Evidence Synthesis

Number 184

Primary Care Screening for Abdominal Aortic Aneurysm: A Systematic Evidence Review for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. HHSA-290-2015-000017-I-EPC5, Task Order No. 3

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AHRQ Publication No. 19-05253-EF-1
June 2019

This report is based on research conducted by the Kaiser Permanente Research Affiliates Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA-290-2015-000017-I-EPC5, Task Order No. 3). The findings and conclusions in this document are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: Ernest Sullivent, MD, MPH, and Iris Mabry-Hernandez, MD, at AHRQ; current and former members of the U.S. Preventive Services Task Force who contributed to topic deliberations; Frank Lederle, MD, former director at the Minneapolis Veterans Affairs Center for Epidemiological and Clinical Research for his longstanding support and expertise in this field; and Shannon Robalino, MS, Smyth Lai, MLS, and Katherine Essick, BS, at the Kaiser Permanente Center for Health Research for technical and editorial assistance.
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Structured Abstract

Objective: To systematically review evidence about the benefits and harms of ultrasound-based abdominal aortic aneurysm (AAA) screening and small aneurysm treatment in primary care populations, including subpopulations of older adults, women, smokers, racial/ethnic subgroups, and those with a family history of AAA.

Data Sources: We performed a search of MEDLINE, PubMed (Publisher Supplied only), the Database of Abstracts of Reviews of Effects, and the Cochrane Collaboration Registry of Controlled Trials for relevant English-language studies published between January 2012 and September 14, 2018. Additionally, we re-evaluated all studies included in the 2014 USPSTF review. We supplemented searches by examining bibliographies from retrieved articles and consulting outside experts. We searched Federal Agency trial registries for ongoing and/or unpublished trials.

Study Selection: Two investigators independently reviewed identified abstracts and full-text articles against a set of *a priori* inclusion and quality criteria. Resolution of disagreements occurred through discussion with a third reviewer. We included the following study designs: randomized controlled trials (RCTs) for the effectiveness of screening and small aneurysm treatment interventions; randomized controlled trials and large cohort studies for rescreening effectiveness and screening/rescreening harms; and randomized controlled trials, large cohort studies, and vascular survey registries for small aneurysm treatment harms.

Data Analysis: One investigator abstracted data into evidence tables and a second investigator checked accuracy. We qualitatively synthesized the data for each Key Question and meta-analyzed trial results for Key Questions 1 and 3. Our analyses utilized the Peto method to pool odds ratios (for AAA-related mortality, rupture, and operations) and the DerSimonian and Laird random effects model to pool calculated risk ratios (for all-cause mortality). Subgroup-specific results were abstracted and qualitatively synthesized from any included studies reporting outcomes for our *a priori* list of subgroups.

Results: Based on four fair- to good-quality, population-based RCTs (N=124,929), the invitation for screening men aged 65 years and older was associated with a 35 percent reduction in AAA-related mortality and a 38 percent reduction in AAA rupture rate; screening was also associated with a 43 percent reduction in the number of emergency surgeries. There was no statistically significant difference, however, in all-cause mortality at 12 to 15-year followup. Based on eight heterogeneous, short-term rescreening studies (N= 8,018) with a variety of protocols (rescreening annually to 5 years with a total of 1 to 6 repeated scans), AAA-related mortality up to 5 to 12 years appears to be rare (< 3%) among those with normal aortas (< 3 cm) on the initial scan. Upon rescreening, few aortas (0 to 2.2%) expanded to > 5 cm at 5 years and 0 to 15 percent had progressed at 10 years. One-time screening is associated with a nearly 44 percent more surgeries in the invited group compared to the control group (K=5, N=175,085; Peto OR 1.44 [95% Confidence Interval [CI], 1.34 to 1.55]), largely driven by elective operations (Peto OR 1.75 [95% CI, 1.61 to 1.90]). There was no statistically significant difference in 30-day mortality rates in the invited versus control groups for either elective surgeries or emergency surgeries at the 12- to 15-year followup. Five studies generally showed no significant long-term differences

in quality of life, anxiety, and depression scores between those who screen positive and those who screen negative up to 12 months. Four fair-to-good quality studies (N=3,314) of small aneurysm (4.0 to 5.4 cm) treatment demonstrate that endovascular repair (EVAR) and open repair are associated with no difference in AAA-related mortality or all-cause mortality compared to surveillance. Early open repair, however, was found to significantly reduce the rate of rupture compared with surveillance. These four trials show an approximately 50 to 100 percent increase in procedures in the early surgery group and no difference in 30-day mortality rates. Complications such as cardiac, pulmonary, and renal events reported in registry databases were generally comparable to those reported in the trials, with the exception of reintervention rates for open repair, which were higher in the registries than in the open trial reporting this outcome. Seven fair-quality, short-term drug trials (N= 1,553) of antibiotic, antihypertensive medications, and mast cell stabilizers showed no overall effect on AAA growth compared to placebo. Propranolol trials, however, reported high withdrawals due to adverse events, but other drugs appear to be well-tolerated.

There are limited data on screening effectiveness or harms in subpopulations; outcomes were rarely reported by subpopulation and when available, the data are fraught with methodologic limitations. For small aneurysm treatment, available evidence from registry data (k=3, N=14,424) shows that women have higher surgical complications and postoperative mortality compared with men. Two trials reported no differences in all-cause mortality associated with open surgical repair of small aneurysm by age, sex, or smoking history.

Limitations: Trials included mostly white men outside of the United States. Information for subgroups and about rescreening was limited.

Conclusions: A one-time invitation for AAA screening in men aged 65 years and older was associated with decreased AAA-related mortality and rupture rates but had little or no effect on all-cause mortality. Screening is associated with higher rates of elective surgery, but there are no long-term differences in the quality of life in those who screen positive. Treatment of small, screen-detected AAA with early open or EVAR surgery did not result in improved health outcomes compared with surveillance but result in more elective surgeries. There are limited data on pharmacotherapy treatment of small aneurysms showing no statistically significant effect on AAA growth rates. There are limited data on screening effectiveness or harms in subpopulations; small aneurysm surgical complication rates appear to be greater in women than in men.

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Chapter 1. Introduction

Condition Background

Condition Definition

An abdominal aortic aneurysm (AAA) is a weakening in the wall of the abdominal aorta with resultant increased pressure leading to aneurysm formation.[1] A large proportion of AAAs are asymptomatic until the development of rupture. AAA rupture can be acute and is associated with a high mortality rate.[1-3]

An AAA is most commonly defined as an arterial diameter of 3.0 centimeters (cm) or larger.[2, 4] This threshold is more than two standard deviations above the average diameter of the abdominal aorta (2.0 cm) in both men and women.[5] The abdominal aorta diameter varies by age, sex, and body size, which may influence the accuracy of this definition in some subgroups.[5] An AAA is less frequently defined as a maximum infrarenal aortic diameter being at least 1.5 times larger than the expected infra-renal aortic diameter.[4] Aneurysms measuring 3 to 5.4 cm are commonly referred to as small aneurysms and those ≥5.5 cm are referred to as large aneurysms.

Prevalence and Burden

The incidence of AAA in the general population appears to be shifting over time. Previous prevalence rates of AAAs reported in population-based screening studies conducted 1 to 2 decades ago in the United States (U.S.), United Kingdom (UK), Australia, Sweden, and Italy ranged from 1.6 to 7.2 percent of the general population aged 60 to 65 years or older.[6-15] More recent studies, however, have reported a decline in AAA prevalence among screened men aged 65 years and older over the past 2 decades in the United Kingdom,[16-18] New Zealand,[19] Sweden,[10, 20, 21] and Denmark,[22] with reported prevalence rates ranging from 1.2 to 3.3 percent. This trend is thought to be largely due to a decrease in smoking prevalence over time.

Age, sex, and smoking influence subpopulation prevalence of AAA. The prevalence of AAA differs substantially by sex: 1.6 to 8.8 percent in men versus 0.2 to 6.2 percent in women, and the ratio of prevalence is generally 4 to 6 times greater in men than women.[6, 9, 11, 23-25] Age has also been found to influence the incidence of AAA, with the prevalence of AAAs increasing with age.[7, 11, 26-28] In a self-referred, self-pay screening cohort study (n=3,056,455) the risk of AAA was found to increase notably as age increased (age 55 to 59 years [adjOR 2.76, 95% CI, 2.55 to 3], age 75 to 79 years [adjOR 20.43, 95% CI, 18.99 to 21.99] as compared to those <55 years).[29] The same cohort reported a much higher risk for smokers as compared to non-smokers (adjOR 2.61 [95% CI, 2.47 to 2.74] for individuals smoking more than 0.5 packs a day for ≤10 years; adjOR 8.96 [95% CI, 8.57 to 9.36] in individuals smoking more than 0.5 packs a day > 35 years).[29] Additionally, the trend in prevalence found in another U.S.-based cohort study found that the lifetime risk of developing an AAA was 10.5 percent in current smokers, 6.3 percent in former smokers, and only 2 percent in never smokers.[30]

In 2016, AAAs were responsible for 3,787 deaths in the United States and were recorded as contributing to 151,493 deaths globally in 2013.[31] Each year, approximately 200,000 people are diagnosed with AAAs in the United States, about 15,000 of whom develop AAAs large enough to be considered high risk for rupture.[1] A rupture is often fatal; an estimated 81 percent of patients die if their aneurysm ruptures, with approximately one-third of patients dying prior to reaching the hospital.[32] Recent registry data report that in hospital mortality associated with ruptured AAA is estimate to be 53 percent and 65 percent in the United States and the United Kingdom, respectively.[33] One meta-analysis estimates that in-hospital mortality of those with rupture who survive until surgery has been estimated to range from 4 to 38 percent (pooled mortality 21%).[32] Mortality rates from ruptured AAA following intervention appear to be higher among women compared with men.[34, 35] The vast majority of deaths from ruptured AAAs occur after the age of 65 years.[36-39]

Data on the total societal economic burden of AAAs are currently not available. From 2009–2012, Medicare actual payments per AAA repair ranged from approximately $32,000 to $48,000. Indirect costs (e.g., disability) add substantially to the economic burden of AAA.[40]

Etiology and Natural History

Although the direct causes for the development of AAAs are not fully understood, studies have suggested that smoking,[3, 41, 42] atherosclerosis,[43, 44] degeneration of the aortic wall,[2] and inflammation[45, 46] may all contribute to the development of AAAs. In addition to the genetically linked connective tissue disorders (e.g. Ehlers-Danlos syndrome), evidence suggesting that genetics and family history play a role in AAA development have continued to emerge, with polymorphisms in several genes associated with AAA development being identified.[3, 47-51]

While the expansion rate of AAAs can vary substantially, the rate of expansion accelerates for larger aneurysms.[52] Rapid rate of aneurysm expansion greater than 1 cm per year is commonly used in decision-making about elective repair of AAAs less than 5.5 cm but the predictive value of expansion as an index of rupture risk is less clear.[53]

The annual risk of aneurysm rupture varies substantially among individuals. A recent analysis of individual patient-level data found that each 0.5 cm increase in aneurysm diameter results in an increased growth rate of 0.5 mm/year and that rupture rates doubled.[54] Further, among males with a 3.0 cm AAA, the average growth rate was 1.3 mm/year, and for those with a 5.0 cm AAA the growth rate increased to 3.6 mm/year. Rupture rates similarly increased from 0.05 per 100 person-years in men with AAAs 3.0 in diameter to 0.64 per 100 person-years in those with a 5.0 cm AAA. Although women have a much lower prevalence of AAAs, they are up to 4 times more likely to have their aneurysms rupture than men.[26, 54]

Risk Factors

Risks Factors for Developing AAAs

The most important risk factors for the development of AAA include advanced age,[29, 55] male

sex,[29, 56] smoking,[3, 4, 56, 57] and family history of AAA.[4, 57, 58] Other potential risk factors include a history of other vascular aneurysms,[6, 59] greater height,[60] atherosclerosis,[60] (including peripheral[6, 61] coronary artery disease,[62, 63] cerebrovascular disease,[59, 62] hypercholesterolemia,[60] and hypertension.[4, 60, 64] In recent years, genome-wide association studies have identified four new risk loci for AAA.[50]Protective factors include Black, Hispanic, and Asian race, being female, and having diabetes mellitus.[29, 65-68]

Risk Factors for AAA Growth

A rigorous systematic review and individual patient data meta-analysis of 18 studies involving 15,475 patients examined the factors affecting the growth of small AAAs.[69] Among all factors examined, smoking was the only risk factor that was independently associated with the increased risk of small AAA growth (point growth rate: 0.35; 95% confidence Interval [CI], 0.23 to 0.48 millimeters [mm] per year), and diabetes was independently associated with lower risk of AAA growth (-0.51; 95% CI, -0.70 to -0.32 mm per year). Age, sex, arterial blood pressure, pulse pressure, and history of cardiovascular diseases were statistically associated with AAA growth in unadjusted analyses; the apparent associations became nonstatistically significant in adjusted analyses.

Although peripheral artery disease (PAD) and coronary artery disease (CAD) have been shown to be major risk factors or indicators for AAA presence,[6, 62] two recent meta-analyses have shown a likely negative association with AAA growth.[61, 63] Similarly, despite the positive association of hypertension with AAA presence, another meta-analysis that looked at 20 studies with 6,619 patients found no association of hypertension with AAA expansion rates (standard mean difference [SMD] 0.03, 95% CI, -0.01 to 0.17, P=0.19).[64]

Risk Factors for AAA Rupture

If an aneurysm is allowed to expand without intervention, or if the initial size of an aneurysm is large, the risk of aneurysm rupture is significant.[3, 70-75] Older age, female sex, smoking, and higher arterial or pulse blood pressure are also associated with increased risk of rupture in patients with small AAAs.[69, 76] The risk in women has been reported to be almost 4 times greater than the rupture risk in men (Hazard ratio [HR] 3.76, 95% CI, 2.58 to 5.47).[69] In addition, current smokers have been reported to have double the risk of aneurysm rupture than ever smokers or nonsmokers (HR 2.02, 95% CI, 1.33 to 3.06). Other potential pathogenic factors contributing to rupture include peak AAA wall stress[77, 78] and a rapidly progressing expansion rate.[3, 4, 72, 79]

Rationale for Screening and Screening Strategies

Identifying screening strategies that could reduce mortality and other adverse health outcomes is critical, since most AAAs are asymptomatic and have a high mortality rate if allowed to progress to rupture. Several strategies, including ultrasound, computed tomography (CT), and physical examination can be used to identify AAAs.

Ultrasonography is noninvasive and easy to perform and has high sensitivity (94% to 100%) and specificity (98% to 100%)[3, 4, 80-84] for detecting AAAs. CT scanning is another method that can

be used to detect AAAs. CT scans are more reproducible than ultrasound, with over 90 percent of measurements being within 2 mm of the original scan.[3] Although CT is an accurate tool for identifying AAAs, it is not promoted as a screening method due to radiation exposure. The Society for Vascular Surgery recommends the use of CT scanning for operative planning due to its precision, reproducibility, and ability to determine the morphology of the AAA and presence of renal arteries and occlusive disease;[3] CT has been used in at least one screening trial.[85, 86]

While physical examination for the detection of AAAs has also been used in practice, such exams have a low sensitivity, especially in detecting smaller aneurysms or in obese patients. A case-control study estimated the sensitivity of detecting an AAA ≥3.0 cm to be 68 percent (95% CI, 60 to 76%) with a specificity of 75 percent (95% CI, 68 to 82%).[87] A meta-analysis of 15 cohort screening studies with asymptomatic patients estimated sensitivity to be even lower, at 39 percent.[88] This approach is not recommended for screening or preoperative planning.

Treatment Approaches for Large Aneurysms

Treatment guidelines for AAAs vary by aneurysm diameter.[3, 4] Because larger AAA size is associated with higher rupture risk,[3, 70] it is standard practice in men to consider surgical repair of aneurysms over 5.5 cm (as risk of aortic rupture < 5.5cm is low) or those > 4.0 cm that have rapid growth indicated by an increase in 1.0 cm diameter in the previous 12 months.[3, 4] Open repair has been a long-standing treatment for aneurysm repair. However, since its first published use in the early 1980s, endovascular repair has transformed AAA repair and has become the far more common approach to repair intact AAAs. In the United States, endovascular aneurysm repair (EVAR) comprises 80 percent of all intact aneurysm repairs and 52 percent of ruptured AAA repairs.[89] There are several advantages to EVAR which have contributed to its increased popularity, including a reduced operative time, avoidance of general anesthesia, less postoperative pain, and reduced blood loss.[4, 90] The reduced short-term postoperative morbidity and mortality associated with EVAR is balanced with the increased risk of endoleaks, requiring lifelong monitoring with ultrasound or computed radiography imaging.[91, 92]

Current Clinical Practice in the United States and Recent Recommendations

Ultrasound is the primary technology used to screen patients for AAA.[3, 28, 93] It is preferred to both physical examination and CT scans because it is inexpensive and noninvasive, can be easily implemented by both primary care and specialty clinics, and has optimal sensitivity and specificity.[3, 28, 93] Ultrasound screening has been widely accepted as the primary approach for detecting AAAs by both primary care physicians and vascular surgeons.[3, 4, 84, 94] Four U.S.-based guidelines recommend one-time ultrasound screening in 65- to 75-year-old ever-smoking men (**Appendix B Table 1**).[3, 95-97] Two recommend extending screening to men with a family history at younger ages (≥55 years and ≥60 years),[3, 95] and one guideline promotes screening for women ≥65 years if they have a family history or history of tobacco use.[3]

Once an AAA is detected, the management of the aneurysm depends on its size, the risk of rupture, and the risk of operative mortality.[3, 95, 98] Ninety percent or more of identified

aneurysms, however, are below the threshold for immediate surgery (3.0 to 5.5 cm).[8, 10, 99, 100] The currently recommended standard of care is to maintain ultrasound surveillance at regular intervals for patients with small AAAs because the risk of rupture is negligible.[3, 95, 98] Several guideline groups propose various surveillance intervals for monitoring the growth of small AAAs until the aneurysm reaches a diameter that is appropriate for surgical intervention (**Appendix B Table 1**). Compliance with surveillance recommendations has been reported as low (65%).[101] The universal standard for elective repair is that patients with AAAs with a diameter of 5.5 cm or more should be referred to a vascular surgeon for surgical intervention with either open repair or EVAR.[28, 95, 102] This recommendation is based on randomized controlled trials with populations consisting mainly of men; as a result, the aneurysm size needed for surgical intervention may be different in women.[28, 102] The Society of Vascular Surgery guidelines reflect this in their recommendation to repair AAAs in women between 5.0 cm and 5.4 cm.[3] Despite these guidelines, the proportion of AAAs repaired before they reach the 5.5 cm threshold ranges from 6.4 to 29.0 percent in various countries.[103] Recent analyses from the 2013 U.S. National Surgical Quality Improvement Program data demonstrate that 39.2 percent of repairs of intact AAAs in men occur in aneurysms below the 5.5 cm threshold and 17.2 percent of repairs of intact AAAs in women occur below 5.0 cm; in contrast, early surgical repair is much less frequent in United Kingdom.[104]

Previous USPSTF Recommendation

In 2014, the United States Preventive Services Task Force (USPSTF) found good-quality evidence to recommend one-time screening for AAA by ultrasonography in *asymptomatic men aged 65 to 75 years who have ever smoked* (B Recommendation).[93] The USPSTF concluded that the benefits of screening do not clearly outweigh the possible harms and recommended that clinicians selectively offer screening for AAA *in men ages 65 to 75 years who have never smoked* rather than routinely screening all men in this group (C Recommendation).[93]Also, the USPSTF recommended against routine screening for AAA in *asymptomatic women who have never smoked* (D Recommendation) and determined that there was insufficient evidence for screening *women aged 65 to 75 years who have ever smoked* (I statement).[93]

Chapter 2. Methods

Scope and Purpose

This systematic review will provide updated evidence regarding the effectiveness of one-time and repeated screening for AAAs, the associated harms of screening, and the benefits and harms of available treatments for small AAAs (3.0 to 5.0 cm) identified through screening. The USPSTF will use this review to update its 2014 recommendation for primary care practices.[93] This review included all trials from the previous review[105] that met current inclusion/exclusion criteria as well as newly identified studies.

Key Questions and Analytic Framework

Using the USPSTF's methods (detailed in **Appendix A**), we developed an analytic framework (**Figure 1**) and five Key Questions (KQs).

The KQs include:

1. What are the effects of one-time screening for abdominal aortic aneurysm (AAA) on health outcomes in an asymptomatic population aged 50 years or older?
   a. Do the effects of one-time screening for AAA vary among subpopulations (i.e., by age, sex, smoking status, family history, or race/ethnicity)?
2. What are the effects of rescreening for AAA on health outcomes or AAA incidence in a previously screened, asymptomatic population without AAA on initial screening?
   a. Do the effects of rescreening for AAA vary among subpopulations (i.e., by age, sex, smoking status, family history, or race/ethnicity)?
   b. Do the effects of rescreening for AAA vary by the time interval between screenings?
3. What are the harms of one-time and repeated screening for AAA?
   a. Do the harms of one-time and repeated screening for AAA vary among subpopulations (i.e., by age, sex, smoking status, family history, or race/ethnicity)?
4. What are the effects of treatment (pharmacotherapy or surgery) on intermediate and health outcomes in an asymptomatic, screen-detected population with small AAAs (i.e., aortic diameter of 3.0 to 5.4 cm)?
   a. Do the effects of treatment of small AAAs vary among subpopulations (i.e., by age, sex, smoking status, family history, or race/ethnicity)?
5. What are the harms of treatment in an asymptomatic, screen-detected population with small AAAs (i.e., aortic diameter of 3.0 to 5.4 cm)?
   a. Do the harms of treatment of small AAAs vary among subpopulations (i.e., by age, sex, smoking status, family history, or race/ethnicity)?

Data Sources and Searches

In addition to considering all studies from the previous review for inclusion in the current

review, we performed a comprehensive search of MEDLINE, PubMed (publisher supplied only), the Database of Abstracts of Reviews of Effects, and the Cochrane Collaboration Registry of Controlled Trials for studies published between January 2013 and September 14, 2018. A research librarian developed and executed the search, which was peer-reviewed by a second research librarian (**Appendix A**).

In addition, we examined the reference lists of other previously published reviews, meta-analyses, and primary studies to identify additional potential studies for inclusion. We supplemented our searches with suggestions from experts and articles identified through news and table-of-contents alerts. We also searched ClinicalTrials.gov (https://ClinicalTrials.gov/) for ongoing trials (**Appendix H**). We imported the literature from these sources directly into EndNote® X7 (Thomson Reuters, New York, NY).

Study Selection

Two reviewers independently reviewed the titles and abstracts of all identified articles to determine whether studies met inclusion and exclusion criteria for design, population, intervention, and outcomes (**Appendix A Table 1**). Two reviewers then independently evaluated the full-text article(s) of all potentially included studies against the complete inclusion and exclusion criteria. Disagreements in the abstract and/or full-text review were resolved by discussion and consultation with a third reviewer if necessary. Excluded studies and reasons for exclusion are listed in **Appendix D**.

We developed an *a priori* set of criteria for inclusion and exclusion of studies based on our understanding of the literature (**Appendix A Table 1**). For KQ1 and KQ2, examining the effectiveness of one-time and repeated screening, we considered randomized controlled trials (RCTs) and large cohort studies (n ≥1000) of asymptomatic adult populations. For KQ4, examining the effectiveness of treating small AAAs, we considered only RCTs of asymptomatic adult populations with AAAs identified as being small (3.0 to 5.4 cm). For KQ3 and KQ5, examining the harms of screening for AAAs and of treating small AAAs, we were more inclusive and considered RCTs, observational studies, and registry data related to surgical harms. For KQ5, we considered only populations of adults with asymptomatic, small aneurysms. For all KQs, the only screening modality that we considered was ultrasound. We did not consider physical examinations due to literature reporting unfavorable sensitivity and specificity of this diagnostic method.[87] Further, we did not consider CT or magnetic resonance imaging (MRI) screening, as these modalities are not readily available in primary care. For KQ2, we accepted targeted screening as being defined as screening based on one or more patient risk factors or screening based on prediction/prognostic modeling. For KQs related to the treatment of small AAAs, we considered surgical intervention (open or EVAR) or pharmacotherapeutic interventions (statins, ACE-inhibitors, beta-blockers, or antibiotics) compared with surveillance, usual care, or placebo. We limited our included studies to those published in English and those that were deemed good- or fair-quality by using items from the Newcastle-Ottawa Scale[106] and USPSTF quality rating standards.[107] The outcomes that were reviewed are fully listed in **Appendix A Table 2**.

Quality Assessment and Data Abstraction

Two reviewers applied USPSTF design-specific criteria and items from the Newcastle-Ottawa Scale[106, 107] to assess the methodological quality of all eligible studies (**Appendix A Table 2**). We assigned each study a quality rating of "good," "fair," or "poor." Discordant quality ratings were resolved by discussion or by a third reviewer and adjudicated as needed. Studies rated as poor quality were excluded from the review.

Good-quality RCTs were those that met all or nearly all of the specified quality criteria (e.g., comparable groups were assembled initially and maintained throughout the study, followup was 90% or higher, assessment procedures were described and blinded if they involved direct interview, randomization methods were described, allocation was concealed), whereas fair-quality studies did not meet all these criteria but did not have serious threats to their internal validity related to design, execution, or reporting. Intervention studies rated as poor quality generally had several important limitations, including at least one of the following risks of bias: very high attrition (generally > 40%), differential attrition between intervention arms (generally > 20%); lack of baseline comparability between groups without adjustment; or problematic issues in trial conduct, analysis, or reporting of results (e.g., possible selective reporting; inappropriate exclusion of participants from analyses; questionable validity of allocation or assessment procedures).

Good-quality observational studies had an unbiased selection of the nonexposed cohort and adequate ascertainment of exposure. These studies addressed a population without the outcome of interest at the beginning of the study, and they had reliable outcome measures, blinded assessment, low attrition, adjustment for potential confounders, and no other important threats to internal validity. Observational studies were downgraded to fair if they were unable to meet the majority of good-quality criteria. Poor-quality observational studies had multiple threats to internal validity and were excluded from the review.

One reviewer extracted data from all included studies rated as fair- or good-quality directly into summary tables (Microsoft Word®; Microsoft Corporation, Redmond, WA), and a second reviewer checked the data for accuracy. Elements abstracted included population characteristics (e.g., baseline demographics, concurrent conditions, family history of AAA, smoking status, and cardiovascular disease [CVD] risk factors), as well as study design elements (e.g., recruitment procedures, inclusion/exclusion criteria, followup and population adherence), intervention characteristics (including post-screening management), and relevant outcomes.

Health outcomes included the number of participants experiencing an event and incidence rates. For KQs 1, 2, and 3 (efficacy and harms of screening), we abstracted the reported incidence and prevalence of AAA, incidence of ruptured aneurysms, and mortality (all-cause, AAA-related, and operative mortality). In addition, we extracted information on the number and circumstance (i.e., emergency or elective) of surgical interventions reported in each study and any adverse events related to screening (e.g., changes in quality of life, anxiety) that were reported. In our previous review, we included the shorter-term outcomes from the screening trials, but in the current report we only report outcomes from the longest-term followup. We also did not include the Viborg Vascular (VIVA) trial mortality data due to our inability to capture the independent

contribution of AAA screening within the multicomponent screening program. We did include AAA prevalence and data related to AAA procedures. For KQs 4 and 5 (efficacy and harms related to treating small AAAs), we abstracted data related to the dose and duration of the pharmaceutical intervention, surgical details (if reported), AAA growth rate, the number and circumstance (i.e., emergency or elective) of surgical interventions, incidence of aneurysm rupture, and mortality (all-cause, AAA-related, and operative mortality). For adverse events, we extracted all that were reported but specifically looked for incidences of reinterventions, endoleaks, device migration, conversion to open surgery, and hospital readmission within 30 days of surgery.

Data Synthesis and Analysis

We synthesized data separately for each KQ. Specifically, we provide a narrative summary of the included studies regarding study design and setting, internal validity and major factors threatening the interval validity, and important characteristics about patients and interventions.

For Key Question 1, we examined all-cause mortality, AAA-related mortality, rupture, and emergency surgeries for the comparison of screening versus no screening. We pooled calculated risk ratios and used the DerSimonian & Laird[108] (DL) random effects model as the primary analysis for all-cause mortality, since statistical heterogeneity was very low (I^2=0%, τ^2 = 0.0). Because of the relatively small number of trials being pooled, we also conducted a sensitivity analysis using the restricted maximum likelihood method, which tends to result in more conservative (larger) estimates of τ^2 when there are fewer than five to ten trials being pooled. As expected, results showed slightly larger confidence intervals and were consistent with the DL model with respect to statistical significance, so only DL analyses are reported. For AAA-related mortality, rupture, and emergency surgeries, we used the Peto method to pool odds ratios. Odds ratios were calculated based on the numbers of events and participants in each study arm. The Peto method was chosen because events were very rare (occurred in fewer than 1% of participants in most study arms) and trials had a similar number of participants in both study arms.[109] All statistical testing was two-sided and we considered 0.05 as significant. We examined statistical heterogeneity across trials with the I^2 statistic and chi-square test of heterogeneity.

We did not conduct meta-analysis of the rescreening studies included in Key Question 2 because of substantial differences in patient population, length of followup, and outcomes reported. We provide a narrative summary of results and reported outcomes including incidence of large AAA, AAA ruptures, AAA procedure data, and AAA-related mortality and all-cause mortality.

To analyze the harms of screening versus no screening in Key Question 3, we examined 30-day mortality after elective surgery, 30-day mortality after emergency surgery, overall operations, elective operations, emergency operations, and quality of life (QOL) measures. The 30-day mortality after elective surgery and 30-day mortality after emergency surgery outcomes were not pooled since there were only two trials reporting these outcomes. The Peto method was used to pool overall operations, elective operations, and emergency operations, as described under KQ1. All statistical testing was two-sided, and we considered 0.05 as significant. We examined heterogeneity across trials with the I^2 statistic and chi-square test of heterogeneity. Because of

the substantial difference in quality-of-life measurements and insufficient reporting of data (e.g. lack of variation parameters), we were unable to pool these data in the studies of screening versus no screening.

We narratively describe the treatment study results for Key Questions 4 and 5 and present the data in tables. We did not conduct meta-analysis of the treatment trials due to the small number of studies of each intervention type.

