National Institute for Health and Care Excellence

Final

Abdominal aortic aneurysm: diagnosis and management

Evidence review E: Non-surgical interventions for slowing aneurysm growth and reducing the risk of rupture

NICE guideline NG156

Methods, evidence and recommendations

March 2020

Final

This evidence review was developed by the NICE Guideline Updates Team

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN: 978-1-4731-3452-2

Contents

Non-surgical interventions for slowing aneurysm growth and reducing the risk of rupture

Review question

Which non-surgical interventions (including drug treatment and risk factor management) are effective in slowing aneurysm expansion and reducing the risk of rupture?

Introduction

This review question aims to determine the effectiveness of nonsurgical interventions (including antiplatelet, antihypertensive, lipid-lowering medication, antibiotics and lifestyle interventions) in slowing abdominal aortic aneurysm (AAA) expansion and reducing the risk of rupture.

PICO table

Table 1: Inclusion criteria

Parameter	Inclusion criteria
Population	People with a confirmed AAA >3cm in diameter who have not undergone aortic surgery
Interventions	Antiplatelet therapy (aspirin, clopidogrel, ticlopidine, cilostazol, prasugrel, ticagrelor, or any other antiplatelet drugs) Anticoagulant drugs (heparin, warfarin, NOACs (dabigatran, rivaroxaban, apixaban)) Antihypertensive drugs (calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers (β-blockers; e.g. metoprolol, propranolol), angiotensin-II receptor antagonists, thiazide/ thiazide-like diuretics, or any other antihypertensive drugs) Lipid-lowering therapy (statins) Antibiotics (doxycycline, roxithromycin, azithromycin) Diabetic control, including metformin COPD control Smoking cessation Physical therapy/exercise Diet Weight control Control of alcohol consumption
Comparators	Placebo, no intervention or each other
Outcomes	AAA rupture AAA growth/expansion Surgery/referral for surgery Mortality (all-cause; cardiovascular (e.g. fatal myocardial infarction, fatal stroke, other vascular deaths; AAA-related); survival Nonfatal cardiovascular events (e.g. nonfatal myocardial infarction, nonfatal stroke, or transient ischaemic attack (TIA)) Major amputation

Parameter	Inclusion criteria
	Quality of life Adverse effects Resource use and cost

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in Appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

A Cochrane systematic review (Rughani et al. 2012) assessing medical treatment for small AAA (5.5 cm in diameter or smaller) was used as a source of randomised controlled trials (RCTs) relevant to this review question. The review was chosen since its broad inclusion criteria (any type, method, duration, timing, mode of delivery and dose of medical treatment) would have covered interventions of interest in this NICE review. Since the systematic review was published in 2012, the NICE Guideline Updates Team performed literature searches to identify RCTs published after the systematic review. Data were extracted from the systematic review, individual RCTs within it, and RCTs identified from update literature searches to compare and evaluate the efficacy of non-surgical interventions for slowing aneurysm expansion or reducing the rate of rupture. Although RCTs were judged to be the optimal study design for this question, quasi-randomised controlled trials were also considered for inclusion.

Studies were excluded if they:

- were not in English
- were not full reports of the study (for example, published only as an abstract)
- were not peer-reviewed.

Clinical evidence

Included studies

The 2012 Cochrane systematic review included 7 RCTs (reported across multiple publications) out of 1,614 records identified from initial literature searches. One RCT included in the Cochrane review was not a full report; it was published as a conference abstract with no other data publically available. Thus it was excluded from this NICE review.

The update literature search performed by NICE in December 2017 found 916 abstracts, of which 17 were ordered. Of the 17 full manuscripts reviewed, 3 studies were considered relevant to this review question.

Overall, 9 RCTs (6 from the Cochrane review, and 3 from the update searches) were included.

Excluded studies

The list of papers excluded at full-text review, with reasons, is given in Appendix H.

Summary of clinical studies included in the evidence review

A summary of the included studies is provided in the tables below.

Table 2: Cochrane systematic review

Study	Details
Rughani G, Robertson L, and Clarke M (2012) Medical treatment for small abdominal aortic aneurysms. The Cochrane database of systematic reviews (9), CD009536	Study design: systematic review Location: UK Population: people of any age with an asymptomatic AAA <5.5 in the maximum external antero-posterior diameter Sample size: 6 RCTs including 1,063 participants Follow-up: up to 5.3 years Interventions: antibiotics and propranolol Comparators: placebo Outcomes: AAA expansion rates, proportion of patients referred for aneurysm surgery, mortality, and adverse events.

Individual studies within the systematic review

Table 3: Antibiotics

Study	Details
Høgh A, Vammen S, Ostergaard L, et al. (2009) Intermittent roxithromycin for preventing progression of small abdominal aortic aneurysms: long-term results of a small clinical trial. Vasc Endovascular Surg;43(5):452-6	Study design: multicentre, double blind, randomised controlled trial Location: Denmark Population: men with AAAs ≥3.0 cm and <5.0 cm in diameter Sample size: 84 Follow-up: 5.27 years Intervention: roxithromycin Comparators: placebo Outcomes: mean annual rate of aneurysm expansion (average change in anteroposterior diameter), and the number of patients referred for surgery when AAA diameter exceeded 5.0 cm
Karlsson L, Gnarpe J, Bergqvist D, et al. (2009). The effect of azithromycin and Chlamydophilia pneumonia infection on expansion of small abdominal aortic aneurysms--a prospective randomized double-blind trial. J Vasc Surg. 2009 Jul;50(1):23-9	Study design: multicentre, double-blind, randomised controlled trial Location: Sweden Population: people ≤80 years with AAAs ≥3.5 cm and ≤4.9 cm in diameter Sample size: 247 Follow-up: up to 3 years Intervention: azithromycin Comparators: placebo Outcomes: mean annual rate of aneurysm expansion (average change in anteroposterior diameter), and change in aneurysmal volume
Mosorin M, Juvonen J, Biancari F, et al. (2001)Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind,	Study design: multicentre, double-blind, randomised controlled trial Location: Finland

Study	Details
placebo-controlled pilot study. J Vasc Surg. 34(4):606-10	Population: people with AAAs ≥3.0 cm in diameter, or a ratio of infrarenal to suprarenal aortic diameter of 1.2 cm or more Sample size: 34 Follow-up: median of 18 months Intervention: doxycycline Comparators: placebo Outcomes: expansion rate (median change in anterior-posterior diameter), and the number of patients who had AAA rupture or repair
Vammen S, Lindholt JS, Ostergaard L, et al. (2001) Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion. Br J Surg. 88(8):1066-72	Study design: multicentre, double-blind, randomised controlled trial Location: Denmark Population: people with asymptomatic AAA ≥3.0 cm in diameter Sample size: 92 Follow-up: mean of 1.5 years Intervention: roxithromycin Comparators: placebo Outcomes: mean annual rate of aneurysm expansion (average change in anteroposterior diameter), and the number of patients referred for surgery when AAA diameter exceeded 5.0 cm, mortality and adverse events

Table 4: Propranolol

Study	Details
Lindholt JS, Henneberg EW, Juul S, et al. (1999) Impaired results of a randomised double blinded clinical trial of propranolol versus placebo on the expansion rate of small abdominal aortic aneurysms. Int Angiol. 1999 Mar;18(1):52-7	Study design: multicentre, double-blind, randomised controlled trial Location: Denmark Population: men with AAAs ≥3.0 cm and <5.0 cm in diameter Sample size: 54 Follow-up: up to 2 years Intervention: Propranolol Comparators: Placebo Outcomes: mean annual rate of aneurysm expansion (average change in anteroposterior diameter), adverse events, and quality of life
Propanolol Aneurysm Trial Investigators. Propranolol for small abdominal aortic aneurysms: results of a randomized trial. J Vasc Surg. 2002 Jan;35(1):72-9	Study design: multicentre, double-blind, randomised controlled trial Location: Canada Population: people with asymptomatic AAA ≥3.0 cm and <5.0 cm in diameter Sample size: 552 Follow-up: mean of 2.5 years Intervention: Propranolol Comparators: Placebo Outcomes: mean annual rate of aneurysm expansion (mean change in anterior-posterior diameter, as well as the transverse diameter), mortality, elective resection of AAA, and quality of life

New studies identified

Table 5: Antibiotics

Study	Details
Meijer CA , Stijnen T, Wasser MNJ, et al. (2013) Doxycycline for stabilization of abdominal aortic aneurysms: A randomized trial. Annals of Internal Medicine 159(12), 815-823	Study design: multicentre, double-blind, randomised controlled trial Location: Netherlands Population: people with AAAs ≥3.5 cm and ≤5.0 cm in diameter & people with larger aneurysms who were unfit for repair Sample size: 286 Follow-up: up to 1.5 years Intervention: doxycycline Comparators: placebo Outcomes: mean change in aortic diameter at 6, 12 and 18 months, the number of participants who underwent elective surgery, and adverse events

Table 6: ACE-inhibitors and Calcium channel blockers

Study	Details
Bicknell CD, Kiru G, Falaschetti E, et al. (2016) An evaluation of the effect of an angiotens inconverting enzyme inhibitor on the growth rate of small abdominal aortic aneurysms: A randomized placebo-controlled trial (AARDVARK). European Heart Journal 37(42), 3213-3221	Study design: multicentre, randomised controlled trial Location: UK Population: people ≥55 years with AAAs ≥3.0 cm and <5.5 cm in diameter Sample size: 227 Follow-up: up to 2 years Intervention: perindopril arginine 10 mg, or amlodipine 5 mg Comparators: placebo Outcomes: mean annual rate of aneurysm expansion (average change in anteroposterior diameter), the number of AAAs that reached 5.5 cm in diameter, the number of patients who underwent elective surgery, adverse events

Table 7: Exercise

Study	Details
Tew GA, Moss J, Crank H, et al. (2012) Endurance exercise training in patients with small abdominal aortic aneurysm: a randomized controlled pilot study. Archives of physical medicine and rehabilitation 93(12), 2148-53	Study design: multicentre, single-blind, randomised controlled trial Location: UK Population: people between 50 and 85 years with asymptomatic infrarenal AAAs ≥3.0 cm and <5.0 cm in diameter Sample size: 28 Follow-up: 12 weeks Intervention: Exercise training Comparators: Standard care Outcomes: Mean change in aneurysm diameter

See Appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See Appendix F for full GRADE tables.

Economic evidence

Included studies

An initial literature search was conducted jointly for all review questions by applying standard health economic filters to a clinical search for AAA. This search returned a total of 5,173 citations. Following review of all titles and abstracts, no studies were identified as being potentially relevant to the review question. No full texts were retrieved, and no studies were included as economic evidence.

An update search was conducted in December 2017, to identify any relevant health economic analyses published during guideline development. The search yielded 814 abstracts; all of which were not considered relevant to this review question. As a result no additional studies were identified.

Excluded studies

No studies were retrieved for full-text review.

Evidence statements

Antibiotics

- Very-low evidence from 3 RCTs, including 462 people with small aneurysms, could not differentiate annual AAA growth rates between patients who received antibiotics and those who did not receive antibiotics. Subgroup analysis of 2 RCTs indicated that annual AAA growth rates were lower in people who received macrolides compared with those who received placebo, whereas 1 RCT indicated that annual growth rates were higher in people who received doxycycline compared with those who received placebo.
- Low- to moderate-quality evidence from 5 RCTs, including up to 743 people with small aneurysms, could not differentiate rates of referral for AAA repair, aneurysm rupture, all-cause mortality, and adverse event between people who received antibiotics and those who did not.

Propranolol

- Very low-quality evidence from 2 RCTs, including up to 606 people with small aneurysms, could not differentiate annual AAA growth rates, rates of referral for AAA repair, aneurysm rupture, and all-cause mortality between people who received propranolol and those who did not.
- Low-quality evidence from 2 RCTs, including 606 people with small aneurysms, reported higher rates of adverse events leading to treatment discontinuation in people who received propranolol compared with those who did not.

ACE-inhibitors

- Low- to moderate-quality evidence from 1 RCT, including up to 152 people with small aneurysms, could not differentiate annual AAA growth rates, rates of referral for AAA repair, all-cause mortality and adverse events leading to treatment discontinuation between people who received ACE inhibitors and those who did not.

Calcium channel blockers

- Low- to moderate-quality evidence from 1 RCT, including up to 151 people with small aneurysms, could not differentiate annual AAA growth rates, rates of referral for AAA repair, all-cause mortality and adverse events leading to treatment discontinuation between people who received calcium channel blockers and those who did not.

Exercise

- Low- to moderate-quality evidence from 1 RCT, including up to 25 people with small aneurysms, could not differentiate AAA growth rates between people who participated in exercise training and those who received standard care without exercise training.

Research recommendations

RR2. What are the benefits and harms of macrolides (such as azithromycin) for reducing AAA growth rates and the risk of rupture?

