, the study authors accounted for and reported on all missing data.

Selective reporting

The authors of Yang 2006 specified their hypothesis using results from previously published work. They clearly stated their primary and secondary outcomes and reported data on all outcomes.

Other potential sources of bias

We considered the Yang 2006 study to be at low risk of other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Metoprolol compared to placebo for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm

As only one study, Yang 2006, met the inclusion criteria, we were unable to pool data or perform a meta-analysis. Therefore, we reported the individual estimates from the study in a narrative synthesis. The included study did not measure mortality at five years but at two shorter time points of 30 days and six months postoperation. Results indicated no clear evidence that metoprolol reduced all-cause or cardiovascular mortality at 30 days: the incidence of all-cause mortality was 1/111 in the metoprolol group and 6/116 in the placebo group (odds ratio (OR) 0.17, 95% confidence interval (CI) 0.02 to 1.41) while the incidence of cardiovascular mortality at 30 days was 1/111 and 5/116 in the metoprolol and placebo groups respectively (OR 0.20, 95% CI 0.02 to 1.76). One participant in each treatment group died of causes related to AAA (OR 1.05, 95% CI 0.06 to 16.92). Nonfatal cardiovascular events occurred in 12/111 in the metoprolol group and 9/116 in the placebo group at 30 days (OR 1.44, 95% CI 0.58 to 3.57). At six months, metoprolol did not significantly reduce the rate of all-cause mortality (OR 0.71, 95% CI 0.26 to 1.95) or cardiovascular deaths (OR 0.73, 95% CI 0.23 to 2.39). The incidence of AAA-related death was not measured at six months. The incidence of nonfatal cardiovascular events was similar between the two treatment groups at six months (OR 1.41, 95% CI 0.59 to 3.35). For these outcomes, we downgraded the quality of the evidence to low. The quality of evidence was downgraded due to imprecision, as only one study with a small number of participants met the inclusion criteria, the number of events was low, and the result was consistent with benefit and harm. No participant had to undergo an amputation. Quality of life was not reported.

Yang 2006 reported on adverse events in the form of study drug discontinuation (due to bronchospasm, hypotension, or bradycardia) and intraoperative hypotension or bradycardia. However, data on study drug discontinuation and the incidence of intraoperative hypotension or bradycardia were not available for the subgroup of AAA participants. In the overall study of 496 participants, the study authors reported that the incidence of intraoperative complications was significantly higher in the metoprolol group ($P < 0.01$). Hypotension occurred in 54% of metoprolol participants (46% required treatment) compared to 41% of placebo participants (34% required treatment). Bradycardia occurred in 35% and 10% of metoprolol and placebo participants, respectively, of whom 22% and 7% required treatment. However, given that these outcomes are based on a population of participants who had undergone vascular surgery for other conditions, we cannot generalise the results to participants with AAA.

DISCUSSION

Summary of main results

Only one study fulfilled the inclusion criteria of this review. The study was a randomised controlled trial in which 496 participants undergoing non-cardiac vascular surgery received either metoprolol or placebo (Yang 2006). We received data on a subgroup of 227 participants who underwent AAA repair from the study author. Results of the study indicate that metoprolol is not associated with a reduction in the rate of all-cause or cardiovascular mortality at either 30 days or six months. No participant had to undergo an amputation. Quality of life was not reported. Adverse drug effects were reported for the whole study population and were not available for the subgroup of participants with AAA. We downgraded the quality of the evidence due to imprecision, as only one study with a small number of participants met the inclusion criteria, the number of events was low, and the result was consistent with benefit and harm.

Overall completeness and applicability of evidence

Currently, there is a severe lack of evidence concerning the effectiveness of pharmacological prophylaxis in the prevention of cardiovascular events in AAA patients. The one included study was relatively small and tested one beta-blocker against a placebo at 30 days and six months follow-up. Therefore, the results of this study are not widely applicable to the AAA population and the follow-up period was relatively short to study mortality and cardiovascular events in such participants. Recent evidence has questioned whether beta-blockers are of any perioperative value and suggests they may be harmful (Bolsin 2013). As there are many different drugs available, it is important to test these drugs, not just against a placebo but also against each other. Furthermore, it is important to establish if a combination of drugs would yield a better outcome than one drug alone.