Subpopulation Methods

We prespecified subpopulations of interest in the KQs. These populations were selected based on analysis of subpopulation considerations in the previous review and recommendation, established characteristics associated with the development of AAA, and feedback received from three Key Informants during the scoping phase. During the data abstraction phase, we catalogued the availability and characteristics of subgroup analyses (i.e., whether analyses were *a priori*, post hoc, or unclear) for each subpopulation of interest for each trial and subsequently audited these results. Using this audit, formal subgroup analyses were prioritized based on the number of contributing studies and the credibility of subgroup analyses, with subpopulation-specific trials and *a priori* analyses given more weight. This process was aided by subpopulation credibility ratings conducted by our team based on the guidance from Whitlock et al.[110]

We then entered data from subgroup analyses into summary tables for the prioritized analyses of age, sex, smoking status, family history, and race/ethnicity. In addition to outcomes, subgroup summary tables included information relevant to the credibility of each trial's subgroup analyses, such as the interaction testing for heterogeneity of treatment effect if it were available. Direct evidence from within-study comparisons was emphasized over across-study comparisons, which can be confounded by differences in populations and their risk factors.

Based on a limited number of contributing studies for subgroup analyses, we did not pool results but analyzed them qualitatively.

Grading the Strength of the Body of Evidence

We graded the strength of the overall body of evidence for each Key Question. We adapted the Evidence-based Practice Center approach,[111] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[112] Our method explicitly addresses four of the five Evidence-based Practice Center-required domains: consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (i.e., study limitations). We did not address the fifth required domain—directness—as it is implied in the structure of the Key Questions (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

Consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). Reporting bias was rated as suspected, undetected, or not applicable (e.g., when there was insufficient evidence for a particular outcome). Study quality reflects the quality ratings of the individual trials and indicates the degree to which the included studies for a given outcome have a high likelihood of adequate protection against bias. The body-of-evidence limitations field highlights important restrictions in answering the overall Key Question (e.g., lack of replication of interventions, nonreporting of outcomes important to patients).

We graded the overall strength of evidence as high, moderate, or low. "High" indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effects. "Moderate" indicates moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate. "Low" indicates low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effect and to change the estimate. A grade of "insufficient" indicates that evidence is either unavailable or does not permit estimate of an effect. At least two independent reviewers rated the overall strength of evidence for each intervention type. We resolved discrepancies through consensus discussion involving more reviewers.

Expert Review and Public Comment

A draft Research Plan for this review was available for public comment from August 10, 2017, to September 6, 2017. In response to comments, the USPSTF expanded the scope of the evidence review to include cardiovascular events (e.g., myocardial infarction, stroke) and mortality related to cardiovascular disease to more fully evaluate the benefits and harms of treatment of small AAAs (i.e., pharmacotherapy such as statins and antihypertension medications). The USPSTF made other minor modifications as appropriate, such as clarifying that surveillance alone would be included as a comparator for KQ 4. The draft version of this report was reviewed by experts and USPSTF Federal Partners and will be posted for public comment on the USPSTF Web site. Comments received during any period were reviewed, considered, and addressed as appropriate.

USPSTF Involvement

We worked with four USPSTF members at key points throughout this review, particularly when determining the scope and methods for this review and developing the Analytic Framework and Key Questions. After revisions reflecting the public comment period, the USPSTF members approved the final analytic framework, KQs, and inclusion and exclusion criteria. The Agency for Healthcare Research and Quality (AHRQ) funded this review under a contract to support the work of the USPSTF. An AHRQ Medical Officer provided project oversight, reviewed the draft report, and assisted in the external review of the report.

Chapter 3. Results

Literature Search

We screened 3,946 abstracts and assessed 137 full-text articles for inclusion; 50 articles were reviewed for Key Questions 1–3 and 87 articles were reviewed for Key Questions 4 and 5 (**Appendix A Figure 1**). After screening the full-text articles, 33 studies (in 70 articles) were included in our systematic review.[7, 12-15, 22, 36, 75, 113-174] The full list of included studies and their ancillary articles as available in **Appendix C**. The list of excluded studies (with reasons for exclusion) are available in **Appendix D**.

KQ1. What Are the Effects of One-Time Screening for AAA on Health Outcomes in an Asymptomatic Population Aged 50 Years or Older?

Summary of Results

Four large, population-based screening RCTs of men aged 65 years and older examined the effectiveness of one-time AAA screening and found that AAA prevalence varies from 4 to 7.6 percent, with the majority of screen-detected AAAs being small in size (≤ 4 to 4.5 cm).[12, 15, 113, 143, 147, 155, 170] One more contemporary screening trial in the same population solely contributed to outcomes of prevalence and number of operations and reports a 3.3 percent prevalence, reflecting a temporal decline in the disease.[146] The invitation for screening men aged 65 years and older was associated with a 35 percent reduction in AAA-related mortality, a 38 percent reduction in AAA rupture rate, and a 43 percent reduction in the number of emergency surgeries. There was no statistically significant difference, however, in all-cause mortality at 12- to 15-year followup.

Study Characteristics

Two fair- and two good-quality population-based screening RCTs from the United Kingdom, Denmark, and Australia assessed the efficacy of AAA screening in population-based settings: the Multicentre Aneurysm Screening Study (MASS) (n=67,770);[12, 134, 135, 170, 171] the Chichester, United Kingdom, screening trial (n=15,382);[13, 36, 113, 173] the Viborg County, Denmark, screening trial (n=12,639);[14, 143-145, 147] and the Western Australia screening trial (n=38,480) (**Appendix E Tables 1 and 2**).[7, 15, 154, 155, 168] These four RCTs were included in the previous review, with new long-term data reported in the Western Australia trial[15] included in this update. One additional population-based screening trial in Denmark (VIVA) is discussed in detail under Key Question 3 but is mentioned here due to its contribution to AAA prevalence in a screened population and number of operations.[146] All trials identified potential participants aged 64 or 65 years and older from population registries or regional health directories. The MASS trial identified participants from four centers in the United Kingdom; the Chichester trial included nine general practices in

Chichester; the Viborg trial included the population from Viborg County; and the Western Australia trial included participants from a capital city and satellite towns. Reported mean (or median) ages ranged from 67.7 to 72.6 years, and the oldest study participants were 83 years old. One study, the Chichester trial,[14] included women,[25] while the other three recruited only men. Other than age and sex, no studies reported outcomes in the screened and control groups by any other demographic information.

Two trials provide some risk factor information.[15, 147] The Viborg trial, which described AAA-related comorbidity risk factor information from hospital discharge data, indicated that 26.5 percent of all participants had at least one cardiovascular risk factor or chronic obstructive pulmonary disease (COPD).[145, 147] The Western Australia trial reported cardiovascular comorbidity and risk factor information for the screened group and analyzed the association between the risk factor and AAA diagnosis, but risk factor data were not collected for the control group nor were they linked to mortality outcomes.[15] Three studies had no trial exclusions; only the MASS trial excluded patients who (1) were identified by their primary care physicians as too high risk to be screened, (2) were terminally ill, or (3) had other serious health problems or prior AAA repair.

All trials randomized participants to one of two groups: the invited group received a letter invitation for one-time ultrasound screening, while the control group received usual care. All trials considered "normal" aortic diameter to be less than 3 cm and defined AAA as ≥3.0 cm. Three of the RCTs (MASS, Viborg, Chichester) further prescribed specific postscreening surveillance protocols for AAA ≥3.0 cm with repeat ultrasounds,[113, 147, 170] while one trial (Western Australia) sent initial ultrasound results to primary care physicians for management.[15] In the MASS trial, those with aortic diameters 3.0 to 4.4 cm were rescanned yearly, 4.5 to 5.4 cm were rescanned at 3-month intervals, and ≥5.5 cm were urgently referred to a vascular surgeon.[170] In the Viborg trial, individuals with ectatic aortic size 2.5 to 2.9 cm were offered a repeat scan at 5 years, AAAs 3.0 to 4.9 cm were offered annual scans, and AAA ≥5.0 cm were referred to vascular surgery.[147] In the Chichester trial, patients with AAAs 3.0 to 4.4 cm were rescanned annually, 4.5 to 5.9 cm were rescanned every 3 months, and 6 cm or greater were referred to vascular surgeon, as were those with increase of diameter of 1 cm or more per year (**Appendix E Table 1 and 2**).[113]

The primary outcome reported in trials was AAA-specific mortality (defined as all AAA-related deaths plus all deaths within 30 days of AAA surgical repair); all four trials also reported AAA rupture rate and all-cause mortality as benefit outcomes. Mortality data and causes of death were ascertained from death certificates in all studies, and three of the RCTs additionally involved an independent blinded review of autopsy reports and/or hospital records for all AAA-related deaths. Mean or median followup in these four population-based screening trials ranged from 12.8 to 15 years, with short-term results published at 3- to 5-year intervals; this report focuses solely on the longest-term followup. Local and national health departments, research councils, and heart foundations funded these studies.

The MASS trial[12, 134, 135, 170, 171] stands out as the highest quality of the four trials: it had the greatest number of participants, the highest adherence to screening, and clear reporting of randomization, allocation, blinding of outcome assessors and confirmation of equal followup in

the invited and control groups. All trials appeared to use intention-to-treat analysis; adherence to screening varied from the lowest adherence in the Western Australia trial (62.5% of invited attended screening) to the highest adherence in the MASS trial (80.2% adherence). Three studies reported low loss-to-followup rates in participants with AAA: MASS trial (70% retention rate at 13-year followup in men with an AAA detected at the initial scan),[170] Viborg trial (75.1% retention rate in invited group; 58.0% in control group at 52-month followup),[147] and Western Australia trial (87.1% retention in invited group; 84.9% in the control group at 3.6-year followup).[15]

Detailed Results (Male Only; Female Results in KQ1a)

AAA Prevalence in Screened Population

AAA prevalence (≥3.0cm) on the initial screen for male attenders in the four population-based screening trials varied from as low as 3.9 percent in the Viborg trial[147] to as high as 7.6 percent in the Chichester trial[113] (**Table 1**). Notably, the Chichester and Western Australia trials reported the highest AAA prevalence rates and they recruited older participants (Chichester median age 72 years, Western Australia mean 72.7 years compared to mean ages of 67.7 and 69.2 years in the Viborg and MASS trials). The VIVA trial[146] reported a prevalence of AAAs (619/25,078 [3.3%]) similar to the older Viborg trial[147]; both trials were conducted in the same geographic area. Four of the five trials (MASS, Chichester, Western Australia, and VIVA)[12, 13, 15, 113, 143, 146, 155, 170] reported the prevalence of AAA by size at initial screening, with MASS, VIVA, and Western Australia trials reporting that the majority of AAAs (87 to 93%) detected were small (measuring < 5.5 cm). The overall prevalence of large AAAs (≥5 cm or ≥5.5 cm) in the screened population was consistent across studies and was reported as 0.3 to 0.6 percent (**Appendix E Table 3**).

Effect of Population Screening on All-Cause Mortality and AAA-Related Mortality

A meta-analysis of all-cause mortality of the four screening trials[15, 113, 147, 170] (N=124,929) using relative risk (RR) estimates with the DerSimonian and Laird (DL) method showed a result that when rounded, yielded a nonstatistically significant pooled result (RR 0.99 [95% CI, 0.98 to 1.00]; I^2=0%) (**Figure 2**). None of the individual screening trials reported a statistically significant reduction in all-cause mortality (**Table 2**) with screening except MASS (HR 0.97 [95% CI, 0.95 to 0.99]).[170] Individually calculated RR point estimates ranged from 0.98 to 1.00 with none reaching statistical significance.

Pooled analysis of AAA-related mortality of the four trials[15, 113, 147, 170] (N=124,929) showed a statistically significant 35 percent reduction associated with invitation to screening (Peto OR 0.65 [95% CI, 0.57 to 0.74], I^2=80%) (**Figure 3**) with high heterogeneity. We estimate a number needed to screen of 305 men (95% CI, 248 to 411) to prevent one AAA death. The results lost statistical significance, however, with REML method (data not shown). Individual trial results demonstrate that the MASS and Viborg trials found a statistically significant AAA-related mortality benefit in the invited group compared with the control group at the longest followup time points, while Chichester study reported a hazard ratio that was less than 1 but was not statistically significant (**Table 2**).

Effect of Population Screening on AAA Rupture

Pooled results of the four trials[15, 113, 147, 170] (N=124,929) showed a statistically significant reduction in ruptures associated with the invitation to screening (Peto OR 0.62 [95% CI, 0.55 to 0.70]; I^2=53%) (**Figure 3**). We estimate a number needed to screen of 246 men (95% CI, 207 to 311) to prevent one AAA rupture. Individual study results for AAA rupture rate show mixed results with calculated Peto ORs ranging from 0.46 to 1.11, with the beneficial effect favoring invitation to screening reaching statistical significance in three trials (MASS, Western Australia, and Viborg)[15, 147, 170] (**Table 1**).

Emergency Operations

Pooled results at the longest followup of the five trials[15, 113, 146, 147, 170] (N=175,085) showed a reduction in emergency operations in the invited group (Peto OR 0.57 [95% CI, 0.48 to 0.68]; I^2=27%) (**Figure 4**). We estimate that screening 1000 men for AAA would reduce the number of emergency procedures by 2 (95% CI, 2 to 2). Individual trial results show that results for number of emergency surgeries were as follows: MASS, Viborg, and Western Australia trials reported significantly fewer emergency surgeries in the invited group at the longest-term followup (MASS: Peto OR 0.50, [95% CI, 0.39 to 0.64]; Viborg: Peto OR: 0.47, [95% CI, 0.29 to 0.77]; Western Australia Peto OR 0.60 [95% CI, 0.37 to 0.95]), while Chichester and VIVA showed similar nonsignificant trends (Chichester: Peto OR 0.77 [95% CI, 0.41 to 1.48]; VIVA;OR 0.82 (95% CI, 0.53 to 1.27) (**Table 1**, **Figure 4**).

KQ1a. Do the Effects of One-Time Screening for AAA Vary Among Subpopulations (i.e., by Age, Sex, Smoking Status, Family History, or Race/Ethnicity)?

Summary of Results

Available subgroup analyses are scant, and their analytical credibility is mixed. The Viborg[147] and Western Australia[15] trials, both of which were population-based screening trials, reported subanalyses, with substantial limitations suggesting that there is no differential screening effect based on age. While our review scope included adults age 50 and older, none of the trials recruited patients younger than 64 years of age. Only the Chichester[36, 113] trial, also a population-based screening trial, examined AAA screening in women, showing a low prevalence of AAA in women, with most screen-detected AAAs measuring 3.0 to 3.9 cm.[13, 36] There was no difference in AAA rupture rate among women at 10-year followup or in AAA-related or all-cause mortality at 5 years between the invited and control groups, but the trial was underpowered. While the Western Australia trial reported that smoking is associated with a higher risk of all-cause mortality (OR 1.59 [95% CI, 1.47 to 1.72]) and AAA-related mortality (OR 2.95 [95% CI, 1.04 to 8.43]) in the screened group,[15] it did not compare outcomes in the unscreened control for comparison and therefore does not address modification of intervention effectiveness by smoking status.

Study Characteristics and Results

Age

The oldest participants in the four major screening trials ranged from 73 years in the Viborg trial[147] to 83 years old in the Western Australia trial[15] (**Appendix E Table 2**). Viborg and Western Australia were the only two population-based screening trials reporting AAA-related mortality outcomes stratified by age, suggesting that there is no differential screening effect on mortality by age (**Appendix F Table 1**).[15, 147] Neither of these subgroup analyses was reported as prespecified, however. Further randomization was not stratified to ensure baseline characteristic similarities and the trials were not powered to detect differences in the age subgroups. No formal interaction testing was performed. The 13-year followup of the Viborg trial performed a subgroup analysis of men aged 64 to 65 years (N=5,429) showing a similar AAA-related mortality benefit in the 64- to 65-year-old age group compared with the 66- to 73-year-old age group (N=7,210) (HR 0.36 [95% CI, 0.14 to 0.93] in 64- to 65-year-olds; HR 0.33 [95% CI, 0.18 to 0.62] in 66- to 73-year-olds).[93] The Western Australia trial showed no AAA-related mortality benefit in the invited group of 65- to 74-year-olds (N=26,505) AAA-related mortality: Rate Ratio 0.92 [95% CI, 0.62 to 1.36]) at 12.8-year followup.[15] These results were similar to findings for the entire trial, which had an age range of 64 to 83 years (N=38,480) AAA-related mortality: Rate Ratio 0.91 [95% CI, 0.68 to 1.21]).[15] A rate ratio was not provided for all-cause mortality.

Sex

Of the four population-based screening trials, only the Chichester study[13, 36, 113] recruited female participants aged 65 to 80 years (59% of participants were women; n=9,342 women) (**Appendix E Table 2**). While this trial prespecified its subgroup analysis and allowed for within-study comparisons by sex, the trial was insufficiently powered to detect AAA-related mortality or all-cause mortality differences in women and no formal interaction testing was performed.

A greater proportion of women than men in the invited group refused screening; for example, in the 65-year-old cohort, 27.3 percent of invited women refused screening compared with 19.5 percent of men; in the 76- to 80-year-old cohort, 41.7 percent of invited women refused screening, while 33.8 percent of men refused. The prevalence of AAA in the screened group was 6 times lower in women than in men (1.3% vs. 7.6%) (**Table 1**).[13, 36, 113] Prevalence by age group revealed a time delay in AAA development compared with men: no women were diagnosed with AAA at the age of 65 years, 1 percent were diagnosed at ages 66 to 70 years, 1.8 percent at ages 71 to 75 years, and 1.6 percent at ages 76 to 80 years. Seventy-five percent of AAAs were small, measuring 3.0 to 3.9 cm; fifteen percent of AAAs were ≥ 5.0 cm. All-cause mortality in women at 5 years was similar in the invited and control groups (10.7% vs. 10.2%). AAA-specific mortality in women was low in both groups at 5-year followup (3 deaths [0.06%] in the invited group and 2 deaths [0.04% in the control group; no statistical analysis) and not reported at longer followup (**Table 2**). The rupture rate was low (0.2%) in both the invited and control groups at 10-year followup (**Table 1**). Similarly, emergency repairs were rare in both the invited and control groups at 5 years (0.02%). All-cause mortality and AAA-related mortality were not reported for women at 10-year followup. AAA-related mortality was reported in the entire unscreened population in Chichester, and while more than half of the AAA-related deaths in men

occurred before age 80 years, the majority (70%) of AAA-related deaths in women occurred among those ages 80 years and older.[13, 36, 113]

Smoking

Only the Western Australia trial[15] reported outcomes by smoking status in the screened group (**Appendix F Table 2**). The analysis had low subgroup credibility: it was unclear if this analysis was prespecified as the study was not powered to detect subpopulation differences. There was no formal test for interaction performed; and no comparisons in the unscreened group were reported. Results showed that smoking was associated with a higher risk of all-cause mortality (OR 1.59 [95% CI, 1.47 to 1.72]) and AAA-related mortality (OR 2.95 [95% CI, 1.04 to 8.43]) in the screened group of men aged 64 to 83 years.[15] This trend was more pronounced among those ages 65 to 74 years; however, no formal analysis was performed to explore if there is a differential screening effect based on smoking status.

Race/Ethnicity and Family History

None of the population-based screening RCTs reported AAA family history or race/ethnicity descriptive data for participants in order to allow for the analysis of screening benefits among these subpopulations. Of note, all studies were conducted in majority-Caucasian populations (**Appendix E Table 1**).

KQ2. What Are the Effects of Rescreening for AAA on Health Outcomes or AAA Incidence in a Previously Screened, Asymptomatic Population Without AAA on Initial Screening?

Summary of Results

No trial-level evidence examined the effectiveness of one-time screening plus rescreening compared to one-time screening alone. Eight heterogeneous, prospective cohort studies recruited screen-negative participants and administered various rescreening protocols (rescreening every 1 to 5 years with 1 to 6 repeated scans) and reported the proportion of initially normal or ectatic aneurysms that reach 5.0 or 5.5 cm at the repeat scan. These studies report that AAA-related mortality over 5 to 12 years is rare (< 3%) among those with normal aortas (< 3 cm) on the initial scan. Upon rescreening, few aortas grew to > 5 cm (0 to 2.2%) at 5 years[121, 123, 138] and 0 to 15 percent had progressed at 10 years.[120] Four studies reported no AAA ruptures or AAA-related deaths[121, 138, 167, 169] at 4- to 5-year followup; one study reported 2.4 percent ruptures at median 7.9-year followup.[120] Overall, this heterogeneous body of literature was too limited to make conclusions about the effectiveness of rescreening.

Study Characteristics

Five fair-quality prospective studies,[121, 123, 165, 167, 169] two good-quality cohort studies[119, 120, 125, 138, 151, 156] and one fair-quality case-control study[148] examined the yield of rescreening

participants who initially screened negative for AAA (**Appendix E Table 4**). Six of these studies were available in the previous review[105] and two of the studies[167, 169] are new; one screening program has updated data.[156] Two of these studies analyzed subsamples of the Aneurysm Detection and Management (ADAM) Veterans Affairs trial of open versus surveillance strategies for small AAAs.[121, 138] Additionally, three studies were based in the United Kingdom: a subsample of the Gloucestershire screening study[156] a hospital screening program,[123] and a Chichester screening program separate from the Chichester trial.[165] Two of the cohort studies were conducted in Sweden, [167, 169] and one of these was exclusively in in women.[167, 169] The case-control study was a subsample of the Viborg screening trial; however, data were only considered from the cohort of participants with ectatic aortas who were offered rescreening. The size of the rescreened cohorts ranged from 33[167] to 2,692[169] participants; samples of those with normal or ectatic aortas were derived from larger screening programs and had mean followup ranging from 4 to 10 years. The Gloucestershire population-based screening program published their observations over the 25-year history of the program with a proportion being followed for at least 10 years.[120, 156] (**Appendix E Table 4**).

The definition of "normal" or "ectatic" aortas differed; inclusion criteria for selection of the rescreening cohort based on aortic diameter were defined as follows: 2.5 or 2.6 to 2.9 cm,[121, 123, 148, 156, 167, 169] less than 2.5 cm,[169] or less than or equal to 3 cm.[138, 165, 169] Ultrasound measurement techniques varied, with some measurements obtained using inner-to-inner wall measurements,[119, 120, 125, 151, 156] leading edge,[167, 169] or unspecified measurements.[121, 123, 138, 148, 165] Repeat screening occurred at various intervals after the initial normal scan as follows: annually,[121, 123,156] once at 3 to 5 years,[138, 148, 167, 169] and every 2 years.[165] Participants had a total of one,[138, 148, 167, 169] five,[121, 165] or six [156] scans after initial screening over the study duration; one study[123] did not report total number of scans.

Benefit outcomes (**Tables 3 and 4**) reported in these trials included all-cause mortality,[121, 156, 167, 169] AAA-related mortality,[121, 138, 156, 167, 169] AAA rupture[121, 138, 156, 165, 167, 169] and large-AAA incidence.[121, 123, 138, 148, 156, 165, 167] Six of these studies reported the use of procedures (**Table 3**).[121, 138, 148, 156, 167, 169]

Most studies included men 65 years and older, with only one study including men ages 50 years and older (**Appendix E Table 5**).[138] The mean age of participants ranged from 65– to 70 years. One Swedish study[167] solely recruited 70-year-old women, and one study[138] reported the inclusion of few female participants (2.4% women). The remaining studies solely recruited men. Additionally, the two studies that followed subgroups from the ADAM trial[121, 138] and one Swedish study[167] included risk factor information.

Overall, this group of observational studies is limited because: a small number of participants with normal aortas was included; all but a single study exclusively recruited men; cohort study designs did not have matched controls, and the primary focus of most studies was growth rate because the followup time for most studies was 5 years. This time frame would be too short to expect the development of AAA-related health outcomes.

Detailed Results

Large AAA incidence

While all studies reported the percentage of participants with initially normal scans who eventually developed AAA ≥ 3.0 cm, we were interested in the percentage of participants whose normal or ectatic aortas expanded to near or greater than the surgical threshold (≥ 5.0 or 5.5 cm) during the followup period. Four studies reported that none of the initially normal or ectatic aortas expanded to > 5 cm at a mean of 4 to 10 year followup (**Table 3**).[138, 148, 165, 167] Three other studies report that some of the normal aortas did progress to large AAAs on rescreening. One study (N=223) reported that 1.3 percent of aortas initially measuring 2.5 to 2.9 cm expanded to > 5.0 cm at a mean of 5.9 years of followup,[121] and one study (N=358) reported that 2.2 percent of aortas 2.6 to 2.9 cm expanded to ≥ 5.5 cm at 5.4-year mean followup.[123] A large cohort from the Gloucestershire screening program (N=1233) with longer followup reported that 14.7 percent of aortas measuring 2.6 to 2.9 cm expanded to ≥ 5.5 cm at 7.8-year mean followup.[156] The Gloucestershire publication provided estimates of large-AAA development (≥ 5.5 cm) based on growth measurements after an initial measurement of 2.6 to 2.9 cm as follows: 0.5 percent at 5 years, 10.0 percent at 10 years, 28.0 percent at 15 years; and 25.6 percent at 20 years.

Effect of Rescreening on All-Cause Mortality and AAA-Related Mortality

Only four rescreening studies reported rates of all-cause mortality, finding variable results (**Table 4**). Two studies with 5-year followup and small sample sizes reported 5.0 percent (2/40) and 15.2 percent (5/33) mortality rates in those with initial aortas of 2.5 to 2.9 cm.[167, 169] One of these studies additionally reported a 5.1 percent (136/2652) mortality rate among those with initial aortas < 2.5 cm.[169] One study (N=1233) of individuals with an initial aortic diameter of 2.6 to 2.9 cm reported a high mortality rate (30.7%) among participants at mean 7.8-year followup.[156] It is unclear how best to interpret these findings given the fact that most were not powered to detect differences in mortality and had followup time periods that were too short to fully evaluate health outcomes. Additionally, it is probable that mortality rates were confounded by variations in followup time and comorbidities contributing to competing causes of death unrelated to AAAs.

Five studies reported the incidence of AAA-related mortality in those with normal or ectatic aortas.[121, 138, 156, 167, 169] Rates were low overall and ranged from 0 to 2.4 percent (**Table 4**). Four of these studies with mean followup ranging from 4 to 5.9 years reported no AAA-related deaths.[121, 138, 167, 169] The Gloucestershire screening program (N=547) reported 2.4 percent had died of AAA-related causes by 10 years.[120, 156]

Effect of Rescreening on AAA Rupture

Reported AAA rupture rates were low in participants with ectatic or "normal" aortas (**Table 3**). Four studies that included participants with an initial aortic diameter of 2.5 to 2.9 cm reported no ruptures at a mean of 4.0 to 5.9 years of followup.[121, 138, 167, 169] The Gloucestershire screening program (N=547) of patients with an initial aortic diameter of 2.6 to 2.9 cm and a median of 7.9-year followup reported that 2.4 percent had experienced a rupture.[120, 156] Three studies did not

report rupture rates.[123, 148, 165]

AAA Procedures and Operative Mortality

AAA-related surgeries and operative mortality were rare (**Tables 3 and 4**). Four studies reported no AAA procedures at 4 to 5.9 years of followup;[121, 138, 167, 169] however, the Gloucestershire screening program reported that 11.5 percent of those with initial 2.6 cm to 2.9 cm aortas had undergone a procedure by the median 7.9-year followup; 90 percent of these were elective surgeries.[120] In this publication, 30-day operative mortality rate of 11.1 percent (7/63) after emergency and elective repair combined, with a 7.0 percent operative mortality after elective repair; most deaths occurred in those with ruptured aortas.[120] Two studies reported no operative deaths[167, 169] (**Table 4**).

KQ2a. Do the Effects of Rescreening for AAA Vary Among Subpopulations (i.e., by Age, Sex, Smoking Status, Family History, or Race/Ethnicity)?

Summary of Results

There were no trials available to examine the differential effectiveness of rescreening by subpopulation. Nearly all rescreening cohort studies were performed in Caucasian men and most did not perform subgroup analyses. Scant available data had low credibility. Only one good-quality rescreening study[138] at 4 years reported AAA-related health outcomes and captured risk factor information; however, there were no AAA-related deaths or ruptures reported in this study. A single rescreening study among women (N=25)[167] reported AAA-related health outcomes, but it was too small to make any comparisons with the other all-male studies. Two studies[138, 169] reported multi-regression analyses suggesting that current smoking is an independent risk factor for the development of AAA at rescreening, and another study's univariate analysis shows a similar trend for smoking status among women.[167]

Study Details

Only four of the rescreening studies provided data on screening in subgroups[138, 165, 167, 169] For all but one study,[138] it was unclear whether the subanalyses were prespecified. Additionally, there was a lack of a proper control group in these studies and the overall study sizes were small, making the subgroup analysis credibility low. The conclusions about the effects of rescreening in subgroups were limited by lack of adequate reporting of health outcomes by subpopulation, as well as by the heterogeneity of study rescreening protocols and short followup times.

Results

AAA Incidence 3.0 cm by Subgroup

Both the articles by Lederle et al. 2000[138] (N= 2622) and Svensjo et al. 2014[169] (n=2059) examined numerous risk factors among participants (> 10 risk factors). Both studies reported that current smoking was an independent risk factor for AAA development based on a multivariable regression analysis. Lederle et al. found that current smokers were three times as likely to develop AAAs (OR 3.09 [95% CI, 1.74 to 5.50). Other risk factors (including age, family history, race, and sex) were not found to be independently associated with AAA development. Similarly, in the article by Svensjo et al.,[169] current smoking was found to be independently associated with AAA development (OR 2.78, [95% CI, 1.38 to 5.57]). In the Soderberg study (N=25), approximately half of those who progressed from small AAAs to large AAAs at the 5-year rescreening were current smokers (7/12; p =0.01). The other ADAM subset study[121] (N=223), however, reported that a multivariate logistic regression analysis did not identify any risk factors independently associated with the development of AAAs. The subset of the Chichester screening[165] study showed that the screening yield among patients rescreened every two years diminishes with age and multiple repeat scans.

AAA Incidence ≥5 cm by Subgroup

The development of large AAAs in the rescreening trials was rarely reported by subpopulation. Lederle et al. 2000[138] and Scott et al. 2001[165] collected risk factor information, and both reported zero incident AAAs ≥ 5 cm at 4- and 10-year rescreening, respectively. Likewise, none of the aneurysms in the all-women Soderberg study[167] progressed to ≥ 5.0 cm at 5 years.

AAA-Related Health Outcomes by Subgroup

Of the eight rescreening studies, only the ADAM subset study[138] collected risk factor information and reported health outcomes. Lederle reports AAA-related mortality by age, race, smoking history, and family history (along with > 10 other patient characteristics) but there were zero AAA-related deaths or ruptures in the 4-year followup period among those with initial aortas < 3.0 cm. Scott et al. 2001[165] reports AAA-related mortality by age but does not provide the denominator for the age groups provided. Therefore, no comparative analysis can be done. None of the studies reported within-study subgroup analyses by sex although several studies recruited a single sex: one study included all women[167] and five recruited all men.[123, 148, 156, 165, 169] There was such substantial heterogeneity across these studies (e.g., rescreening intervals, followup time, mean baseline aortic diameter) that comparisons across studies would not be appropriate.