RR3. What are the benefits of and harms metformin for reducing AAA growth rates and the risk of rupture?

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee considered that the outcomes that matter most are a reduction in the risk of aneurysm rupture, as well as a reduction in the rate of AAA repair (or referrals for AAA repair).

The quality of the evidence

The committee noted that pooled analysis of data from 2 RCTs assessing roxithromycin (a macrolide) and 1 RCT assessing doxycycline (a tetracycline) indicated that antibiotics had no effect on the annual AAA growth rates. Further review of a subgroup analysis of the individual effects of each antibiotic showed that roxithromycin significantly reduced annual growth rates, compared with placebo, whereas people who received doxycycline had significantly higher annual growth rates compared with those who received placebo. The committee noted that, although the reported increase in aneurysm growth rates associated with doxycycline was statistically significant, it was unlikely to be clinically significant. In relation to roxithromycin, the committee noted that the antibiotic is not licensed for use in the UK. With this in mind, they were wary about extrapolating the evidence on roxithromycin to other macrolides within its class, and drafting recommendations that could affect thousands of people with AAA. The committee agreed that it was appropriate to make a research recommendation to encourage research into whether macrolides, which are licensed for use in the UK, can be used to reduce the rate of AAA expansion.

The committee discussed the evidence on other types of non-surgical inte`rventions (propranolol, ACE-inhibitors, and calcium channel blockers), and considered that the identified studies demonstrated that these interventions had no effect on AAA growth rates, or rates of referral for surgical repair. The committee also noted that insufficient or no evidence was identified for other interventions of interest (such as exercise,

diet, smoking cessation and control of alcohol consumption). Bearing in mind that non-surgical interventions are not used to reduce the rate of aneurysm growth, in practice, the committee agreed that it was not necessary to make recommendations.

The committee noted that evidence from observational studies has demonstrated that people with diabetes are less likely to experience AAA growth or rupture, and it has been proposed that this protective effect is due to the antidiabetic drug, metformin. The committee noted that no trials assessing metformin were identified from literature searches. They agreed that well-conducted RCTs which demonstrate a causal relationship between metformin and a reduction in aneurysm growth would allow clinicians to have confidence in using it as an alternative to surgical repair. As a result, the committee agreed to draft a research recommendation.

Benefits and harms

The committee noted potential harms associated with inappropriate or prolonged use of antibiotics – notably, population-level sequelae due to antibiotic resistance. They agreed that robust evidence was needed to demonstrate that the benefits of using antibiotics to treat small AAAs offset any harms resulting from antibiotic resistance.

The committee noted that the studies that assessed propranolol reported that significant numbers of participants receiving propranolol experienced adverse events that lead to them discontinuing treatment; so much so that the trials were stopped early. The committee discussed whether it was necessary to draft a “do not use” recommendation to mitigate any harm that could be caused by propranolol. However they agreed not to draft any recommendations as it is not used in practice for AAA alone and is unlikely to be used in the future.

The committee noted that many people with AAA are likely to receive ACE inhibitors or calcium channel blockers for treating other conditions. They agreed that both medications can have unpleasant side effects so clinicians would not prescribe them unless absolutely necessary (in line with their respective indications). As a result, the committee agreed that there was no need to make any recommendations for ACE inhibitors or calcium channel blockers.

Cost effectiveness and resource use

The committee noted that all the interventions considered in this review are already used in practice to treat conditions other than AAA. Since the committee believed that a lack of recommendations would have no impact in practice, they concluded that there would also be no impact on NHS costs and resources.

Other factors the committee took into account

No other factors were discussed by the committee.

Appendices

Appendix A – Review protocols

Review protocol for non-surgical interventions for slowing aneurysm growth and reducing the risk of rupture

Review question 6	Which non-surgical interventions (including drug treatment and risk factor management) are effective in slowing aneurysm expansion and reducing the risk of rupture?
Objectives	To determine the effectiveness of nonsurgical interventions (including antiplatelet, antihypertensive, lipid-lowering medication, antibiotics or lifestyle interventions) in slowing aneurysm expansion and reducing the risk of rupture
Type of review	Intervention
Language	English only
Study design	Systematic reviews of study designs listed below Randomised controlled trials Quasi-randomised controlled trials
Status	Published papers only (full text) No date restrictions
Population	People with a confirmed abdominal aortic aneurysm >3cm in diameter who have not undergone aortic surgery
Intervention	Antiplatelet therapy (aspirin, clopidogrel, ticlopidine, cilostazol, prasugrel, ticagrelor, or any other antiplatelet drugs) Anticoagulant drugs (heparin, warfarin, NOACs (dabigatran, rivaroxaban, apixaban)) Antihypertensive drugs (calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers (β-blockers; e.g. metoprolol, propranolol), angiotensin-II receptor antagonists, thiazide/ thiazide-like diuretics, or any other antihypertensive drugs) Lipid-lowering therapy (statins (simvastatin, pravastatin, atorvastatin etc)) Antibiotics (doxycycline, roxithromycin, azithromycin) Diabetic control, including metformin COPD control Smoking cessation Physical therapy/exercise Diet Weight control Control of alcohol consumption
Comparator	Placebo, no intervention or each other
Outcomes	AAA rupture AAA growth/expansion Surgery/referral for surgery Mortality (all-cause; cardiovascular (e.g. fatal myocardial infarction, fatal stroke, other vascular deaths; AAA-related); survival Nonfatal cardiovascular events (e.g. nonfatal myocardial infarction, nonfatal stroke, or transient ischaemic attack (TIA)) Major amputation Quality of life Adverse effects Resource use and cost

Review question 6	Which non-surgical interventions (including drug treatment and risk factor management) are effective in slowing aneurysm expansion and reducing the risk of rupture?
Other criteria for inclusion / exclusion of studies	Exclusion: Non-English language Abstract/non-published People who have previously undergone aortic surgery Pharmacological interventions not available in the UK
Baseline characteristics to be extracted in evidence tables	Age Sex Size of aneurysm Comorbidities Ethnicity
Search strategies	See Appendix B.
Review strategies	Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. The update of Rughani et al's 2012 Cochrane review (ongoing at the time of protocol development) of medical treatment for small AAAs (those <5.5cm) will be used as the evidence base for pharmacological interventions Cochrane has agreed to share their excluded studies lists with NICE; the analyst will review these and extract those papers excluded for having a population with AAAs >5.5cm – these will be used to supplement the Cochrane review Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. All key findings from evidence will be presented in GRADE profiles and further summarised in evidence statements.
Key papers	• Myers,Jonathan, McElrath,Mary, Jaffe,Alyssa, Smith,Kimberly, Fonda,Holly, Vu,Andrew, Hill,Bradley. A randomized trial of exercise training in abdominal aortic aneurysm disease. Med Sci Sports Exerc 2014;46(1):2-9 • Rughani G, Robertson L, Clarke M. Medical treatment for small abdominal aortic aneurysms. Cochrane Database Syst Rev. 2012 Sep 12;9:CD009536 c: • Høgh A, Vammen S, Ostergaard L, Joensen JB, Henneberg EW, Lindholt JS. Intermittent roxithromycin for preventing progression of small abdominal aortic aneurysms: long-term results of a small clinical trial. Vasc Endovascular Surg. 2009 Oct-Nov;43(5):452-6 • Karlsson L, Gnarpe J, Bergqvist D, Lindbäck J, Pärsson H. The effect of azithromycin and Chlamydophilia pneumonia infection on expansion of small abdominal aortic aneurysms--a prospective randomized double-blind trial. J Vasc Surg. 2009 Jul;50(1):23-9 • Lindholt JS, Henneberg EW, Juul S, Fasting H. Impaired results of a randomised double blinded clinical trial of propranolol versus placebo on the expansion rate of small abdominal aortic aneurysms. Int Angiol. 1999 Mar;18(1):52-7 • Mosorin M, Juvonen J, Biancari F, Satta J, Surcel HM, Leinonen M, Saikku P, Juvonen T. Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study. J Vasc Surg. 2001 Oct;34(4):606-10 • Propanolol Aneurysm Trial Investigators. Propranolol for small abdominal aortic aneurysms: results of a randomized trial. J Vasc Surg. 2002 Jan;35(1):72-9 • Vammen S, Lindholt JS, Ostergaard L, Fasting H, Henneberg EW. Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion. Br J Surg. 2001 Aug;88(8):1066-72

Appendix B – Literature search strategies

Clinical search literature search strategy

Main searches

Bibliographic databases searched for the guideline

- Cumulative Index to Nursing and Allied Health Literature - CINAHL (EBSCO)
- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE Epub Ahead of Print (Ovid)
- MEDLINE In-Process (Ovid)

Identification of evidence for review questions

The searches were conducted between November 2015 and October 2017 for 31 review questions (RQ). In collaboration with Cochrane, the evidence for several review questions was identified by an update of an existing Cochrane review. Review questions in this category are indicated below. Where review questions had a broader scope, supplement searches were undertaken by NICE.

Searches were re-run in December 2017.

Where appropriate, study design filters (either designed in-house or by McMaster) were used to limit the retrieval to, for example, randomised controlled trials. Details of the study design filters used can be found in section 4.

This search was constructed in two parts. The first part was covered by a Cochrane Review and the Medline strategy for the Cochrane searches can be found in D.3.

The NICE guidance Information Services search below covered an update of a Cochrane Review

Search strategy review question 6

Medline Strategy, searched 27th June 2017 **Database: Ovid MEDLINE(R) 1946 to June Week 3 2017** **Search Strategy:**
1 Aortic Aneurysm, Abdominal/
2 (aneurysm* adj4 (abdom* or thoracoabdom* or thoraco-abdom* or aort* or spontan* or juxtarenal* or juxta-renal* or juxta renal* or paraerenal* or para-renal* or para renal* or suprarenal* or supra renal* or supra-renal* or short neck* or short-neck* or shortneck* or visceral aortic segment*)).tw.
3 AAA*.tw.
4 or/1-3
5 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
6 (Hydroxymethylglutaryl-CoA adj4 Reductase adj4 Inhibitor*).tw.

Medline Strategy, searched 27th June 2017
Database: Ovid MEDLINE(R) 1946 to June Week 3 2017
Search Strategy:

7 statin*.tw.
8 (hmg-CoA adj4 Reductase adj4 Inhibitor*).tw.
9 exp Platelet Aggregation Inhibitors/
10 (antithrombocytic* adj4 agent*).tw.
11 antiplatelet*.tw.
12 (platelet adj4 (inhibitor* or antiaggregant* or anti-aggregant*)).tw.
13 (blood adj4 platelet adj4 antagonist*).tw.
14 Anticoagulants/
15 anticoagulant*.tw.
16 (indirect adj4 thrombin adj4 inhibitor*).tw.
17 Antihypertensive Agents/
18 (anti-hypertensive* or antihypertensive* or anti hypertensive*).tw.
19 Anti-bacterial Agents/
20 ((anti-bacterial or antibacterial or anti bacterial or anti-mycobacterial or antimycobacterial or anti mycobacterial or bacteriocidal*) adj4 (agent* or compound*)).tw.
21 (antibiotic* or bacteriocide*).tw.
22 Hypoglycemic Agents/
23 (diabet* adj4 control*).tw.
24 ((antidiabetic or anti-diabetic or anti diabetic) adj4 (agent* or medication* or medicine* or drug*)).tw.
25 (anti-hyperglycemic* or antihyperglycemic* or anti hyperglycemic* or anti-hyperglycaemic* or antihyperglycaemic* or anti hyperglycaemic* or hypoglycemic* or hypoglycaemic*).tw.
26 Motor Activity/
27 ((motor or physical* or locomotor or supervis*) adj4 activit*).tw.
28 exp Exercise/ or Exercise Therapy/
29 (exercise* or exercisi* or kinesiotherap*).tw.
30 exp Physical Fitness/
31 Physical endurance/
32 fitness*.tw.
33 (walk* or swim* or jog* or cycl* or bicycl* or gym*).tw.
34 ((physical* or keep* or cardio* or aerobic or fitness or endurance) adj4 (fit* or activit* or active or train* or therap*)).tw.
35 (aerobic adj4 condition*).tw.
36 Muscle strength/
37 (muscle adj4 strength*).tw.
38 Smoking Cessation/
39 "Tobacco Use Cessation"/
40 ((cigarette* or smok* or tobacco or nicotine*) adj4 (cessation or withdrawal or ceas*)).tw.
41 ((quit* or stop* or giv* or abstin* or abstain*) adj4 (tobacco or cigarette or smoking or nicotine*)).tw.
42 (smoking adj4 (therap* or rehab*)).tw.
43 (cessation adj4 (treat* or therap* or assist* or advice or advis* or program* or interven* or service*)).tw.
44 exp Diet/
45 (diet or diets or dieting).tw.
46 (health* adj4 eat*).tw.
47 exp Food/
48 food*.tw.