Quality of the evidence

The quality of reporting in the single included study was good. With the exception of failing to report the methods used to conceal allocation of treatments, the study authors provided adequate information on the process of randomisation and blinding. As such, we deemed the study to be at a low risk of selection, performance, and detection bias. Additionally, the study authors accounted for all missing data and reported data on all primary and secondary outcomes, and therefore minimised the chances of attrition and performance bias. For all outcomes, we downgraded the quality of the evidence to low. We downgraded the quality of evidence for imprecision, as there was only one included study with a small

number of participants, the number of events was small, and the confidence intervals (CI) indicated both benefit and harm.

Potential biases in the review process

We, the authors of this Cochane review, were neither involved in the included study nor in any of the excluded studies. Furthermore, we do not have any commercial or other conflict of interest. The search was as comprehensive as possible and two review authors independently assessed all studies for inclusion. We are confident that we have included all relevant studies and attempted to reduce bias in the review process. However, the possibility remains that we may have missed studies that have not been published.

Agreements and disagreements with other studies or reviews

This is an update of a Cochrane review first published in 2014 and the first systematic review to measure the effectiveness of pharmacological prophylaxis in reducing cardiovascular morbidity and mortality in AAA patients. One prospective study of AAA participants who were followed up over a median of 4.7 years determined that, in those who survived AAA repair, beta-blocker use was associated with a significantly lower incidence of all-cause mortality (hazard ratio (HR) 0.6, 95% CI 0.5 to 0.9) and cardiovascular mortality (HR 0.7, 95% CI 0.4 to 0.9) (Kertai 2004). After adjusting for clinical risk factors and beta-blocker use, the same study showed that long-term use of statins showed a reduction in both all-cause and cardiovascular mortality (HR 0.4, 95% CI 0.3 to 0.6; and HR 0.3, 95% CI 0.2 to 0.6 respectively). Therefore, it would appear that statins reduce cardiovascular risk regardless of beta-blocker use. However, this was a prospective cohort study with no randomisation and therefore likely to be at high risk of bias.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the one study that met the inclusion criteria of this Cochrane review, there is insufficient evidence to draw any conclusions about the effectiveness of cardiovascular prophylaxis in reducing mortality and cardiovascular events in people with AAA. Although the study was of low risk of bias, we downgraded the quality of the evidence for imprecision, as only one study with a small number of participants was available, the number of events was small, and the result was consistent with benefit and harm. Further good-quality randomised controlled trials are required. There are a wide range of prophylactic treatments for AAA patients that need to be tested for effectiveness and other outcomes, such as adverse side effects and quality of life. They also need to be tested at long-term endpoints, such as five years or greater. The introduction of AAA screening programmes in the UK has provided a valuable tool to identify patients with AAA and therefore potentially modify risk factors in those at high cardiovascular risk. However, until adequate evidence regarding the efficacy and acceptability of interventions is available, definitive conclusions cannot be made.

Implications for research

The results of this systematic review confirm the need for large randomised controlled trials with longer follow-up (five years or greater) to determine the effectiveness of pharmacological prophylaxis in preventing mortality and cardiovascular events in AAA patients. At present, patients with AAA are offered a wide range of pharmacological prophylaxes including antiplatelet drugs, antihypertensives, and lipid-lowering drugs. Future research should test the available drugs to find the most effective strategy, whether that be one drug alone or a combination of treatments. Moreover, the acceptability of such interventions needs to be assessed. Thus, any future studies should also analyse the secondary effects of such interventions, including adverse side effects and quality of life.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Yang 2006