KQ3. What Are the Harms Associated With One-Time and Repeated Screening?

Summary of Results

All four population-based screening RCTs (2 fair-, 2 good-quality) provide information on operative mortality and the number of surgeries for AAA, showing an increase in elective surgeries among the intervention group compared with the control group, but no difference in operative mortality.[12, 15, 113, 147, 168, 170] One new fair-quality population-based screening trial, VIVA,[22, 146] which looked at the impact of screening for multiple cardiovascular conditions, provides the number of elective and emergency operations among those screened. Overall, there were approximately 40% percent more surgeries in the invited group than the control group (K=5, N=175,085; Peto OR 1.44 [95% CI, 1.34 to 1.55]), which is largely driven by elective operations (k=5; N=175,085; Peto OR 1.75 [95% CI, 1.61 to 1.90]). There was no statistically significant difference in 30-day mortality rates among the invited versus control groups for either elective surgeries or emergency surgeries at 12- to 15-year followup.

Three small quality of life observational studies report mixed results.[141, 150, 174] These studies, in addition to the two population-based screening RCTs that reported quality of life scores,[12, 15, 168, 170] generally showed no substantial differences in quality of life, anxiety or depression scores between those who screened positive and those who were unscreened or screened negative for AAAs based on one-time screening.

Study Characteristics

Four population-based AAA screening trials previously described for KQ1 also provide data on harms (**Tables 1 and 2**).[15, 113, 147, 170] These four RCTs were included in the previous review with the addition of updated long term followup data available from the Western Australia trial.[15] One additional new multicomponent population-based Danish screening trial, Viborg Vascular (VIVA), was included in this current review of harms to estimate elective surgeries.[146] VIVA enrolled 50,156 men aged 65 to 74 years from 2008 to 2011. Participants were randomized to screening versus no screening for hypertension, PAD, and AAA. After screening, VIVA participants who had confirmed AAA or PAD were counseled on the need to initiate preventive interventions including walking, smoking cessation, a low-fat diet, and cholesterol testing, with aspirin and statin therapy prescribed to those meeting a total cholesterol threshold value (**Appendix E Tables 1 and 2**).[146] An interim analysis at a median of 4.4 years of followup reported number of operations, all-cause mortality and AAA-related outcomes, including causes of death based on death certificates. The effects of AAA screening alone could not be independently assessed with respect to all-cause mortality or AAA-mortality because there were multicomponent screening interventions administered, however the number of surgeries were included in this review as these would almost exclusively be expected due to AAA screening.

One study (MASS) reported quality of life differences over time between screened and unscreened populations.[12, 170] This MASS subsample[12, 170] plus four additional studies measured various quality of life questionnaires for screened populations with and without AAA diagnoses,

comparing prescreening baseline scores to repeated scores at 1 to 15 months after screening (**Appendix E Tables 1 and 6**).[15, 141, 150, 168, 174] All of these quality of life studies were available in the previous review. [105] Two studies were subsamples from the screened arms in the MASS (N=1956; 599 AAAs, 631 normal aortas, 726 not invited for screening)[12, 170] and Western Australia (N=365; 120 AAA, 245 normal aortas) trials;[15, 168] two additional observational comparisons were analyzed from population-based screening programs in Gloucestershire (N=161; 61 AAAs, 100 normal aortas)[150] and Sweden (N= 69; 24 AAAs, 45 normal aortas);[174] and one small observational study analyzed screened participants in a rural Australian screening study (N=183 completed postscreening questionnaire; 35 AAAs, 89 normal aortas)[141] The studies reported quality of life outcomes using: Short-form 36 (SF-36),[12, 15, 141, 168, 170, 174] EQ-5D,[15, 168] and EuroQOL EQ-5D.[12, 15, 168, 170] Mood (anxiety or depression) was measured with the Hospital Anxiety and Depression scale (HADS),[15, 141, 168] the General Health Questionnaire (GHQ),[150] and a VAS anxiety scale.[150] Questionnaires were administered prior to screening, after screening, or in selected subgroups of those with screen-detected AAAs undergoing surgery or surveillance. Timing of questionnaires was up to 12 months after a specific event.

Detailed Results

Operative Mortality

30-Day Postoperative Mortality From Elective Surgeries

Two of the four population-based screening trials report 30-day operative mortality from elective surgeries, showing no difference among those invited to screening and those in the control group (**Table 2**).[15, 170] The MASS[170] and Western Australia[15] trials reported no statistically significant difference in 30-day mortality from elective surgeries between the invited and control groups at 12.8 to 13.1 year followup (n=1827; MASS: RR 0.76 [95% CI, 0.40 to 1.45]; Western Australia: RR 0.82 [95% CI, 0.43 to 1.57]) (**Figure 5**).

30-Day Postoperative Mortality From Emergency Surgeries

The MASS[170] and Western Australia[15] screening trials report 30-day operative mortality from emergency surgeries and show similar results (**Table 2**). They showed no statistically significant difference in 30-day mortality from emergency surgery between the invited and control groups at 12.8 to 13.1-year followup (n=316; MASS: RR 0.98 [95% CI, 0.68 to 1.43]; Western Australia: RR 1.43 [95% CI, 0.90 to 2.25] (**Figure 5**).

Number of Operations

All AAA Operations

As would be expected, in all five screening trials,[15, 113, 146, 147, 170] there were more AAA-related operations in the invited group than the control group, with 1.1 to 2.9 percent of the screened group undergoing surgical repair (**Table 1**). Based on pooled data from the five trials (n=175,085), there were nearly 40 percent more surgeries in the invited group compared to the control group (Peto OR 1.44 [95% CI, 1.34 to 1.55]; I^2=74%) (**Figure 4**). We estimate the

screening program would increase the total number of operations per 1000 men by 6 (95% CI, 5 to 8). Overall, the majority of operations in the screening group were elective, with few emergency surgeries reported. This pattern was not consistent across the studies, however, when examining the control group proportionality for elective and emergency surgery.

Elective Operations

Elective operations were consistently more common in the screened group than in the control group in all five trials,[15, 113, 146, 147, 170] with surgery rates ranging from 1.0 to 2.8 percent in those screened versus 0.4 to 2.2 percent in the control group (**Table 1**). The pooled analysis of these five trials (N=175,085) confirmed this finding and showed a higher elective operation rate in the screened group than in the control group (Peto OR 1.75 [95% CI, 1.61 to 1.90]; I^2=89%) (**Figure 4**). We estimate that screening 1000 men for AAA would increase the number of elective operations by 8 procedures (95% CI, 6 to 9).

Emergency Operations

These outcomes are discussed under Key Question 1, benefits of screening.

Quality of Life

Results from five studies (n=2,734) were mixed but generally showed no substantial, long-term differences in quality of life, anxiety, or depression scores between those who screened positive and negative for AAAs (**Appendix E Table 6**).[12, 15, 141, 146, 150, 168, 170, 174] Of note, the QOL and mood scales administered in these studies have no established minimally clinically important differences in AAA populations. MASS (n=1,956) reported that SF-36 QOL measures were similar between participants who screened positive for AAA at 6 weeks and unscreened controls.[12, 170] Compared with the screen negative group, the group with screen-detected AAAs had statistically significantly poorer anxiety, physical health, mental health, and self-rated health and health index QOL scores at 6 weeks, but all measures were within age-matched population norms. . Further, comparisons between screen-detected participants undergoing surgery and surveillance showed initial differences at 3 months in the mental health component of the SF 36 and EQ-5D self-rating, but other measures were similar between the groups and the scores improved slightly by 12-month followup.

The Western Australia trial subsample (n=365) reported no statistically significant difference in self-perceived general health changes from baseline to 12-month followup between those with and without an AAA.[15, 168] Validated quality of life measures were only reported at 12 months for the screen positive and screen negative groups with higher physical functioning in the screen negative group but, without changes from baseline comparisons between the groups provided. Similar findings were reported in a study of Swedish men and women (n=69).[174] The study reported that even though those who screened positive showed a statistically significant decrease from baseline in several SF-36 domains (i.e., physical functioning, social functioning, and mental health); SF-36 scores were not different at baseline or at 12 months after screening in those who screened positive compared to those who screened negative for AAAs. In the Gloucestershire Screening program (n=161),[150] the group with screen detected AAAs and normal

aortas both had modest (up to 2 points out of an 80-point scale) reductions in anxiety levels based on GHQ scores 1 month after screening; there were no differences between the groups in prescreen scores or post screening GHQ scores or visual analogue anxiety scores. In a study conducted in rural Australia (n=183),[141] only the screen-negative group had a statistically significant improvement in the SF-36 dimensions of general health, social function, and freedom from bodily pain, but SF-36 scores were not different 6 months after screening in those with AAAs compared to those without AAAs. Small numbers make these results imprecise.

Rescreening Harms

There were no RCTs to assess the harms of rescreening versus no rescreening in those with normal sized aortas (< 3.0cm) on initial screening. No studies examined QOL outcomes for rescreening.

Six fair-quality cohort studies examined procedure rates in rescreened cohorts.[121, 138, 148, 156, 167, 169] Five of these studies showed a low procedure rate (0 to 4%) up to 5-year followup; [121, 138, 148, 167, 169] a single study with a mean 7.8-year followup reported a higher rate of 10.9 percent (**Table 3**).[156]

KQ3a. Do the Harms of One-Time and Repeated Screening for AAA Vary Among Subpopulations (i.e., by Age, Sex, Smoking Status, Family History, or Race/Ethnicity)

Summary of Results

Overall, there is very little information on screening harms reported by subpopulation and what is reported has low credibility as it is unlikely to have been prespecified or powered to detect subpopulation differences. Available scant data from a single trial (Western Australia) suggest a trend of higher postoperative mortality after elective repair associated with screening (compared to no screening) in older age groups but no differential screening effect on number of operations by age.[15]

Results

Operative Mortality

The Western Australia trial reported lower rates of 30-day postoperative mortality from elective AAA surgeries attributed to screening (versus no screening) in those who were 65 to 74 years of age compared with the entire trial population age (64 to 83 years) (**Appendix F Table 1**).[15] No statistical testing was performed to compare summary estimates (HR and CIs) for age bands, nor was interaction testing performed to test differential treatment effects by age. Authors reported that 1.6 percent (6/368) died among the narrower age band (65-74 years), whereas 3.4 percent (18/536) of the entire study population died within 30 days of elective repair; unscreened control group 30-day mortality was 4.0 percent and 4.1 percent in the younger age band and entire trial

population, respectively. This 30-day postoperative mortality trend was less pronounced for 30-day postoperative mortality following emergency surgery (**Appendix F Table 1**).

Number of Operations

The Western Australia trial reported no differential screening effect in the number of elective and emergency AAA surgeries attributed to screening (versus no screening) in those who were 65 to 74 years of age compared with those who were 64 to 83 years of age.[15] For elective AAA surgeries, authors report the similar relative rate of elective surgeries among the narrower age band compared with the entire study population for the screened and unscreened groups (screened: 2.77% vs. 2.78% in younger age band and entire study population; unscreened: 2.08% vs. 2.15% in the narrower age band and entire study population). This was similar to the findings for emergency surgeries (screened: 0.11% vs. 0.14% in younger age band and entire study population; unscreened: 0.20 % vs. 0.23% in narrower age band and entire study population) and overall operations (**Appendix F Table 3**).

While the Western Australia trial reported a subgroup analysis concluding that ever-smokers had a higher rate of elective operations compared to never-smokers (4.19% vs. 1.24%, OR 3.47 [95% CI, 2.54 to 4.75]), this analysis did not provide comparative ORs for the unscreened group and therefore did not test the differential effect of screening by smoking status (**Appendix F Table 4**).[15]

Quality of Life

There is no information on quality of life reported for subpopulations.

KQ4. What Are the Effects of Treatment (Pharmacotherapy or Surgery) on Intermediate and Health Outcomes in an Asymptomatic, Screen-Detected Population With Small AAAs (i.e., Aortic Diameter of 3.0 to 5.4 cm)?

Summary of Results

Four trials evaluated the comparative effectiveness of early surgical repair versus surveillance for small aneurysms (4 to 5.4 cm): two evaluated the effectiveness of early open surgery[140, 163] and two evaluated early EVAR interventions.[118, 158] All four of these trials showed no difference in all-cause mortality or AAA-related mortality between the intervention and control groups up to 8 to 12 years for open repair[140, 163] and at up to 2.6 years for EVAR.[118, 158]

Seven pharmacotherapy efficacy trials examining antibiotics, antihypertensive medications, or mast cell stabilizers were identified in this updated review.[114, 132, 133, 152, 153, 164, 166] In all included trials, pharmacotherapy intervention showed no overall impact on AAA growth compared to placebo. Conclusions are limited by a small number of trials evaluating each medication and trial durations, which were too short to expect the development of AAA-related events or changes in

health outcomes.

Study Characteristics

Early Open Surgery Versus Surveillance

Two good-quality RCTs[140, 162] evaluated the comparative effectiveness of open repair versus surveillance for small AAAs. These two trials were available in the previous review.[105] The ADAM trial[139, 140] (N=1,136) recruited participants from a U.S. Veteran Affairs (VA) AAA screening program from 1992 to 1997, who were aged 50 to 79 years with AAAs measuring 4.0 to 5.4 cm. The UK Small Aneurysm Trial (UKSAT)[75, 115, 128, 130, 161-163] (N=1,090) recruited patients from 93 U.K.-based hospitals from 1991 to 1995, who were aged 60 to 76 years with AAAs measuring 4.0 to 5.5 cm. The mean age in these trials was 68.1 years with nearly all men (99.2% men) and 69.3 years with mostly men (82.5% men) in ADAM and UKSAT, respectively. Over one-third of participants in both trials were current smokers. Additionally, ADAM reported that 12.9 percent of participants had a family history of AAA. There were a large proportion of participants in both trials with hypertension, however, CVD was higher in the ADAM trial (41.9% coronary disease, 12.4% cerebrovascular disease) than UKSAT (14% probable ischemic heart disease). The mean baseline AAA diameters were similar in the trials (4.7 cm[140] and 4.6 cm[162]) although measurement in ADAM was via CT measurement rather than ultrasound (**Appendix E Tables 7 and 8**).

The intervention group in both trials received open surgical repair by local surgeons using their usual clinical pre/intra/postoperative management within 6 weeks[140] or 3 months[162] of AAA identification. Fidelity to the assigned intervention arm was high with 520 patients (92.4%) in the UKSAT trial and 527 (92.6%) in the ADAM trial receiving procedures after a mean followup period of approximately 5 years. Control groups received surveillance every 3 to 6 months depending on AAA diameter. Participants in the surveillance arm were referred for surgical intervention if AAA reached 5.5 cm or rapidly increased by 1 cm/year, 0.7 cm in 6 months, or if symptoms developed. By the end of 5-year followup, 349 (61.6%) in the ADAM surveillance group and 321 (60.9%) patients in the UKSAT surveillance group had undergone open surgical repairs. By the end of 12-year followup, 401 (76.1%) patients in the UKSAT surveillance group had undergone open surgical repair.

Both studies actively managed patients for a mean of approximately 5 years (4.6 years UKSAT; 4.9 years ADAM).[140, 162, 163] In addition to 5-year followup at the end of active management, the UKSAT trial reported results at 8 and 12 years.[161-163] Followup rates were high, with over 99 percent of patients followed up after 12 years in the UKSAT trial, and approximately 86 percent in the ADAM trial after 5 years for primary outcomes.[140, 163]

Early EVAR Versus Surveillance

Two fair-quality RCTs (Comparison of Surveillance versus Aortic Endografting for Small Aneurysm Repair [CAESAR],[118] Positive Impact of endoVascular Options for Treating Aneurysm earLy [PIVOTAL] trial[158] evaluated the impact of early EVAR compared to surveillance among patients with small aneurysms. These two trials were available in the

previous review in the previous review.[105] CAESAR (N=360) recruited participants from 20 European and Western Asian hospitals from 2004 to 2008, aged 50 to 79 years with AAAs measuring 4.1 to 5.4 cm.[117, 118] PIVOTAL (N=728) recruited participants from 70 U.S. sites from 2005 to 2010, aged 40 to 90 years with AAAs measuring 4.0 to 5.0 cm. The mean age was similar in both trials (68.9 vs. 70.5 years),[157, 158] and the majority of participants were men (95.8% [CAESAR] and 86.6% [PIVOTAL]). Mean AAA diameters were 4.7 cm [CAESAR] and 4.4 cm [PIVOTAL]. Notably, there was a higher proportion of smoking patients and patients with coronary artery disease (CAD) in the PIVOTAL trial compared to CAESAR (smoking: 91.0% vs. 55.3%, CAD: 55.4% vs. 39.2%, respectfully) (**Appendix E Tables 7 and 8**).

In the intervention group, patients received EVAR as soon as possible [CAESAR][118] or within 30 days [PIVOTAL][158] of randomization. The control group received surveillance every 6 months and were offered surgery when AAAs reached 5.5 cm or enlarged at a rate of > 1cm/year [CAESAR] or ≥0.5 cm/6 months [PIVOTAL], or if aneurysms became symptomatic [CAESAR] (**Appendix E Tables 7**). Fidelity to the assigned intervention was high with 322 patients (88.9%) who were allocated to the early EVAR group receiving EVAR procedures in the PIVOTAL trial, and 171 (94.0%) receiving early EVAR in CAESAR. In each trial, four patients received open surgery instead of EVAR in the early EVAR group. Of patients randomized to surveillance, 71 (39.9%) in the CAESAR trial and 108 (30.1%) in the PIVOTAL trial received EVAR by the end of followup (**Table 8**).

The CAESAR trial reported results at a median followup of 2.6 years,[118] and the PIVOTAL trial reported results at 1.7-year mean followup.[158] Both RCTs conducted interim analyses and found that detection of meaningful difference in primary outcomes between EVAR and surveillance was unlikely if patient enrollment were to continue (i.e. futility).[118, 158] Thus, both trials subsequently stopped recruiting patients early, but they completed scheduled followups in those who had already been enrolled. Likely due to early stopping of enrollment, the two studies did not adequately achieve balance between randomized arms in important prognostic factors such as family history, sex, and diabetes.

Detailed Results

Open Repair Versus Surveillance

All-Cause Mortality

Both trials found no significant differences in all-cause mortality at any followup time between those receiving early open repair versus surveillance (**Table 5**).[140, 162, 163] At 5-year followup, the ADAM trial reported slightly more deaths in the intervention group than in the control group (25.1% vs. 21.5%; RR 1.21 [95% CI, 0.95 to 1.54),[140] while UKSAT reported slightly more deaths among those in the control group (30.6% vs. 46.7%, RR 0.91 [95% CI, 0.72 to 1.16]),[162, 163] but neither finding was statistically significant. At 12-year followup UKSAT reported a similar trend; however, the difference was not statistically significant (adjRR 0.88 [95% CI, 0.75 to 1.02). An individual patient data (IPD) analysis (n=2,226) of patients randomized to both trials showed no survival benefit at approximately 5 years in both the unadjusted (HR 0.96, [95% CI, 0.81 to 1.14]) and adjusted analyses (HR 0.99, [95% CI, 0.83 to 1.18]).[126]

AAA-Related Mortality

Similar to the findings for all-cause mortality, both trials found no significant differences in AAA-related mortality at any followup time period (**Table 5**).[140, 162, 163] At 5-year followup, the ADAM trial reported nearly identical rates of AAA-related mortality among those who received open repair versus surveillance (3.0% vs. 2.6%, HR 1.15 [95% CI, 0.58 to 2.31]).[140] Mortality rates in UKSAT were slightly higher at 5 years of followup and more deaths were observed in the surveillance group compared with those receiving surgery, but the difference was not significant (5.7% [IG] vs. 6.6% [CG], RR 0.86 [95% CI, 0.54 to 1.36]).[162, 163] At 12 years of followup, UKSAT reports an AAA-related mortality rate of 6.9 percent in the intervention group and 9.5 percent in the surveillance group.[163]

Rupture

Ruptures were rare events in both trials; however, early open repair significantly reduced the rate of rupture compared with those undergoing surveillance at each followup interval (**Table 6**).[140, 162, 163] The ADAM trials reported a rupture rate of 0.4 percent in the early intervention group compared with 1.9 percent in the surveillance group (RR 0.18 [95% CI, 0.04 to 0.81]).[140] Rates were slightly higher in UKSAT at 5-year followup but remain significantly different between treatment groups (1.2% vs. 3.2%, RR 0.33 [95% CI, 0.13 to 0.83]).[162, 163] At 12 years of followup, UKSAT reported that 2.3 percent of the early surgery group and 4.5 percent of the surveillance group experienced AAA rupture (RR 0.51 [95% CI, 0.26 to 0.99]).[163]

All Operations

As expected, overall there were more surgical interventions in the early surgery groups than in the surveillance group (**Table 6**). The ADAM trial reported only overall procedures (IG: 92.6% vs. CG: 61.6%) and did not break them down into emergency versus elective.[140] In UKSAT the majority of surgical interventions were elective at each followup timepoint.[162, 163] At 12 years of followup there were notably fewer emergency surgeries in the early surgery group compared with those undergoing surveillance (3 [0.5%] vs. 6 [1.1%], but emergency surgeries overall were rare.[163]

Early EVAR Versus Surveillance

All-Cause Mortality

Both EVAR trials found no significant differences in all-cause mortality at 1.7- to 2.6-year followup between those receiving early EVAR and those undergoing surveillance (**Table 7**).[118, 158] At 2.6 years, CAESAR reports similar rates of all-cause mortality between treatment groups (5.5% vs. 4.5%) with a HR (CG vs. IG) of 0.76 (95% CI, 0.30 to 1.93).[118] Likewise, PIVOTAL found no difference in all-cause mortality between those receiving early EVAR versus surveillance at 1.7 years (4.1% vs. 4.1%, HR 1.01 [95% CI, 0.49 to 2.07]).[158]

AAA-Related Mortality

Similar to the findings for all-cause mortality, both trials found no significant difference in AAA-related mortality at any followup time period (**Table 7**).[118, 158] Events were rare and findings in both trials were nearly identical in each treatment group (1 [0.5%] vs. 1 [0.6%] in CAESAR; 2 [0.5%] vs. 1 [0.3%] in PIVOTAL). The relative risks were nonsignificant with wide confidence intervals. Conclusions are limited by low event rates.

Rupture

Ruptures were rarely reported in either trial, making comparisons challenging (**Table 8**). Both trials report zero ruptures among those receiving early EVAR and few events among those undergoing surveillance (2 [1.1%] in CAESAR; 1 [0.3%] in PIVOTAL).[118, 158]

All Operations

Again, as anticipated, there were more total surgical interventions in the early surgery groups than in the surveillance group (**Table 8**). In both trials, the majority of surgeries were elective. with more elective surgeries reported in the intervention groups (CAESAR 94.0% vs 39.9%; PIVOTAL 88.9% vs 30.1% received surgery).[118, 158] Emergency surgeries were rare events. PIVOTAL reported only a single emergency surgery in the surveillance group, and there was mention of emergency surgeries in the early EVAR group. CAESAR did not report emergency surgeries as an outcome.

Pharmacotherapy Versus Placebo

Study Characteristics

Three good-quality[114, 132, 164] and four fair-quality[133, 152, 153, 166] placebo-controlled RCTs investigated the effectiveness of antibiotics, antihypertensives, or mast cell stabilizers on small AAA growth. These trials, conducted in Finland,[153] Denmark,[131, 132, 166, 172] Sweden,[133, 166] the Netherlands,[152] the United Kingdom,[114, 136, 166] and Canada,[164] recruited participants from vascular referral centers, as well as from community/population screening programs, who had small AAAs ranging from 3 or 3.5 cm to 4.9 or 5.4 cm in diameter. Three of these trials[114, 152, 166] are new since the previous review. The mean AAA diameter at baseline ranged from 3.3 to 4.4 cm (**Appendix E Table 8**).

The trials recruited mostly men, with women comprising 0 to 18.5 percent of the trial participants (**Appendix E Table 8**). The mean age ranged from 68.4 to 72.5 years and the mean percent of current smokers in the trials ranged from 25 to 60 percent. Only two trials reported the proportion of participants with a positive family history for AAA as 14 percent[133] and 25.2 percent.[152] The history of CVD was prevalent in the studies, ranging from approximately a third to a half of participants in the trials reporting this baseline characteristic. Sample sizes ranged from 32[153] to 552.[164]

All but one included trial examined the role of either antibiotics or antihypertensives on AAA

growth compared to placebo—four trials studied the effects of antibiotics on AAA growth[132, 133, 152, 153] and two studied antihypertensive medication effects on growth.[114, 164] Of the trials of antibiotics, two examined macrolide antibiotics (roxithromycin 300 mg daily for 28 days,[131, 132, 172] azithromycin 600 mg daily for 3 days followed by 600 mg once per week for 15 weeks)[133] and two of these trials studied doxycycline at different doses (100 mg[152] or 150 mg[153] daily for 3 to 18 months). There were two antihypertensive trials: one used propranolol 20 mg twice per day titrated up to target dose of 80 to 120 mg twice per day for 2.5 years[164] and one administered an ACE-inhibitor, (perindopril 10 mg daily) or a calcium channel blocker (amlodipine 5mg daily) for 2 years.[114, 136] The final trial examined a mast cell inhibitor, pemirolast 40 mg twice daily.[166] The treatment duration ranged from 28 days[132] to 2.5 years.[164] The control group received a matching placebo in all trials (**Appendix E Table 8**).

The seven trials' primary outcome was AAA growth. Two antibiotic trials of azithromycin and doxycycline[133, 153] reported the median and interquartile range (IQR) of annual growth rates, while the other five trials reported the mean annual growth rate of the aneurysm (mm/year).[114, 132, 152, 164, 166] Ultrasound measurements were performed using aortic anterior-posterior diameters in all trials with four using the larger of the axial or transverse measurement planes.[132, 133, 153, 166] Only one trial (PAT) reported using outer-to-outer wall measurements, while one trial reported using the external diameter measured in the longitudinal plane[114, 136] and another reported using the anterior posterior diameter from inner to inner wall.[152] Two trials clearly reported a standard AAA size threshold for surgical repair: PAT[164] and Hogh et al.[131, 132, 172] referred all AAAs at greater than or $\geq$ 5 cm to surgery. The assumption for the remainder of studies is that repair was performed according to local standard clinical practice. Only two trials measured patient adherence to medications with pill counts (**Appendix E Table 7**).[114, 152] Followup time in the trials was 1 to 5 years. Additionally, two of the trials reported quality of life outcomes using Screen QOL[142] or SF-36[164] scales (see KQ5 harms).

Detailed Results

AAA Growth Rates

All seven trials reported no significant beneficial impact of pharmacotherapy on AAA growth (**Table 9**).[114, 131-133, 136, 152, 153, 164, 166, 172] One trial of doxycycline compared with placebo reported that the intervention group had a statistically significantly *greater* growth in aneurysm size compared with those taking placebo (4.1 mm vs. 3.3 mm; difference 0.8 mm [95% CI, 0.1 to 1.4 mm]).[152] This trial included participants with larger AAAs who were unfit for surgery. The remaining six trials showed no statistically significant difference in growth rates between the intervention and control groups.[114, 132, 133, 153, 164, 166] Four of these trials[114, 132, 153, 164] showed a nonsignificant lower mean growth rate in the intervention group, with differences ranging from 0.5 mm/year[164] to 1.5 mm/year.[153] Conversely, one trial showed identical mean growth rates of 2.2 mm/year (median IQR) in the intervention and control groups,[133] and one trial of pemirolast showed a nonsignificant greater aneurysm growth rate in the intervention group compared with those taking placebo (2.71 mm/year vs. 2.04 mm/year).[166]

All-Cause Mortality

Few studies reported the impact of pharmacotherapy on all-cause mortality and those that did found mixed trends without statistical significance (**Table 10**). Three antibiotic trials[133, 152, 153] and one beta-blocker trial[164] report rates of all-cause mortality. PAT reported a higher mortality rate among those in the treatment group compared with those taking placebo, however the difference was nonsignificant (12% vs. 9.6%, p = 0.36).[164] This same trend was reported in the study of doxycycline by Mosorin et al. (23.5% vs. 20.0%, significance NR).[153] In the remaining studies, there were more deaths observed in the control group, however these events overall were too rare to make any conclusions about effects on all-cause mortality at 1.5- to 2.5-year followup.

AAA-Related Mortality

Again, few studies reported the impact of pharmacotherapy on AAA-related mortality and those that did found mixed results (**Table 10**). Only three trials—two antibiotic trials[133, 152] and one beta-blocker trial[164]—reported this outcome. Two of the three trials report the same number of events between treatment groups, while one trial reports a slightly higher rate among those taking placebo.[152] Events overall were rare (0 to 2 events in each group), thereby limiting conclusions.

AAA Rupture

Five trials reported instances of AAA rupture between treatment groups and again found mixed results (**Table 9**).[114, 152, 153, 164, 166] The event rates were very low in these trials: two trials reported no ruptures in both the intervention and control groups,[114, 166] and three trials had 0 to 2 events in each group (control group rates 0% to 1.4%), making it difficult to make conclusions about the medication's effect on rupture at 1- to 2.5-year followup.

All Operations

Total AAA-related procedures are reported in all seven pharmacotherapy trials; however, only five specify surgeries as emergency or elective procedures.[132, 133, 152, 153, 164] Results showed a mixed pattern and statistical testing was not performed. Rates of total AAA-related procedures varied widely by study (range 2 to 40% in control groups), with two studies[133, 166] reporting more surgeries in the intervention group, three studies[152, 153, 164] reporting more surgeries in the control group and one study[114] reporting nearly identical rates of surgery in the intervention and control groups (**Table 9**). One trial did not report procedures by treatment group.[132]

Two doxycycline trials[152, 153] and one propranolol trial[164] reported elective AAA surgeries with mixed results (**Table 9**). One doxycycline study[152] reported similar rates of elective surgeries between treatment groups (IG: 14.6% vs. CG: 15.5%), while the other doxycycline trial[153] reported more elective repairs in the control group compared to the intervention group (IG: 11.8% vs. CG: 40%; statistical information NR). Similarly, PAT reported more elective surgeries in the control group than in the treatment group (20.3% vs. 26.5%; statistical information NR).[164]

The same three studies reporting elective surgeries also reported emergency surgeries, finding mixed results. (**Table 9**).[152, 153, 164] These emergency surgeries were rare, with 0 to 2 events in each group (0% to 1.4% in the control groups), again limiting conclusions about these medications' effects on emergency surgery rates at 1.5- to 2.5-year followup.

KQ4a. Do the Effects of Treatment of Small AAAs Vary Among Subpopulations (i.e., by Age, Sex, Smoking Status, Family History, or Race/Ethnicity)?