Medline Strategy, searched 27th June 2017 **Database: Ovid MEDLINE(R) 1946 to June Week 3 2017** **Search Strategy:**
49 (weight adj4 (manag* or control* or maintain* or achiev* or goal* or health*)).tw.
50 exp Alcohol-Related Disorders/
51 (alcohol* adj4 (use* or abus* or drink* or reduc* or intake or consum* or control* or abstain* or abstinen* or depend* or addict* or chonic*)).tw.
52 exp Pulmonary Disease, Chronic Obstructive/
53 Lung diseases, obstructive/
54 (COPD* or COAD* or COBD* or AECB*).tw.
55 (chronic adj4 obstruct* adj4 (disease* or airway*)).tw.
56 (chronic* adj4 (airflow* or airway* or bronch* or lung* or respirat* or pulmonary) adj4 obstruct*).tw.
57 exp Muscarinic Antagonists/
58 ((muscarinic adj4 antagonist*) or (antimuscarinolytic* or antimuscarinic* or LAMA or SAMA)).tw.
59 exp Adrenergic beta-2 Receptor Agonists/
60 ((beta-2 or beta2 or "beta 2") adj4 (agonist* or agent* or stimula*)).tw.
61 exp Glucocorticoids/
62 (glucocorticoid* or glucocortoid* or corticosteroid*).tw.
63 exp Expectorants/
64 (expectorants or mucolytic*).tw.
65 exp Antitussive Agents/
66 ((cough adj4 suppressant) or antitussive*).tw.
67 (cough* adj4 (relie* or depressant*)).tw.
68 (anticough or anti-cough).tw.
69 Theophylline/
70 theophylline.tw.
71 or/5-70
72 4 and 71
73 animals/ not humans/
74 72 not 73
75 limit 74 to english language
76 limit 75 to ed=20120501-20171220

Note: RCT, Systematic Review and Observational study filters appended to strategy.

Cochrane review

Rughani G, Robertson L, Clarke M. Medical treatment for small abdominal aortic aneurysms. Cochrane Database Syst Rev. 2012 Sep 12;9:CD009536 c

CENTRAL Strategy, searched May 2012 **Search Strategy:**
#1 MeSH descriptor Aortic Aneurysm explode all trees
#2 (aort* near3 (balloon* or dilat* or bulg* or ruptur* or expan*))
#3 (aneury*)
#4 (AAA*)
#5 (#1 OR #2 OR #3 OR #4)
#6 (grow* or expan* or diameter* or ruptur* or size or dilat* or measur*):ti,ab,kw
#7 (#5 AND #6)

Health Economics literature search strategy

Sources searched to identify economic evaluations

- NHS Economic Evaluation Database – NHS EED (Wiley) last updated Dec 2014
- Health Technology Assessment Database – HTA (Wiley) last updated Oct 2016
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Search filters to retrieve economic evaluations and quality of life papers were appended to the population and intervention terms to identify relevant evidence. Searches were not undertaken for qualitative RQs. For social care topic questions additional terms were added. Searches were re-run in September 2017 where the filters were added to the population terms.

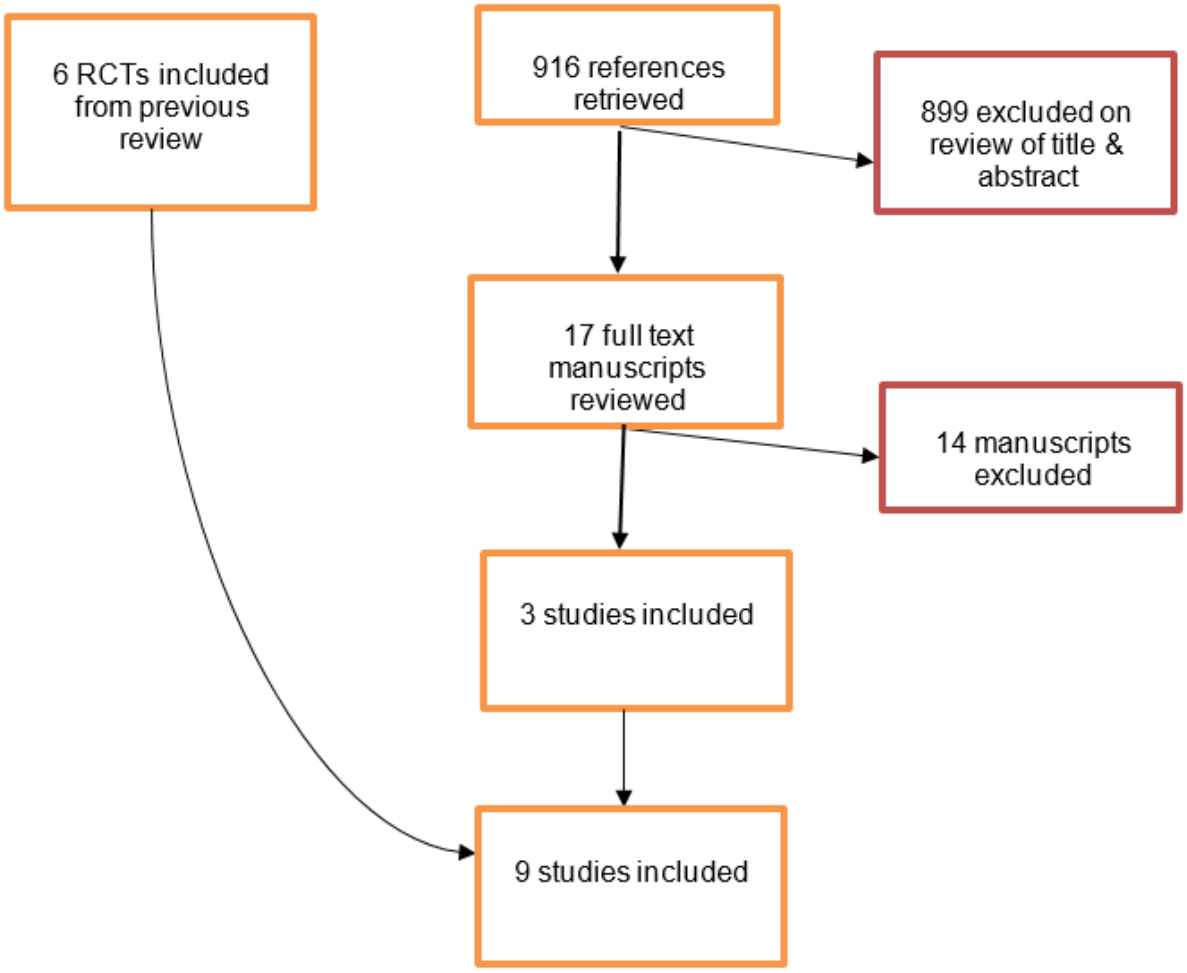
Health economics search strategy

Medline Strategy
Economic evaluations 1 Economics/ 2 exp "Costs and Cost Analysis"/ 3 Economics, Dental/ 4 exp Economics, Hospital/ 5 exp Economics, Medical/ 6 Economics, Nursing/ 7 Economics, Pharmaceutical/ 8 Budgets/ 9 exp Models, Economic/ 10 Markov Chains/ 11 Monte Carlo Method/ 12 Decision Trees/ 13 econom*.tw. 14 cba.tw. 15 cea.tw. 16 cua.tw. 17 markov*.tw. 18 (monte adj carlo).tw. 19 (decision adj3 (tree* or analys*)).tw. 20 (cost or costs or costing* or costly or costed).tw. 21 (price* or pricing*).tw. 22 budget*.tw. 23 expenditure*.tw. 24 (value adj3 (money or monetary)).tw. 25 (pharmacoeconomic* or (pharmaco adj economic*)).tw. 26 or/1-25 Quality of life 1 "Quality of Life"/

Medline Strategy
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly* or qald* or qale* or qtime*).tw.
7 disability adjusted life.tw.
8 daly*.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health* year* equivalent*.tw.
19 utilit*.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili*.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble*.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

Appendix C – Clinical evidence study selection

Cochrane systematic review update search



Appendix D – Clinical evidence tables

Cochrane systematic review

Full citation	Rughani G, Robertson L, and Clarke M (2012) Medical treatment for small abdominal aortic aneurysms. The Cochrane database of systematic reviews (9), CD009536
Study details	Study type: systematic review Location: UK Aim: To assess the effects of medical treatment on the expansion rate of small abdominal aortic aneurysms. Study dates: literature searched for publications up to May 2012 Follow-up: up to 5.3 years Sources of funding: this study was supported by funding from the UK National Institute of Health Research (NIHR)
Participants	Population: people of any age with an asymptomatic AAA <5.5 in the maximum external antero-posterior diameter measured by ultrasound or computed tomography Sample size: 6 RCTs including 1,558 participants Inclusion criteria: RCTs in which patients were randomly allocated to medical treatment (with the intention of retarding aneurysm expansion) or placebo were included Exclusion criteria: studies in which patients were randomised to medical treatment following surgery or those where patients were randomised to a combination of surgery and medical therapy were excluded
Methods	Literature searches were performed on the Cochrane Central Register of Controlled trials and the Cochrane Vascular Specialised Register (constructed from weekly electronic searches of MEDLINE, Embase, CINAHL, and AMED databases. Additional searches were also performed on the World Health Organisation International Clinical Trials Registry, ClinicalTrials.gov website and the ISRCTN register, and the Netherlands Trial register. Bibliographies of included studies were reviewed to identify any additional studies that were relevant to the review question. Two independent reviewers were involved in study selection, data extraction, and risk of bias assessments. Any disagreements were resolved through discussion.
Interventions	Antibiotics (roxithromycin, azithromycin, and doxycycline), and beta-blockers (propranolol)
Comparison	Placebo
Outcomes measures	AAA expansion rates, proportion of patients referred for aneurysm surgery, mortality, and adverse events

Full citation	**Rughani G, Robertson L, and Clarke M (2012) Medical treatment for small abdominal aortic aneurysms. The Cochrane database of systematic reviews (9), CD009536**
Study Appraisal using AMSTAR (Assessing the Methodological Quality of Systematic Reviews)	1. Was an 'a priori' design provided? Yes 2. Was there duplicate study selection and data extraction? Yes 3. Was a comprehensive literature search performed? Yes 4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? Yes 5. Was a list of studies (included and excluded) provided? Yes 6. Were the characteristics of the included studies provided? Yes 7. Was the scientific quality of the included studies assessed and documented? Yes 8. Was the scientific quality of the included studies used appropriately in formulating conclusions? Yes 9. Were the methods used to combine the findings of studies appropriate? Yes 10. Was the likelihood of publication bias assessed? Yes 11. Was the conflict of interest included? Yes Directness: Directly applicable

Studies included in the systematic review by Rughani et al.

Antibiotics

Full citation	**Høgh A, Vammen S, Ostergaard L, et al. (2009) Intermittent roxithromycin for preventing progression of small abdominal aortic aneurysms: long-term results of a small clinical trial. Vasc Endovascular Surg;43(5):452-6**
Study details	Study type: multicentre, double blind, randomised controlled trial Location: Denmark Aim: to assess whether intermittent, long-term roxithromycin was effective at reducing rates AAA expansion and referral for surgery Study dates: 1994 to 1998 Follow-up: mean, 5.27 years Sources of funding: the study was part funded by the Danish Heart Foundation and the Health Department of Viborg County for financial support
Participants	Population: men with a confirmed AAA ≥3.0 cm in diameter who had not underwent AAA repair Sample size: 84 Inclusion criteria: men with AAAs ≥3.0 cm and <5.0 cm in diameter were included. All participants had no known or suspected allergy to macrolide antibiotics, and had not been receiving antibiotics within 3 months of study commencement. Exclusion criteria: people with AAAs >5.0 cm in diameter were excluded Baseline characteristics: • Mean age: roxithromycin group, 71 years; placebo group, 71 years • Sex: 100% male • Mean aneurysm diameter: roxithromycin group, 3.8 cm; placebo group, 3.7 cm • Comorbidities: not reported
Intervention	Roxithromycin, 300 mg daily for 28 days, given each year the participant remained in the trial
Comparison	Placebo
Outcomes measures	Mean annual rate of aneurysm expansion (average change in anteroposterior diameter), and the number of patients referred for surgery when AAA diameter exceeded 5.0 cm
Risk of bias assessment	1. Random sequence generation (selection bias): Unclear risk – Method of randomisation not reported 2. Allocation concealment (selection bias): Unclear risk – Concealment methods were not explicitly stated