Methods	Study type: double-blind randomised controlled trial Study aim: to test the hypothesis that, at 30 days and 6 months after vascular surgery, the perioperative administration of metoprolol reduces the incidence of cardiac complications defined as cardiac death, nonfatal myocardial infarction (MI), congestive heart failure (CHF), unstable angina, and dysrhythmias requiring treatment Country: Canada Setting: 3 tertiary care centres: General Campus, Hamilton Health Sciences; Victoria Campus, London Health Sciences; and Kingston General Hospital between 1999 and 2002 Recruitment: all patients undergoing vascular surgery were screened for eligibility. Elective vascular surgical patients are evaluated by internists, cardiologists, or anaesthesiologists in preoperative clinics. Screening was also undertaken on the wards when applicable
Participants	Inclusion criteria: patients with American Society of Anesthesiology class 3 or less and undergoing abdominal aortic surgery and infrainguinal or axillofemoral revascularisation Exclusion criteria: current or recent β-blocker use, current amiodarone use, airflow obstruction requiring treatment, history of CHF, history of atrioventricular block, previous adverse drug reactions to β-blockers, and previous participation in the MaVS study Gender: placebo group 184 M/66 F; metoprolol group 193 M/53 F Age: placebo participants mean 65.9 ± 10.0 years; metoprolol participants mean 66.4 ± 10.0 years Co-morbidities: Prior MI: 30 placebo, 37 metoprolol Angina: 25 placebo, 18 metoprolol Diabetes mellitus on treatment: 37 placebo, 54 metoprolol Permanent pacemaker: 1 placebo, 0 metoprolol AAA subgroup: 116 placebo, 111 metoprolol
Interventions	Treatment: metoprolol administered orally or intravenously. Participants weighing ≥ 75 kg received metoprolol 100 mg; participants weighing between 40 and 75 kg received metoprolol 50 mg; and participants weighing ≤ 40 kg received metoprolol 25 mg OR intravenously at 1 mg/mL for 15 minutes. Intravenous (IV) treatment was converted to oral as soon as oral intake was tolerated Control: placebo administered orally as tablet or given intravenously as saline 0.2 mL/kg (to a maximum of 15 mL), diluted with 20 mL of saline for 15 minutes Duration: metoprolol or placebo given orally 2 hours preoperatively. Within 2 hours of surgery, metoprolol or placebo were give intravenously or orally. IV drug administered over 15 minutes every 6 hours. Oral administration was twice daily. Treatment lasted for 5 days or until hospital discharge, whichever occurred sooner Co-interventions: short-acting vasoactive medications including phenylephrine, ephedrine, nitroglycerine, and low-dose dopamine were allowed. Open-label β-blocker use was strongly discouraged except when deemed absolutely necessary by the attending physician. Circumstances for open-label use were generally for rapid heart rate control. Intraoperatively, esmolol, if deemed absolutely necessary, was allowed

Outcomes	Primary outcome: composite of cardiac complications at 30 days postoperation including; cardiac death[1], nonfatal MI[2], CHF[3], unstable angina[4], and dysrhythmia requiring treatment defined as atrial fibrillation or ventricular dysrhythmias[5] [1]Cardiac death was defined as either the ultimate cause of death traceable to an initiating cardiac complication or death in which the cause was not clearly identifiable or was insufficient to account for the demise in a patient who was not expected to succumb at the time of death [2]Nonfatal MI within 3 postoperative deaths diagnosed if ≥ 1 of the following present: chemical evidence of MI or new Q waves > 0.04 s on 2 contiguous leads. Beyond 3 days, nonfatal MI was determined by attending physicians with supporting documentation of hospital chart, troponins, and pre- and postoperative electrocardiograms [3]Unstable angina diagnosed by attending physician when anginal symptoms necessitated a change in medications, coronary revascularisation, or intensive care admission [4]CHF was diagnosed clinically with the requisite radiographic evidence [5]Dysrhythmia requiring treatment was defined as one of the following: ventricular fibrillation requiring counter shock, ventricular tachycardia requiring counter shock or medication, or atrial fibrillation > 15 minutes in duration requiring counter shock or medication Secondary outcomes: • Study drug discontinuation due to bronchospasm, advanced heart blocks, hypotension (systolic blood pressure < 90 mmHg) or bradycardia (50 beats/min). • Reoperation or amputation. • Intraoperative hypotension and bradycardia requiring treatment by the attending anaesthesiologists.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was constructed in blocks of 4 by the study statistician"
Allocation concealment (selection bias)	Unclear risk	Comment: Methods of concealment of allocation are not stated. Insufficient information to permit judgement of low or high risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients, investigators, and all caretakers were blinded to the study randomisation. Blinding of randomisation was maintained throughout clinical decisions on reducing or discontinuing the study medication"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All data were collected by the participating centres and evaluated by the adjudication committee in a blinded fashion"