Summary of Results

Subpopulation information was rarely reported among treatment studies for small AAAs. For trials of early intervention via open surgery compared with surveillance, the available trials reported limited data on the subpopulations of sex, age, and smoking status. Only UKSAT, with a 12-year followup, and the IPD MA, which pooled 5- to 8-year followup data from ADAM and UKSAT, reported all-cause mortality by sex, finding no differential effect.[126, 162, 163] Both trials reported the impact of age on all-cause mortality, utilizing slightly different age cutoffs, but did not report differential all-cause mortality treatment effect by age at 4.9 and 12-year followup. UKSAT reported no differences in all-cause mortality by smoking status but did not report outcomes in smokers for each treatment arm so no conclusions could be made about differential treatment effect of early surgery by smoking status. Neither trial of early EVAR compared with surveillance reports data by subpopulation.

None of the pharmacotherapy trials reported health outcomes by subgroup. One small doxycycline trial and one propranolol trial performed limited subgroup analyses, which did not support treatment effect modification by age or smoking status. These available analyses would be considered exploratory at best, particularly given that the subgroup methodologies were of low quality and overall trial results do not support a AAA growth benefit.

Detailed Results

Open Surgery Versus Surveillance

Age

Both ADAM and UKSAT reported no statistically significant treatment modification in all-cause mortality by age.[140, 163] These subgroup analyses were prespecified with adjustment for confounders and interaction testing was performed (**Appendix F Table 5**). In the ADAM trial, there was no statistically significant interaction with respect to mortality between treatment groups and age (age strata: 50 to 59 years, 60 to 69 years, 70 to 79 years) at a mean of 4.9-year followup; confidence intervals were overlapping for each age group (p interaction not reported).[140] Likewise, in UKSAT there were similar results seen by age group (age strata: 60 to 66 years, 67 to 71 years, 72 to 76 years) at 12-year followup.[163] There was no significant interaction between treatment group and age with respect to all-cause mortality (p interaction

=0.15). Subgroup-specific effect modification is unlikely, particularly given that the overall trial results showed no difference between the early surgery and surveillance groups.

Sex

Both ADAM and UKSAT conducted subgroup analysis by sex for all-cause mortality.[140, 162, 163] The vast majority of participants (>90%) in the ADAM trial and UKSAT were male and white. Only the UKSAT reported outcomes by sex with a prespecified analysis, adjustment for confounders and interaction testing. ADAM had planned a subgroup analysis by sex (only 0.8% of participants were women); however, results were not reported separately and are only available as pooled data in the IPD MA.[126] In UKSAT no sex-specific subgroup differences in all-cause mortality were found (men: n=902; adjHR 0.9 [95% CI, 0.76 to 1.06]; women: n=188 adjHR 0.89 [95% CI, 0.62 to 1.28]; p-value for interaction=0.76).[163] Through 12 years of followup, UKSAT found similar numbers of deaths in men and women in the early repair group (men: 63.8%; women: 66.3%) and slightly more deaths among women than men in the surveillance group (men: 65.4%; women: 73.1%) (**Appendix F Table 6**).[163] Likewise, the Filardo IPD MA (n=2,226) pooled sex-specific all-cause mortality outcomes from UKSAT and ADAM, with up to 8-year followup showing no differential effect by sex (men: adjHR 1.01 [95% CI, 0.84 to 1.21]; women: 0.96 [95% CI, 0.49 to 1.86]; p interaction not performed).[126] No other outcomes were reported by sex subgroup.

Smoking Status

Only UKSAT reports all-cause mortality outcomes by smoking status (current smokers or never smokers compared to former smokers) showing no differences in all-cause mortality by smoking status at 10-year followup. No outcomes were reported in the intervention and control groups by smoking status for comparison, therefore this subanalysis does not test whether there is a treatment modification by smoking status. (**Appendix F Table 7**).[161-163]

Neither trial reported outcomes for early surgery compared with surveillance by family history or race/ethnicity.

EVAR Versus Surveillance

Neither of the two trials comparing early EVAR surgery to surveillance reported data on subpopulation effects.[117, 118, 157, 158]

Pharmacotherapy Versus Surveillance

Credible subgroup analyses examining differential treatment effectiveness by subpopulation were not available among the pharmacotherapy studies. Two limited analyses are reported: one antibiotic study of doxycycline[153] includes a subpopulation analysis of aneurysm growth by smoking status (patients with COPD and/or smoking habit), and one propranolol trial[164] includes a subpopulation analysis of all-cause mortality by age. Neither of these trials reported whether the subanalyses were prespecified, whether they adjusted for confounders, or whether interaction testing was performed. Other subgroup analyses described in the pharmacotherapy studies were

not considered because they did not actually examine any treatment effect modification by subpopulation (i.e., interaction between treatment assignment and subpopulation).

Mean growth rates in patients with a smoking habit and/or COPD in one small doxycycline trial (n=32) were reported.[153] Confidence intervals for mean growth rates for treatment and control groups in smokers compared to the entire study population were wide and overlapping. One propranolol trial simply stated "age had no impact on the efficacy of propranolol" but had any other details.[164]

None of the trials reported subpopulation analyses of treatment effectiveness by family history or race/ethnicity.

KQ 5. What Are the Harms of Treatment in an Asymptomatic, Screen-Detected Population With Small AAAs (i.e., Aortic Diameter of 3.0 to 5.4 cm)?

Summary of Results

The two trials, ADAM and UKSAT,[127, 137, 140, 163] reported harms of open repair versus surveillance. These trials report rates of intervention and associated mortality, finding a 50 percent higher rate of procedures in the early intervention group compared with the control group, however no difference in 30-day postoperative mortality. Readmission rates at 30 days postoperation were higher in the early intervention group in the ADAM trial than in the surveillance group, however major surgical complications were lower in the early intervention group. Quality of life results were mixed in the early open versus surveillance trials, but generally showed declines in both treatment groups over time with no statistically significant difference observed between the groups up to 1 to 2 years post randomization. The ADAM trial showed higher general health scores in the early repair group in the first 2 years, however this difference did not persist over time. One trial reported higher rates of impotence in the early repair group.

Two trials of early EVAR versus surveillance (PIVOTAL[158] and CAESAR[118]) report an approximately 100 percent higher procedure rate in the early intervention group compared with the surveillance group but no difference in 30-day postoperative mortality (**Table 11**). In the CAESAR trial, the rate of complications was consistently higher among those receiving early EVAR compared with those undergoing surveillance: the number of patients with any adverse events, any morbidity at 30 days postoperation related to repair, endoleaks at 1 year, and reinterventions. Rates were similar for any major morbidity over the trial duration between treatment groups. Conversely, the PIVOTAL trial largely reported similar rates of adverse events between groups at 30 days and 1-year postoperation and reinterventions.

In general, national and international registries report clinically important harms rates that were similar to those reported in the trials.

With the exception of the two propranolol trials reporting high rates of discontinuation due to adverse events, other medications (including other antihypertensive medications [ACE-inhibitor, Ca-channel blocker] and antibiotics) appear to be well tolerated based on few trial withdrawals reported from a small number of studies per drug class.

Study Characteristics

The two trials of early open surgery[127, 137, 140, 163] and the two trials of early EVAR[118, 122, 124, 158] discussed in detail above report data on harms (**Table 11**). The surgical harms considered in this review included surgical procedures, 30-day postoperative mortality, surgical complications including readmissions, and quality of life. In addition to the seven pharmacotherapy RCTs described in KQ4,[114, 132, 133, 152, 153, 164, 166] one additional RCT of propranolol versus placebo provided harms data only.[142]

Five fair-quality registry studies assessing outcomes after EVAR reported harms data for small aneurysm repair[116, 129, 149, 159, 160] (**Table 12, Appendix E Table 9**). Three[116, 149, 159] of the five registries are new since the last review.[105] The five registry publications that prospectively examined EVAR complication rates with subgroup reporting for small sized AAAs < 5.5cm were: the Vascunet international registry (N=12,610 small AAAs),[116] the Australian Safety and Efficacy Register of New Interventional Procedures-Surgical ASERNIP-S)[129] (N= 478) , the U.S. VSGNE (N= 1,336)[149] and ACS NSQIP (N=5,126),[159] and the European Collaborators on Stent/Graft Techniques for Aortic Aneurysm Repair [EUROSTAR]) (N=1,962).[160]

The two largest and most contemporary registries were the Vascunet[116] and NSQIP.[159] The Vascunet international registry from 11 countries reported data on small AAA (< 5.5 cm) repair with EVAR and open repair from 2010 to 2013; this registry represents the largest registry included in the review and captured greater than 90 percent of repairs done in the majority of the participating countries during the time period represented. The mean age and the sex of the subgroup with small AAAs were not reported, nor was the mean followup time. The ACS NSQIP is a nationally validated, U.S.-based, risk-adjusted dataset of surgical procedures that provided complication rates for open and EVAR procedures of small AAAs from 2011 to 2015 with outcomes reported by size quartile, including 3.5 to 5 cm and 5.01 to 5.5 cm. The mean age was 72.3 years and the population comprised 21.9 percent females. Approximately one-third were smokers. The ASERNIP-S registry from Australia reported complication rates for small AAA (≤ 5.5 cm) repaired by EVAR from 1999 to 2001 with mandatory reporting by vascular surgeons during the time period. The mean age was 75 years with a population comprising 15.9 percent women and 11 percent smokers; the median followup was 3.2 years. The VSGNE registry reported complication rates for small AAAs (< 5.5cm) repaired by EVAR and open surgery from 2003 to 2011 from a voluntary collaboration among vascular surgeons, cardiologists, and radiologists from 30 community and academic hospitals in New England. The mean age was 71 years, and the population comprised 26.2 percent women and 88.5 percent smokers; the mean followup was 1 year. The EUROSTAR is an international registry from 17 European countries and 110 institutions reporting complications of elective EVAR for small AAA (4.0–5.4 cm) repair from 1997 to 2002. The mean age of the population was 69.7 years and participants were primarily men (only 7% were female); mean followup was 1.7 years (**Appendix E Table 9**).

The two EVAR-only registries, ASERNIP[129] and EUROSTAR,[160] reported endoleaks and reinterventions, as well as 30-day operative mortality. The three registries that included both EVAR and open repair reported 30-day operative mortality,[116, 149, 159] reinterventions,[159] readmissions,[159] and/or other complications.[159]

Harms Associated With Early Open Surgery Versus Surveillance

Detailed Results for RCTs

Operative Mortality

Both the ADAM trial and UKSAT reported similar 30-day postoperative mortality rates in the early open repair and surveillance groups (**Table 11**).[140, 163] In the ADAM trial, 30-day operative mortality (defined as death within 30 days of an unruptured AAA repair) at 5 years was 2.1 percent in the early surgery group compared with 1.8 percent in the surveillance group.[140] Conversely, at 12-year followup, the 30-day operative mortality (defined as AAA-related death within 30 days of elective repair) in the early surgery group of UKSAT was 5.0 percent compared with 6.3 percent in the surveillance group (**Table 11**).[163]

Surgical Complications

The ADAM trial reported 30-day readmissions and (non-fatal) complications associated with AAA repairs in both the early open repair and surveillance groups, finding no significant higher rates of readmission in the early surgery group, but slightly lower complication rates (**Table 11**).[140] In this trial, patients in the early open surgery group had a nonstatistically significant higher rate of 30-day readmission for complications after surgery (20.5% vs. 16.5%) and a lower risk of any surgical complications (52.3% vs. 56.8%, p=0.026) compared those who received later surgery in the surveillance group. Further, the event rate for total *major* complications was higher in the surveillance group than the early treatment group (4.6% to 7.6%), with a significantly higher risk of surgery-related myocardial infarction reported in the surveillance group (1.0% vs. 3.8%, p=0.0051). UKSAT did not report morbidity outcomes associated with surgery and only reports a readmission rate in the early surgery group (6.3%) without a comparator.[163]

Quality of Life

Both UKSAT and ADAM reported quality of life, although only UKSAT reported numerical data (**Appendix E Table 10**).[127, 137, 140, 163] The UKSAT trial reported the change of quality of life, measured with the Medical Outcomes Study SF-20, 1 year after randomization.[127] The SF-20 has several domains, including physical, role, and social functioning; mental health, health perception, and bodily pain with a total score ranging from 0 to 100 (higher score equals better health). The physical function domain decreased in both groups 1 year after randomization with no statistically significant difference in this change over time between the open repair and surveillance groups. The mental health domain showed no change in mean difference over time for each group or between the groups.

The ADAM trial measured quality of life using the SF-36 every 6 months through 3.5 to 8 years of followup (mean 4.9 years).[137] There was a statistically significant decrease in all SF-36 subscales observed over time for the entire population ($p<0.001$), however no difference was observed between the early repair group and the surveillance group in all SF-36 subscales. The exceptions to this was that the early repair group had a statistically higher general health score compared to the surveillance group ($p<0.001$) with significantly higher scores during the 6-month to 2-year time points ($p <0.05$); this difference did not persist beyond 2 years.

The ADAM trial additionally reported a statistically higher risk of developing impotence in patients in the early open repair group compared to the surveillance group from the 18-month time point to 4 years ($p<0.03$).[137] Exact numerical data was not presented.

Detailed Results for Registries

30-day Operative Mortality

The two largest and most contemporary registries capturing open repairs of small aneurysms reported a 30-day operative mortality rate of 3.1 percent[116] and 3.5 percent[159] (**Table 12**). The VSGNE registry reported lower rates of operative mortality for EVAR and open repair procedures combined (0.7% in men and 1.1% in women).[149] These operative mortality rates are in the range between the rates reported in the two early open repair trials (ADAM and UKSAT).[140, 163]

Reintervention

Only one registry reports reintervention rates following open repair of small aneurysms. NSQIP reports a return to the operating room required in 9.1 percent of open repairs at 30 days postintervention (**Table 12**).[159] This reintervention rate is higher than the data reported in the ADAM trial (IG 1.7%, CG 1.2%).[140]

Readmissions

Only one registry reported readmission rates following open repair of small aneurysms. The NSQIP reports readmission rates for small AAAs at 30-day postintervention as 6.2 percent following open repair (**Table 12**).[159] This figure is similar to that reported in the trials.

Complications

One registry of both open and EVAR reports complication rates following open repair of small aneurysms. NSQIP reports overall 30-day morbidity for open repair as approximately 69.4 percent at 30 days postintervention, with the most common complication being bleeding. (**Table 12**).[159] This is slightly higher than the complication rate reported in the ADAM trial (52.3% any complication; timing NR). [140]

Harms Associated With Early EVAR Versus Surveillance

Detailed Results for RCTs

Operative Mortality

Thirty-day operative mortality after EVAR in both CAESAR and PIVOTAL was rare; only one patient died in the early EVAR group in each trial (0.6% in CAESAR and 0.3% in PIVOTAL), while no patients died undergoing repair in the surveillance group in CAESAR and one patient died in PIVOTAL (**Table 11**).[118, 158]

Complications

Complications were variably reported in the two trials.[118, 158] In the CAESAR trial, the percentage of patients with any adverse events was significantly higher in the early repair group compared to the surveillance group (19% vs. 5%, p<0.01) at 32.4 month followup as was the percentage of patients with any major morbidity related to repair at 30 days (18% vs. 6%, p=0.01) (**Table 11**).[118] Similar rates of any major morbidity over the trial duration, however, were observed in both treatment groups (3.3% vs. 2.8%, p=0.99). Additionally, similar rates of endoleaks were recorded within 30 days between treatment groups (16% vs. 10%, p=0.23), but the early EVAR group had significantly more endoleaks at 1 year (12 vs. 2%, p=0.028) and significantly more reinterventions than those undergoing surveillance (6% vs. 0%, p=0.03). Most of the endoleaks in the early EVAR group were type 2 endoleaks.[118]

The PIVOTAL trial largely reported adverse events within 30 days postintervention.[158] Endoleak was the most common adverse event, occurring at similar rates in the early intervention and surveillance groups at 30 days postintervention (12% vs. 10%) and 1 year (26% vs. 35%) (**Table 11**). Total other complications reported within 30 days of intervention, including endograft or peripheral thromboses, wound infections, and systemic complications, occurred in with 15 percent frequency in EVAR recipients, with no difference between treatment groups. Additionally, the PIVOTAL trial reported that 3.7 percent and 4.6 percent of patients required reintervention in the early surgery and surveillance groups, respectively.[158]

Quality of Life

Both trials report quality of life at baseline and at 6 to 24 months followup using the SF-36[122] or EQ-5D[124] scales, and show no differences in quality of life changes between the treatment groups at longer followup. The CAESAR trial[122] reports that quality of life improved in the early EVAR group but worsened in the surveillance group over the short term. There were statistically significant and modestly greater mean differences in overall quality of life (5.4 [2.1 to 8.8]), physical function (3.8 [0.5 to 7.2]) and mental health (6.0 [2.7 to 9.3]) favoring the early EVAR group compared to the surveillance group from baseline to 6 months after randomization. These results were not sustained, however, and no longer statistically significant through the mean 3-year followup. PIVOTAL[124] reported no statistically significant differences in quality of life changes between the early EVAR versus surveillance groups in any of the EQ-5D dimensions or utility scores at 12-month or 24-month followup compared to baseline (**Appendix E Table 10**).

Detailed Results for Registries

30-Day Operative Mortality

The two largest and most contemporary registries capturing EVAR of small aneurysms reported a 30-day operative mortality rate for EVAR of 0.7 percent (Vascunet and NSQIP)[116,159] The two oldest registries (ASERNIP and EUROSTAR) reported slightly higher mortality rates from EVAR at 1.1 percent (ASERNIP) and 1.6 percent (EUROSTAR) (**Table 12**).[129, 160] VSGNE reported 30-day operative mortality for EVAR and open repair procedures combined as 0.7 percent in men and 1.1 percent in women.[149] The two most contemporary registries have 30-day postoperative complication rates that are comparable to the rates reported in the early EVAR trials.

Reintervention

Two registries of EVAR for small aneurysms report rates of reintervention following surgery. ASERNIP reports a reintervention rate within 30 days of EVAR of 3 percent[129] (**Table 12**). NSQIP reports a return to the operating room required for 3.4 percent of EVAR procedures at 30 days following surgery.[159] These reintervention rates are comparable to the trial data from CAESAR and PIVOTAL for EVAR (CAESAR IG 5.7%, CG 0; PIVOTAL: IG 3.7%, CG 4.6%).[118, 158]

Readmissions

Only one registry reported readmission rates following EVAR repair of small aneurysms. The NSQIP reports readmission rates for small AAAs at 30-day postintervention as 6.8 percent following EVAR (**Table 12**).[159]

Endoleaks Following EVAR

Endoleaks are one of the most commonly reported complications after EVAR. ASERNIP reports the occurrence of endoleaks at 9.6 percent within 30 days of surgery and 20.3 percent at followup (mean 3.2 years);[129] however, incomplete followup (23% lost to followup at study completion) limits this data (**Table 12**). EUROSTAR reports the rate of endoleaks at 31.0 percent at 4 years.[160] Trial data from CAESAR and PIVOTAL reported similar incidence of endoleaks at 30 days as ASERNIP, ranging from 10 to 16 percent at 30 days postintervention. Endoleak incidence by type is reported in **Table 11**.[118, 158]

Complications

Two EVAR registries (ASERNIP[129] and EUROSTAR[160]) and the one registry of both open and EVAR (NSQIP)[159] report complication rates following intervention. ASERNIP reports significant postoperative complications in 29 percent of individuals at 30 days after EVAR: 10.7 percent of patients experienced procedural and device complications; 13.4 percent experienced systemic complications, and 8 percent had access site and lower limb complications (**Table 12**). EUROSTAR reported that 12.0 percent of patients experienced systemic complications (defined

as cardiac, pulmonary, renal, cerebral, or gastrointestinal complications) at 30 days after EVAR; 2.8 percent had cardiac complications, and 1.6 percent had pulmonary complications over the mean 1.7 years of followup.[160] NSQIP reports overall morbidity for EVAR as 11.4 percent at 30 days postoperation; the most common complication was bleeding.[159] This registry data showing 11 to 29 percent complication rates at 30 days postintervention is within the range seen in the trial data (CAESAR: IG 18% vs. CG 6%; PIVOTAL: IG and CG 15% complications not including endoleak).[118, 158]

Harms Associated With Pharmacotherapy

Overall, the trials of antibiotic interventions show that these medications were well tolerated. Both doxycycline trials report similar withdrawals or discontinuations due to adverse events in the treatment and placebo groups at a mean of 1.5 years of followup (**Table 13**). The doxycycline trial by Mosorin et. al.[153] (N=32) reported that the active drug was well tolerated in most patients; one patient in the doxycycline group and one in the placebo group discontinued the drug due to an allergic reaction (5.9% vs. 6.7%). The other doxycycline trial (N=286 analyzed) suggested no statistically significant difference in adverse events leading to study withdrawal (7.6% vs. 2.1%; difference 5.5 [-6.3 to 17.1]).[152] In the azithromycin trial[133] (n=211), 13 patients in the treatment group and 8 patients in the control group reported side effects due to gastrointestinal side effects, arthralgias, or allergic reactions at 1.5 years (12.3% vs. 7.6%; no statistical difference reported). In the Roxithromycin trial (N=84),[132] there were no adverse events or drop outs reported at 2-year followup.

Both propranolol trials report high rates of discontinuation due to adverse events,[142, 164] while the AARDVARK trial of an ACE inhibitor and a calcium-channel blocker suggests that these other antihypertensive medications are generally well tolerated (**Table 13**).[114] In the PAT trial (N=539), there was a higher rate of drug discontinuation in the propranolol group compared with placebo at 2.5 years (42.4% vs. 26.8%, difference 15.6% [7.6% to 23.5%]).[164] Likewise, the propranolol group had a higher rate of trial withdrawals due to adverse events (37.7% vs. 21.3%; difference 16.4% [8.7% to 24.0%]). In the small Danish propranolol trial (N=54) a substantial and statistically significantly greater proportion of patients dropped out compared with the placebo group at 2 years of followup (60% vs. 28%; RR 5.7 [1.5-22.2].[142] The most commonly cited reasons for these dropouts were death, serious cardiac arrhythmia, dyspepsia, headache, and dizziness in the intervention group. The AARDVARK trial (N=224) with the active ACE inhibitor and calcium-channel blocker arms had generally low withdrawals due to adverse events attributed to study medications at 2 years of followup (2.7% and 5.6% in the ACE inhibitor and calcium-channel blocker groups, respectively).[114] Additionally, 4.1 percent (3/73) and 1.4 percent (1/72) from the ACE inhibitor and calcium-channel blocker groups, respectively, switched to another class of medication due to cough. Similarly, the only trial of a mast cell stabilizer [AORTA trial] (N=168 analyzed single active drug vs. placebo arm) reported high rates of any adverse events (approximately 80%) and serious adverse events (approximately 18%) in both the intervention and placebo groups; a higher percentage of participants withdrew in the placebo group compared to the treatment arms at 1-year followup (1/84 [2.5%] vs. 8/84 [9.5%]).[166]

Two propranolol trials[142, 164] report quality of life generally showing no difference between the

intervention and control groups. One study reports a decline in screenQL in both the intervention and control groups through 2 years without a significant difference between the groups,[142] and the other study reports no significant difference in SF-36 scores between the propranolol and control groups at one month post randomization.[164]

KQ5a. Do the Harms of Treatment of Small AAAs Vary Among Subpopulations (i.e., by Age, Sex, Smoking Status, Family History, or Race/Ethnicity)?

Summary of Results

Scant data have been reported for harms among subpopulations. The only available evidence comes from surgical registries due to no trial data being available to examine harms in subpopulations. Existing evidence from three surgical registries shows higher 30-day operative mortality and secondary complications among women compared with men for both EVAR and open repair of small aneurysms.

Detailed Results

Overall, registry data show a higher rate of post-operative mortality following elective repair of small AAAs in women compared with men, regardless of the surgical technique. One registry study[116] reports higher rates of 30-day postoperative mortality in women compared with men for both open repair and EVAR for small AAAs; this pattern remains consistent regardless of age (≥80 and <80-year olds). For example, in those less than 80 years of age, the 30-day postoperative mortality is 2.5 percent in men and 3.0 percent in women for open repair, and 0.4 percent in men and 1.1 percent in women for EVAR. In those ≥80 years of age, postoperative mortality for open repair was 3.4 percent in men and 9.7 percent in women, while intervention via EVAR was associated with a postoperative mortality of 0.6 percent in men and 1.3 percent in women. One registry shows a similar pattern for AAA repair (EVAR and open reported combined) with a 30-day postoperative mortality of 0.7 percent in men and 1.1 percent in women.[149] Further, one registry reports lower clinical success rates following surgery in women at 3-year and 5-year followup compared to men. The difference observed was greatest at 5 years, with 93 percent (+/- 1) of men and only 70 percent (+/- 16%) of women having clinical success.[129]

The two early open repair versus surveillance trials, ADAM and UKSAT,[140, 163] and the two early EVAR versus surveillance trials, CAESAR and PIVOTAL,[118, 158] did not report harms by subpopulation. Additionally, none of the pharmacotherapy trials reported harms data by subpopulation.

Chapter 4. Discussion

Summary of Review Findings

We have provided a summary of the evidence by Key Question (**Table 14**).

What Is New Since the Previous Review

Since our previous systematic review,[105] we have added: 1) the longest-term followup available from the last of the four population-based RCTs confirming the reduction in AAA-related mortality and rupture associated with screening balanced by the already known increase in elective procedures; 2) a few more small rescreening cohort studies offering little additional information to a heterogeneous literature; 3) no new small aneurysm early surgery versus surveillance trials beyond ADAM, UKSAT, PIVOTAL, CAESAR which concluded no benefit from early surgical repair over surveillance of small aneurysms; 4) a few additional pharmacotherapy trials showing no benefit; and 5) newer, contemporary registry data citing complication rates from EVAR and open repair generally comparable to those cited in the aforementioned small aneurysm surgery trials.

Overall Summary by Key Question

Our meta-analyses demonstrate that offering one-time screening to men ages 65 to 75 years reduces AAA-related mortality, AAA rupture, and emergency surgeries over 13 to 15 years of followup (KQ1). These benefits appear within the first 3 to 5 years after initial screening and are sustained at least through the maximum observed time of 15 years.[105] While our meta-analysis showed no statistically significant all-cause mortality benefit, others have reported a modest benefit that just reaches statistical significance using alternate pooling methods.[175-177] Their findings are driven by the MASS trial, which contributes half of the combined screening-trial population and is the only trial with a statistically significant all-cause mortality benefit (HR 0.97 [95% CI, 0.95 to 0.99]).[170] Balancing those benefits of screening, our review of harms included those same four trials plus a more contemporary trial (VIVA)[146] showing that there were nearly 50 percent more surgeries in the screening group than in the control group, largely driven by twice as many elective operations in the screening group. There was no statistically significant difference in 30-day postoperative mortality rates in the screening versus control groups for either elective surgeries or emergency surgeries at 12 to 15 years of followup, nor were there clinically meaningful sustained differences in quality of life or mood between those who screened positive and those who were unscreened or screen-negative based on a heterogeneous group of small studies. The harms of overdiagnosis and overtreatment, including harms of CT surveillance (exposure to radiation and intravenous contrast), were not addressed in the population-based trials but may be important considerations given that the vast majority of screen-detected aneurysms are small in size.

To inform rescreening intervals (KQ2), we included eight heterogeneous prospective observational studies following patients for 5 to 12 years. They estimated that 0 to 15 percent of

aortas < 3 cm progress to > 5 cm over 10 years and that AAA-related mortality is rare among those whose initial screen is negative. Arguably, these studies' primary outcomes were aneurysm growth, and they were underpowered and too short to detect AAA-related health outcomes. Unlike the robust literature available examining growth rates for small AAAs,[76] such a literature base does not exist for subaneurysmal or ectatic aortas. Nonetheless, the competing causes of mortality at 10 years, particularly in those with accelerated growth (smokers, those with known coronary disease),[138] as well as the likelihood that incident AAAs will be small in size make rescreening benefit likely modest, at best.

We examined the evidence on the benefits (KQ4) and harms (KQ5) of surgical or pharmacotherapy interventions for small AAAs (4 to 5.4 cm) following the rationale that: the benefit of AAA screening depends on detection and intervention at a threshold at which the rupture risk reductions outweigh surgical harms; size is currently the only available predictor of rupture risk; and the vast majority of screen-detected AAAs are small in size. The four trials of early surgical intervention at 4 to 5.4 cm compared with surveillance (until standard 5.5 cm surgical threshold) show no all-cause or AAA-related mortality differences, but more elective surgeries without any differences in 30-day postoperative mortality. The literature addressing effectiveness of pharmacotherapy on slowing AAA growth rates for the small AAAs showed no statistically significant benefit; these studies were too short in duration to accrue AAA-related health outcomes. Aside from the propranolol trials which showed high withdrawal rates due to adverse events, the remaining studies of antihypertensive, antibiotic, mast cell inhibitor studies showed that these drugs were generally well tolerated, albeit ineffective, therapies.

Direct and Indirect Evidence for Screening by Risk Factor

Since the population-based screening trials almost exclusively recruited Caucasian men aged 65 to 75 years and generally did not report outcomes by subpopulation, one critical question is whether these findings can be extrapolated to other populations. In the absence of trial data, assessing generalizability requires understanding contextual evidence about contemporary prevalence, natural history, and treatment effectiveness.

Subpopulation considerations for older adults, women, smokers, and those with family history are addressed below; more detailed references can be found in **Appendix G**.

Age

Age thresholds for screening have been variably recommended in clinical practice (**Appendix B Table 1**).[3, 93, 96] While AAA prevalence and rupture risk increase with older age, so do the comorbidities complicating surgical candidacy and contributing to competing causes of mortality. Overall, expanding screening eligibility to older adults would only prevent AAA-related deaths in those who are surgical candidates with life expectancies long enough to realize the AAA benefits. Direct evidence presented in our systematic review shows that the mean age at recruitment in the population-based trials ranged from 68 to 73 years, with the oldest participants up to 83 years in one of the trials.[15] Literature examining a possible differential screening effect by age is limited by lack of power, distribution and range of ages reported, and number of studies examining these subgroup issues. Nonetheless, two of the population-based screening trials

(Viborg and Western Australia) reporting subgroup analyses by age show similar relative benefits in AAA-related mortality estimates in older or younger age groups as compared with the overall trial results. None of the included population-based screening trials included adults younger than 64 years of age.