Full citation	Høgh A, Vammen S, Ostergaard L, et al. (2009) Intermittent roxithromycin for preventing progression of small abdominal aortic aneurysms: long-term results of a small clinical trial. Vasc Endovascular Surg;43(5):452-6
	3. Blinding of participants and personnel (performance bias): Unclear risk – Incomplete blinding. Participants and observers blinded but blinding was broken once by the principal investigator 4. Blinding of outcome assessment (detection bias): Unclear risk – Insufficient information was available 5. Incomplete outcome data (attrition bias): Unclear risk – There were no reported exclusions post-randomisation; however there was inadequate reporting of the numbers of participants remaining in the trial at each follow-up interval. 6. Selective reporting (reporting bias): Low risk – Although the numbers referred to surgery in each group was not presented, members of the Cochrane collaboration contacted the authors to obtain data of the separate group numbers 7. Other bias: Unclear risk – Authors describe the risk of information bias as low but do not state methods used to reduce intra/inter observer variations Overall risk of bias: Moderate – insufficient information available to ascertain the quality of this study Directness: directly applicable

Full citation	**Karlsson L, Gnarpe J, Bergqvist D, et al. (2009). The effect of azithromycin and Chlamydophilia pneumonia infection on expansion of small abdominal aortic aneurysms--a prospective randomized double-blind trial. J Vasc Surg. 2009 Jul;50(1):23-9**
Study details	Study type: multicentre, double-blind, randomised controlled trial Location: Sweden Aim: was to evaluate the effect of azithromycin on the expansion rate of small AAAs Study dates: 2002 to 2005 Follow-up: up to 3 years Sources of funding: the drug manufacturer provided the study medication but had no involvement in any trial management or data analysis
Participants	Population: people with a confirmed AAA ≥3.0 cm in diameter who had not underwent AAA repair Sample size: 247 Inclusion criteria: people ≤80 years with AAAs ≥3.5 cm and ≤4.9 cm in diameter were included Exclusion criteria: AAA <3.5 cm or AAA ≥5.0 cm, age ≥ 81 years, intolerance to macrolide antibiotics, creatinine clearance <40 mL/minute and medication with ergotamine Baseline characteristics: Mean age: azithromycin group, 71 years; placebo group, 71 years Sex: azithromycin group, 84% male; placebo group, 79% male Median aneurysm diameter: azithromycin group, 4.0 cm; placebo group, 4.0 cm Previous myocardial infarction: azithromycin group, 31%; placebo group, 35% Asthma: azithromycin group, 4%; placebo group, 4% COPD: azithromycin group, 4%; placebo group, 8% Diabetes: azithromycin group, 5%; placebo group, 4% Hypertension: azithromycin group, 64%; placebo group, 61%
Intervention	Azithromycin, 600 mg daily for 3 days, and then weekly for 15 weeks
Comparison	Placebo
Outcomes measures	Mean annual rate of aneurysm expansion (average change in anteroposterior diameter), and change in aneurysmal volume
Risk of bias assessment	1. Random sequence generation (selection bias): Low risk – Participants were randomised by computer generated codes in blocks of 4 in a 1:1 proportion. 2. Allocation concealment (selection bias): Low risk – Code was kept centrally and adequately concealed.

Full citation	**Karlsson L, Gnarpe J, Bergqvist D, et al. (2009). The effect of azithromycin and Chlamydophilia pneumonia infection on expansion of small abdominal aortic aneurysms--a prospective randomized double-blind trial. J Vasc Surg. 2009 Jul;50(1):23-9**
	3. Blinding of participants and personnel (performance bias): Low risk – Participants and observers were blinded until 'all analyses... were completed' 4. Blinding of outcome assessment (detection bias): Low risk – Participants and observers were blinded until 'all analyses... were completed' 5. Incomplete outcome data (attrition bias): Unclear risk – Follow up for the rest of the trial was not as clear, namely inadequate reporting of the numbers of participants remaining in the trial at each follow up interval. 6. Selective reporting (reporting bias): Low risk – Continuous variables were presented as medians and inter-quartile ranges: the Cochrane review states that the authors were contacted and stated that this was done because the underlying data were 'slightly skew. 7. Other bias: Low risk – no other risk of bias issues were identified Overall risk of bias: Low Directness: directly applicable

Full citation	**Mosorin M, Juvonen J, Biancari F, et al. (2001) Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study. J Vasc Surg. 34(4):606-10**
Study details	Study type: multicentre, double-blind, randomised controlled trial Location: Finland Aim: to investigate the efficacy of doxycycline in reducing the expansion of small AAAs Study dates: 1997 to 1998 Follow-up: median of 18 months Sources of funding: the drug manufacturer provided the study medication and performed randomisation of participants to treatment arms
Participants	Population: people with a confirmed AAA ≥3.0cm in diameter who had not underwent AAA repair Sample size: 34 Inclusion criteria: people with AAAs ≥3.0 cm in diameter, or a ratio of infrarenal to suprarenal aortic diameter of 1.2 or more were included Exclusion criteria: AAAs >5.5 cm in diameter Baseline characteristics: • Mean age: doxycycline group, 68.6 years; placebo group, 68.1 years • Sex: doxycycline group, 94% male; placebo group, 86% male • Median aneurysm diameter: doxycycline group, 3.1 cm; placebo group, 3.5 cm • Diabetes: doxycycline group, 23.5% %; placebo group, 6.6% % • Hypertension: doxycycline group, 47.0% %; placebo group, 33.3% • COPD: doxycycline group, 11.7%; placebo group, 26.6%
Intervention	Doxycycline, 150 mg daily for three months
Comparison	Placebo
Outcomes measures	Expansion rate (median change in anterior-posterior diameter), and the number of patients who had AAA rupture or repair
Risk of bias assessment	1. Random sequence generation (selection bias): Unclear risk – Method of randomisation not clearly reported 2. Allocation concealment (selection bias): Unclear risk – Concealment methods were not explicitly stated 3. Blinding of participants and personnel (performance bias): Low risk – Participants were blinded to group allocations 4. Blinding of outcome assessment (detection bias): Low risk – Observers were blinded to group allocations 5. Incomplete outcome data (attrition bias): High risk – Attrition and exclusions reported, but the number and handling of censored cases was not clarified.

Full citation	**Mosorin M, Juvonen J, Biancari F, et al. (2001) Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study. J Vasc Surg. 34(4):606-10**
	6. Selective reporting (reporting bias): High risk – Study methodology did not outline that multiple interim analyses would be performed. This may have been done to overemphasise protective effect of doxycycline. Authors used medians and interquartile ranges without demonstrating or stating that the data was not normally distributed. 7. Other bias: High risk – There were considerable differences in baseline characteristics between treatment arms however these were not found to be statistically significant due to the study's small sample size. Overall risk of bias: High Directness: directly applicable

Full citation	**Vammen S, Lindholt JS, Ostergaard L, et al. (2001) Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion. Br J Surg. 88(8):1066-72**
Study details	Study type: multicentre, double-blind, randomised controlled trial Location: Denmark Aim: to investigate the effect of roxithromycin on the expansion rate of small AAA Study dates: 1994 to 1998 Follow-up: mean of 1.5 years Sources of funding: the study was part funded by the Danish Heart Foundation and the Health Department of Viborg County for financial support
Participants	Population: people with a confirmed AAA ≥3.0cm in diameter who had not underwent AAA repair Sample size: 92 Inclusion criteria: people with asymptomatic AAA ≥3.0 cm in diameter were included Exclusion criteria: known or suspected allergy to macrolide antibiotics or related products, current or previous use of macrolide antibiotics within 3 months of study commencement, or AAAs >5.0 in diameter Baseline characteristics: • Mean age: roxithromycin group, 72 years; placebo group, 73 years • Sex: proportions not reported • Mean aneurysm diameter: roxithromycin group, 3.8 cm; placebo group, 3.7 cm • Comorbidities: not reported

Full citation	**Vammen S, Lindholt JS, Ostergaard L, et al. (2001) Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion. Br J Surg. 88(8):1066-72**
Intervention	Roxithromycin, 300 mg daily for 28 days; given each year the participant remained in the trial
Comparison	Placebo
Outcomes measures	Mean annual rate of aneurysm expansion (average change in anteroposterior diameter), and the number of patients referred for surgery when AAA diameter exceeded 5.0 cm, mortality and adverse events
Risk of bias assessment	1. Random sequence generation (selection bias): Unclear risk – Method of randomisation not reported 2. Allocation concealment (selection bias): Low risk – Authors state that the person involved in randomisation was separated from (had no contact with) other people involved with the study 3. Blinding of participants and personnel (performance bias): Unclear risk – Insufficient information was provided 4. Blinding of outcome assessment (detection bias): Unclear risk – Insufficient information was available 5. Incomplete outcome data (attrition bias): Low risk – Rates of attrition were relatively low and similar between groups 6. Selective reporting (reporting bias): Low risk – No serious concerns relating to reporting bias were identified 7. Other bias: Low risk – no other risk of bias issues were identified Overall risk of bias: Low Directness: directly applicable

Propranolol

Full citation	**Lindholt JS, Henneberg EW, Juul S, et al. (1999) Impaired results of a randomised double blinded clinical trial of propranolol versus placebo on the expansion rate of small abdominal aortic aneurysms. Int Angiol. 1999 Mar;18(1):52-7**
Study details	Study type: multicentre, double-blind, randomised controlled trial Location: Denmark Aim: to assess whether propranolol was effective at reducing rates AAA expansion and referral for surgery Study dates: not specified Follow-up: up to 2 years Sources of funding: the study was part funded by the Danish Heart Foundation and the Health Department of Viborg County for financial support
Participants	Population: people with a confirmed AAA ≥3.0 cm in diameter who had not underwent AAA repair Sample size: 54 Inclusion criteria: men with AAAs ≥3.0 cm and <5.0 cm in diameter were included Exclusion criteria: AAA >5.0 cm, people who were already taking beta-blockers, history of cardiac failure, COPD, asthma, arrhythmia, Morbus Raynaud or intermittent claudication • Mean age: propranolol group, 68.7 years; placebo group, 69.6 years • Sex: 100% male • Median aneurysm diameter: propranolol group, 3.5 cm; placebo group, 3.5 cm • Comorbidities: not reported
Intervention	Propranolol, 40 mg twice daily until the end of the study
Comparison	Placebo
Outcomes measures	Mean annual rate of aneurysm expansion (average change in anteroposterior diameter), adverse events, and quality of life
Risk of bias assessment	1. Random sequence generation (selection bias): Unclear risk – Method of randomisation was not reported 2. Allocation concealment (selection bias): Unclear risk – Concealment methods were not explicitly stated 3. Blinding of participants and personnel (performance bias): Low risk – Authors stated that participants were blinded to treatments 4. Blinding of outcome assessment (detection bias): Low risk – Authors stated that investigators were blinded to treatment allocations

Full citation	**Lindholt JS, Henneberg EW, Juul S, et al. (1999) Impaired results of a randomised double blinded clinical trial of propranolol versus placebo on the expansion rate of small abdominal aortic aneurysms. Int Angiol. 1999 Mar;18(1):52-7**
	5. Incomplete outcome data (attrition bias): Low risk – Unequal but non-significantly different attrition was reported between both treatment arms. These were well reported, but lacked a summary figure for the total number discontinuing in each group due to adverse effects of treatment. 6. Selective reporting (reporting bias): Unclear risk – Unclear risk – Trial was stopped prematurely after 2 years due to high dropout rates (presumably due to adverse events) but it was unclear what impact this had on the trial results. 7. Other bias: Low risk – no other risk of bias issues were identified Overall risk of bias: Moderate – insufficient information was available to ascertain the quality of this study Directness: directly applicable

Full citation	**Propanolol Aneurysm Trial Investigators. Propranolol for small abdominal aortic aneurysms: results of a randomized trial. J Vasc Surg. 2002 Jan;35(1):72-9**
Study details	Study type: multicentre, double-blind, randomised controlled trial Location: Canada Aim: to investigate whether propranolol decreases the growth rate of small abdominal aortic aneurysms Study dates: not reported Follow-up: mean of 2.5 years Sources of funding: not reported
Participants	Population: people with asymptomatic AAA ≥3.0 cm in diameter who had not underwent AAA repair Sample size: 552 Inclusion criteria: people with asymptomatic AAA ≥3.0 cm and <5.0 cm in diameter were included. Some participating centres only included people with AAA ≥3.0 cm and ≤4.5 cm). Exclusion criteria: contraindications to beta-blockers, clinical need for betablockers, or an AAA that was known to have grown less than 2 mm in the past year Baseline characteristics: • Mean age: propranolol group, 68.7 years; placebo group, 69.1 years • Sex: propranolol group, 85.7% male; placebo group, 82.3% male • Mean aneurysm diameter: propranolol group, 3.8 cm; placebo group, 3.8 cm