Yang 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Completion of the study protocol was similar in the placebo (77.6%) and treatment groups (75.2%). Discontinuation of the study protocol was also similar in the placebo and treatment groups; primary outcome event (30 and 25,respectively); patient/family/physician preference (27 and 14, respectively); open-label β-blockers (24 and 14, respectively); patient death (3 and 0, respectively), atrioventricular block (2 and 3, respectively), bronchospasm (1 and 4, respectively); and other reason (11 and 13, respectively)." Comment: All missing data accounted for and similarly balanced across the two treatment groups. Low risk of attrition bias
Selective reporting (reporting bias)	Low risk	Quote: "Our results show that the RRR achieved with perioperative metoprolol in the vascular population is smaller than previously reported and is not significant" Comment: Authors commented on study results in relation to expected outcomes from other published reports. Furthermore, all of the primary and secondary prespecified outcomes were reported
Other bias	Low risk	The study appears to be free from other sources of bias

Abbreviations: CHF: congestive heart failure; IV: intravenous; MI: myocardial infarction; RRR: relative risk reduction

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

Study	Reason for exclusion
Ashes 2013	The study did not report if there was a subgroup of participants with abdominal aortic aneurysm (AAA). We attempted to contact the study author to see if these data were available but we could not make contact
Berwanger 2015	The study authors reported that 6.6% of participants had undergone vascular surgery but it did not report the number, if any, with AAA. We attempted to contact the study author to see if these data were available but we could not make contact

(*Continued*)

Cesanek 2008	This study examined beta-blocker-related complications in patients undergoing vascular surgery. We contacted the study authors for outcome data for AAA participants but they did not respond to communication
DECREASE Study	The principal investigator of the DECREASE Study was dismissed for misconduct including failing to obtain patient written informed consent and negligent data collection. A full copy of the report issued by the Erasmum Medical Centre can be found here: Erasmus MC Follow-Up Committee 2012
Durazzo 2004	A subgroup of 56 participants underwent a AAA repair but specific outcome data for these participants were not presented. Through personal communication, the study author confirmed that these data were not available
Kouvelos 2011	The study did not report if there was a subgroup of participants with AAA. We attempted to contact the study author to see if these data were available but we could not make contact
Kouvelos 2013	Of the 262 participants studied, 66% were taking antiplatelets, 19% anticoagulants, 23% calcium antagonists, 33% angiotensin-converting enzyme (ACE) inhibitors and 15% were taking angiotensin II receptors prior to randomisation. Outcomes in this study could not be attributed to one specific drug and therefore we excluded this study
Mackey 2006	Prospective study that measured the incidence of perioperative myocardial ischaemic injury in high-risk vascular surgery patients. It was not a randomised controlled trial and it did not administer drugs
Mangano 1996	The study did not report if there was a subgroup of participants with AAA. We attempted to contact the study author to see if these were available but we could not make contact
NCT01225094	Intervention is curcumin, which is a natural health product
Neilipovitz 2012	Patients in this study were taking co-medications (angiotensin drugs, calcium channel blockers, beta blockers, acetylsalicylic acid, clopidogrel) that we planned to assess in this review. Outcomes in this study could not be attributed to one specific drug and therefore we excluded this study
POBBLE Trial	Of the 103 participants included in this study, 38% underwent aortic repair. However the study did not present outcome data for this subgroup. We attempted to retrieve these data but the study authors did not respond to our communication
POISE Study	Following personal communication, the study author confirmed that data for the AAA participants were not available
Qu 2014	The study did not report if there was a subgroup of participants with AAA. We attempted to contact the study author to see if the data were available but we could not make contact
Schouten 2011	The study did not report if there was a subgroup of participants with AAA. We attempted to contact the study author to see if the data were available but we could not make contact
Xia 2014	The study did not report if there was a subgroup of participants with AAA. We attempted to contact the study author to see if the data were available but we could not make contact
Xia 2015	The study did not report if there was a subgroup of participants with AAA. We attempted to contact the study author to see if the data were available but we could not make contact

Abbreviations: AAA: abdominal aortic aneurysm; ACE: angiotensin-converting enzyme.