Indirect evidence in older age groups shows that a large proportion of AAA burden (prevalence and ruptures) occurs in older age groups. One analysis of 3.6 million self-referred participants (2003 to 2008) reported AAA prevalence of 0.05 percent for 40- to 50-year-olds, increasing to 3.5 percent in 91- to 100-year-olds,[178] with nearly half of those with AAA ≥ 5 cm found in 70- to 79-year-olds.[179] A large, prospective population-based study in the United Kingdom (2002 to 2014) reported that the annual rate of AAA acute events in men doubles every decade, increasing from 55 events per 10,000 patient-years for men aged 65 to 74 years to 298 events per 10,000 patient-years for men aged ≥ 85 years.[38] Two-thirds of ruptures were found in those aged ≥ 75 years.

While AAA prevalence rises with age, so do surgical complications, including mortality. A 2017 meta-analysis of nine observational studies (N=25,723) of EVAR with study periods of 1995 to 2012 reported statistically significant higher pooled 30-day postoperative mortality (3.73% vs. 1.68%) in octogenarians compared to younger adults, along with more pulmonary (3.32% vs. 1.38%) and renal complications (3.67% vs. 1.86%) and more endoleaks (25.83% vs. 21.30%). Total complications, however, were similar between the groups.[180] An analysis of VA data (2002 to 2010) reported that functional status is an independent predictor of 30-day postoperative mortality for AAA repair (open and EVAR).[181] This relationship was stronger in octogenarians (≥ 80 years) compared to the younger cohort. An analysis of National Inpatient Sample data (2005 to 2009) reported that postoperative mortality and length of stay increased with every decade ($p<0.05$).[182]

Some evidence suggests that older adults are less likely to benefit from screening. In a retrospective study of individuals referred to a vascular laboratory, patients with screen-detected AAAs were older (mean age of 72.8 years) and more likely to have competing comorbidities compared to individuals with AAAs detected in the screening trials; as a consequence, these patients were also less likely to undergo elective repair (21.5%) or full surveillance (48%), often due to poor health.[183] Less than half (47.5%) were alive at the mean followup of 7.5 years (SD 2.8), with over half (56.8%) of deaths due to cardiac or cerebrovascular disease.

Overall, decisions about upper age thresholds for screening would ideally use this indirect evidence, balancing the increased burden, comorbidities, surgical complication rates for open versus EVAR, and life expectancy. Externally validated surgical mortality risk tools are available to inform these decisions for the individual patient;[184, 185] patients with advanced age and comorbidities may particularly benefit from use of these tools although predictive performance of these tools has recently been called into question.[186]

Women

One of the most controversial issues in AAA screening is whether to screen women at higher risk for developing AAA.[187] Offering screening to women smokers is tempting, but the balance of

benefits and risks remains uncertain. The Chichester trial, which provides the only direct evidence, reported no AAA-related mortality benefit in women, but it was underpowered for this outcome.[36] The trial reported a prevalence for women that was one-sixth of the prevalence for males in the trial (1.3% vs. 7.6%) and most AAA-related deaths occurred in women aged > 80 years (70% vs. < 50% in men). Given the much lower prevalence, it would not be feasible to conduct an adequately powered population-based screening trial in women.

Indirect evidence reveals a complex set of issues in women. The prevalence of AAA in women has consistently been reported to be less than men.[23, 30] The best available evidence is a meta-analysis of eight studies with over 1.5 million women ages 60 years and older screened as part of population-based registries and self-referred/purchased screening programs reporting a pooled prevalence of 0.74 percent (95% CI, 0.53 to 1.03); individual study prevalence ranged from 0.37 percent to 1.53 percent.[23] Prevalence rises with increasing age and smoking exposure with the lowest prevalence in never smokers (0.28% pooled prevalence) followed by ever smokers (1.34% pooled prevalence), and highest prevalence in current smokers: (3 studies ranging from 2.08% to 4.63%). Heterogeneity for these pooled prevalence numbers, however, was high (I^2 > 80% to 90% in most cases), making precise estimates elusive. U.S.-based observational data from the ARIC study confirms the pattern that current female smokers have been shown to have a lifetime prevalence consistent with that of male former smokers (8.2% and 8.1%) and double that of males who have never smoked (3.9%).[30] Such trends have been confirmed in other studies[11, 188-190] with one study noting that smoking has a greater effect on AAA development in women compared with men (p interaction=0.002).[188]

Despite this lower prevalence, small AAAs in women appear to have a higher risk of rupture[69, 75, 79, 191] and rupture at a later age than men.[36, 191-196] Studies have estimated one-quarter to nearly one-third of women had a diameter of AAA below current 5.5 cm threshold at time of rupture,[191, 197] leading some to suggest that lowering the AAA diameter definition of the disease and surgical intervention threshold for women is warranted.[198] Others have argued that that unlike in men, absolute diameter may not be the best predictor of rupture in women given smaller body surface area. They have proposed aortic size index (ASI=diameter[cm]/body surface area [m^2]) as a more accurate prognostic marker.[199, 200] From a population perspective, despite the relatively higher risk of AAA rupture in women, the absolute risk of AAA-related death in women, even in an enriched population of female smokers, is much lower than men because of the overall lower prevalence of AAA in women. In a prospective U.K.-based cohort study of 1.2 million women (median age 55 years) followed for up to 12 years, 330 current smokers (0.028%) and 164 female never-smokers (0.014%) died of AAA.[201]

Efforts to reduce the risk of rupture-related death in women with surgical repair are counterbalanced by robust data reporting higher complications, including 30-day postoperative mortality rates,[193-195, 202, 203] in-hospital mortality,[204] major complications,[195, 203, 205] and readmissions[194] after elective open repair or EVAR in women compared with men. These findings hold after adjusting for confounding variables including aortic diameter. A few studies report no statistically significant differences in postoperative mortality,[191, 205, 206] but they comprise a small proportion of the overall literature. Concerns about poorer surgical outcomes in women who have more complex anatomy and smaller vessels, making EVAR technically challenging, have led some experts to caution against considering lower thresholds for surgical

intervention in women.[207] One simulation model and one observational study suggest that there is short-term harm associated with early surgical intervention in women prior to reaching 5 and 5.5 cm, respectively, compared to surveillance.[208, 209]

A recent model examined the effectiveness of screening women aged ≥ 65 years utilizing contemporary assumptions of prevalence, AAA growth rates, operative harms, and non-AAA-related mortality rates.[210] The discrete event simulation model estimated that invitation to one-time screening in women aged 65 years would yield 0.31 percent of the population having AAAs diagnosed, resulting in a 23 percent increase in AAA detection, 21 percent increase in elective repair, 4 percent reductions in rupture and emergency repairs, 3 percent reduction in AAA-related deaths in women aged 65 to 95 years (or 7% in women aged 65 to 75 years). These benefits were balanced by a 33 percent increase in overdiagnosis (AAAs that would have remained asymptomatic) and 13 percent increase in overtreatment (repair of screen-detected AAAs that resulted in AAA-related death or surgery) compared with no screening. This model estimated that it would require 3,900 screening invitations to avoid one AAA-death, which is higher than estimated in other models for men (number needed to invite to screening was 700 in men).[20] Authors note that an analysis for female smokers was deliberately not performed although this population is often cited as one that should be considered for targeted screening. Again, these confidence intervals for prevalence, even from this most relevant recent meta-analysis, are wide, with high heterogeneity, so there remains uncertainty in the precision of these inputs. It may be useful to perform a similar future decision analysis for female smokers where the point prevalence in ever-smoking women based on a meta-analysis was estimated to be 1.34 percent (95% CI, 0.82 to 2.19),[23] but again data about certain inputs (e.g., prevalence, attendance, incidental detection rates, growth and rupture rates, operative mortality, competing mortality) for female smokers is limited to inform such a model.

Smoking

There is no direct evidence for examining possible differential screening effects in smokers. Given that smoking is such a dominant contributor to AAA development, benefits of screening from population-based trials (which included both smokers and nonsmokers) are likely generalizable to subpopulations of smokers. Indirect evidence shows that smoking is the strongest predictor of AAA prevalence,[29, 30, 38, 69, 211] growth, and rupture rates.[69] There is a dose response relationship as greater smoking exposure is associated with higher ORs for AAA[29, 179] little is known about the role of passive smoking. Even with substantial declines in the overall prevalence of AAA in the past two decades since the screening trials were conducted,[183] prevalence in male smokers aged 65 to 75 years matches that of the population-based screening trials as reported in one VA analysis (N=9,751; 2000 to 2011). The prevalence of AAA in male smokers was 7.1 percent with a shift to smaller AAAs (3 to 4.4 cm [77.9%], 4.5 to 5.4 cm [15.5%], ≥ 5.5 cm [6.6%]);[212] compared with the MASS trial where 12 percent of AAAs were ≥ 5.5 cm in all men.[12] The highest risk for AAA rupture is also seen in male smokers (274/100,000 per year) compared to other groups again favoring a higher yield with a more targeted approach to screening.[38] While smoking contributes to higher overall surgical mortality and increased rates for cardiorespiratory and septic complications for a host of different types of surgery,[213] none of the AAA operative prognosis risk models includes smoking as an independent mortality risk factor.

Family History

There is no direct evidence from screening trials examining the role of family history in differential screening effectiveness or harms. Family history, however, remains an independent predictor of AAA development with at least a doubling of risk.[58, 214] A Danish population-based twin study following 65,820 twins (414 with AAA) suggests that there is a substantial genetic component contributing to the disease.[215] They reported a 77 percent heritability with monozygotic twins sharing triple the concordance of dizygotic twins. Similar results were found in the Swedish Twin Registry.[216] Definitions of "positive family history" and published estimates of AAA prevalence in those with a family history vary widely and are obtained using a variety of methodology, including offering screening ultrasound to family members of index AAA patients, documenting pedigrees based on family history recall of index AAA patients, and population-based screening ultrasound screening studies with family history questionnaires. The VIVA trial (N=18,614 screened; 569 with a positive family history based on questionnaire) was the only analysis we identified estimating the prevalence of familial AAA based on population-based screening.[217] VIVA investigators reported the prevalence of AAA in 65- to 74-year-old men as 6.7 percent in those with at least one first-degree relative with an AAA. This is double the prevalence of those without a family history (3.0%). Having a female relative with the disease was associated with higher AAA risk (OR 4.32 if female first-degree relative; OR 1.61 if male relative). These trends were confirmed in other small studies of family history.[218-220] At this time, there is a lack of evidence to determine if AAAs in those with family histories exhibit differences in natural history or surgical success rates to alter the net screening benefits.

Race/Ethnicity

Population-based screening trials were almost exclusively in Caucasians. Our systematic review identified no studies that addressed race/ethnicity differences for any questions related to screening, treatment, or harms. Estimates from approximately 2010 show that Blacks,[29, 211] Hispanics, and Asians have lower risk of AAA than Whites and Native Americans.[29] Despite lower prevalence, Blacks present for repair with more advanced aneurysms (VQI data N=17,346; VQI 2009 to 2014)[221] and higher in hospital mortalities following open surgical repair (Medicare data (2005 to 2009).[222] At this time, there is scant evidence to understand how race/ethnicity may change the screening benefits/risks tradeoff.

Screening Strategies

Narrowing Versus Expanding Eligible Populations

The desire for a more targeted, high-risk approach to screening to enrich yield is particularly relevant given declines in AAA prevalence in men over the past 2 decades. Recent population-based screening programs in Europe and New Zealand report substantial declines in AAA prevalence in men aged 65 years and older largely attributed to declines in smoking, with more recent AAA prevalence reported at 1.3 to 1.7 percent.[156, 183] England's National Health Service has an 80 percent uptake of their screening guidelines where men aged 65 to 74 years are eligible for screening regardless of risk factors and reports between a 1 to 3 percent prevalence (2015 to

2017 NHS data).[223, 224] On the other hand, limiting screen-eligible populations to only 'high risk' populations inherently results in missed cases. For example, critics note the substantial rupture rates and AAA-related deaths that occur in women (at least 33% of ruptured AAA hospitalizations and 41% of AAA-related deaths), while nonsmokers account for about 22 percent of AAA-related deaths.[225-227] This must be balanced against potential harms. Any attempt to expand screened populations (e.g., extending to all men regardless of smoking history, increasing upper age threshold, or adding women) would invariably increase small aneurysm detection. Based on United States data showing that a substantial proportion of small aneurysms are repaired despite lack of evidence of benefit over surveillance,[104] the degree to which surgeries and consequent surgical harms will ensue from broadening the eligibility for screening remains a concern.

Using large-scale cohort data, investigators have attempted to identify different targeted approaches that are able to detect more clinically significant AAAs with the same or better efficiency than the USPSTF-recommended approach. One initial study developed and tested a novel multivariable risk factor score using data from the Western Australia screening trial.[228] Results found that 50 percent of the male population would need to be screened to detect 75 percent of aneurysms 4 cm or greater, while screening ever-smoking males would detect 87 percent of these aneurysms, but require screening about two-thirds of men. From this early study, authors concluded that mass screening remained preferable to selective screening, but they recognized that risk-prediction models based on better data might alter this conclusion.

Risk Prediction Models for Screening

In the absence of robust studies comparing various screening approaches, risk-prediction models have been developed to provide a more accurate prediction of a person's AAA risk by calculating a score based on an individual's personal characteristics. Two risk-prediction models have been developed utilizing data from 3.1 million individuals who volunteered to provide medical history data and undergo ultrasound screening.[29, 179] The models were developed to calculate risk for developing AAAs ≥ 3 cm and ≥ 5 cm, respectively. The analyses confirmed that male sex, older age, and smoking history are strong independent contributors of risk, but also quantified the independent contribution of family history and CVD morbidity (**Appendix G Table 1**). Protective factors that modified an individual's risk for developing AAA included Black, Hispanic, or Asian ethnicity, diabetes, diet, exercise, and smoking cessation.

To estimate the efficiency of the proposed risk-scoring approach, the authors used National Health and Nutrition Examination Survey (NHANES) data to estimate AAA prevalence in the United States population. They then modeled the efficiency of applying the risk-scores at different thresholds for age groups of 50 to 75 years or 50 to 84 years. Their results indicate that using risk-scores may result in higher-yield screening strategies than the current USPSTF recommendation. Although these are promising results, the risk-prediction models lack external validation and such external validation would be necessary prior to clinical application.

Incidental AAA on Computed Tomography Examination

AAA ultrasound screening implementation has been relatively low in the United States (< 50% uptake).[229] Given the high rate of imaging for other indications, the question arises whether many more individuals could be considered adequately screened based on pre-existing imaging. The estimates for the prevalence of incidental AAAs are wide-ranging: from as low as 1 percent (in men and women mean age 74 with abdominal ultrasound, CT or MRI for other indications)[230] or 2 percent (in VA men mean age 73 during CTs of abdomen and pelvis)[231] to 5.8 percent (men and women ages 50 years and older during abdominal CT scans)[232] to as high as 9.1 percent (65- to 74-year-old men during CT colonography).[233] Given redundancy rates of 31 to 42.6 percent[229, 234] with duplicative imaging (e.g., abdominal CT and targeted AAA screening ultrasound done in a single patient), it is tempting to use pre-existing CT or MRI imaging results. On the other hand, studies have identified problems with documentation at several stages. One study reported that when CT scans for other indications were re-interpreted specifically for AAAs, only 65 percent of AAAs were identified in the original interpretation.[232] Another study reported that 77 percent of reports from scans for other indications made no mention of whether AAAs were present or absent leaving primary care physicians uncertain whether or not the aorta was measured.[234] Furthermore, there is evidence that incidental AAAs are neither well documented by clinicians or well surveilled with only one-quarter of incidental AAAs discovered during hospitalization reported in hospital discharge summaries and three-quarters of incidental AAAs completing subsequent imaging for surveillance.[235] One retrospective cohort found that for 61.4 percent of incidental AAAs found on CT scan, there was no electronic record documentation from the primary care physician of the results within 3 months of the imaging study.[231] One solution to the documentation issue may be for screening ultrasound orders to trigger radiology departments to search preexisting imaging and then re-read these images specifically for AAAs. The sensitivity of this approach has been shown to be high (97.2% sensitivity).[229, 236] Based on these limited data, radiology reports from previous CT scanning may not necessarily be an adequate substitute for recommended AAA screening, since it is not clear how completely CT scans for other purposes identify incidental AAAs, how adequately radiology reports document the presence or absence of AAAs or how effectively these patients will be surveilled compared with those detected in a structured screening program.

Limitations Due to Our Approach

As per USPSTF methods, we limited our results to studies that met the USPSTF's fair- or good-quality criteria.[107] For three of the Key Questions (KQ2, KQ4, KQ5), there were too few studies or the studies were too clinically or statistically heterogeneous for pooling.[109] Our *a priori* methods focused on five Key Questions, so there remain important issues specifically about subpopulations that were addressed as contextual questions. In these cases, we used a best-evidence approach and summarized our finds in the introduction and discussion sections rather than the results section.

Limitations of the Evidence

Screening

The four, large population-based screening trials provide a robust evidence base supporting the effectiveness of one-time screening in older Caucasian men for AAA. There is no direct evidence addressing AAA-related mortality benefit in other subpopulations including women and racial/ethnic minorities. Furthermore, these trials began recruiting participants during an era that pre-dated the current widespread implementation of aggressive CVD risk factor management and reductions in smoking prevalence. The contemporary AAA prevalence and therefore the yield of screening, have declined over the intervening time although some models from outside the United States have estimated that screening men remains effective.[20, 237] Nonetheless, there remains a lack of U.S. population-based estimates in accurate and contemporary AAA prevalence as AAA screening uptake is low and screen detected prevalence may underestimate true disease prevalence. This is true for subpopulations as well. The current body of heterogeneous studies comprising the rescreening literature in our review is inadequate to support practice of repeated screening. Harms studies addressing the quality of life changes associated with screening are a heterogeneously designed group of observational studies largely comparing quality of life in those who screen negative and those with screen positive. This limits our ability to conclude whether screening is harmful to patients' quality of life.

Treatment

With the exception of 30-day postoperative mortality, postsurgical complications in small AAA surgery trials and registries were inconsistently defined, making it difficult to understand the complications of surgery. Publications from currently available surgical registries will continue to provide important information about AAA repair complications.

Because the vast majority of screen-detected AAAs are small, treatments that could possibly improve health outcomes for those identified with small AAAs could substantially improve screening benefit. The available pharmacotherapy trials were largely underpowered and too short in duration to capture health outcomes so larger pharmacotherapy trials using CVD-related medications and other medications could illuminate other treatments to improve mortality in those with small AAAs.

Emerging Issues

One study reporting a lack of dose-response relationship between atherosclerotic burden in other vascular territories (carotid, lower extremity) and AAA suggests that these diseases occur in parallel rather than as simple causal pathway.[238] Nonetheless, most consider those identified with AAA to warrant the CVD risk management strategies for those at high risk for CVD events (statin, HTN control, smoking cessation). There is some emerging interest in exploring the potential effects of AAA screening on CVD mortality by identifying those at increased risk for future CVD events and providing aggressive CVD risk modification.[239-241] MASS reported

ischemic heart disease-related deaths in screened and unscreened groups, showing no difference at 13 years;[170] however, it is uncertain whether contemporary standards of practice including widespread use of statins and hypertension control might change that finding.[242] On the other hand, those identified with AAA would already be candidates for aggressive CVD risk management based on ASCVD predicted 10-year risk of > 7.5 or 10 percent.[243, 244]

Future Research

Ongoing research currently focuses on pharmacologic strategies to delay AAA growth. Single, small, in-progress studies explore the role of drugs in halting aneurysm expansion from diverse medication classes including: antibiotic, angiotensin receptor blockers, aldosterone receptor blockers, platelet aggregation inhibitors, stem cells, and immunosuppressant drugs. Other in-progress research includes screening yield in various populations; cardiovascular patients; primary care and estimates of growth rates of aneurysms (**Appendix H**). We are not aware of any large contemporary ongoing population-based screening trials other than the long-term followup from VIVA,[146] which has an estimated study completion date of 2023. The ongoing DANCAVAS multicomponent screening trial uses CT rather than ultrasound for AAA screening.[86, 245]

Several areas of research could help inform the benefit of screening for AAA in U.S.-based populations.

- Well-conducted cohort studies examining rescreening benefits (growth rates and health outcomes) are needed for those who initially screen negative for AAA to determine the benefit and timing of an additional screening ultrasound.
- External validation of risk prediction models that have already been developed will allow policymakers to assess their value for making more individualized screening recommendations.
- Studies that capture the current prevalence of AAAs in the United States including important subpopulations would help to inform the relevance of older population-based screening trials to the current US-based population.
- Surgical RCTs or large registries comparing AAA thresholds for repair in women are needed to fully understand the complexity of screening in women.
- Studies examining systems approaches to improving implementation of evidence-based AAA screening and surveillance guidelines in the United States are needed.

Conclusions

Consistent with the previous review, trials demonstrate screening benefit in men aged 65 to 75 years, no benefit for earlier surgical repair over surveillance of small aneurysms (4 to 5.4 cm). New, albeit limited, evidence shows no benefit for pharmacologic therapies including antihypertensive, antibiotic, mast cell stabilizer medications. Newer national and international registries confirm complication rates for repair of small aneurysms that are generally comparable to those reported in the trials. The most substantial contributions to the screening literature have

been contextual evidence related to prevalence, natural history and surgical complication risks in subpopulations, particularly women. Because there is no direct trial evidence evaluating screening effectiveness in subpopulations and no externally validated risk assessment tools; decision analysis models populated with meta-analytic estimates of prevalence, yield, and surgical complication rates would be considered the best available evidence to date. We identified one such decision analysis for women and concluded that screening women would require five times the number of screenings to prevent one AAA-related death compared with men. There is a lack of precision in estimates of contemporary AAA prevalence in subpopulations (i.e., women, older adults, smokers, those with family history), with and without additional risk factors making conclusions challenging.

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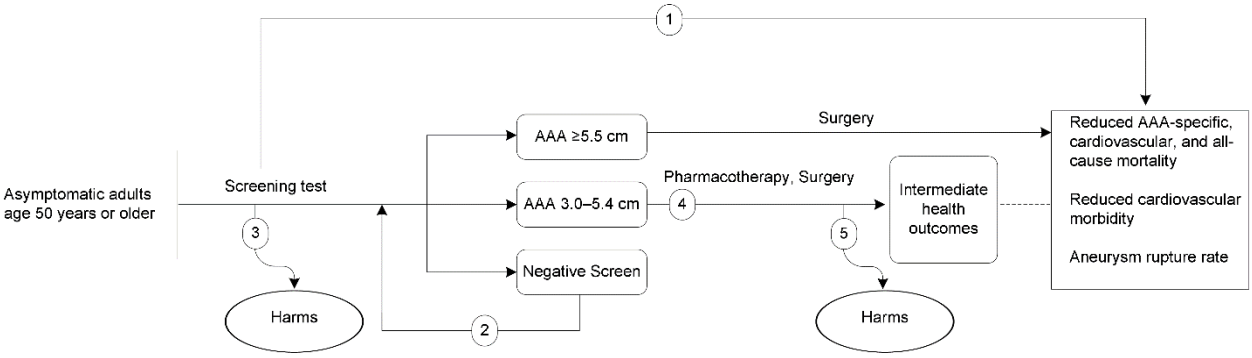
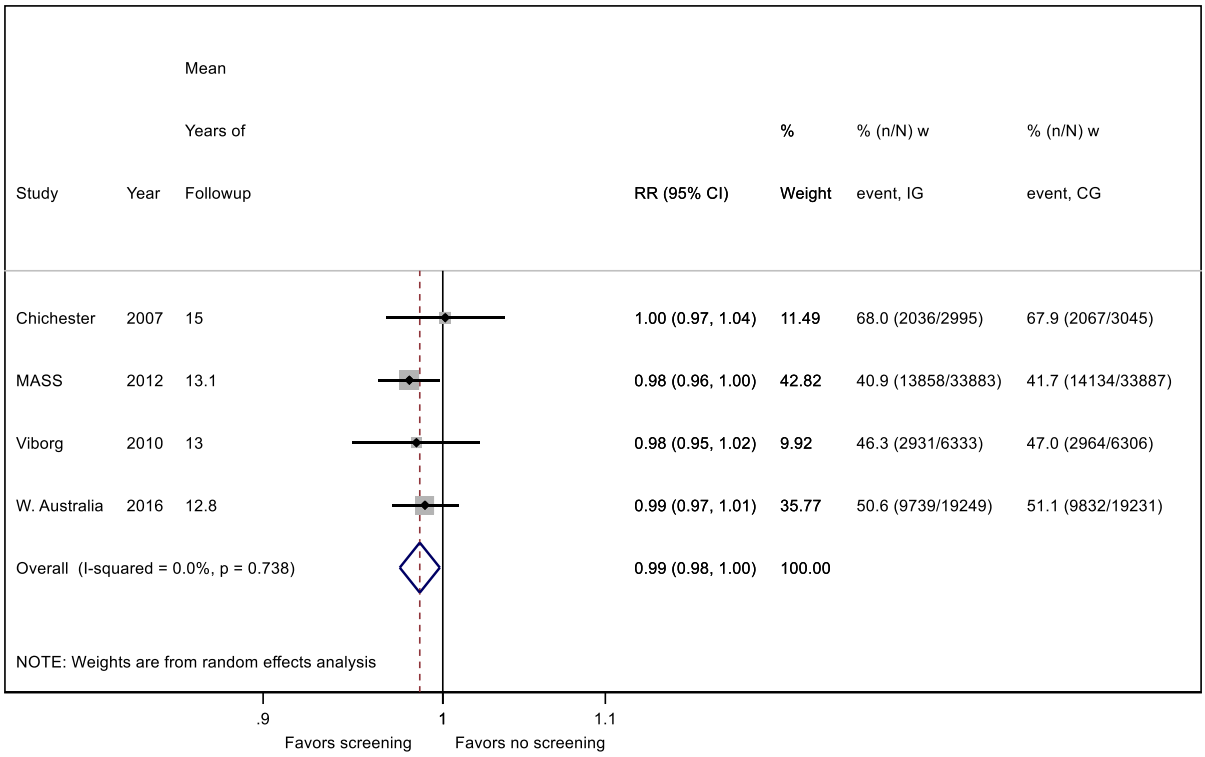
Figure 1. Analytic Framework



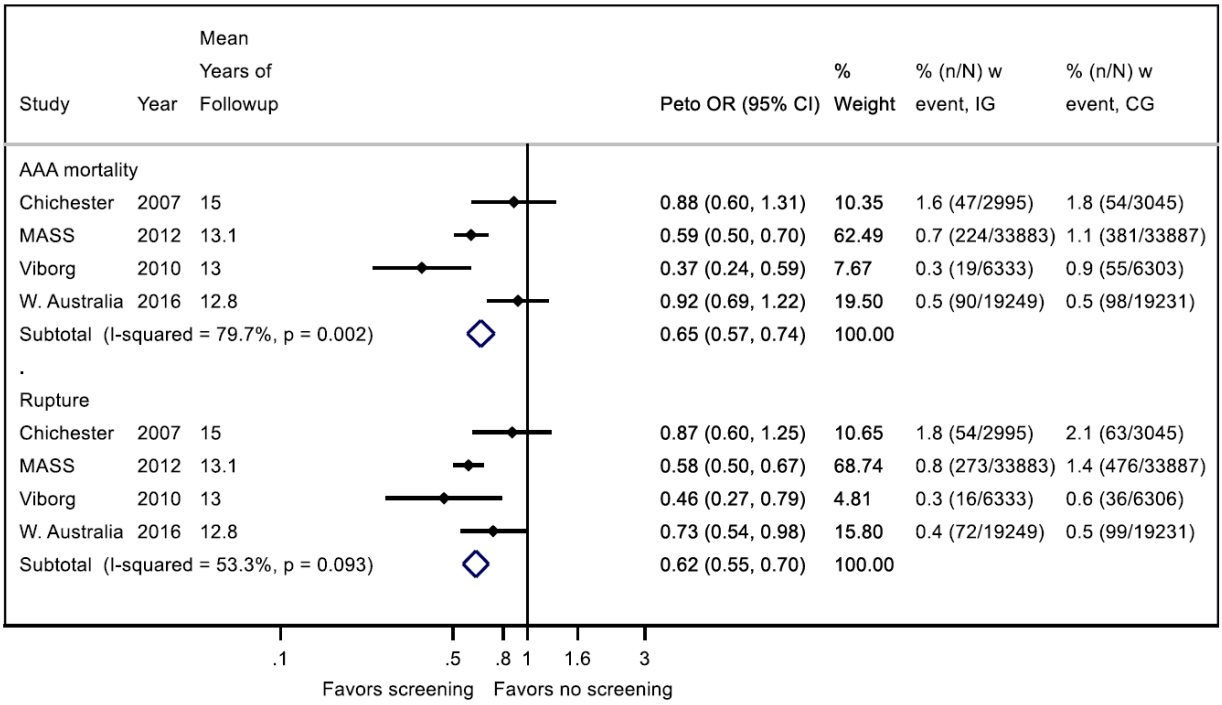
Abbreviations: AAA = abdominal aortic aneurysm; cm = centimeter.