Full citation	**Propanolol Aneurysm Trial Investigators. Propranolol for small abdominal aortic aneurysms: results of a randomized trial. J Vasc Surg. 2002 Jan;35(1):72-9**
	• Angina: propranolol group, 12.1%; placebo group, 17.4% • Heart failure: propranolol group, 1.1%; placebo group, 2.9% • Hyperlipidaemia: propranolol group, 33.5%; placebo group, 33.7% • Hypertension: propranolol group, 36.0%; placebo group, 35.5% • Myocardial infarction: propranolol group, 16.5%; placebo group, 17.4% • Diabetes: propranolol group, 5.9%; placebo group, 6.5%
Intervention	Propranolol in increasing doses from 20 mg twice daily to a target dose of 80 to 120 mg twice daily
Comparison	Placebo
Outcomes measures	Mean annual rate of aneurysm expansion (mean change in anterior-posterior diameter, as well as the transverse diameter), mortality, elective resection of AAA, and quality of life
Risk of bias assessment	1. Random sequence generation (selection bias): Low risk – Randomisation was performed using computer-generated sequences 2. Allocation concealment (selection bias): Low risk – Authors report that “personnel used the next (randomisation) number in the particular stratum” and were not aware “of the treatment allocation before randomisation or throughout the study” 3. Blinding of participants and personnel (performance bias): Low risk – Patient and investigator blinding was maintained throughout the study 4. Blinding of outcome assessment (detection bias): Low risk – Patient and investigator blinding was maintained throughout the study 5. Incomplete outcome data (attrition bias): High risk – Limited details of participants who were lost to follow-up were reported. The reporting of adverse events for 49 patients who stopped the drug was vaguely recorded as ’other’. Finally, there was inadequate reporting of the numbers of participants remaining in the trial at each follow-up interval. 6. Selective reporting (reporting bias): Unclear risk – There was insufficient reporting of reasons for stopping the study drug early, and how this may have affected the overall results 7. Other bias: Low risk – no other risk of bias issues were identified Overall risk of bias: Moderate Directness: directly applicable

New studies identified from update searches

Antibiotics

Full citation	Meijer CA, Stijnen T, Wasser MNJ, et al. (2013) Doxycycline for stabilization of abdominal aortic aneurysms: A randomized trial. Annals of Internal Medicine 159(12), 815-823
Study details	Study type: multicentre, double-blind, randomised controlled trial Location: Netherlands Aim: to investigate whether doxycycline inhibits AAA progression Study dates: 2008 to 2011 Follow-up: up to 1.5 years Sources of funding: this study was funded by the Netherlands Organisation for Health Research and Development, and the NutsOhra fund
Participants	Population: people with a confirmed AAA ≥3.0cm in diameter who had not underwent AAA repair Sample size: 286 Inclusion criteria: people with AAAs ≥3.5 cm and ≤5.0 cm in diameter, people with larger aneurysms who were unfit for repair, and people who declined repair were included. Exclusion criteria: people with AAAs between 5.1-5.5 cm in diameter who were expected to receive surgery, creatinine levels <40ml/min/1.73m^{2,} alanine aminotransferase levels more than 3 times the reference value, hypersensitivity to doxycycline, or a life expectancy <2 years Baseline characteristics: • Mean age: doxycycline group, 70 years; placebo group, 70 years • Sex: doxycycline group, 83% male; placebo group, 80% male • Mean aneurysm diameter: doxycycline group, 4.3 cm; placebo group, 4.3 cm • Diabetes: doxycycline group, 15%; placebo group, 14% • History of cardiovascular disease: doxycycline group, 58%; placebo group, 46% • Use of antihypertensive medication: doxycycline group, 66%; placebo group, 65%
Intervention	Doxycycline, 100 mg per day
Comparison	Placebo

Full citation	**Meijer CA, Stijnen T, Wasser MNJ, et al. (2013) Doxycycline for stabilization of abdominal aortic aneurysms: A randomized trial. Annals of Internal Medicine 159(12), 815-823**
Outcomes measures	Mean change in aortic diameter at 6, 12 and 18 months, the number of participants who underwent elective surgery, and adverse events
Risk of bias assessment	1. Random sequence generation (selection bias): Low risk – randomisation was performed using computer-generated permuted blocks of 10 in 8 strata (by sex, statin use, and AAA diameter (≤5.0 cm or >5.0 cm) 2. Allocation concealment (selection bias): Unclear risk – Concealment methods were not explicitly stated 3. Blinding of participants and personnel (performance bias): Low risk – Authors stated that all patients were blinded to treatment allocations 4. Blinding of outcome assessment (detection bias): Low risk – Authors stated that pharmacy collaborators and trial investigators were blinded to treatment allocations 5. Incomplete outcome data (attrition bias): Low risk – Losses to follow-up were reported and clearly explained. Furthermore, investigators conducted analyses using and intention-to-treat approach 6. Selective reporting (reporting bias): Low risk – No serious concerns relating to reporting bias were identified 7. Other bias: Low risk – No other risk of bias issues were identified Overall risk of bias: Low Directness: directly applicable

ACE inhibitors and calcium channel blockers

Full citation	**Bicknell CD, Kiru G, Falaschetti E, et al. (2016) An evaluation of the effect of an angiotens inconverting enzyme inhibitor on the growth rate of small abdominal aortic aneurysms: A randomized placebo-controlled trial (AARDVARK). European Heart Journal 37(42), 3213-3221**
Study details	Study type: multicentre, randomised controlled trial Location: UK Aim: to investigate whether ACE-inhibition reduces small AAA growth rates Study dates: 2011 to 2013 Follow-up: up to 2 years Sources of funding: the study was part funded by the National Institute for Health Research (NIHR), and the manufacturer provided the trial drug at no charge
Participants	Population: people with a confirmed AAA ≥3.0cm in diameter who had not underwent AAA repair Sample size: 227 Inclusion criteria: people ≥55 years with AAAs ≥3.0 cm and <5.5 cm in diameter, and a systolic BP <150mmHg were included Exclusion criteria: already taking ACE inhibitors, Angiotensin II receptor blockers, or a calcium channel blocker (with the exception of 5 mg amlodipine), renal artery stenosis (>50%), serum creatinine of >180 mmol/L, or a clinically significant medical condition (including reduced life expectancy of <2 years) Baseline characteristics: • Mean age: perindopril group, 71.6 years; amlodipine group, 71.5 years; placebo group, 70.7 years • Sex: perindopril group, 97% male; amlodipine group, 92% male; placebo group, 94% male • Mean aneurysm diameter: perindopril group, 4.05 cm; amlodipine group, 4.03 cm; placebo group, 4.06 cm • Diabetes: perindopril group, 2.7%; amlodipine group, 8.3%; placebo group, 10.1%
Intervention	Perindopril arginine 10 mg, or amlodipine 5 mg
Comparison	Placebo
Outcomes measures	Mean annual rate of aneurysm expansion (average change in anteroposterior diameter), the number of AAAs that reached 5.5 cm in diameter, the number of patients who underwent elective surgery, adverse events,
Risk of bias assessment	1. Random sequence generation (selection bias): Low risk – participants were randomly assigned to treatment arms on a 1:1:1 basis using randomly permuted blocks of varying sizes by an independent statistician 2. Allocation concealment (selection bias): Unclear risk – Concealment methods were not explicitly stated

Full citation	**Bicknell CD, Kiru G, Falaschetti E, et al. (2016) An evaluation of the effect of an angiotens inconverting enzyme inhibitor on the growth rate of small abdominal aortic aneurysms: A randomized placebo-controlled trial (AARDVARK). European Heart Journal 37(42), 3213-3221**
	3. Blinding of participants and personnel (performance bias): Unclear risk – Authors stated that the drugs were not identical in appearance but were dispensed in identical opaque bottles. Authors then stated that technically patients could have investigated the composition of their prescribed trial drug. 4. Blinding of outcome assessment (detection bias): Low risk – Authors stated that neither ultrasonographers nor site investigators were aware of which tablets had been prescribed to each patient 5. Incomplete outcome data (attrition bias): Low risk – Rates of attrition were relatively low and similar between groups 6. Selective reporting (reporting bias): Low risk – No serious concerns relating to reporting bias were identified 7. Other bias: Low risk – No other risk of bias issues were identified Overall risk of bias: Low Directness: directly applicable

Exercise

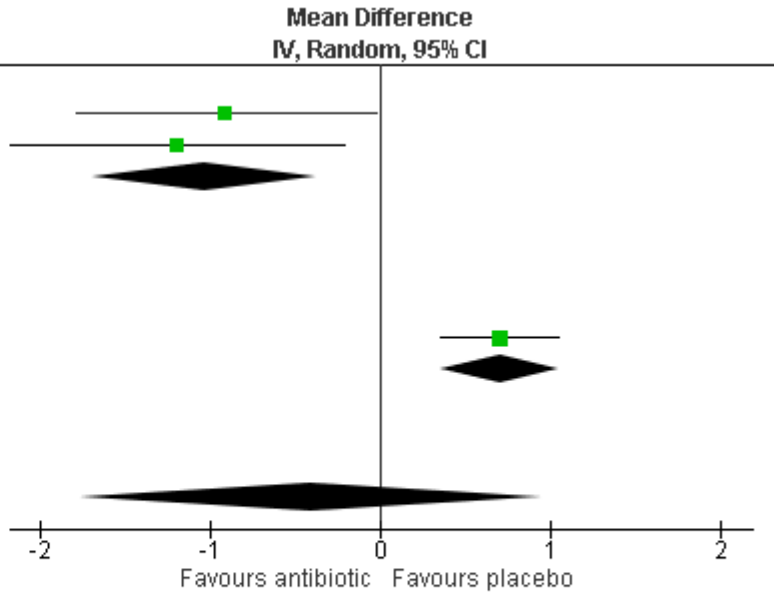
Full citation	**Tew GA, Moss J, Crank H, et al. (2012) Endurance exercise training in patients with small abdominal aortic aneurysm: a randomized controlled pilot study. Archives of physical medicine and rehabilitation 93(12), 2148-53**
Study details	Study type: multicentre, single-blind, randomised controlled trial Location: UK Aim: to investigate the feasibility of endurance exercise training in patients with small AAA Study dates: 2010 to 2011 Follow-up: 12 weeks Sources of funding: not reported; however authors reported no conflicts of interest
Participants	Population: people with a confirmed AAA ≥3.0cm in diameter who had not underwent AAA repair Sample size: 28 Inclusion criteria: people between 50 and 85 years with asymptomatic infrarenal AAAs ≥3.0 cm and <5.0 cm in diameter were included Exclusion criteria: contraindications to exercise testing and training (e.g., severe hypertension, unstable angina, and uncontrolled cardiac arrhythmias), and current participation in regular purposeful exercise (≥30min, ≥3 times per week) Comorbidities: • Mean age: exercise group, 71 years; standard care group, 74 years • Sex: exercise group, 90.9% male; standard care group, 78.6% male • Mean aneurysm diameter: exercise group, 4.1 cm; standard care group, 3.9 cm • Comorbidities: • Coronary artery disease: exercise group, 36.3 %; standard care group, 21.4% • Peripheral artery disease: exercise group, 0%; standard care group, 42.8% • Hypertension: exercise group, 54.5%; standard care group, 85.7% • Diabetes: exercise group, 18.2%; standard care group, 14.3%
Intervention	Exercise training
Comparison	Standard care
Outcomes measures	Mean change in aneurysm diameter
Risk of bias assessment	1. Random sequence generation (selection bias): Unclear risk – Randomisation was performed; however methods were not clearly specified

Full citation	Tew GA, Moss J, Crank H, et al. (2012) Endurance exercise training in patients with small abdominal aortic aneurysm: a randomized controlled pilot study. Archives of physical medicine and rehabilitation 93(12), 2148-53
	2. Allocation concealment (selection bias): Unclear risk – Concealment methods were not explicitly stated 3. Blinding of participants and personnel (performance bias): Low risk – It was not possible to blind participants of group allocations; however this is unlikely to bias results 4. Blinding of outcome assessment (detection bias): High risk – Investigators were not blinded of group allocations 5. Incomplete outcome data (attrition bias): Low risk – There were few losses to follow-up; all of which were explained 6. Selective reporting (reporting bias): Low risk – All relevant outcomes were reported appropriately 7. Other bias: Low risk - No other risk of bias issues were identified Overall risk of bias: Moderate Directness: directly applicable