DATA AND ANALYSES

Comparison 1. Metoprolol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality, 30 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Cardiovascular death, 30 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 AAA-related death, 30 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Nonfatal cardiovascular event, 30 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 All-cause mortality, 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Cardiovascular death, 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Nonfatal cardiovascular event, 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Metoprolol versus placebo, Outcome 1 All-cause mortality, 30 days.

Review: Pharmacological treatment of vascular risk factors for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm

Comparison: 1 Metoprolol versus placebo

Outcome: 1 All-cause mortality, 30 days

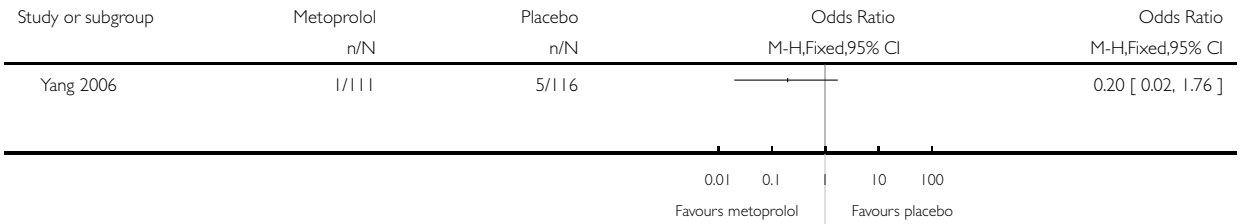
Study or subgroup	Metoprolol n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Yang 2006	1/111	6/116		0.17 [0.02, 1.41]

Analysis 1.2. Comparison 1 Metoprolol versus placebo, Outcome 2 Cardiovascular death, 30 days.

Review: Pharmacological treatment of vascular risk factors for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm

Comparison: 1 Metoprolol versus placebo

Outcome: 2 Cardiovascular death, 30 days

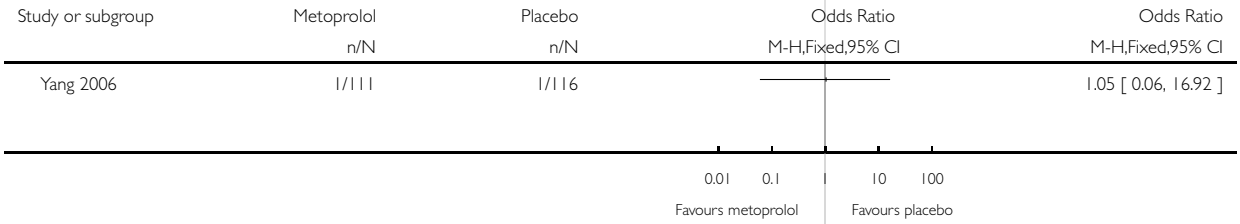


Analysis 1.3. Comparison 1 Metoprolol versus placebo, Outcome 3 AAA-related death, 30 days.

Review: Pharmacological treatment of vascular risk factors for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm

Comparison: 1 Metoprolol versus placebo

Outcome: 3 AAA-related death, 30 days

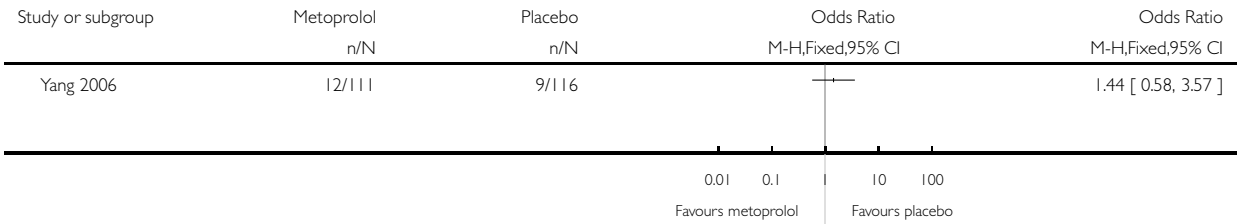


Analysis 1.4. Comparison 1 Metoprolol versus placebo, Outcome 4 Nonfatal cardiovascular event, 30 days.