Figure 2. Pooled Analysis of All-Cause Mortality (Male-Only) in One-Time Screening Trials



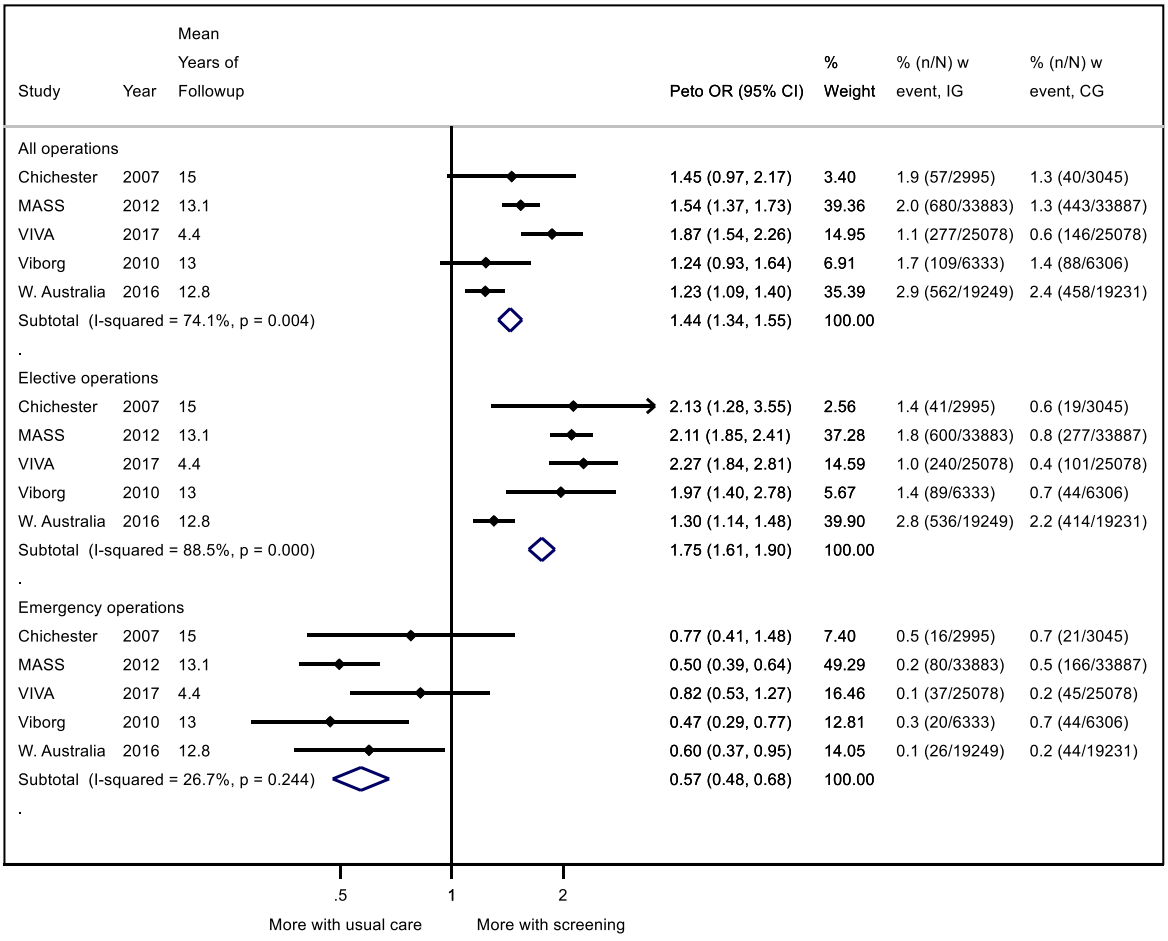
Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = population size; n = sample size; RR = relative risk

Figure 3. Pooled Analysis of AAA-Related Mortality and Ruptures (Male-Only) in One-Time Screening Trials



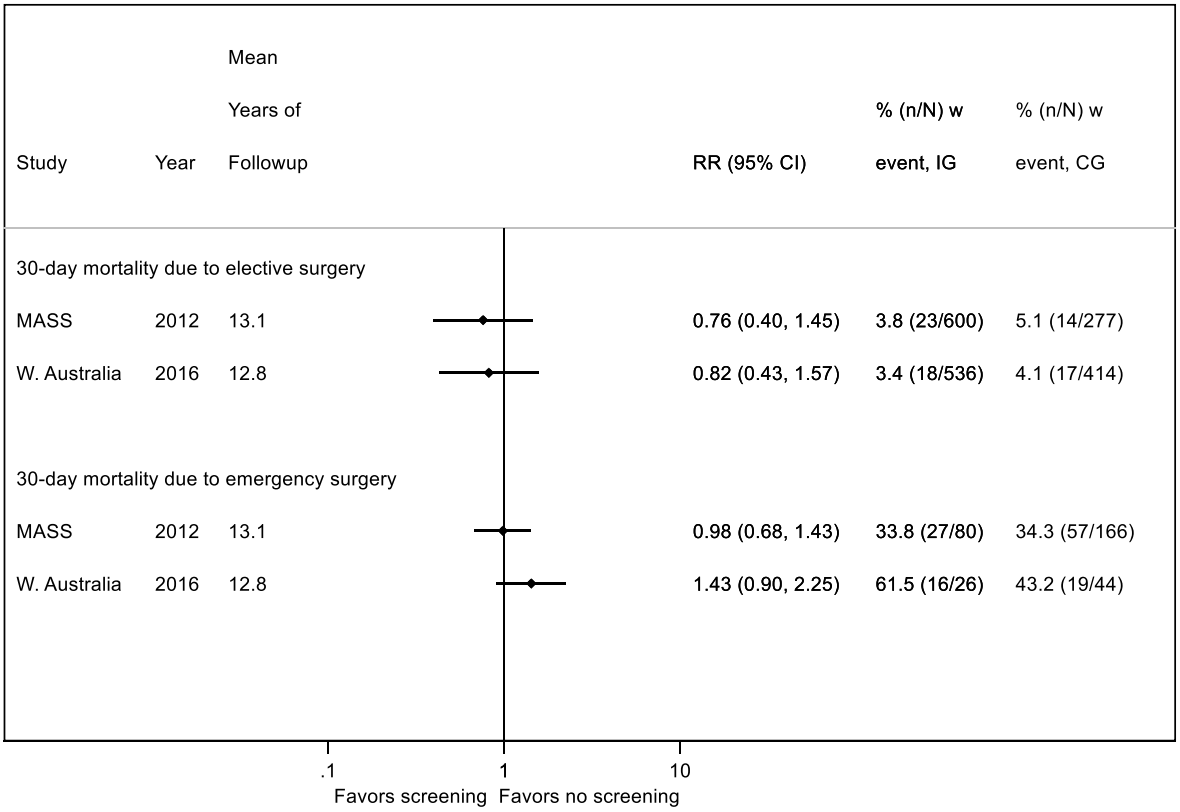
Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = population size; n = sample size; OR = odds ratio

Figure 4. Pooled Analysis of Operations (Male-Only) in One-Time Screening Trials



Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = population size; n = sample size; OR = odds ratio

Figure 5. Forest Plot of 30-Day Mortality (Male Only) Due to Elective and Emergency Surgery in One-Time Screening Trials



Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = population size; n = sample size; RR = relative risk

Table 1. AAA Prevalence, Rupture, and Surgery Data for One-Time Screening Trials (KQ1)

Author, Year Trial name Quality	Mean Followup, years	Group	N Analyzed	AAA Prevalence, n (%)	AAA Rupture, n (%)	HR (95% CI) for AAA Rupture	OR for AAA Rupture*	All AAA Procedures, n (%)	Elective Surgery, n (%)	Emergency Surgery, n (%)	HR (95% CI) for Emergency Surgery	OR (95% CI) for Emergency Surgery*
Ashton, 2007[113] Chichester (men only) Fair	15[†]	IG	2,995[‡]	170[§] (7.6)	54 (1.8)	0.88 (0.61 to 1.26)	0.87 (0.60 to 1.25)	57 (1.9)	41 (1.4)	16 (0.5)	NR	0.77 (0.41 to 1.48)
		CG	3,045[‡]	NR	63 (2.1)			40 (1.3)	19 (0.6)	21 (0.7)		
Scott, 2002[13, 36] Chichester (women only) Fair	10[†]	IG	4,682	40 (1.3)[‖]	10 (0.2)	NR	1.11 (0.45 to 2.72)	6 (0.1)	5 (0.1)	1 (0.02)[‖]	NR	Not Calculated
		CG	4,660	NR	9 (0.2)			NR	NR	2 (0.02)[‖]		
Thompson, 2012[170] MASS Good	13.1	IG	33,883	1,334 (4.9)	273 (0.8)	0.57 (0.49 to 0.66)	0.58 (0.50 to 0.67)	680 (2.0)	600 (1.8)	80 (0.2)	NR	0.50 (0.39 to 0.64)
		CG	33,887	NR	476 (1.4)			443 (1.3)	277 (0.8)	166 (0.5)		
Lindholt, 2010[14, 147] Viborg Good	13	IG	6,333	191 (3.9)[¶]	16 (0.3)	0.44 (0.24 to 0.79)	0.46 (0.27 to 0.79)	109 (1.7)	89 (1.4)	20 (0.3)	0.50 (0.15 to 1.65)[#]	0.47 (0.29 to 0.77)
		CG	6,306	NR	36 (0.6)			88 (1.4)	44 (0.7)	44 (0.7)		
Lindholt, 2017[22, 146] VIVA Fair	4.4[†]	IG	25,078	619 (3.3)	NR	NA	NA	277 (1.1)	240 (1.0)	37 (0.1)	0.81 (0.53 to 1.26)[**]	0.82 (0.53 to 1.27)
		CG	25,078	NR	NR			146 (0.6)	101 (0.4)	45 (0.2)		
McCaul, 2016[15] Western Australia Fair	12.8	IG	19,249	879 (7.2) [‡‡]	72[§§]	NR	0.73 (0.54-0.98)	562 (2.9)	536 (2.78)[‖‖]	26 (0.14)[¶¶]	NR	0.60 (0.37-0.95)
		CG	19,231	NR	99			458 (2.4)	414 (2.15)	44 (0.23)[¶¶]		

Table 1. AAA Prevalence, Rupture, and Surgery Data for One-Time Screening Trials (KQ1)

*Calculated, Peto OR
†Median
‡ Due to updated computer systems & the correction of data, 391 men were excluded from the original data
§ N analyzed for prevalence: 2,216
‖ From 5yr reported data; N analyzed for prevalence: 3052
¶ N analyzed for prevalence: 4816. Prevalence reported at 4.3yr (median) followup[14] NR in 13 year follow-up results.
# Hazard ratio for emergency surgery without rupture; HRs reported separately for emergency surgery with rupture: 0.44 (95% CI, 0.24-0.79).
** Likely confounded by co-screening and resulting treatment
‡‡ N analyzed for prevalence: 12,203
§§ p=0.04
‖‖ p<0.001
¶¶ Total surgery for rupture

Abbreviations: AAA = abdominal aortic aneurysm; CG = control group; CI = confidence intervals; HR = hazard ratio; IG = intervention group; MASS = Multicenter Aneurysm Screening Study; N = population size; n = sample size; NA = not applicable; NR = not reported; OR = odds ratio

Table 2. All-Cause and AAA-Related Mortality Data for One-Time Screening Trials (KQ1)

Author, Year Trial name Quality	Mean Followup, years	Group	N Analyzed	All-cause mortality, n (%)	HR (95% CI)	RR (95% CI)*	AAA-related mortality, n (%)	HR (95% CI)	OR (95% CI)*	30 day mortality for elective repairs, n (%)	RR (95% CI)*	30 day mortality for emergency repairs, n (%)	RR (95% CI)*
Ashton, 2007[113] Chichester (men only) Fair	15[†‡]	IG	2,995[§]	2036 (68.0)	1.01 (0.95 to 1.07)	1.00 (0.97 to 1.04)	47 (1.6)	0.89 (0.6 to 1.32)	0.88 (0.60 to 1.31)	NR	Not calculated	NR	Not calculated
		CG	3,045[§]	2067 (67.9)			54 (1.8)			NR		NR	
Scott, 2002[13, 36] Chichester (women only) Fair	10[‡]	IG	4,682	503 (10.7)[‖]	NR	Not calculated	3 (0.06)[‖]	NR	Not calculated	NR	Not calculated	NR	Not calculated
		CG	4,660	476 (10.2)[‖]			2 (0.04)[‖]			NR		NR	
Thompson, 2012[170] MASS Good	13.1	IG	33,883	13,858 (40.9)	0.97 (0.95 to 0.99)	0.98 (0.96-1.00)	224 (0.7)	0.58 (0.49 to 0.69)	0.59 (0.50 to 0.70)	23 (3.8)[¶]	0.76 (0.40 to 1.45)	27 (33.8)[#]	0.98 (0.68 to 1.43)
		CG	33,887	14,134 (41.7)			381 (1.1)			14 (5.1) [¶]		57 (34.3)[#]	
Lindholt, 2010[147] Viborg Good	13	IG	6,333	2,931 (46.3)	0.98 (0.93 to 1.03)	0.98 (0.95-1.02)	19 (0.3)	0.34 (0.20 to 0.57)	0.37 (0.24 to 0.59)	NR	Not calculated	NR	Not calculated
		CG	6,306	2,964 (47.0)			55 (0.9)			NR		NR	
McCaul, 2016[15] Western Australia Fair	12.8[‡] (range, 11.6 to 14.2)	IG	19,249	9739 (50.6)	NR**	0.99 (0.97-1.01)	90 (0.46)	0.91 (0.68 to 1.21)**	0.92 (0.69 to 1.22)	18 (3.4)[‡‡]	0.82 (0.43 to 1.57)	16 (61.5)[§§]	1.43 (0.90 to 2.25)
		CG	19,231	9832 (51.1)			98 (0.51)			17 (4.1)[‡‡]		19 (43.2)[§§]	

* Calculated

† Male subgroup only

‡ Median

§ Due to updated computer systems & the correction of data, 391 men were excluded from the original data

Table 2. All-Cause and AAA-Related Mortality Data for One-Time Screening Trials (KQ1)

‖ from 5yr reported data
¶ N Analyzed for IG: 600, CG: 277
# N Analyzed for IG: 80, CG: 166
** Rate ratio (95% CI). Rate ratios reported as AAA-related and non-AAA deaths, not available for ACM.
N Analyzed for IG: 536, CG: 414
§§ N Analyzed for IG: 26, CG: 44

Abbreviations: AAA = abdominal aortic aneurysm; ACM = all-cause mortality; CG = control group; CI = confidence intervals; HR = hazard ratio; IG = intervention group; MASS = Multicenter Aneurysm Screening Study; N = population size; n = sample size; NA = not applicable; NR = not reported; OR = odds ratio; RR = relative risk

Table 3. AAA Prevalence, Rupture, and Surgery Data for Rescreening Studies (KQ2)

Study, Year USPSTF Quality	Mean Followup, years	N Analyzed	Initial Aorta Size range	Large AAA Incidence, n (%)	AAA Rupture, n (%)	All AAA Procedures, n (%)	Elective Surgery, n (%)	Emergency Surgery, n (%)
D'Audiffret, 2002[121] Fair	5.9	223	2.5-2.9 cm	> 5 cm: 3 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)
Deveraj, 2008[123] Fair	5.4	358	2.6-2.9 cm	≥ 5.5 cm: 8 (2.2)	NR	NR	NR	NR
Oliver-Williams, 2018[120, 156] Good	7.8	1233	2.6-2.9 cm	≥5.5 cm: 181 (14.7)	13 (2.4)*	134 (10.9)	124 (10.1)	10 (0.8)
	7.9*	547	2.6-2.9 cm	> 5.4 cm: 87 (15.9)	13 (2.4)	63 (11.5)	57 (10.4)	6 (1.1)
Lederle, 2000[138] Good	4	2622	≤3.0 cm	> 5 cm: 0	0 (0)	0 (0)	NR	NR
Lindholt, 2000[148] Fair	5	248	2.5-2.9 cm	> 5 cm: 0	NR	0 (0)	NR	NR
Scott, 2001[165] Fair	10	649	< 3.0 cm	>5 cm: 0	NR	NR	NR	NR
Soderberg, 2017[167] Fair	5	33† 25 rescreened	2.5-2.9 cm	>5 cm: 0	0 (0)	1 (4)	1 (4)‡	0
Svensjo, 2014[169] Fair	5	2652 2041 rescreened	<2.5 cm	NR§	0	0	0	0

* From median followup of 7.9 years (2.7 to 11-year range)[120]
† One woman was misclassified with a normal (2.1cm) aorta at rescanning and was excluded from further analysis
‡ One participant was diagnosed with a 4.5cm AAA at 5yr followup and was then electively repaired.
§ Did not report >5cm AAA incidence
‖ Of those rescreened (n=38)

Abbreviations: AAA = abdominal aortic aneurysm; cm = centimeter; N = population size; n = sample size; NR = not reported

Table 4. All-Cause and AAA-Related Mortality Data for Rescreening Studies (KQ2)

Study, Year USPSTF Quality	Mean followup, years	N Analyzed	All-cause mortality, n (%)	AAA-related mortality, n (%)	Operative mortality, n (%)
D'Audiffret, 2002[121] Fair	5.9	223	8 (3.6)	0 (0)	NR
Deveraj, 2008[123] Fair	5.4	358	NR	NR	NR
Oliver-Williams, 2018[120, 156] Good	7.8	1233	379 (30.7)	14 (2.4)*	7 (11.1)*
Lederle, 2000[138] Good	4	2622	NR	0 (0)	NR
Lindholt, 2000[148] Fair	5	248	NR	NR	NR
Scott, 2001[165] Fair	10	649	NR	NR	NR
Soderberg, 2017[167] Fair	5	33 (2.5-2.9 cm AAA diameter group)	5 (15.2)	0 (0)	0 (0)
Svensjo, 2014[169] Fair	5	2652 (<2.5 AAA diameter group)	136 (5.1)	0 (0)	0 (0)
		40 (2.5-2.9 cm AAA diameter group)	2 (5)	0 (0)	0 (0)

* AAA-related mortality from median followup of 7.9 years (2.7 to 11-year range)[120]

Abbreviations: AAA = abdominal aortic aneurysm; cm = centimeter; N = population size; n = sample size; NR = not reported

Table 5. All-Cause and AAA-Related Mortality Data for Open Versus Surveillance Trials for Small AAA (KQ4)

Study, Year Quality	Mean Followup, years	Treatment group	N Analyzed	All-cause mortality, n (%)	HR (95% CI)	RR (95% CI)*	AAA-related mortality, n (%)	HR (95% CI)	RR (95% CI)*
Lederle, 2002[140] ADAM Good	4.9	IG	569	143 (25.1)	1.21 (0.95 to 1.54)†	1.17 (0.95 to 1.44)	17 (3.0)	1.15 (0.58 to 2.31) †	1.13 (0.57 to 2.24)
		CG	567	122 (21.5)			15 (2.6)		
Powell, 2007[162, 163] UKSAT Good	4.6	IG	563	159 (30.6)	0.91 (0.72 to 1.16)	0.99 (0.82 to 1.20)	32 (5.7)	NR	0.86 (0.54 to 1.36)
		CG	527	150 (46.7)			35 (6.6)		
	12	IG	563	362 (64.3)	0.88 (0.75 to 1.02)ǂ	0.96 (0.88 to 1.05)	36 (6.9)	NR	0.67 (0.45 to 1.02)
		CG	527	352 (66.8)			50 (9.5)		

*Calculated

†Author reported RR

ǂ Primary adjustment made for age, sex, initial abdominal aortic aneurysm diameter, smoking status, mean of left and right ankle-brachial pressure indices, forced expiratory volume in 1s and aspirin use (missing values for 33 patients)

Abbreviations: AAA = abdominal aortic aneurysm; ADAM = Abdominal aortic aneurysm Detection and Management study; CG = control group; CI = confidence interval; HR = hazard ratio; IG = intervention group; N = population size; n = sample size; NR = not reported; RR = relative risk; UKSAT = the UK Small Aneurysm Trial

Table 6. AAA Growth Rate, Rupture, and Surgery Data for Open Versus Surveillance Trials for Small AAAs (KQ4 and KQ5)

Study, Year Quality	Mean Followup, years	Treatment group	N Analyzed	Mean AAA Growth Rate, mm/year (IQR)	AAA Rupture, n (%)	RR (95% CI)*	All AAA procedures, n (%)	Elective Surgery, n (%)	Emergency Surgery, n (%)
Lederle, 2002[140] ADAM Good	4.9	IG	569	NA	2 (0.4)	0.18 (0.04 to 0.81)	527 (92.6)	NR	NR
		CG	567	3.2 (1.6 to 4.2)†	11 (1.9)		349 (61.6)	NR	NR
Powell, 2007[162, 163] UKSAT Good	4.6	IG	563	NA	6 (1.2)	0.33 (0.13 to 0.83)	520 (92.4)	517 (91.8)	3 (0.5)
		CG	527	3.3 (2.0 to 5.3)‡	17 (3.2)		321 (60.9)	NR	NR
	12	IG	563	NR	13 (2.3)§	0.51 (0.26 to 0.99)	528 (93.8)	525 (93.3)	3 (0.5)
		CG	527	NR	24 (4.5)		401 (76.1)	395 (75.0)	6 (1.1)

*Calculated

†Average growth at 3 years

‡Median

§ Deaths from ruptures, plus two additional whose group was not reported

Abbreviations: AAA = abdominal aortic aneurysm; ADAM = Abdominal aortic aneurysm Detection and Management study; CI = confidence interval; HR = hazard ratio; IQR = interquartile range; mm = millimeter(s); N = population size; n = sample size; NA = not applicable; NR = not reported; RR = relative risk; UKSAT = the UK Small Aneurysm Trial

Table 7. All-Cause and AAA-Related Mortality Data for EVAR Versus Surveillance Trials for Small AAA (KQ4)

Study, Year Quality	Mean Followup, years	Treatment group	N Analyzed	All-cause mortality, n (%)	HR (95% CI)	RR (95% CI)*	AAA-related mortality, n (%)	HR (95% CI)	RR (95% CI)*
Cao, 2011[118] CAESAR Fair	2.6†	IG	182	10 (5.5)	0.76 (0.30 to 1.93)‡	1.22 (0.49 to 3.03)	1 (0.5)	NR	0.98 (0.06 to15.52)
		CG	178	8 (4.5)			1 (0.6)		
Ouriel, 2010[158] PIVOTAL Fair	1.7	IG	366	15 (4.1)	1.01 (0.49 to 2.07)	0.99 (0.49 to 1.99)	2 (0.5)	NR	1.98 (0.18 to 21.72)
		CG	362	15 (4.1)			1 (0.3)		

* Calculated
† Median
‡CG vs. IG

Abbreviations: AAA = abdominal aortic aneurysm; CAESAR = Comparison of surveillance versus Aortic Endografting for Small Aneurysm Repair; CG = control group; CI = confidence intervals; EVAR = endovascular aneurysm repair; HR = hazard ratio; IG: intervention group; N = population size: n = sample size; NA = not applicable; NR = not reported; PIVOTAL = Positive Impact of Endovascular Options for Treating Aneurysms Early; RR = relative risk

Table 8. AAA Growth Rate, Rupture, and Surgery Data for EVAR Versus Surveillance Trials for Small AAAs (KQ4 and KQ5)

Study, Year Quality	Mean Followup, years	Treatment group	N Analyzed	AAA Growth Rate, mm/year	AAA Rupture, n (%)	All AAA Procedures, n (%)	Elective Surgery (EVAR), n (%)	Emergency Surgery, n (%)
Cao, 2011[118] CAESAR Fair	2.6¶	IG	182	NR	0	175 (96.2)	171 (94.0)†	NR
		CG	178	1.5*	2 (1.1)	85 (47.8)	71 (39.9) ‡	NR
Ouriel, 2010[158] PIVOTAL Fair	1.7	IG	366	NR	0	326 (89.1)	322 (88.9)§	NR
		CG	362		1 (0.3)	112 (30.9)	108 (30.1)‖	1 (0.3)

* Mean increase in patients who were never repaired (at time of analysis)
† 4 patients (2.3%) received repair via open surgery
‡ 14 patients (7.9%) received repair via open surgery
§ 5 patients (1.4%) received repair via open surgery
‖ 3 patients (0.8%) received repair via open surgery
¶ Median

Abbreviations: AAA = abdominal aortic aneurysm; CAESAR = Comparison of surveillance versus Aortic Endografting for Small Aneurysm Repair; CG = control group; CI = confidence intervals; EVAR = endovascular aneurysm repair; IG: intervention group; mm = millimeter; N = population size: n = sample size; NA = not applicable; NR = not reported; PIVOTAL = Positive Impact of Endovascular Options for Treating Aneurysms Early

Table 9. AAA Growth Rate, Rupture, and Surgery Data for Pharmacotherapy Versus Placebo Trials for Small AAAs (KQ4 and KQ5)

Study, Year Quality	Comparison	Mean Followup, years	Treatment group	N Analyzed	Mean AAA Growth Rate, mm/year	AAA Rupture, n (%)	All AAA Procedures, n (%)	Elective Surgery, n (%)	Emergency Surgery, n (%)
Bicknell, 2016[114] AARDVARK Good	Perindopril (IG1) or amlodipine (IG2) vs. placebo	2	IG1	73	1.77 (0.2)**	0 (0)	10 (13.7) ††	NR	NR
			IG2	72	1.81 (0.2)**	0 (0)	11 (15.3) ††	NR	NR
			CG	79	1.68 (0.2)**	0 (0)	11 (13.9) ††	NR	NR
Hogh 2009[132] Good	Roxithromycin vs. placebo	5	IG	42	1.16¶	NR	29 (34.5)#	29 (34.5)#	NR
			CG	42	2.52¶	NR			NR
Karlsson 2009[133] Fair	Azithromycin vs. placebo	1.5	IG	106	2.2 (0.12 to 0.36)§	1 (0.94)	16 (15.1)	15 (14.1)‡	1 (0.9)‡
			CG	105	2.2 (0.09 to 0.34)§	NR	13 (12.4)	NR	NR
Meijer, 2013[152] Fair	Doxycycline vs. placebo	1.5	IG	144	4.1 (3.6 to 4.5) ‡‡	0 (0)	21 (14.6)	21 (14.6)	0 (0)
			CG	142	3.3 (2.8 to 3.7) ‡‡	2 (1.4)	24 (16.9)	22 (15.5)	2 (1.4)
Mosorin 2001[153] Fair	Doxycycline vs. placebo	1.5	IG	17	1.5 (0.0 to 3.0)†	1 (5.9)	3 (17.6)	2 (11.8)	1 (5.9)
			CG	15	3.0 (0.3 to 6.0)†	0 (0)	6 (40.0)	6 (40.0)	0 (0)
PAT Investigators, 2002[164] PAT Good	Propranolol vs. placebo	2.5	IG	276	2.1 (0.29)*	1 (0.4)	57 (20.6)	56 (20.3)	1 (0.4)
			CG	272	2.6 (0.30)*	2 (0.7)	74 (27.2)	72 (26.5)	2 (0.7)
Sillensen, 2015[166] AORTA Fair	Pemirolast vs. placebo	1	IG	84	2.71 (2.25 to 3.16)§§	0 (0)	6 (7.1)	NR	NR
			CG	84	2.04 (1.58 to 2.50)§§	0 (0)	2 (2.4)	NR	NR

* While patients were taking the study drug assigned; values reported as mean growth rate (SD); p=0.10
†Median (IQR); p-value was not significant
‡Assumed
§Median (IQR); p=0.85
¶p=0.055
Total referred to surgery because AAA was >5.0 cm (treatment group NR)
** Mean (SE), difference NS (IG1, p=0.78, IG2, p=0.68)
†† Number of patients reaching 5.5 cm or being referred to/having surgery
‡‡Mean (95% CI), based on a linear mixed model and adjusted for incomplete data. Mean between group difference (95% CI), mm: 0.8 (0.1 to 1.4); p = 0.016

Table 9. AAA Growth Rate, Rupture, and Surgery Data for Pharmacotherapy Versus Placebo Trials for Small AAAs (KQ4 and KQ5)

[§§]Adjusted mean change (95% CI); p = 0.189; doses of 10 mg and 25 mg are also reported; there was no significant difference in growth rate found between treatment groups

Abbreviations: AAA = abdominal aortic aneurysm; AARDVARK = Aortic Aneurysmal Regression of Dilation: Balue of ACE-Inhibition on RisK trial; AORTA = the Anti-inflammatory Oral Treatment of AAA; CG = control group; IG = intervention group; N = population size; n = sample size; NR = not reported; PAT = propranolol Aneurysm Trial; vs = versus

Table 10. All-Cause and AAA-Related Mortality Data for Pharmacotherapy Versus Placebo Trials for Small AAA (KQ4)

Study, Year USPSTF Quality	Comparison	Mean followup, years	Treatment group	N Analyzed	All-cause mortality, n (%)	HR (95% CI)	AAA-related mortality, n (%)	HR (95% CI)
Hogh 2009[132] Good	Roxithromycin vs. placebo	5	IG	NR	NR	NR	NR	NR
			CG	NR	NR		NR	
Karlsson 2009[133] Fair	Azithromycin vs. placebo	1.5	IG	106	5 (4.7)	NR	0	NR
			CG	105	8 (7.6)		0	
Meijer, 2013[152] Fair	Doxycycline vs. placebo	1.5	IG	144	2 (1.4)	NR	0 (0)	NR
			CG	142	5 (3.5)		1 (0.7)	
Mosorin 2001[153] Fair	Doxycycline vs. placebo	1.5	IG	17	4 (23.5)*	NR	NR	NR
			CG	15	3 (20.0)*		NR	
PAT Investigators, 2002[164] PAT Good	Propranolol vs. placebo	2.5	IG	57	33 (12.0)	NR	2 (0.7)	NR
			CG	74	26 (9.6)		2 (0.7)	
Bicknell, 2016[114] AARDVARK Good	Perindopril (IG1) or amlodipine (IG2) vs. placebo	2	IG1	73	NR	NR	NR	NR
			IG2	72	NR		NR	
			CG	79	NR		NR	
Sillensen, 2015[166] AORTA Fair	Pemirolast vs. placebo	1	IG	84	NR	NR	NR	NR
			CG	84	NR		NR	

* Defined as being "unrelated to aneurysm"

Abbreviations: AAA = abdominal aortic aneurysm; AARDVARK = Aortic Aneurysmal Regression of Dilation: Value of ACE-Inhibition on RisK trial; AORTA = the Anti-inflammatory Oral Treatment of AAA; CG = control group; IG = intervention group; N = population size; n = sample size; NR = not reported; PAT = propranolol Aneurysm Trial; vs = versus

Table 11. Harms Data in Studies of Treatment for Small AAAs (KQ5)

Comparison	Study	Mean Followup, years	Treatment Group	N Analyzed	30-day Operative Mortality, n (%)	Reintervention, n (%)	Endoleak, n (%)	Readmission in 30 days, n (%)	Complication, n (%)
Open surgery vs. surveillance	Lederle, 2002[140] ADAM	4.9	IG	526	Elective repairs: 11 (2.1)* Emergency: NR Overall: NR	*Timing NR* IG: 9 (1.7%) CG: 4 (1.2%)	NA	108 (20.5)†	Timing NR *Any complication:* 275 (52.3)‡ Major complications: *MI:* 5 (1.0)‡ *Stroke:* 3 (0.6) *Pulmonary embolism:* 4 (0.8) Amputation: 2 (0.4) Paraplegia: 0 Dialysis: 2 (0.6)
			CG	340	Elective repairs: 6 (1.8)* Emergency: NR Overall: NR		NA	56 (16.5)†	Timing NR *Any complication:* 193 (56.8)‡ Major complications: *MI:* 13 (3.8)‡ *Stroke:* 2 (0.6) *Pulmonary embolism:* 1 (0.3) Amputation: 2 (0.4) Paraplegia: 2 (0.6) Dialysis: 2 (0.6)
	Powell, 2007[163] UKSAT	12.0	IG	526	Elective: 26 (5.0) Emergency: 3 (100) Overall (including after emergency repair): 29 (5.5)§	NR	NA	30 (6.3)‖	NR
			CG	389	Elective repairs: 25 (6.3) Emergency: 4 (66.7) Overall (including after emergency repair): 29 (7.2)§	NR	NA	NR	NR

Table 11. Harms Data in Studies of Treatment for Small AAAs (KQ5)