Appendix E – Forest plots

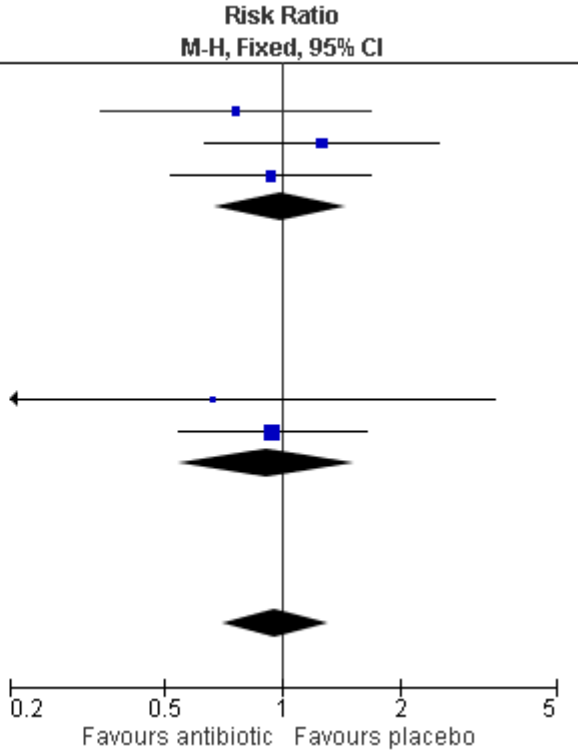
Antibiotics: AAA expansion

Study or Subgroup	Antibiotic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Macrolides								
Hogh 2009	1.61	1.5	42	2.52	2.5	42	32.3%	-0.91 [-1.79, -0.03]
Vammen 2001	1.56	2.4	43	2.75	2.4	49	31.2%	-1.19 [-2.17, -0.21]
Subtotal (95% CI)			**85**			**91**	**63.5%**	**-1.03 [-1.69, -0.38]**
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%								
Test for overall effect: Z = 3.09 (P = 0.002)								
1.1.2 Tetracycline								
Meijer 2013	2.8	1.5	144	2.1	1.5	142	36.5%	0.70 [0.35, 1.05]
Subtotal (95% CI)			**144**			**142**	**36.5%**	**0.70 [0.35, 1.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.95 (P < 0.0001)								
Total (95% CI)			**229**			**233**	**100.0%**	**-0.41 [-1.77, 0.95]**
Heterogeneity: Tau² = 1.28; Chi² = 21.13, df = 2 (P < 0.0001); I² = 91%								
Test for overall effect: Z = 0.59 (P = 0.55)								
Test for subgroup differences: Chi² = 20.96, df = 1 (P < 0.00001), I² = 95.2%								



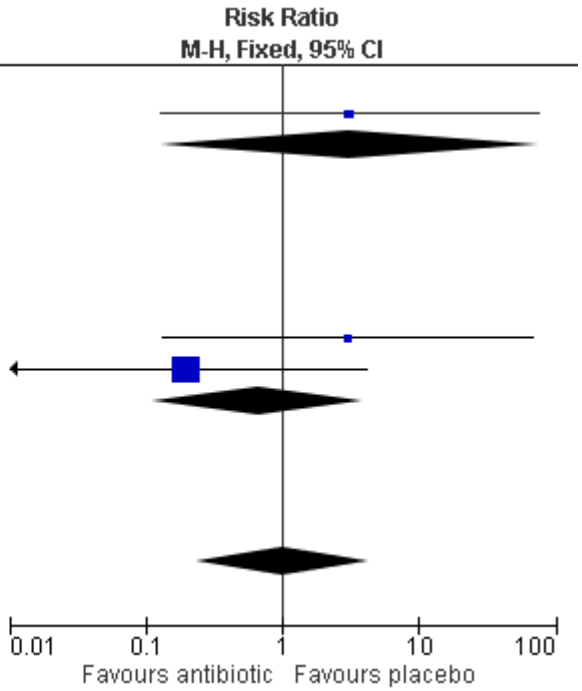
Antibiotics: referral to surgery

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Macrolide						
Vammen 2001	8	43	12	49	17.5%	0.76 [0.34, 1.68]
Karlsson 2009	16	122	13	125	20.0%	1.26 [0.63, 2.51]
Hogh 2009	14	42	15	42	23.4%	0.93 [0.52, 1.68]
Subtotal (95% CI)		**207**		**216**	**60.8%**	**0.99 [0.67, 1.47]**
Total events	38		40			
Heterogeneity: Chi² = 0.94, df = 2 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.04 (P = 0.96)						
2.1.2 Tetracycline						
Mosorin 2001	2	17	3	17	4.7%	0.67 [0.13, 3.50]
Meijer 2013	21	144	22	142	34.5%	0.94 [0.54, 1.63]
Subtotal (95% CI)		**161**		**159**	**39.2%**	**0.91 [0.54, 1.53]**
Total events	23		25			
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
Total (95% CI)		**368**		**375**	**100.0%**	**0.96 [0.70, 1.31]**
Total events	61		65			
Heterogeneity: Chi² = 1.14, df = 4 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.79)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%						



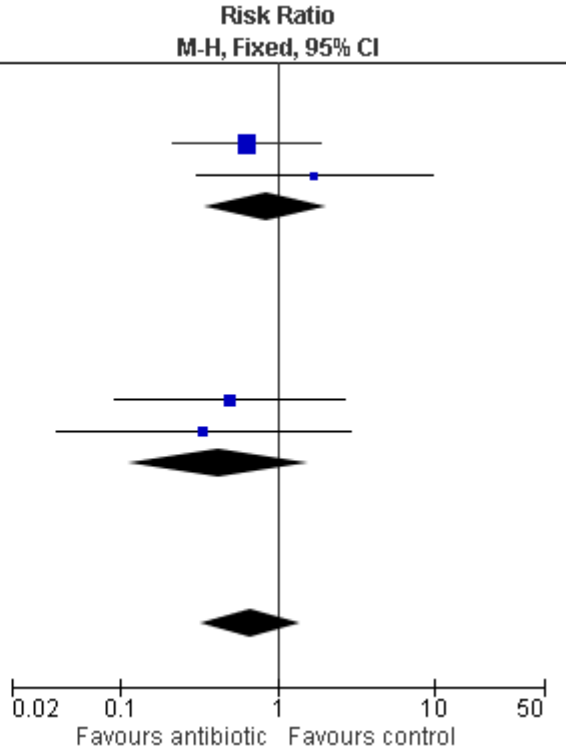
Antibiotics: rupture

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Macrolide						
Karlsson 2009	1	122	0	125	14.1%	3.07 [0.13, 74.71]
Subtotal (95% CI)		**122**		**125**	**14.1%**	**3.07 [0.13, 74.71]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
3.1.2 Tetracycline						
Mosorin 2001	1	17	0	17	14.2%	3.00 [0.13, 68.84]
Meijer 2013	0	144	2	142	71.7%	0.20 [0.01, 4.07]
Subtotal (95% CI)		**161**		**159**	**85.9%**	**0.66 [0.11, 3.87]**
Total events	1		2			
Heterogeneity: $Chi^2 = 1.51$, df = 1 (P = 0.22); $I^2 = 34\%$						
Test for overall effect: Z = 0.46 (P = 0.65)						
Total (95% CI)		**283**		**284**	**100.0%**	**1.00 [0.23, 4.33]**
Total events	2		2			
Heterogeneity: $Chi^2 = 2.05$, df = 2 (P = 0.36); $I^2 = 3\%$						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: $Chi^2 = 0.68$, df = 1 (P = 0.41), $I^2 = 0\%$						



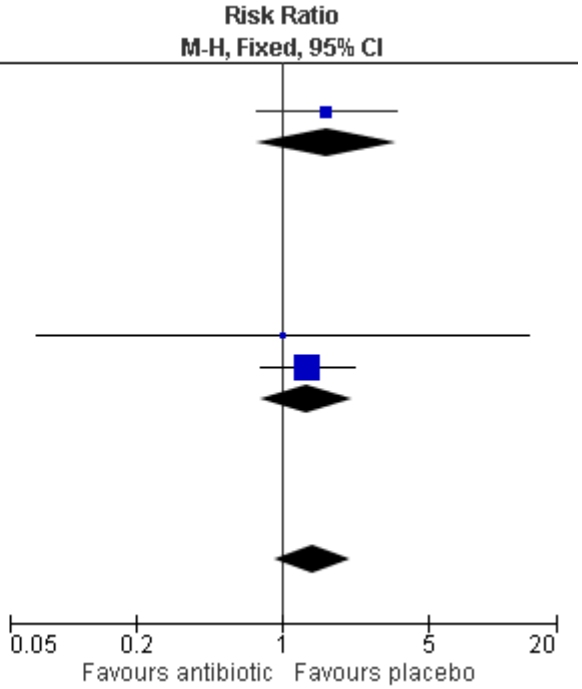
Antibiotics: all-cause mortality

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Macrolide						
Hogh 2009	0	42	0	42		Not estimable
Karlsson 2009	5	122	8	125	47.0%	0.64 [0.22, 1.90]
Vammen 2001	3	43	2	49	11.1%	1.71 [0.30, 9.75]
Subtotal (95% CI)		**207**		**216**	**58.2%**	**0.84 [0.34, 2.08]**
Total events	8		10			
Heterogeneity: Chi² = 0.88, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
4.1.2 Tetracycline						
Meijer 2013	2	144	4	142	24.0%	0.49 [0.09, 2.65]
Mosorin 2001	1	17	3	17	17.9%	0.33 [0.04, 2.89]
Subtotal (95% CI)		**161**		**159**	**41.8%**	**0.42 [0.11, 1.59]**
Total events	3		7			
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.27 (P = 0.20)						
Total (95% CI)		**368**		**375**	**100.0%**	**0.67 [0.32, 1.40]**
Total events	11		17			
Heterogeneity: Chi² = 1.65, df = 3 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.28)						
Test for subgroup differences: Chi² = 0.71, df = 1 (P = 0.40), I² = 0%						



Antibiotics: adverse events

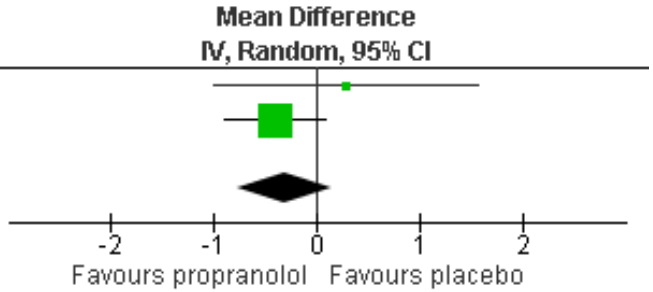
Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.1 Macrolide						
Hogh 2009	13	42	8	42	26.5%	1.63 [0.75, 3.51]
Subtotal (95% CI)		**42**		**42**	**26.5%**	**1.63 [0.75, 3.51]**
Total events	13		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.22)						
5.1.2 Tetracycline						
Mosorin 2001	1	17	1	17	3.3%	1.00 [0.07, 14.72]
Meijer 2013	28	144	21	142	70.1%	1.31 [0.78, 2.20]
Subtotal (95% CI)		**161**		**159**	**73.5%**	**1.30 [0.78, 2.16]**
Total events	29		22			
Heterogeneity: $Chi^2 = 0.04$, df = 1 (P = 0.84); $I^2 = 0\%$						
Test for overall effect: Z = 1.02 (P = 0.31)						
Total (95% CI)		**203**		**201**	**100.0%**	**1.39 [0.91, 2.12]**
Total events	42		30			
Heterogeneity: $Chi^2 = 0.26$, df = 2 (P = 0.88); $I^2 = 0\%$						
Test for overall effect: Z = 1.51 (P = 0.13)						
Test for subgroup differences: $Chi^2 = 0.22$, df = 1 (P = 0.64), $I^2 = 0\%$						



Propranolol: AAA expansion

Study or Subgroup	Propranolol Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lindholt 1999	3.12	2.4	30	2.84	2.4	24	12.8%	0.28 [-1.01, 1.57]
Propranolol trial 2002	2.2	2.8	277	2.6	3.1	275	87.2%	-0.40 [-0.89, 0.09]
Total (95% CI)			**307**			**299**	**100.0%**	**-0.31 [-0.77, 0.15]**

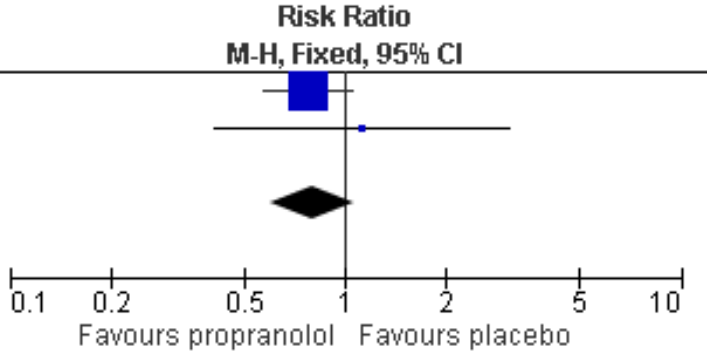
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 1.33 (P = 0.18)



Propranolol: referral to surgery

Study or Subgroup	Propranolol Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Propranolol trial 2002	56	277	72	275	92.9%	0.77 [0.57, 1.05]
Lindholt 1999	7	30	5	24	7.1%	1.12 [0.41, 3.09]
Total (95% CI)		**307**		**299**	**100.0%**	**0.80 [0.59, 1.07]**
Total events	63		77			