Review: Pharmacological treatment of vascular risk factors for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm

Comparison: 1 Metoprolol versus placebo

Outcome: 4 Nonfatal cardiovascular event, 30 days

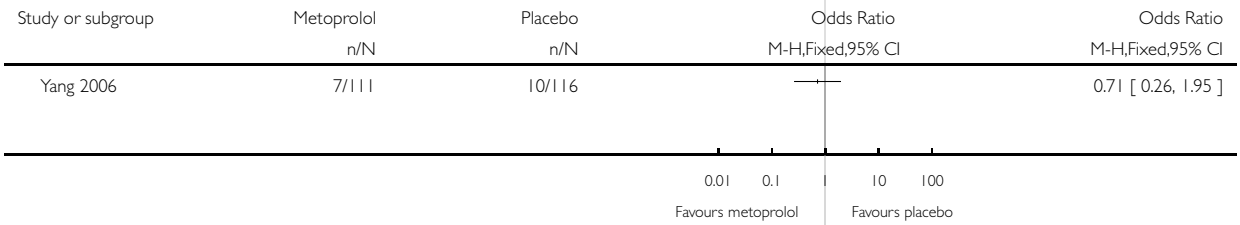


Analysis 1.5. Comparison 1 Metoprolol versus placebo, Outcome 5 All-cause mortality, 6 months.

Review: Pharmacological treatment of vascular risk factors for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm

Comparison: 1 Metoprolol versus placebo

Outcome: 5 All-cause mortality, 6 months



Analysis 1.6. Comparison 1 Metoprolol versus placebo, Outcome 6 Cardiovascular death, 6 months.

Review: Pharmacological treatment of vascular risk factors for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm

Comparison: 1 Metoprolol versus placebo

Outcome: 6 Cardiovascular death, 6 months

Study or subgroup	Metoprolol n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Yang 2006	5/111	7/116		0.73 [0.23, 2.39]

Analysis 1.7. Comparison 1 Metoprolol versus placebo, Outcome 7 Nonfatal cardiovascular event, 6 months.

Review: Pharmacological treatment of vascular risk factors for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm

Comparison: 1 Metoprolol versus placebo

Outcome: 7 Nonfatal cardiovascular event, 6 months

Study or subgroup	Metoprolol n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Yang 2006	13/111	10/116		1.41 [0.59, 3.35]

APPENDICES

Appendix 1. CENTRAL search strategy

#1	MESH DESCRIPTOR Aortic Aneurysm EXPLODE ALL TREES	559
#2	((aort* near3 (balloon* or dilat* or bulg* or rupture or expan*))):TI,AB,KY	438
#3	(aneury* near3 (abdominal or thoraco*)):TI,AB,KY	460
#4	AAA*:TI,AB,KY	693
#5	MESH DESCRIPTOR Vascular Surgical Procedures	523
#6	(vascular near3 surg*):TI,AB,KY	1408
#7	(infrarenal near3 surg*):TI,AB,KY	30
#8	(noncardiac near3 surg*):TI,AB,KY	175
#9	(non-cardiac near3 surg*):TI,AB,KY	122
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	2969
#11	indobufen	81
#12	MESH DESCRIPTOR Platelet Aggregation Inhibitors EXPLODE ALL TREES	8224
#13	MESH DESCRIPTOR Phosphodiesterase Inhibitors EXPLODE ALL TREES	5416
#14	MESH DESCRIPTOR Tetrazoles	1790
#15	(antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg*) :TI,AB,KY	2881
#16	(((platelet or thromboxane or thrombocyte or cyclooxygenase or cyclo-oxygenase or phosphodiesterase or fibrinogen or PAR-1) near3 (antagonist or inhibitor))):TI,AB,KY	2178
#17	((gp* or glycoprotein* or protease or P2Y12 or TXA2) near3 inhibit*):TI,AB,KY	2957
#18	thienopyridine:TI,AB,KY	230