Comparison	Study	Mean Followup, years	Treatment Group	N Analyzed	30-day Operative Mortality, n (%)	Reintervention, n (%)	Endoleak, n (%)	Readmission in 30 days, n (%)	Complication, n (%)
EVAR vs. surveillance	Cao, 2011[118] CAESAR	2.6¶	IG	175	Elective: 1 (0.6) Emergency: NR Overall: NR	10 (5.7)‡	*Within 30-days*# Type 1: 2 (1.2) Type 2: 25 (14.6) Type 3: 0 (0) Unknown: 1 (0.6) *At 1 year*# Type 1: 0 (0) Type 2: 19 (10.9) Type 4: 1 (0.6), unknown: 1 (0.6)	NR	*Within 30-days* Any morbidity related to repair: 31 (17.7)‡ Any major morbidity: 6 (3.4) Any device-related morbidity: 3 (1.7) *At 32.4 months* Any morbidity: 34 (19.1) Any major morbidity: 6 (3.3) Cumulative probabilities of adverse events: 19.8% (36mo); 21.2% (54 mo)**
			CG	85	Elective: 0 (0) Emergency: NR Overall: NR	0‡	*Within 30-days*# Type 1: 1 (1.4) Type 2: 4 (5.6) Type 3: 1 (1.4) Unknown: 1(1.4) *At 1 year*# Type 1 (0) Type 2: 2 (2.4) Type 4 0 (0) Unknown: 0 (0)	NR	*Within 30-days* Any morbidity related to repair: 5 (6.0)‡ Any major morbidity: 4 (4.7) Any device-related morbidity: NR *At 32.4 months* Any morbidity: 10 (5.1) Any major morbidity: 5 (2.8) Cumulative probabilities of adverse events: 4.0% (36mo); 14.8% (54mo)
	Ouriel, 2010[158] PIVOTAL	1.7	IG	322	1(0.3)	*Timing NR* 12 (3.7)	*Within 30-days* Overall: 36 (11.9) Type 1: 0 Type 2: 34 (11.3) Type 3: 1 (0.3) Type 4: 1 (0.3) *At 1 year*	20 (4.6; group NR)	*Within 30-days* Endograph migration: 1 (0.3) Superficial wound infection: 8 (2.5) Endograph thrombosis: 4 (1.2) Deep vein thrombosis: 1 (0.3)

Table 11. Harms Data in Studies of Treatment for Small AAAs (KQ5)

Comparison	Study	Mean Followup, years	Treatment Group	N Analyzed	30-day Operative Mortality, n (%)	Reintervention, n (%)	Endoleak, n (%)	Readmission in 30 days, n (%)	Complication, n (%)
							Overall: 72 (26.1) Type 1: 2 (0.7) Type 2: 67 (24.4) Type 3: 1 (0.3) Type 4: 2 (0.7)		Serious cardiac event: 17 (5.3) Serious pulmonary event: 4 (1.2) Serious renal event: 6 (1.9)
			CG	109	1 (0.9)	*Timing NR* 5 (4.6)	*Within 30-days* Overall: 10 (10.3) Type 1: 1 (1.0) Type 2: 4 (9.3) Type 3: 0 (0) Type 4: 0 (0) *At 1 year* Overall: 30 (35.1) Type 1: 2 (2.4) Type 2: 29 (33.4) Type 3: 0 (0) Type 4: 0 (0)		*Within 30-days* Endograph migration: 0 Superficial wound infection: 1 (0.9) Endograph thrombosis: 3 (2.8) Deep vein thrombosis: 0 Serious cardiac event: 9 (8.3) Serious pulmonary event: 1 (0.9) Serious renal event: 1 (0.9)

* Operative mortality associated with the repair of unruptured AAA
† Timing NR
‡ $p < 0.05$
§ N analyzed for overall 30-day operative mortality, IG: 528, CG: 401
‖ From 1 -year followup data; the use of bifurcated grafts (12/30, 40%) was associated with a 2-fold increase in the risk of reoperation, p=0.03
¶ Median
# Denominator is those that received EVAR: IG: 171; CG: 7; At 1 year: IG: Type 2: 19 (10.9%), Type 4: 1 (0.6%), unknown: 1 (0.6%); CG: Type 2: 2 (2.4%)
** $p<0.001$

Abbreviations: AAA = abdominal aortic aneurysm; ADAM = Abdominal aortic aneurysm Detection and Management study; CAESAR = Comparison of surveillance versus Aortic Endografting for Small Aneurysm Repair; CG = control group; EVAR = endovascular aneurysm repair; IG: intervention group; MI = myocardial infarction; N = population size: n = sample size; NA = not applicable; NR = not reported; PIVOTAL = Positive Impact of Endovascular Options for Treating Aneurysms Early; UKSAT = the UK Small Aneurysm Trial

Table 12. Harms Data in Registry Studies (KQ5)

Study Registry	Mean Followup, years	N Analyzed	Surgical technique(s) included	30-day Operative Mortality, n (%)	Reintervention, n (%)	Endoleak, n (%)	Readmission in 30 days, n (%)	Complication, n (%)
Budtz-Lilly, 2017[116] Vascunet	NR	12,610	EVAR, open	Open: 391 (3.1)* EVAR: 88 (0.7)*	NR	NR	NR	NR
Golledge, 2007[129] ASERNIP-S‖	3.2†	478	EVAR	5 (1.1)	*Within 30-days* 13 (3)‡	*Within 30-days* Type 1: 10 (2.1) Type 2: 35 (7.3) Type 4: 1 (0.2) 97 (20.3) patients had endoleak on followup imaging ≥ 30 days after procedure	NR	*Within 30-days* *Significant postop complications reported in 138 (29%)* 52 procedural & device complications occurred in 51 (10.7) patients 72 systemic complications were noted in 64 (13.4) of patients 41 access site and lower limb complications in 39 patients (8%)
Lo, 2013[149] Vascular Study Group of New England	1.0	1,336	EVAR, open	Men: 7 (0.7) Women: 4 (1.1)	NR	NR	NR	NR
Overbey, 2017[159] ACS NSQIP	NR	5,126	EVAR, open	56 (1.1) Open: 25 (3.5)§ EVAR: 31 (0.7)§	214 (4.2) Open: 64 (9.1) EVAR: 150 (3.4)	NR	348 (6.8) Open: 44 (6.2) EVAR: 304 (6.8)	Open: Overall morbidity within 30 days of surgery: 69.4% Pneumonia: 34 (4.8) Acute renal failure: 18 (2.3) Sepsis: 12 (1.7) Septic shock: 19 (2.7) Cardiac arrest: 19 (2.7) MI: 24 (3.4) Pulmonary embolism: 3 (0.4) Stroke: 5 (0.7) Bleeding complications: 460 (65.2)

Table 12. Harms Data in Registry Studies (KQ5)

Study Registry	Mean Followup, years	N Analyzed	Surgical technique(s) included	30-day Operative Mortality, n (%)	Reintervention, n (%)	Endoleak, n (%)	Readmission in 30 days, n (%)	Complication, n (%)
								Ischemic colitis: 34 (4.8) Lower extremity ischemia: 15 (2.1) EVAR: Overall morbidity within 30 days of surgery: 11.4% Pneumonia: 24 (0.5) Acute renal failure: 15 (0.3) Sepsis: 20 (0.4) Septic shock: 6 (0.1) Cardiac arrest: 14 (0.3) MI: 46 (1.0) Pulmonary embolism: 5 (0.1) Stroke: 12 (0.3) Bleeding complications: 296 (6.6) Ischemic colitis: 16 (0.4) Lower extremity ischemia: 56 (1.3) Combined: Pneumonia 58 (1.1) Acute renal failure: 33 (0.6) Sepsis: 32 (0.6) Septic shock: 25 (0.5) Cardiac arrest: 33 (0.6) MI: 70 (1.4) Pulmonary embolism: 8 (0.2) Stroke: 17 (0.3) Bleeding complications: 756 (14.7)

Table 12. Harms Data in Registry Studies (KQ5)

Study Registry	Mean Followup, years	N Analyzed	Surgical technique(s) included	30-day Operative Mortality, n (%)	Reintervention, n (%)	Endoleak, n (%)	Readmission in 30 days, n (%)	Complication, n (%)
								Ischemic colitis 50 (0.01) Lower extremity ischemia 71 (1.4)
Peppelenbosch, 2004[160] EUROSTAR	1.7	1,962	EVAR	31 (1.6)	NR	*Event at 4 years* Type I proximal:5.3% distal: 11.3% Type III: 14.4%	NR	Timing NR *Cardiac:* 55 (2.8) *Pulmonary:* 31 (1.6) *Early procedure or device-related:* 57 (2.9) *30-day systemic complications combined*: 235 (12.0)

* Defined as hospital death or death within 30 days of surgery
† Median
‡ Reinterventions ≤ 30 days after surgery; ≥ 30 days after surgery: 50 patients underwent 72 additional interventions by open (20 times in 16 patients [5 had an EVAR procedure]), EVAR (52 times in 39 patients), or combined approaches
§ N analyzed for 30-day operative mortality; Open n=705, EVAR n=4471
‖ Registry does not report whether they include emergency surgeries

Abbreviations: AAA = abdominal aortic aneurysm; ACS NSQIP: American College of Surgeons National Surgical Quality Improvement Program; ASERNIP-S = Australian Safety and Efficacy Register of New Interventional Procedures-Surgical; EVAR = endovascular aneurysm repair; IG: intervention group; MI = myocardial infarction; N = population size: n = sample size; NA = not applicable; NR = not reported

Table 13. Harms Data in Studies of Treatment for Small AAA (KQ5): Pharmacotherapy Versus Placebo

Study	Drug name	Mean Followup, years	Treatment Group	N Analyzed	Readmission in 30 days, n (%)	Trial Withdrawals due to AEs related to study medication, n (%)	Complication, n (%)
Bicknell, 2016[114] AARDVARK	Perindopril (IG1); amlodipine (IG2)	2.0	IG1	73	NR	2 (2.7)	*Serious AEs** 19 (26.0)
			IG2	72	NR	4 (5.6)	*Serious AEs** 12 (16.7)
			CG	79	NR	0 (0)	*Serious AEs** 16 (20.2)
Hogh 2009[132]	Roxithromycin	2.0	IG	40	NR	0 (0)	No adverse events were reported
			CG	44	NR	0 (0)	No adverse events were reported
Karlsson 2009[133]	Azithromycin	1.5	IG	106	NR	3 stopped taking medication	13 (12.3)†
			CG	105	NR	2 stopped taking medication	8 (7.6)†
Lindholt, 1999[142]	Propranolol	2.0	IG	30	NR	18‡	*Serious cardiac arrhythmia:* 1 (3.3)§ *Dyspepsia:* 3 (10.0)§ *Headache:* 2 (6.7)§ *Dizziness:* 3 (10.0)§
			CG	24	NR	7‡	*Serious cardiac arrhythmia:* 0 (0)§ *Dyspepsia:* 1 (4.2)§ *Headache:* 1 (4.2)§ *Dizziness:* 0 (0)§
Meijer, 2013[152]	Doxycycline	1.5	IG	144	NR	11 (7.6)	*Abdominal pain, nausea, diarrhea* 5 (3.5)
			CG	142	NR	3 (2.1)	*Abdominal pain, nausea, diarrhea* 11 (7.7)
Mosorin 2001[158]	Doxycycline	1.5	IG	17	NR	1 (5.9)‖	No adverse events were reported
			CG	15	NR	1 (6.7)‖	No adverse events were reported
PAT Investigators, 2002[164] PAT	Propranolol	2.5	IG	267	NR	104 (37.7)¶	Patients who stopped their medication before surgery or the end of study: 117 (42.4) Reasons for permanently stopping study drug:# *Fatigue:* 24 (8.7)

Table 13. Harms Data in Studies of Treatment for Small AAA (KQ5): Pharmacotherapy Versus Placebo

Study	Drug name	Mean Followup, years	Treatment Group	N Analyzed	Readmission in 30 days, n (%)	Trial Withdrawals due to AEs related to study medication, n (%)	Complication, n (%)
							Heart failure: 7 (2.5) *Bradycardia/AVB:* 11 (4) *Claudication/Raynaud's disease:* 1 (0.4)
			CG	272	NR	58 (21.3)	Patients who stopped their medication before surgery or the end of study: 73 (26.8) Reasons for permanently stopping study drug:[#] *Fatigue:* 12 (4.4) *Heart failure:* 2 (0.7) *Bradycardia/AVB:* 1 (0.4) *Claudication/Raynaud's disease:* 3 (1.1)
Sillensen, 2015[166] AORTA	Pemirolast	1.0	IG1	84	NR	7 discontinued intervention (not specific); 1 withdrew	*Any AE: 67 (79.8)* *Any SAE: 15 (17.9)* *Serious cardiac disorder: 4 (4.8)*
			CG	84	NR	14 discontinued intervention (not specific); 8 withdrew	*Any AE: 68 (80.9)* *Any SAE): 15 (17.9)* *Serious cardiac disorder: 5 (5.9)*

***** None of the recorded SAEs were deemed to be related to the trial medications.
† All patients in CG had GI symptoms and 2 stopped taking meds. In IG: 3 stopped taking meds (1 due to diarrhea, 1 due to arthralgia, 1 had allergic reaction [found to be to antihypertensive med, not study med])
‡ Cumulated drop-outs
§ Withdrew due to complications; subset of complications. Full list of complications listed in Figure 18 of article.
‖ Discontinued the medication due to an allergic reaction
¶ $p<0.0001$
# Complete list available in Table 2 of article

Abbreviations: AAA = abdominal aortic aneurysm; AARDVARK = Aortic Aneurysmal Regression of Dilation: Value of ACE-Inhibition on RisK trial; AORTA = the Anti-inflammatory Oral Treatment of AAA; AVB = atrioventricular block; CG = control group; EVAR = endovascular aneurysm repair; GI = gastrointestinal; IG = intervention group; MI = myocardial infarction; N = population size; n = sample size; NR = not reported; PAT = propranolol Aneurysm Trial; PVD = peripheral vascular disease; SAE = serious adverse events; vs = versus

Table 14. Summary of Evidence

Key Question	Sub-population	Studies (k), Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ1: What are the effects of one-time screening for abdominal aortic aneurysm (AAA) on health outcomes in an asymptomatic population age 50 years or older?	Entire study population	K=4 (0 new studies; 1 trial with longer followup) N=124,929	Invitation for one-time screening in men aged 65 years and older was associated with a 35% reduction in AAA-related mortality, 38% reduction in AAA rupture rate, and a 43% reduction in the number of emergency operations, but no statistically significant difference in all-cause mortality at 12 to 15-year followup.	Reasonably consistent and precise	--	Moderate to high	These population-based screening trials were set in the 1990s in mostly Caucasian males aged 65 to 75 years. Since this time, AAA prevalence has declined along with smoking prevalence, and medical management of CVD has changed.
KQ1a: Do the effects of one-time screening for AAA vary among subpopulations (i.e., by age, sex, smoking status, family history, or race/ethnicity)?	Age	K=2 (0 new studies;1 trial with longer followup) N=51,119	The Viborg and Western Australia population-based screening trials reported subanalyses with substantial limitations suggesting that there is no differential screening effect based on age.	Consistent; imprecise	Subanalyses were not prespecified, stratified at randomization to ensure baseline comparability, adjusted for confounders, or powered to detect subgroup differences; no heterogeneity testing was performed.	Low	Both trials were conducted in mostly Caucasian older men.
	Sex	K=1 N=9,342	There was no difference in AAA rupture rate at 10-year followup, or in mortality (both AAA-related & all-cause) at 5 years between the invited and control groups. Most AAA ruptures occur ≥ age 80 years in women.	Consistency NA (1 study) imprecise	Underpowered for health outcomes	Low	Population was older Caucasian women in Chichester, UK.

Table 14. Summary of Evidence

Key Question	Sub-population	Studies (k), Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
	Smoking	K=1 N=19,249	Results showed that smoking was associated with a higher risk of all-cause mortality (OR 1.59 [95% CI, 1.47 to 1.72]) and AAA-related mortality (OR 2.95 [95% CI, 1.04 to 8.43]) in the screened group of men aged 64 to 83 years. This trend was more pronounced in the age group of 65 to 74-year olds, however no formal analysis was performed to explore if there is a differential screening effect based on smoking status.	Consistency NA (1 study); Imprecise	Subanalyses were not prespecified or powered to detect subgroup differences; no heterogeneity testing was performed to determine if there is modification in the effect of screening in smokers.	Low	Trial was conducted in mostly Caucasian older men.
KQ2: What are the effects of rescreening for AAA on health outcomes or AAA incidence in a previously screened, asymptomatic population without AAA on initial screening?	Entire study population	K=8 (2 new studies) N=8,018	Studies rescreened participants with various rescreening protocols (rescreening annually to 5 years with 1 to 6 repeated scans), demonstrating that AAA-related mortality over 5 to 12 years is rare (<3%) among those with normal aortas (< 3 cm) on the initial scan. Upon rescreening, few aortas grew to > 5 or ≥5.5 cm (0 to 2.2%) at 5 years and 0 to 15% had progressed at 10 years. Four studies reported no AAA ruptures or AAA-related deaths at 4 to 5-year followup; one study reported 2.4% ruptures at 7.9 year median followup.	Inconsistent; Imprecise	Heterogeneous rescreening protocols. A small number of participants with normal aortas were included in these studies; all but a single study was exclusively in men; there are no matched controls in most studies; the primary focus of most studies was growth rate as the followup time for most studies was 5 years, which is a timeframe too short to expect the development of AAA-related health outcomes.	Low	Mostly men (only one trial conducted in women). All but one trial conducted outside of the US.
KQ2a: Do the effects of rescreening for AAA vary among subpopulations (i.e., by age, sex, smoking status, family	Sex	K=1 (1 new) (n=33 women) remaining 7 KQ2 studies in men	One small study in women was too small to compare to other rescreening studies in men.	Consistency NA; Imprecise	Few studies reporting outcomes by subpopulation; most studies did not report if subgroup analyses were prespecified and studies tested numerous risk factors. Overall	Low	Small study of women conducted outside of the US.

Table 14. Summary of Evidence

Key Question	Sub-population	Studies (k), Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
history, or race/ethnicity)?	Smoking	k=3 (2 new) N=4,706	Two studies report multiregression analyses suggesting that current smoking is an independent risk factor for the development of AAA at rescreening and another univariate analysis in a study of solely women shows a similar trend for smoking, however the number developing AAAs over the rescreening interval was small.	Consistent; Imprecise	rescreening literature limited by lack of adequate reporting; heterogeneity of study rescreening protocols; and short follow-up times with focus on growth rates rather than health outcomes.	Low	Studies were conducted in mostly men.
KQ3: What are the harms associated with one-time and repeated screening?	Entire study population	K=5 (1 new study) N=175,085	There were approximately 40% more surgeries in the invited group compared to the control group (K=5, N=; Peto OR 1.44 [95%CI, 1.34 to 1.55]), largely driven by elective operations (Peto OR 1.75 [95% CI, 1.61 to 1.90]). There was no statistically significant difference in 30-day operational mortality rates in the invited versus control groups for either elective surgeries or emergency surgeries at the 12 to 15-year followup.	Consistent; reasonably precise	---	Moderate	Trials were conducted in mostly Caucasian older men.
KQ3a: Do the harms of one-time and repeated screening for AAA vary among subpopulations (i.e., by age, sex, smoking status, family history, or race/ethnicity)	Age	K= 1 (0 new studies but longer term followup available N= 19,571	Single population-based screening trial reports similar number of elective operations and lower 30-day operative mortality after elective and emergency surgery in the younger age subset (65 to 74 years) compared to entire trial population (64 to 83 years).	Consistent NA 1 trial; Imprecise	Subanalyses were not prespecified, stratified at randomization to ensure baseline comparability, adjusted for confounders, or powered to detect subgroup differences; no heterogeneity testing was performed.	Low	Trial was conducted in mostly Caucasian older men.
KQ4: What are the effects of treatment (pharmacotherapy or surgery)	Entire study population: open versus surveillance	K=2 (0 new) N=2,226	No difference in all-cause mortality, AAA-related mortality but reduction in rupture seen with early open surgery compared to surveillance for small AAAs.	Consistent; Imprecise	Only 2 studies. No differentiation of sizes between 4 to 5.4 cm	Moderate	Trails primarily recruited males with small AAAs (4 to 5.4 cm).

Table 14. Summary of Evidence

Key Question	Sub-population	Studies (k), Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
on intermediate and health outcomes in an asymptomatic, screen-detected population with small AAAs (i.e., aortic diameter of 3.0 to 5.4 cm)?	Entire study population: EVAR versus surveillance	K=2 (0 new) n=1,088	No difference in all-cause or AAA-related mortality with early EVAR compared to surveillance for small AAAs.	Consistent; Imprecise	Both trials were stopped early at interim analysis due to futility.	Moderate	Trails primarily recruited males with small AAAs (4 to 5.4 cm).
	Entire study population: Pharmacotherapy versus placebo	K=7 trials (3 new) N=1,553	Drug trials of antibiotics, antihypertensive medications, a mast cell stabilizer showed no overall effect on AAA growth compared to placebo.	Consistency NA given different drug classes; Imprecise	1 to 2 trials for each medication, followup times too short to expect development of AAA-related events or changes in health outcomes (all-cause mortality, AAA-related mortality, rupture)	Low	Studies were predominantly conducted in males with small AAAs. All trials were conducted outside of the US.
KQ4a: Do the effects of treatment of small AAAs vary among subpopulations (i.e., by age, sex, smoking status, family history, or race/ethnicity)?	Open vs. surveillance by age & sex	K=2 (1 IPD MA of these 2 RCTs) N=2,226	IPD MA available pooling the two early open versus surveillance trials (ADAM and UKSAT) with 5 to 8-year followup reported no differential all-cause mortality effect by sex. The two trials reported no differential all-cause mortality treatment effect by age at 5 and 12-year followup. One of these RCTs (UKSAT) reports no difference in all-cause mortality by smoking status; this subanalysis did not address differential mortality effect of early surgery by smoking status. There is no data on family history or race.	Unknown consistency; Imprecise	Subanalyses by age: one trial did not report interaction testing results. Subanalyses by sex: both prespecified analyses, one trial did not adjust for confounders or report interaction testing	Low	Participants were men and women with small AAAs; analyses were separated by older and younger participants (reported in 5 to 10-year age strata), with and without a smoking history.
	EVAR vs. surveillance	No studies	---	---	---	---	---

Table 14. Summary of Evidence

Key Question	Sub-population	Studies (k), Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
	Pharmaco-therapy by age & smoking	Age: k=1 propranolol RCT (0 new); n=552 Smoking: k=1 doxycycline RCT (0 new); n=32	None of the pharmacotherapy trials report health outcomes by subgroup. One small doxycycline trial and one propranolol trial performed limited subgroup analyses which do not support a treatment effect modification by age or smoking history.	NA single trial for each medication/ imprecise	Too few studies. Available analyses would be considered exploratory, at best particularly given that the subgroup methodologies were of low quality (no prespecification of analysis, adjustment for confounders, or interaction testing) and overall trial results do not support a AAA growth benefit.	Low	
KQ 5: What are the harms of treatment in an asymptomatic, screen-detected population with small AAAs (i.e., aortic diameter of 3.0 to 5.4cm)?	Open vs. surveillance	K=2 trials plus 3 registries (2 new); N=21,298	Two trials of early open repair vs. surveillance reported a 50% higher rate of procedures in the early intervention group with no difference in 30-day operative mortality. Readmission rates at 30 days were similar; and major surgical complications were lower in the early intervention group. QOL results were mixed, but generally showed declines in both the early surgery and surveillance groups over time with no statistically significant difference between the groups up to 1 to 2 years; only the ADAM trial showed higher general health scores in the early repair group in the first 2 years that did not persist over time. One trial reported an increased incidence of impotence in the early repair group at up to 4 years. Registry harms data were generally comparable to the 2 trials with the exception of reintervention rates, which were higher in the registries compared to the ADAM trial.	Reasonably consistent for procedures, 30-day operative mortality; consistency NA for other complications as only reported in 1 trial Reasonably precise for procedures; 30-day mortality and complications imprecise	Surgical morbidity complications not well-reported	Moderate	Registry data from both national and international sources; contemporary.

Table 14. Summary of Evidence

Key Question	Sub-population	Studies (k), Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
	EVAR vs surveillance	K=2 RCTs plus 5 registries (3 new); N=22,600	Two trials of early EVAR vs. surveillance reported approximately 100% more procedures in the early intervention group and similarly rare 30-day operative mortality rates between the groups. In the CAESAR trial, the early intervention group had a higher percentage of patients with any adverse events (19% vs. 5%, p<0.01), any morbidity related to repair at 30 days (18% vs. 6%, p=0.01), endoleaks at 1 year (12% vs. 3%, p=0.028), and reinterventions (6% vs. 0%, p=0.03), but similar rates of any major morbidity over the trial duration (3.3% vs. 2.8%, p=0.99). Conversely, PIVOTAL largely reported similar rates of adverse events at 30 days (12% vs. 10%) and 1 year (26% vs. 35%) and reinterventions (3.7% vs. 4.6%). Reported complication rates from registry data were generally comparable to those rates reported in the above trials for 30-day operative mortality and reinterventions.	Consistent for procedures, 30-day operative mortality, reinterventions, major morbidity; precise for procedures, 30-day mortality, reinterventions	Individual post-operative complications and major morbidities variably reported	Moderate	Registry data from both national and international sources; contemporary.
	Pharmaco-therapy vs. placebo	K=8 (3 new); N=1,598	With the exception of the two propranolol trials reporting high adverse events related discontinuation rates (38% and 60% of the propranolol arms withdrew from the trials); other medications (including other antihypertensive medications [ACE-inhibitors, Ca-channel blocker] and antibiotics) appear to be well-tolerated based on few trial withdrawals reported from 1 to 2 studies per drug class.	Propranolol-consistent, imprecise; Doxycycline-consistent, imprecise; Other drugs-NA for consistency as 1 trial for each drug; imprecise	1 to 2 trials per drug class with limited harms reporting	Low	Predominantly male population with small AAAs. All trials conducted outside of the US.

Table 14. Summary of Evidence

Key Question	Sub-population	Studies (k), Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ5a: Do the harms of treatment of small AAAs vary among subpopulations (i.e., by age, sex, smoking status, family history, or race/ethnicity)?	Sex	K=3 registries (2 new); N= 14,424	There is scant data on harms in subpopulations. No trial data is available to examine harms in subpopulations. Existing evidence shows higher 30-day operative mortality and secondary complications in women compared to men for both EVAR and open repair. No information available for other subpopulations.	Consistent; imprecise	Few registries & nontrial data, few outcomes (mostly 30-day operative mortality).	Moderate	Registry data from both national and international sources; contemporary.