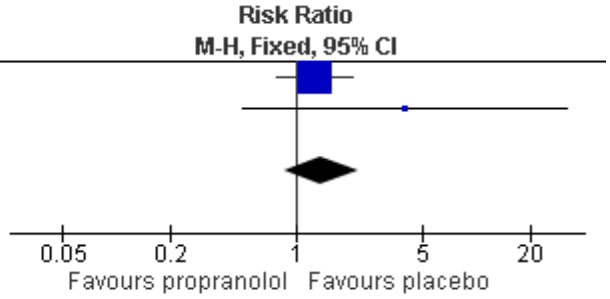
Heterogeneity: Chi² = 0.47, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.52 (P = 0.13)



Propranolol: all-cause mortality

Study or Subgroup	Propranolol Events	Propranolol Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Propranolol trial 2002	33	277	26	275	95.9%	1.26 [0.77, 2.05]
Lindholt 1999	5	30	1	24	4.1%	4.00 [0.50, 31.98]
Total (95% CI)		**307**		**299**	**100.0%**	**1.37 [0.86, 2.19]**
Total events	38		27			

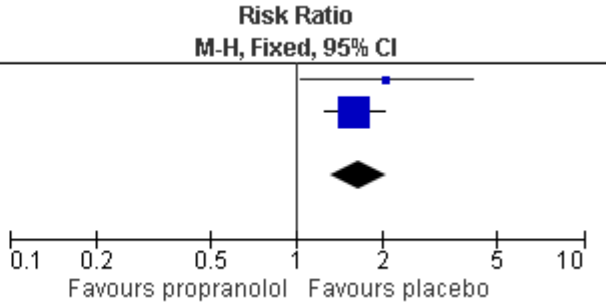
Heterogeneity: Chi² = 1.14, df = 1 (P = 0.29); I² = 12%
Test for overall effect: Z = 1.32 (P = 0.19)



Propranolol: adverse events

Study or Subgroup	Propranolol Events	Propranolol Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lindholt 1999	18	30	7	24	9.6%	2.06 [1.03, 4.10]
Propranolol trial 2002	117	277	73	275	90.4%	1.59 [1.25, 2.02]
Total (95% CI)		**307**		**299**	**100.0%**	**1.64 [1.30, 2.05]**
Total events	135		80			

Heterogeneity: Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 4.26 (P < 0.0001)



Appendix F – GRADE tables

Antibiotics

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Antibiotic	Placebo	Summary of results	
Annual AAA growth rate (mm per year); effects below 0 favour antibiotic									
2 (Hogh 2009, Meijier 2013, Vammen 2001)	RCTs	Serious[1]	Not serious	Very serious[2]	Serious[3]	229	233	MD -0.41 (-1.77,-0.95)	Very low
Median differences in aneurysm growth at 18 month follow-up (mm); effects below 0 favour antibiotic									
1 Mosornin 2001	RCT	Very serious[4,5]	Not serious	N/A	Serious[3]	107	106	Difference in medians: -1.5 mm (Non-significant according to the Mann-Whitney test)	Very low
Referral to AAA surgery; effects below 1 favour antibiotic									
5 (Hogh 2009, Vammen 2001, Meijer 2013, Mosornin 2001, Karlsson 2009)	RCTs	Not serious	Not serious	Not serious	Very serious[6]	368	375	RR 0.96 (0.70, 1.31)	Low
Aneurysm rupture; effects below 1 favour antibiotic									
3 (Meijer 2013, Mosornin 2001, Karlsson 2009)	RCTs	Not serious	Not serious	Not serious	Very serious[6]	283	284	RR 1.00 (0.23, 4.33)	Low
All-cause mortality; effects below 1 favour antibiotic									
5 (Hogh 2009, Vammen 2001, Meijer 2013, Mosornin 2001, Karlsson 2009)	RCTs	Not serious	Not serious	Not serious	Very serious[6]	368	375	RR 0.67 (0.32, 1.40)	Low

Quality assessment						No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Antibiotic**	**Placebo**	**Summary of results**	
Any adverse events; effects below 1 favour antibiotic									
3 (Hogh 2009, Meijer 2013, Mosornin 2001)	RCTs	Not serious	Not serious	Not serious	Serious[7]	203	201	RR 1.39 (0.91, 2.12)	Moderate

1. Insufficient information was available to ascertain risk of bias in the included study, downgrade 1 level.
2. I^2 value greater than 66.7%, downgrade 2 levels.
3. Non-significant result, downgrade 1 level.
4. Considerable differences were observed between baseline characteristics of each study arm, downgrade 1 level.
5. Authors reported some losses to follow-up, but the number and handling of censored cases was not clarified, downgrade 1 level.
6. Confidence interval crosses two lines of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 2 levels
7. Confidence interval crosses one line of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 1 level.

Propranolol

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Antibiotic	Placebo	Summary of results	
Mean difference in annual AAA growth rate (mm per year); effect sizes below 0 favour propranolol									
2 (Propranolol 2002, Lindholt 1999)	RCTs	Very serious[1]	Not serious	Not serious	Serious[2]	307	299	MD -0.31 (-0.77, 0.15)	Very low
Referral to AAA surgery; effect sizes below 1 favour propranolol									
2 (Propranolol 2002, Lindholt 1999)	RCTs	Very serious[1]	Not serious	Not serious	Serious[3]	307	299	RR 0.80 (0.59, 1.07)	Very low
Aneurysm rupture; effect sizes below 1 favour propranolol									
1 Propranolol 2002	RCT	Very serious[1]	Not serious	N/A	Very serious[4]	275	284	RR 0.50 (0.05, 5.44)	Very low
All-cause mortality; effect sizes below 1 favour propranolol									
2 (Propranolol 2002, Lindholt 1999)	RCTs	Very serious[1]	Not serious	Not serious	Serious[3]	307	299	RR 1.37 (0.86, 2.19)	Very low
Adverse events causing discontinuation; effect sizes below 1 favour propranolol									
2 (Propranolol 2002, Lindholt 1999)	RCTs	Very serious[1]	Not serious	Not serious	Not serious	307	299	RR 1.64 (1.30, 2.05)	Low

1. Insufficient details about numbers of patients lost to follow-up, reasons for losses, and numbers of participants remaining at each follow-up interval. Downgrade 1 level.
2. Non-significant result, downgrade 1 level.
3. Confidence interval crosses one line of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 1 level.
4. Confidence interval crosses two lines of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 2 levels.

ACE-inhibitors

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Antibiotic	Placebo	Summary of results	
Mean difference in annual AAA growth rate (mm per year); effect sizes below 0 favour ACE-inhibitor									
1, Bicknell 2013	RCTs	Not serious	Not serious	N/A	Serious[1]	73	79	MD 0.08 (95% CI not reported)	Moderate
Referral to AAA surgery at 2 year follow-up; effect sizes below 1 favour ACE-inhibitor									
1, Bicknell 2013	RCTs	Not serious	Not serious	N/A	Very serious[2]	73	79	RR 1.20 (0.52, 2.79)	Low
All-cause mortality at 2 year follow-up; effect sizes below 1 favour ACE-inhibitor									
1, Bicknell 2013	RCTs	Not serious	Not serious	N/A	Very serious[2]	73	79	RR 0.36 (0.04, 3.39)	Low
Adverse events causing discontinuation; effect sizes below 1 favour ACE-inhibitor									
1, Bicknell 2013	RCTs	Not serious	Not serious	N/A	Very serious[2]	73	79	RR 1.76 (0.77, 4.00)	Low

1. Non-significant result, downgrade 1 level.
2. Confidence interval crosses two lines of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 2 levels.
3. Confidence interval crosses one line of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 1 level.

Calcium channel blockers

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Antibiotic	Placebo	Summary of results	
Mean difference in annual AAA growth rate (mm per year); effect sizes below 0 favour calcium channel blocker									
1, Bicknell 2013	RCTs	Not serious	Not serious	N/A	Serious[1]	72	79	MD 0.12 (95% CI not reported)	Moderate
Referral to AAA surgery at 2 year follow-up; effect sizes below 1 favour calcium channel blocker									
1, Bicknell 2013	RCTs	Not serious	Not serious	N/A	Very serious[2]	72	79	RR 0.87 (0.32, 2.20)	Low
All-cause mortality at 2 year follow-up; effect sizes below 1 favour calcium channel blocker									
1, Bicknell 2013	RCTs	Not serious	Not serious	N/A	Very serious[2]	72	79	RR 1.11 (0.23, 5.34)	Low
Adverse events causing discontinuation; effect sizes below 1 favour calcium channel blocker									
1, Bicknell 2013	RCTs	Not serious	Not serious	N/A	Serious[3]	72	79	RR 1.95 (0.87, 4.37)	Moderate

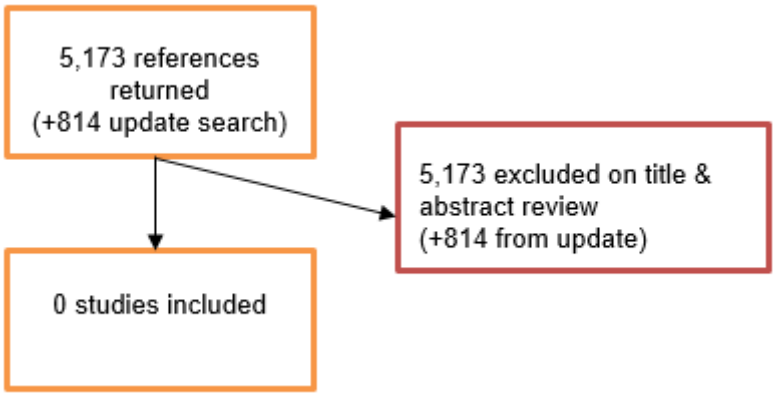
1. Non-significant result, downgrade 1 level.
2. Confidence interval crosses two lines of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 2 levels
3. Confidence interval crosses one line of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 1 level.

Exercise

Quality assessment						No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Antibiotic**	**Placebo**	**Summary of results**	
Mean difference in AAA growth at 3 month follow-up(mm); effect sizes below 0 favour exercise									
1, Tew 2012	RCTs	Serious[1]	Not serious	N/A	Serious[2]	11	14	MD -0.1 (-1.5, 1.2)	Low

1. Assessors were not blinded to treatment allocations, downgrade 1 level.
2. Non-significant result, downgrade 1 level.

Appendix G – Economic evidence study selection



Appendix H – Excluded studies

Clinical studies

No.	Study	Reason for exclusion
1	Bergqvist D, Lindeman JHN, Lindholt JS, et al. (2013) Antimicrobial treatment to impair expansion of abdominal aortic aneurysm (AAA): a systematic review of the clinical evidence. Current vascular pharmacology 11(3), 288-92	Systematic review which included studies that employed multiple study designs. Individual studies were assessed to establish if they met criteria for inclusion in this NICE review.
2	Dunne Jonathan A, Bailey Marc A, Griffin Kathryn J, et al. (2014) Statins: the holy grail of Abdominal Aortic Aneurysm (AAA) growth attenuation? A systematic review of the literature. Current vascular pharmacology 12(1), 168-72	Systematic review which included studies that employed multiple study designs. Individual studies were assessed to establish if they met criteria for inclusion in this NICE review.
3	Gunasekera RC, Moss J, Crank H, et al. (2014) Patient recruitment and experiences in a randomised trial of supervised exercise training for individuals with abdominal aortic aneurysm. Journal of vascular nursing: official publication of the Society for Peripheral Vascular Nursing 32(1), 4-9	This is a qualitative study which used focus groups to assess patients' views on a supervised exercise training programme. The study design and outcomes reported are not in line with the review protocol
4	Kiru G, Bicknell C, Falaschetti E, et al. (2016) An evaluation of the effect of an angiotensin-converting enzyme inhibitor on the growth rate of small abdominal aortic aneurysms: A randomised placebo-controlled trial (AARDVARK). Health Technology Assessment 20(59), 1-180	Conference abstract
5	Kokje VBC, Hamming JF, and Lindeman JHN (2015) Editor's Choice - Pharmaceutical Management of Small Abdominal Aortic Aneurysms: A	Systematic review which included studies that employed multiple study designs. Individual studies were assessed to establish if they met criteria for inclusion in this NICE review.