(*Continued*)

#19	(ticlopidine or Ticlid):TI,AB,KY	1665
#20	(clopidogrel or Plavix):TI,AB,KY	2634
#21	(Prasugrel or Effient or Efient or Prasita):TI,AB,KY	374
#22	(ticagrelor or AZD6140 or Brilinta):TI,AB,KY	278
#23	(elinogrel or PRT060128 or PRT-060128):TI,AB,KY	8
#24	(cangrelor or AR-C6993* or ARC6993*):TI,AB,KY	40
#25	(SCH530348 or SCH-530348):TI,AB,KY	16
#26	E5555:TI,AB,KY	5
#27	(terutroban or Triplion):TI,AB,KY	14
#28	(aspirin* or nitroaspirin or ASA):TI,AB,KY	16259
#29	(acetylsalicylic acid):TI,AB,KY	4352
#30	(acetyl salicylic acid*):TI,AB,KY	102
#31	(triflusal or disgren):TI,AB,KY	95
#32	(Cilostazol or Pletal or Pletaal):TI,AB,KY	436
#33	(dipyridamol* or Persantine):TI,AB,KY	1103
#34	(OPC-13013 or OPC13013):TI,AB,KY	5
#35	(picotamide or picotinamide):TI,AB,KY	41
#36	satigrel:TI,AB,KY	3
#37	vorapaxar:TI,AB,KY	63
#38	indobufen:TI,AB,KY	81
#39	MESH DESCRIPTOR Antihypertensive Agents EXPLODE ALL TREES	22578
#40	MESH DESCRIPTOR Adrenergic beta-Antagonists EXPLODE ALL TREES	9426

(*Continued*)

#41	MESH DESCRIPTOR Angiotensin-Converting Enzyme Inhibitors EXPLODE ALL TREES	5527
#42	MESH DESCRIPTOR Diuretics EXPLODE ALL TREES	5678
#43	MESH DESCRIPTOR Calcium Channel Blockers EXPLODE ALL TREES	7947
#44	(antihypertensi* or anti-hypertensi*):TI,AB,KY	13540
#45	(calcium near3 (antag* or block*)):TI,AB,KY	6255
#46	(amlodipin* or diltiazem or diltiazam or felodipin*):TI,AB,KY	4362
#47	(nicardipin* or nifedipin* or nimodipin*):TI,AB,KY	4603
#48	(nisoldipin* or nitrendipin* or verapamil):TI,AB,KY	2736
#49	diureti*:TI,AB,KY	6368
#50	(angiotensin near3 inhibitor*):TI,AB,KY	5765
#51	(alacepril or altiopril or benazepril or captopril or ceronapril or cilazapril or delapril or derapril):TI,AB,KY	2804
#52	(enalapril or fosinopril or idapril or imidapril or lisinopril):TI,AB,KY	3648
#53	(moexipril or moveltipril or pentopril):TI,AB,KY	38
#54	(perindopril or quinapril):TI,AB,KY	1045
#55	(ramipril or spirapril or temocapril or trandolapril or zofenopril):TI,AB,KY	1351
#56	(ACE next inhibitor*):TI,AB,KY	2565
#57	(adrenergic near3 (antagonist* or block*)):TI,AB,KY	8604
#58	(betablocker* or beta-blocker*):TI,AB,KY	4445
#59	(acebutolol or atenolol or Tenormin):TI,AB,KY	3213
#60	(alprenolol or betaxolol or bisoprolol or bupranolol):TI,AB,KY	1153
#61	(carvedilol or Coreg or carteolol or celiprolol):TI,AB,KY	1218

(*Continued*)