No.	Study	Reason for exclusion
	Systematic Review of the Clinical Evidence. European Journal of Vascular and Endovascular Surgery 50(6), 702-713	
6	Lima RM, Vainshelboim B, Ganatra R, et al. (2017) Exercise Training Improves Ventilatory Efficiency in Patients With a Small Abdominal Aortic Aneurysm: A RANDOMIZED CONTROLLED STUDY. Journal of cardiopulmonary rehabilitation and prevention ,	This study did not assess whether the intervention (exercise training) was effective in slowing aneurysm expansion or reducing the risk of rupture. Instead, investigators assessed the cardiorespiratory responses and exercise capacities of patients after 3 months.
7	McElrath M, Myers J, Chan K, and Fonda H (2017) Exercise adherence in the elderly: Experience with abdominal aortic aneurysm simple treatment and prevention. Journal of vascular nursing : official publication of the Society for Peripheral Vascular Nursing 35(1), 12-20	Study explored cardiopulmonary outcomes of people who underwent exercise testing. No useful data was available relating to reduction in AAA diameter.
8	Murohara T, Kureishi BY, Nishigami K, et al. (2015) Effects of angiotensin-II receptor blocker or calcium channel blocker on abdominal aortic aneurysm growth at presurgical stage. European heart journal. 36, 880-881	Conference abstract
9	Myers J, McElrath M, Jaffe A, et al. (2014) A randomized trial of exercise training in abdominal aortic aneurysm disease. Medicine and science in sports and exercise 46(1), 2-9	Study included people with AAAs less than 3.0 cm in diameter. No details were provided on what proportion of the study population had aneurysms less than 3.0 cm in diameter. Furthermore, the study mainly explored cardiopulmonary outcomes of participants. Data relating to AAA diameter was reported in the form of linear regression coefficients. This was not considered useful for this review question
10	Robertson L, Atallah E, and Stansby G (2014) Pharmacological treatment of vascular risk factors for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm. The Cochrane database of systematic reviews (1), CD010447	Systematic review including studies that assessed outcomes of patients who have undergone aortic surgery. Patients who have undergone aortic surgery are out of scope of this NICE review.
11	Robertson L, Atallah E, and Stansby G (2017) Pharmacological treatment of vascular risk factors for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm. The Cochrane database of systematic reviews 1, CD010447	Systematic review including studies that assessed outcomes of patients who have undergone aortic surgery. Patients who have undergone aortic surgery are out of scope of this NICE review.
12	Salata K, Syed M, Hussain MA, et al. (2017) Renin-angiotensin system blockade does not attenuate abdominal aortic aneurysm growth, rupture rate, or	Systematic review which included studies that employed multiple study designs. Individual studies were assessed to establish if they met criteria for inclusion in this NICE review.

No.	Study	Reason for exclusion
	perioperative mortality after elective repair. Journal of Vascular Surgery ,	
13	Takagi H, Yamamoto H, Iwata K, et al. (2012) Effects of statin therapy on abdominal aortic aneurysm growth: a meta-analysis and meta-regression of observational comparative studies. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 44(3), 287-92	Systematic review of cohort and case-controls studies.
14	Takagi H, Umemoto T, and Alice group (2017) Vitamins and abdominal aortic aneurysm. International angiology : a journal of the International Union of Angiology 36(1), 21-30	Systematic review of case-control studies.
15	Wilmink ABM, Hubbard CSFF, Day NE, Quick CRG. Effect of Propanolol on the expansion of abdominal aortic aneurysms: a randomised study. British Journal of Surgery 2000;87(4):499.	Grey literature considered in the Cochrane review which is only available as a conference abstract

Economic studies

No full text papers were retrieved. All studies were excluded at review of titles and abstracts.

Appendix I – Research recommendations

Research recommendation on macrolides

Research recommendation	What are the benefits and harms of macrolides (such as azithromycin) for reducing AAA growth rates and the risk of rupture?
Population	People with a confirmed abdominal aortic aneurysm >3cm in diameter who have not undergone aortic surgery
Intervention(s)	Macrolides (ideally those that are licensed for use in the UK)
Comparator(s)	Matched placebo
Outcomes	• AAA rupture • AAA growth/expansion • Surgery/referral for surgery • Mortality (all-cause; cardiovascular (e.g. fatal myocardial infarction, fatal stroke, other vascular deaths); AAA-related) • Nonfatal cardiovascular events • Major amputation • Quality of life • Adverse effects • Resource use and cost
Study design	Randomised controlled trial

Potential criterion	Explanation
Importance to patients, service users or the population	Small AAAs are currently managed by monitoring, until the aneurysm reaches a diameter at which surgical repair is needed. There are currently no non-surgical interventions available to prevent AAAs from growing, and subsequently rupturing. Clinical research in this area would be useful for developing a secondary prevention strategy to prevent rupture.
Relevance to NICE guidance	High priority: no recommendations were made on macrolides due to a lack of robust evidence. Further research would allow for recommendations to be possible in future guideline updates.
Current evidence base	Trials assessing the use of the macrolide, roxithromycin, have suggested that the antibiotic may have a role in reducing aneurysm growth; however, it is currently not licensed for use in the UK. As it was not considered appropriate to extrapolate the potential benefits of roxithromycin to other macrolides, more evidence is needed to ascertain the clinical utility of the drug class. Furthermore, in an age of antibiotic stewardship, well-conducted research is needed to demonstrate that any benefits produced by macrolides will offset any harms associated with antibiotic resistance.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a sufficiently large and well defined population available that randomised controlled trials in this area should be feasible.

Research recommendation on metformin

Research recommendation	What are the benefits and harms of metformin for reducing AAA growth rates and the risk of rupture?
Population	People with a confirmed abdominal aortic aneurysm >3cm in diameter who have not undergone aortic surgery
Intervention(s)	Metformin
Comparator(s)	Matched placebo

Research recommendation	What are the benefits and harms of metformin for reducing AAA growth rates and the risk of rupture?
Outcomes	• AAA rupture • AAA growth/expansion • Surgery/referral for surgery • Mortality (all-cause; cardiovascular (e.g. fatal myocardial infarction, fatal stroke, other vascular deaths); AAA-related) • Nonfatal cardiovascular events • Major amputation • Quality of life • Adverse effects • Resource use and cost
Study design	Randomised controlled trial

Potential criterion	Explanation
Importance to patients, service users or the population	Observational study data suggests an association between diabetes and slower aneurysm growth, and it has been proposed that this is caused by taking metformin. Randomised controlled trials are needed to determine whether metformin reduces the rate of aneurysm growth.
Relevance to NICE guidance	High priority: no recommendations were made on metformin in this guideline due to a lack of robust evidence. Further research would allow for recommendations to be possible in future guideline updates.
Current evidence base	No evidence was found that assessed the use of metformin for reducing AAA growth, as well the risk of rupture.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a sufficiently large and well defined population available that randomised controlled trials in this area should be feasible.

Appendix J – Glossary

Abdominal Aortic Aneurysm (AAA)

A localised bulge in the abdominal aorta (the major blood vessel that supplies blood to the lower half of the body including the abdomen, pelvis and lower limbs) caused by weakening of the aortic wall. It is defined as an aortic diameter greater than 3 cm or a diameter more than 50% larger than the normal width of a healthy aorta. The clinical relevance of AAA is that the condition may lead to a life threatening rupture of the affected artery. Abdominal aortic aneurysms are generally characterised by their shape, size and cause:

- Infrarenal AAA: an aneurysm located in the lower segment of the abdominal aorta below the kidneys.
- Juxtarenal AAA: a type of infrarenal aneurysm that extends to, and sometimes, includes the lower margin of renal artery origins.
- Suprarenal AAA: an aneurysm involving the aorta below the diaphragm and above the renal arteries involving some or all of the visceral aortic segment and hence the origins of the renal, superior mesenteric, and celiac arteries, it may extend down to the aortic bifurcation.

Abdominal compartment syndrome

Abdominal compartment syndrome occurs when the pressure within the abdominal cavity increases above 20 mm Hg (intra-abdominal hypertension). In the context of a ruptured AAA this is due to the mass effect of a volume of blood within or behind the abdominal cavity. The increased abdominal pressure reduces blood flow to abdominal organs and impairs pulmonary, cardiovascular, renal, and gastro-intestinal function. This can cause multiple organ dysfunction and eventually lead to death.

Cardiopulmonary exercise testing

Cardiopulmonary Exercise Testing (CPET, sometimes also called CPX testing) is a non-invasive approach used to assess how the body performs before and during exercise. During CPET, the patient performs exercise on a stationary bicycle while breathing through a mouthpiece. Each breath is measured to assess the performance of the lungs and cardiovascular system. A heart tracing device (Electrocardiogram) will also record the hearts electrical activity before, during and after exercise.

Device migration

Migration can occur after device implantation when there is any movement or displacement of a stent-graft from its original position relative to the aorta or renal arteries. The risk of migration increases with time and can result in the loss of device fixation. Device migration may not need further treatment but should be monitored as it can lead to complications such as aneurysm rupture or endoleak.

Endoleak

An endoleak is the persistence of blood flow outside an endovascular stent - graft but within the aneurysm sac in which the graft is placed.

- Type I – Perigraft (at the proximal or distal seal zones): This form of endoleak is caused by blood flowing into the aneurysm because of an incomplete or ineffective seal at either end of an endograft. The blood flow creates pressure within the sac and significantly increases the risk of sac enlargement and rupture. As a result, Type I endoleaks typically require urgent attention.
- Type II – Retrograde or collateral (mesenteric, lumbar, renal accessory): These endoleaks are the most common type of endoleak. They occur when blood bleeds into the sac from small side branches of the aorta. They are generally considered benign because they are usually at low pressure and tend to resolve spontaneously over time without any need for intervention. Treatment of the endoleak is indicated if the aneurysm sac continues to expand.
- Type III – Midgraft (fabric tear, graft dislocation, graft disintegration): These endoleaks occur when blood flows into the aneurysm sac through defects in the endograft (such as graft fractures, misaligned graft joints and holes in the graft fabric). Similarly to Type I endoleak, a Type III endoleak results in systemic blood pressure within the aneurysm sac that increases the risk of rupture. Therefore, Type III endoleaks typically require urgent attention.
- Type IV– Graft porosity: These endoleaks often occur soon after AAA repair and are associated with the porosity of certain graft materials. They are caused by blood flowing through the graft fabric into the aneurysm sac. They do not usually require treatment and tend to resolve within a few days of graft placement.
- Type V – Endotension: A Type V endoleak is a phenomenon in which there is continued sac expansion without radiographic evidence of a leak site. It is a poorly understood abnormality. One theory that it is caused by pulsation of the graft wall, with transmission of the pulse wave through the aneurysm sac to the native aneurysm wall. Alternatively it may be due to intermittent leaks which are not apparent at imaging. It can be difficult to identify and treat any cause.

Endovascular aneurysm repair

Endovascular aneurysm repair (EVAR) is a technique that involves placing a stent –graft prosthesis within an aneurysm. The stent-graft is inserted through a small incision in the femoral artery in the groin, then delivered to the site of the aneurysm using catheters and guidewires and placed in position under X-ray guidance.

- Conventional EVAR refers to placement of an endovascular stent graft in an AAA where the anatomy of the aneurysm is such that the ‘instructions for use’ of that particular device are adhered to. Instructions for use define tolerances for AAA anatomy that the device manufacturer considers appropriate for that device. Common limitations on AAA anatomy are infrarenal neck length (usually >10mm), diameter (usually ≤30mm) and neck angle relative to the main body of the AAA
- Complex EVAR refers to a number of endovascular strategies that have been developed to address the challenges of aortic proximal neck fixation associated with complicated aneurysm anatomies like those seen in juxtarenal and suprarenal AAAs. These strategies include using conventional infrarenal aortic stent grafts outside their ‘instructions for use’, using physician-modified endografts, utilisation of customised fenestrated endografts, and employing snorkel or chimney approaches with parallel covered stents.

Goal directed therapy

Goal directed therapy refers to a method of fluid administration that relies on minimally invasive cardiac output monitoring to tailor fluid administration to a maximal cardiac output or other reliable markers of cardiac function such as stroke volume variation or pulse pressure variation.

Post processing technique

For the purpose of this review, a post-processing technique refers to a software package that is used to augment imaging obtained from CT scans, (which are conventionally presented as axial images), to provide additional 2- or 3-dimensional imaging and data relating to an aneurysm's, size, position and anatomy.

Permissive hypotension

Permissive hypotension (also known as hypotensive resuscitation and restrictive volume resuscitation) is a method of fluid administration commonly used in people with haemorrhage after trauma. The basic principle of the technique is to maintain haemostasis (the stopping of blood flow) by keeping a person's blood pressure within a lower than normal range. In theory, a lower blood pressure means that blood loss will be slower, and more easily controlled by the pressure of internal self-tamponade and clot formation.

Remote ischemic preconditioning

Remote ischemic preconditioning is a procedure that aims to reduce damage (ischaemic injury) that may occur from a restriction in the blood supply to tissues during surgery. The technique aims to trigger the body's natural protective functions. It is sometimes performed before surgery and involves repeated, temporary cessation of blood flow to a limb to create ischemia (lack of oxygen and glucose) in the tissue. In theory, this "conditioning" activates physiological pathways that render the heart muscle resistant to subsequent prolonged periods of ischaemia.

Tranexamic acid

Tranexamic acid is an antifibrinolytic agent (medication that promotes blood clotting) that can be used to prevent, stop or reduce unwanted bleeding. It is often used to reduce the need for blood transfusion in adults having surgery, in trauma and in massive obstetric haemorrhage.