#62	(esmolol or labetalol):TI,AB,KY	1068
#63	(metoprolol or nadolol or nebivolol):TI,AB,KY	3101
#64	(oxprenolol or penbutolol or pindolol):TI,AB,KY	1239
#65	(practolol or propranolol or timolol):TI,AB,KY	6192
#66	*artan:TI,AB,KY	4870
#67	*sartan:TI,AB,KY	4854
#68	*dipine:TI,AB,KY	8436
#69	*olol:TI,AB,KY	13831
#70	*alol:TI,AB,KY	1150
#71	(bumetanide or ethacrynic acid or furosemide or torsemide): TI,AB,KY	1967
#72	*thiazide:TI,AB,KY	4110
#73	epitizide:TI,AB,KY	2
#74	(indapamide or chlorthalidone or metolazone):TI,AB,KY	1055
#75	(amiloride or triamterene or spironolactone):TI,AB,KY	1768
#76	MESH DESCRIPTOR Anticholesteremic Agents EXPLODE ALL TREES	5458
#77	*statin:TI,AB,KY	11508
#78	meglutol:TI,AB,KY	2
#79	mevacor:TI,AB,KY	9
#80	pravachol:TI,AB,KY	5
#81	lescol:TI,AB,KY	47
#82	lipitor*:TI,AB,KY	23
#83	cholestyramine:TI,AB,KY	392
#84	(lipid next lowering):TI,AB,KY	2280

(*Continued*)

#85	(cholesterol next lowering):TI,AB,KY	1182
#86	colestipol:TI,AB,KY	152
#87	gemfibrozil:TI,AB,KY	461
#88	clofibrate:TI,AB,KY	314
#89	(nicotinic NEXT acid):TI,AB,KY	513
#90	ezetimibe:TI,AB,KY	698
#91	MESH DESCRIPTOR Fish Oils EXPLODE ALL TREES	2431
#92	MESH DESCRIPTOR Fatty Acids, Omega-3 EXPLODE ALL TREES	2153
#93	(fatty next acid*):TI,AB,KY	10298
#94	(omega near2 acid*):TI,AB,KY	1840
#95	(*eicosapentanoic or docosahexanoic or docosapentanoic or alpha-linolenic):TI,AB,KY	424
#96	(*eicosapentaen* or icosapentaenoic or docosahexaeno*):TI,AB,KY	2165
#97	(fish near2 oil*):TI,AB,KY	1698
#98	(cod near2 oil):TI,AB,KY	58
#99	MESH DESCRIPTOR Antioxidants EXPLODE ALL TREES	11258
#100	(antioxidant* or anti-oxidant*):TI,AB,KY	6756
#101	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100	114007

(*Continued*)

#102	#10 and #101	522
#103	30/04/2013 TO 29/02/2016:DL	245401
#104	#102 AND #103	137

Appendix 2. Trials registries seaches

World Health Organization International Clinical Trials Registry Platform

27 new records found for abdominal aneurysm

ClinicalTrials.gov

109 new studies found for abdominal aneurysm

ISRCTN Register

10 new results for abdominal aneurysm

WHAT'S NEW

Date	Event	Description
14 October 2016	New citation required but conclusions have not changed	Search rerun. No new studies included, eight new studies excluded. A 'Summary of findings' table was added. No change to conclusions
14 October 2016	New search has been performed	Search rerun. No new studies included, eight new studies excluded

CONTRIBUTIONS OF AUTHORS

LR drafted the protocol, selected studies for inclusion, assessed the quality of studies, performed data analyses, and wrote and updated the review.

EA contributed to the protocol, selected studies for inclusion, assessed the quality of studies, and contributed to the text of the review and review update.

GS contributed to the protocol and the text of the review and review update.

DECLARATIONS OF INTEREST

LR: none known

EA: none known

GS: none known

SOURCES OF SUPPORT

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External sources

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INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [therapeutic use]; Aortic Aneurysm, Abdominal [*complications; mortality]; Cardiovascular Agents [*therapeutic use]; Cardiovascular Diseases [mortality; *prevention & control]; Cause of Death; Metoprolol [*therapeutic use]; Randomized Controlled Trials as Topic; Risk Factors

MeSH check words

Humans