Abbreviations: AAA = abdominal aortic aneurysm; AARDVARK = Aortic Aneurysmal Regression of Dilation: Value of ACE-Inhibition on RisK trial; ADAM = Abdominal aortic aneurysm Detection and Management study; CI = confidence interval; HR = hazard ratio; IQR = interquartile range; mm = millimeter(s); AORTA = the Anti-inflammatory Oral Treatment of AAA; CG = control group; CVD = cardiovascular disease; EVAR = endovascular aneurysm repair; IG = intervention group; K = number of trials; MI = myocardial infarction; N = population size; n = sample size; NA = not applicable; NR = not reported; PAT = propranolol Aneurysm Trial; PVD = peripheral vascular disease; SAE = serious adverse events; vs = versus

Appendix A. Detailed Methods

Literature Search Strategies for Primary Literature

Sources searched:
Cochrane Central Register of Controlled Clinical Trials, via Wiley
Cochrane Database of Systematic Reviews, via Wiley
Database of Abstracts of Reviews of Effects, via Wiley
Medline, via Ovid
PubMed, publisher-supplied

Key:
* = truncation
$ = truncation
ab = word in abstract
kf = keyword heading [word not phrase indexed]
kw = keyword
pt = publication type
ti = word in title

MEDLINE: Screening

Database: Ovid MEDLINE(R) <1946 to September Week 1 2018>, Ovid MEDLINE(R) Daily Update <September 14, 2018>

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1 Aortic Aneurysm, Abdominal/ (17370)
2 abdominal aortic aneurysm$.ti,ab. (15021)
3 1 or 2 (20880)
4 Mass screening/ (95905)
5 (screen$ or rescreen$ or re screen$).ti,ab. (555648)
6 4 or 5 (583442)
7 3 and 6 (1298)
8 limit 7 to (english language and yr="2013 -Current") (293)

MEDLINE: Clinical trials

Database: Ovid MEDLINE(R) <1946 to September Week 1 2018>, Ovid MEDLINE(R) Daily Update <September 14, 2018>

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1 Aortic Aneurysm, Abdominal/ (17370)
2 abdominal aortic aneurysm$.ti,ab. (15021)
3 1 or 2 (20880)
4 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/ (318970)
5 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. (896853)
6 random$.ti,ab. (853765)
7 control groups/ or double-blind method/ or single-blind method/ (178983)
8 clinical trial$.ti,ab. (271317)
9 controlled trial$.ti,ab. (160123)
10 (metaanaly$ or meta analy$).ti,ab. (100793)
11 or/4-10 (1645301)
12 3 and 11 (2052)
13 limit 12 to (english language and yr="2013 -Current") (518)
14 remove duplicates from 13 (467)

Appendix A. Detailed Methods

MEDLINE: Treatment cohort studies

Database: Ovid MEDLINE(R) <1946 to September Week 1 2018>, Ovid MEDLINE(R) Daily Update <September 14, 2018>

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1 Aortic Aneurysm, Abdominal/co, dt, mo, pc, px, rh, su, th [Complications, Drug Therapy, Mortality, Prevention & Control, Psychology, Rehabilitation, Surgery, Therapy] (13967)
2 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ (1761323)
3 Registries/ (73991)
4 cohort$.ti,ab. (385596)
5 2 or 3 or 4 (1940167)
6 1 and 5 (4757)
7 limit 6 to (english language and yr="2013 -Current") (1114)
8 remove duplicates from 7 (1020)

MEDLINE: All key questions [in-process/non-indexed records]

Database: Ovid MEDLINE(R) Epub Ahead of Print <September 14, 2018>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 14, 2018>

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1 abdominal aortic aneurysm$.ti,ab,kf. (1526)
2 limit 1 to (english language and yr="2013 -Current") (1169)
3 remove duplicates from 2 (1168)

Cochrane (Wiley)

Cochrane Database of Systematic Reviews : Issue 9 of 12, September 2017
Database of Abstracts of Reviews of Effects : Issue 2 of 4, April 2015
Cochrane Central Register of Controlled Trials : Issue 8 of 12, August 2017

#1 "abdominal aortic aneurysm":ti,ab,kw
#2 "abdominal aortic aneurysm*":ti,ab,kw
#3 #1 or #2 Publication Year from 2013 to 2017, in Cochrane Reviews (Reviews and Protocols)
#4 #1 or #2 Publication Year from 2013 to 2017, in Other Reviews
#5 #1 or #2 Publication Year from 2013 to 2017 , in Trials

PubMed, publisher-supplied

Search	Query
#5	#4 AND ("2013/01/01"[Date - Publication] : "3000"[Date - Publication]) AND English[Language]
#4	#3 AND publisher[sb]
#3	#1 AND #2
#2	screen*[tiab] OR rescreen*[tiab] OR re screen*[tiab]OR trial[tiab] OR trials[tiab] OR random*[tiab] OR cohort*[tiab] OR longitudinal*[tiab] OR "follow up"[tiab] OR "followed up"[tiab] OR followup*[tiab] OR prospective*[tiab] OR retrospective*[tiab] OR meta analy*[tiab] OR metaanaly*[tiab] OR registry[tiab] OR registries[tiab] OR register[tiab] OR registers[tiab]
#1	abdominal aortic aneurysm*[tiab]

Appendix A. Detailed Methods

Existing Systematic Reviews Search

Sources searched (2014-present)	Number of items retrieved
Agency for Healthcare Research and Quality	0
Canadian Agency for Drugs and Technologies in Health	0
Cochrane Database of Systematic Reviews	13 (file attached)
Database of Abstracts of Reviews of Effects	16 (file attached)
Dynamed	1 (links below)
Health Technology Assessment (Centre for Reviews and Dissemination)	8 (file attached)
Institute of Medicine	0
NHS Health Technology Assessment Programme	6 (links below)
National Institute for Health and Clinical Excellence	2 (links below)
PubMed	187 (file attached)

Cochrane (Wiley)

Cochrane Database of Systematic Reviews : Issue 2 of 12, February 2017
Database of Abstracts of Reviews of Effects : Issue 2 of 4, April 2015
Health Technology Assessment Database : Issue 4 of 4, October 2016

#1	"abdominal aortic aneurysm":ti,ab,kw	642
#2	"abdominal aortic aneurysms":ti,ab,kw	306
#3	#1 or #2 Publication Year from 2014 to 2017, in Cochrane Reviews (Reviews and Protocols)	13
#4	#1 or #2 Publication Year from 2014 to 2017, in Other Reviews	16
#5	#1 or #2 Publication Year from 2014 to 2017, in Technology Assessments	8

Dynamed

Abdominal aortic aneurysm (last updated 12/19/2016)
http://search.ebscohost.com/login.aspx?direct=true&db=dme&AN=114361&site=dynamed-live&scope=site

NHS HTA Programme

HTA - 09/91/39: The development of an algorithm to calculate in individual patients with abdominal aortic aneurysm (AAA) when repair is indicated to improve survival , May 2015
https://www.journalslibrary.nihr.ac.uk/programmes/hta/099139/#/

Calculating when elective abdominal aortic aneurysm repair improves survival for individual patients: development of the Aneurysm Repair Decision Aid and economic evaluation, May 2015
https://www.journalslibrary.nihr.ac.uk/hta/hta19320/ - DUPLICATE

Screening women for abdominal aortic aneurysm, in progress
https://www.journalslibrary.nihr.ac.uk/programmes/hta/1417901/

Endovascular treatment for ruptured abdominal aortic aneurysm, in progress
https://www.journalslibrary.nihr.ac.uk/programmes/sr/167205/

Magnetic Resonance Imaging Using Ultrasmall Superparamagnetic Particles of Iron Oxide to Predict Clinical Outcome in Patients Under Surveillance for Abdominal Aortic Aneurysms, in progress

https://www.journalslibrary.nihr.ac.uk/programmes/eme/112003/

Surveillance following endovascular aortic aneurysm repair, in progress
https://www.journalslibrary.nihr.ac.uk/programmes/hta/157801/

NICE

Endovascular aneurysm sealing for abdominal aortic aneurysm (IPG547), February 2016
https://www.nice.org.uk/guidance/ipg547

Abdominal aortic aneurysm: diagnosis and management, in development
https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0769

PubMed

Search	Query	Items found
#5	Search ((#4) AND English[Language]) AND ("2014/01/01"[Date - Publication] : "3000"[Date - Publication])	187
#4	Search #3 AND systematic[sb]	618
#3	Search #1 OR #2	18887
#2	Search abdominal aortic aneurysm*[tiab] AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])	1424
#1	Search "Aortic Aneurysm, Abdominal"[Mesh] OR abdominal aortic aneurysm*[title]	18334

Appendix A Table 1. Inclusion and Exclusion Criteria

Category	Included	Excluded
Populations	**KQs 1–3:** Asymptomatic adult population **KQs 4, 5:** Asymptomatic adult population with small AAAs (i.e., aortic diameter of 3.0 to 5.4 cm)	**KQs 1–3:** Patients experiencing symptoms related to AAA **KQs 4, 5:** Patients experiencing symptoms related to AAA; populations with AAAs with an aortic diameter larger than 5.4 cm or smaller than 3.0 cm
Setting	Studies conducted in primary care or other settings with a comparable population to primary care (e.g., general unselected population for screening [KQs 1, 3])	
Disease/ condition	AAA (aortic diameter ≥3.0 cm)	
Interventions	**KQs 1–3:** Screening with ultrasound **KQs 4, 5:** Treatment with pharmacotherapy (e.g., statins, angiotensin converting enzyme inhibitors, antibiotics) or surgical intervention	**KQs 1–3:** Screening with physical examination, computed tomography, or magnetic resonance imaging
Comparisons	**KQs 1, 3:** One-time screening vs. no screening **KQs 2, 3:** Repeat screening vs. no rescreening **KQ 4:** Pharmacotherapy vs. placebo, surgery vs surveillance alone	**KQ 2:** Comparison of surveillance interval **KQs 4, 5:** Comparative effectiveness of treatments
Outcomes	**KQs 1, 2:** All-cause mortality, aneurysm-related mortality, cardiovascular disease mortality, aneurysm rupture rate, cardiovascular disease events, and quality of life **KQ 3:** Anxiety and downstream procedures related to false-positive results **KQ 4:** AAA annual growth rate, all-cause mortality, aneurysm-related mortality, cardiovascular disease mortality, aneurysm rupture rate, cardiovascular disease events, and quality of life **KQ 5:** Harms (i.e., serious adverse events from pharmacotherapy or surgery)	
Study Designs	**KQs 1, 4:** Randomized, controlled trials **KQs 2, 3:** Randomized, controlled trials; large cohort studies (sample size >1,000) **KQ 5:** Randomized, controlled trials; large cohort studies (sample size >1,000); vascular surgery registries	**KQs 1, 4:** Case-control, cross-sectional, and cohort studies; editorials, letters, and opinions; cost studies **KQs 2, 3:** Case-control and cross-sectional studies; editorials, letters, and opinions; cost studies
Countries	Studies conducted in countries categorized as “Very High” on the 2016 Human Development Index (as defined by the United Nations Development Programme)	Studies conducted in countries that are not categorized as “Very High” on the 2016 Human Development Index
Language	English only	Languages other than English
Quality	Fair- and good-quality studies	Poor-quality studies

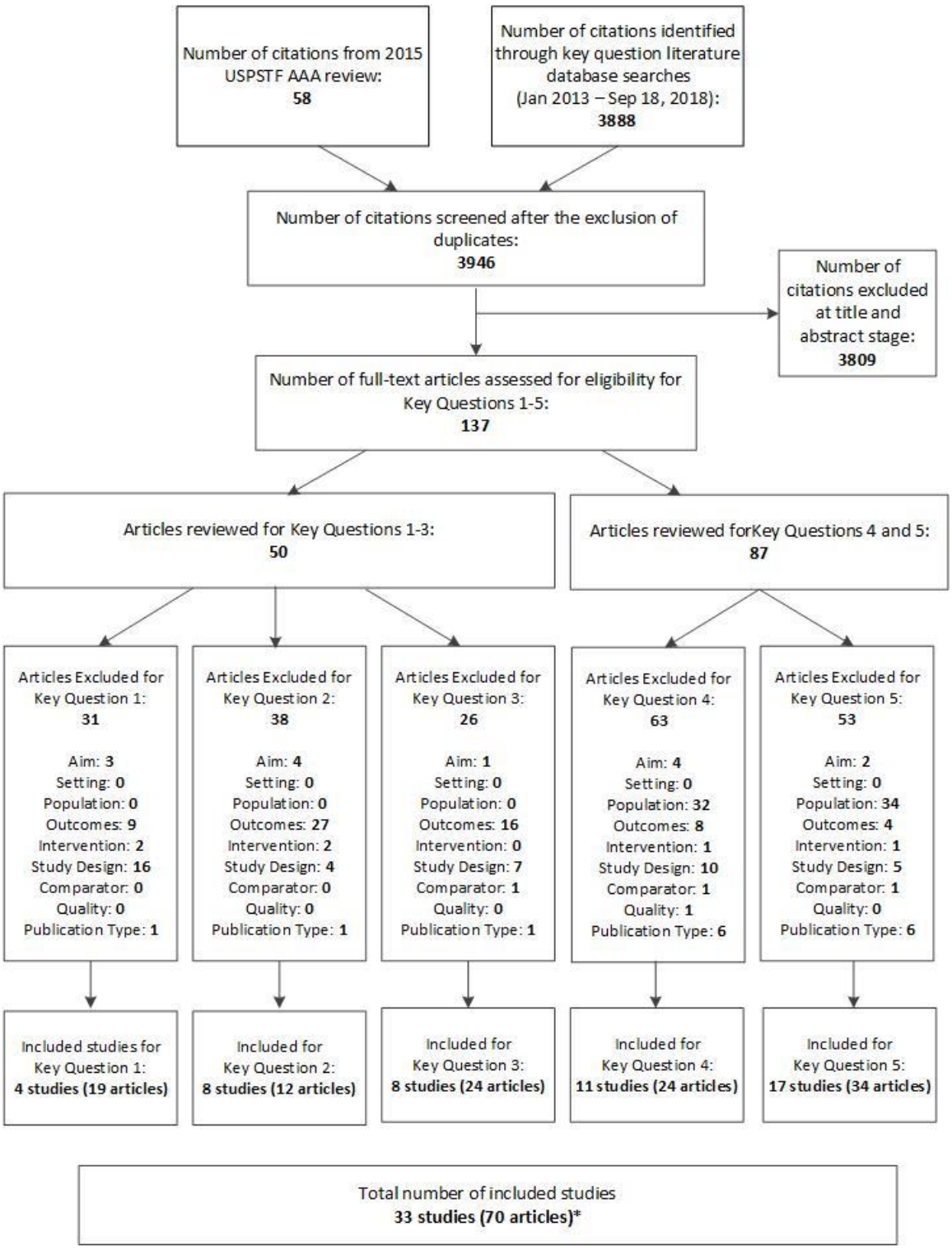
Abbreviations: KQ = Key Question; USPSTF = U.S. Preventive Services Task Force

Appendix A Table 2. Quality Assessment Criteria*

Study Design	Adapted Quality Criteria
Randomized and non-randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods[107]	**Bias arising in the randomization process or due to confounding** • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics **Bias in selecting participants into the study** • CCT only: No evidence of biased selection of sample **Bias due to departures from intended interventions** • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated **Bias from missing data** • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported
Cohort studies, adapted from the Newcastle-Ottawa Scale[106]	• Was there representativeness of the exposed cohort? • Was the non-exposed systematic selected? • Was the ascertainment of exposure reported? • Were eligibility criteria specified? • Were groups similar at baseline? • Was the reading (interpretation) of the pathology results adequate? • Were outcome assessors blinded? • Were measurements equal, valid and reliable? • Was followup long enough for outcomes to occur? • Were the statistical methods acceptable? • Was the handling of missing data appropriate? • Was there adjustment for confounders? • Was there acceptable followup?

* Good quality studies generally meet all quality criteria. Fair quality studies do not meet all the criteria but do not have critical limitations that could invalidate study findings. Poor quality studies have a single fatal flaw or multiple important limitations that could invalidate study findings. Critical appraisal of studies using *a priori* quality criteria are conducted independently by at least two reviewers. Disagreements in final quality assessment are resolved by consensus, and, if needed, consultation with a third independent reviewer.

Appendix A Figure 1. Literature Flow Diagram



*Studies may appear under more than one Key Question.

Appendix B Table 1. Expert Groups' Recommendations of AAA Screening With Ultrasonography

Organization (Year)	Population	Surveillance interval
American College of Cardiology and American Heart Association (2013)[95]	Men ≥ 60 years with a family history Men 65-75 years who have ever smoked Men & women >50 years should be asked if AAA family history	<4.0 cm: every 2 – 3 years 4.0 – 5.4 cm: every 6 – 12 months
American Academy of Family Physicians (NR)[97]	Refers to USPSTF Recommendation Men 65-75 years who have ever smoked Selectively screen men 65-75 years who have never smoked Recommends against routine screening for women who have never smoked	Not stated
American College of Preventive Medicine (2011)[96]	Men 65-75 years who have ever smoked Recommends against routine screening in women	Not stated
Society for Vascular Surgery (2018)[3]	All men and women aged 65-75 years with history of tobacco use Men ≥ 55 years with family history Women ≥ 65 years if family history/smoker	2.5 - 3.0 cm: after 10 years 3.0 - 3.9 cm: every 3 years 4.0 - 4.9 cm: every 12 months 5.0 - 5.4 cm: every 6 months
Canadian Task Force on Preventive Health Care (2017)[175]	Men aged 65-80 years Recommends not screening men aged >80 or women at any age.	Not stated
Public Health England (2015)[246]	Men 65-74 years	3.0 - 4.4 cm: every 12 months 4.5 - 5.4 cm: every 3 months
National Institute for Health and Care Excellence (NICE) DRAFT Guideline (2018)[186]	All men aged ≥ 66 years eligible to self-refer to screening Encourage men ≥ 66 years with risk factors* to be screened Consider screening women aged ≥70 years with risk factors* Risk factors: COPD, family history, history of tobacco use, hyperlipdemia, hypertension, European origin	3.0 - 4.4 cm: every 2 years 4.5 – 5.4 cm: every 3 months

Abbreviations: cm = centimeter(s); COPD = chronic obstructive pulmonary disease

Below is a list of included studies and their ancillary publications (indented below main results publication):

Key Questions 1 & 3

Chichester

Ashton HA, Gao L, Kim LG, et al. Fifteen-year follow-up of a randomized clinical trial of ultrasonographic screening for abdominal aortic aneurysms. The British journal of surgery. 2007;94(6):696-701. PMID: 17514666. https://doi.org/10.1002/bjs.5780.

Scott RA, Wilson NM, Ashton HA, et al. Influence of screening on the incidence of ruptured abdominal aortic aneurysm: 5-year results of a randomized controlled study. The British journal of surgery. 1995;82(8):1066-70. PMID: 7648155.

Scott RA, Bridgewater SG, Ashton HA. Randomized clinical trial of screening for abdominal aortic aneurysm in women. The British journal of surgery. 2002;89(3):283-5. PMID: 11872050. https://doi.org/10.1046/j.0007-1323.2001.02014.x.

Vardulaki KA, Walker NM, Couto E, et al. Late results concerning feasibility and compliance from a randomized trial of ultrasonographic screening for abdominal aortic aneurysm. The British journal of surgery. 2002;89(7):861-4. PMID: 12081734. https://doi.org/10.1046/j.1365-2168.2002.02133.x.

Multicentre Aneurysm Screening Study (MASS)

Thompson SG, Ashton HA, Gao L, et al. Final follow-up of the Multicentre Aneurysm Screening Study (MASS) randomized trial of abdominal aortic aneurysm screening. The British journal of surgery. 2012;99(12):1649-56. PMID: 23034729. https://doi.org/10.1002/bjs.8897.

Ashton HA, Buxton MJ, Day NE, et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. Lancet. 2002;360(9345):1531-9. PMID: 12443589.

Kim LG, Ra PS, Ashton HA, et al. A sustained mortality benefit from screening for abdominal aortic aneurysm. Annals of internal medicine. 2007;146(10):699-706. PMID: 17502630.

Kim LG, Scott RAP, Ashton HA, et al. A prolonged mortality benefit from screening for abdominal aortic aneurysm: seven-year follow-up of the MASS trial. SO: The Vascular Society of Great Britain & Ireland Yearbook 2006. 2006:77.

Thompson SG, Ashton HA, Gao L, et al. Screening men for abdominal aortic aneurysm: 10 year mortality and cost effectiveness results from the randomised Multicentre Aneurysm Screening Study. BMJ. 2009;338:b2307. PMID: 19553269.

Viborg

Lindholt JS, Sorensen J, Sogaard R, et al. Long-term benefit and cost-effectiveness analysis of screening for abdominal aortic aneurysms from a randomized controlled trial. The British journal of surgery. 2010;97(6):826-34. PMID: 20473995. https://doi.org/10.1002/bjs.7001.

Lindholt JS, Juul S, Fasting H, et al. Hospital costs and benefits of screening for abdominal aortic aneurysms. Results from a randomised population screening trial. Eur J Vasc Endovasc Surg. 2002;23(1):55-60. PMID: 11748949. https://doi.org/10.1053/ejvs.2001.1534.

Lindholt JS, Juul S, Fasting H, et al. Screening for abdominal aortic aneurysms: single centre randomised controlled trial. BMJ. 2005;330(7494):750. PMID: 15757960. 10.1136/bmj.38369.620162.82

Lindholt JS, Juul S, Henneberg EW. High-risk and low-risk screening for abdominal aortic aneurysm both reduce aneurysm-related mortality. A stratified analysis from a single-centre randomised screening trial. Eur J Vasc Endovasc Surg. 2007;34(1):53-8. PMID: 17331750. https://doi.org/10.1016/j.ejvs.2006.12.031.

Lindholt JS, Juul S, Fasting H, et al. Preliminary ten year results from a randomised single centre mass screening trial for abdominal aortic aneurysm. Eur J Vasc Endovasc Surg. 2006;32(6):608-14. PMID: 16893663. https://doi.org/10.1016/j.ejvs.2006.06.008.

Western Australia

McCaul KA, Lawrence-Brown M, Dickinson JA, et al. Long-term Outcomes of the Western Australian Trial of Screening for Abdominal Aortic Aneurysms: Secondary Analysis of a Randomized Clinical Trial. JAMA Intern Med. 2016;176(12):1761-7. PMID: 27802493. https://doi.org/10.1001/jamainternmed.2016.6633.

Jamrozik K, Norman PE, Spencer CA, et al. Screening for abdominal aortic aneurysm: lessons from a population-based study. Med J Aust. 2000;173(7):345-50. PMID: 11062788.

Norman PE, Jamrozik K, Lawrence-Brown MM, et al. Western Australian randomized controlled trial of screening for abdominal aortic aneurysm. The British journal of surgery. 2003;90(4):492.

Norman PE, Jamrozik K, Lawrence-Brown MM, et al. Population based randomised controlled trial on impact of screening on mortality from abdominal aortic aneurysm. BMJ. 2004;329(7477):1259. PMID: 15545293. https://doi.org/10.1136/bmj.38272.478438.55.

Spencer CA, Norman PE, Jamrozik K, et al. Is screening for abdominal aortic aneurysm bad for your health and well-being? ANZ J Surg. 2004;74(12):1069-75. PMID: 15574151. https://doi.org/10.1111/j.1445-1433.2004.03270.x.

Key Question 2

d'Audiffret A, Santilli S, Tretinyak A, et al. Fate of the ectatic infrarenal aorta: expansion rates and outcomes. Annals of vascular surgery. 2002;16(5):534-6.

Devaraj S, Dodds SR. Ultrasound surveillance of ectatic abdominal aortas. Ann R Coll Surg Engl. 2008;90(6):477-82. PMID: 18765027. https://doi.org/10.1308/003588408X301064.

Lederle FA, Johnson GR, Wilson SE, et al. Yield of repeated screening for abdominal aortic aneurysm after a 4-year interval. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. Arch Intern Med. 2000;160(8):1117-21. PMID: 10789604.

Oliver-Williams C, Sweeting MJ, Turton G, et al. Lessons learned about prevalence and growth rates of abdominal aortic aneurysms from a 25-year ultrasound population screening programme. Br J Surg. 2018;105(1):68-74. PMID: 29265406. https://doi.org/10.1002/bjs.10715.

Crow P, Shaw E, Earnshaw JJ, et al. A single normal ultrasonographic scan at age 65 years rules out significant aneurysm disease for life in men. The British journal of surgery. 2001;88(7):941-4. PMID: 11442524. https://doi.org/10.1046/j.0007-1323.2001.01822.x.

Darwood R, Earnshaw JJ, Turton G, et al. Twenty-year review of abdominal aortic aneurysm screening in men in the county of Gloucestershire, United Kingdom. Journal of vascular surgery. 2012;56(1):8-13. PMID: 22503187. https://doi.org/10.1016/j.jvs.2011.12.069.

Emerton ME, Shaw E, Poskitt K, et al. Screening for abdominal aortic aneurysm: a single scan is enough. The British journal of surgery. 1994;81(8):1112-3. PMID: 7953333.

McCarthy RJ, Shaw E, Whyman MR, et al. Recommendations for screening intervals for small aortic aneurysms. The British journal of surgery. 2003;90(7):821-6. PMID: 12854107. https://doi.org/10.1002/bjs.4216.

Chichester
Scott RA, Vardulaki KA, Walker NM, et al. The long-term benefits of a single scan for abdominal aortic aneurysm (AAA) at age 65. Eur J Vasc Endovasc Surg. 2001;21(6):535-40. PMID: 11397028. https://doi.org/10.1053/ejvs.2001.1368.

Soderberg P, Wanhainen A, Svensjo S. Five Year Natural History of Screening Detected Sub-Aneurysms and Abdominal Aortic Aneurysms in 70 Year Old Women and Systematic Review of Repair Rate in Women. Eur J Vasc Endovasc Surg. 2017;53(6):802-9. PMID: 28389251. https://dx.doi.org/10.1016/j.ejvs.2017.02.024.

Svensjo S, Bjorck M, Wanhainen A. Editor's choice: five-year outcomes in men screened for abdominal aortic aneurysm at 65 years of age: a population-based cohort study. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2014;47(1):37-44. PMID: 24262320. https://dx.doi.org/10.1016/j.ejvs.2013.10.007.

Additional studies for Key Question 3 (only included for screening harms)

Lesjak M, Boreland F, Lyle D, et al. Screening for abdominal aortic aneurysm: does it affect men's quality of life? Aust J Prim Health. 2012. PMID: 22951209. https://doi.org/10.1071/PY11131.

Viborg Vascular (VIVA)
Lindholt JS, Sogaard R. Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial. Lancet. 2017. PMID: 28859943. https://dx.doi.org/10.1016/s0140-6736(17)32250-x.

Grondal N, Sogaard R, Lindholt JS. Baseline prevalence of abdominal aortic aneurysm, peripheral arterial disease and hypertension in men aged 65-74 years from a population screening study (VIVA trial). Br J Surg. 2015;102(8):902-6. PMID: 25923784. https://dx.doi.org/10.1002/bjs.9825.

Lucarotti ME, Heather BP, Shaw E, et al. Psychological morbidity associated with abdominal aortic aneurysm screening. Eur J Vasc Endovasc Surg. 1997;14(6):499-501. PMID: 9467527.

Wanhainen A, Rosen C, Rutegard J, et al. Low quality of life prior to screening for abdominal aortic aneurysm: a possible risk factor for negative mental effects. Annals of vascular surgery. 2004;18(3):287-93. PMID: 15354629. https://doi.org/10.1007/s10016-004-0021-x.

Key Questions 4 & 5

Open vs Surveillance

ADAM

Lederle FA, Wilson SE, Johnson GR, et al. Immediate repair compared with surveillance of small abdominal aortic aneurysms. N Engl J Med. 2002;346(19):1437-44. PMID: 12000813. https://doi.org/10.1056/NEJMoa012573.

Lederle FA, Wilson SE, Johnson GR, et al. Design of the abdominal aortic Aneurysm Detection and Management Study. ADAM VA Cooperative Study Group. Journal of vascular surgery. 1994;20(2):296-303. PMID: 8040955.

Filardo G, Lederle FA, Ballard DJ, et al. Immediate open repair vs surveillance in patients with small abdominal aortic aneurysms: survival differences by aneurysm size. Mayo Clin Proc. 2013;88(9):910-9. PMID: 24001483. https://dx.doi.org/10.1016/j.mayocp.2013.05.014.

UKSAT

Powell JT, Brown LC, Forbes JF, et al. Final 12-year follow-up of surgery versus surveillance in the UK Small Aneurysm Trial. Br J Surg. 2007;94(6):702-8. PMID: 17514693. https://doi.org/10.1002/bjs.5778.

Brown LC, Powell JT. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. UK Small Aneurysm Trial Participants. Ann Surg. 1999;230(3):289-96; discussion 96-7. PMID: 10493476.

Brown LC, Thompson SG, Greenhalgh RM, et al. Fit patients with small abdominal aortic aneurysms (AAAs) do not benefit from early intervention. J Vasc Surg. 2008;48(6):1375-81. PMID: 19118733. https://doi.org/10.1016/j.jvs.2008.07.014

Fowkes FG, Greenhalgh RM, Powell JT, et al. Length of hospital stay following elective abdominal aortic aneurysm repair. U.K. Small Aneurysm Trial Participants. Eur J Vasc Endovasc Surg. 1998;16(3):185-91. PMID: 9787298.

Greenhalgh RM, Forbes JF, Fowkes FG, et al. The UK Small Aneurysm Trial: design, methods and progress. Eur J Vasc Endovasc Surg. 1995;9(1):42-8. PMID: 7664011.

Powell JT. Long-term outcomes of immediate repair compared with surveillance of small abdominal aortic aneurysms. N Engl J Med. 2002;346(19):1445-52. PMID: 12000814. https://doi.org/10.1056/NEJMoa013527.

Powell JT, Brady AR, Brown LC, et al. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. The UK Small Aneurysm Trial Participants. Lancet. 1998;352(9141):1649-55. PMID: 9853436.

Filardo G, Lederle FA, Ballard DJ, et al. Immediate open repair vs surveillance in patients with small abdominal aortic aneurysms: survival differences by aneurysm size. Mayo Clin Proc. 2013;88(9):910-9. PMID: 24001483. https://dx.doi.org/10.1016/j.mayocp.2013.05.014.

Appendix C. Included Studies

EVAR vs Surveillance

CAESAR

Cao P, De RP, Verzini F, et al. Comparison of surveillance versus aortic endografting for small aneurysm repair (CAESAR): results from a randomised trial. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2011;41(1):13-25. PMID: 20869890. https://doi.org/10.1016/j.ejvs.2010.08.026

Cao P. Comparison of surveillance vs aortic endografting for small aneurysm repair (CAESAR) trial: study design and progress. Eur J Vasc Endovasc Surg. 2005;30(3):245-51. PMID: 16130206.

PIVOTAL

Ouriel K, Clair DG, Kent KC, et al. Endovascular repair compared with surveillance for patients with small abdominal aortic aneurysms. Journal of vascular surgery. 2010;51(5):1081-7. PMID: 20304589. https://doi.org/10.1016/j.jvs.2009.10.113

Ouriel K. The PIVOTAL study: A randomized comparison of endovascular repair versus surveillance in patients with smaller abdominal aortic aneurysms. Journal of vascular surgery. 2009;49(1):266-9. PMID: 19174266. https://doi.org/10.1016/j.jvs.2008.11.048.

Pharmacotherapy vs Placebo

Bicknell CD, Kiru G, Falaschetti E, et al. An evaluation of the effect of an angiotensin-converting enzyme inhibitor on the growth rate of small abdominal aortic aneurysms: a randomized placebo-controlled trial (AARDVARK). European heart journal. 2016;37(42):3213-21. PMID: 27371719. https://doi.org/10.1093/eurheartj/ehw257.

Kiru G, Bicknell C, Falaschetti E, et al. 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 (Winchester, England). 2016;20(59):1-180. PMID: 27488944. https://dx.doi.org/10.3310/hta20590.

Karlsson L, Gnarpe J, Bergqvist D, et al. The effect of azithromycin and Chlamydophilia pneumonia infection on expansion of small abdominal aortic aneurysms--a prospective randomized double-blind trial. Journal of vascular surgery. 2009;50(1):23-9. PMID: 19563951. https://doi.org/10.1016/j.jvs.2008.12.048.

Hogh A, Vammen S, Ostergaard L, et al. Intermittent roxithromycin for preventing progression of small abdominal aortic aneurysms: long-term results of a small clinical trial. Vasc Endovascular Surg. 2009;43(5):452-6. PMID: 19640922. https://doi.org/10.1177/1538574409335037.

Vammen S, Lindholt JS, Ostergaard L, et al. Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion. The British journal of surgery. 2001;88(8):1066-72. PMID: 11488791. https://doi.org/10.1046/j.0007-1323.2001.01845.x.

Hogh A, Vammen S, Joensen J, et al., editors. Intermittent Roxithromycin Treatment for Preventing Small Abdominal Aortic Aneurysms Progression. Long Term Results from a Small Randomised Double-blinded Clinical Controlled Trial2008 2008. PMID: None.

Meijer C, Stijnen T, Wasser M, et al. Doxycycline for stabilization of abdominal aortic aneurysms: A randomized trial. Annals of internal medicine. 2013;159(12):815-23. PMID: 24490266. https://doi.org/10.7326/0003-4819-159-12-201312170-00007.

Mosorin M, Juvonen J, Biancari F, et al. Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study. Journal of vascular surgery. 2001;34(4):606-10. PMID: 11668312. https://doi.org/10.1067/mva.2001.117891.

Propranolol Aneurysm Trial Investigators. Propranolol for small abdominal aortic aneurysms: results of a randomized trial. Journal of vascular surgery. 2002;35(1):72-9. PMID: 11802135.

Sillesen H, Eldrup N, Hultgren R, et al. Randomized clinical trial of mast cell inhibition in patients with a medium-sized abdominal aortic aneurysm. The British journal of surgery. 2015;102(8):894-901. PMID: 25963302. https://doi.org/10.1002/bjs.9824

Additional studies for Key Question 5 (only included for treatment harms)

Open vs Surveillance

ADAM

Lederle FA, Johnson GR, Wilson SE, et al. Quality of life, impotence, and activity level in a randomized trial of immediate repair versus surveillance of small abdominal aortic aneurysm. Journal of vascular surgery. 2003;38(4):745-52. PMID: 14560224.

UKSAT

Forbes JF, Brady AR, Brown LC, et al. Health service costs and quality of life for early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. UK Small Aneurysm Trial Participants. Lancet. 1998;352(9141):1656-60. PMID: 9853437.

EVAR vs Surveillance

CAESAR

De Rango P, Verzini F, Parlani G, et al. Quality of life in patients with small abdominal aortic aneurysm: the effect of early endovascular repair versus surveillance in the CAESAR trial. Eur J Vasc Endovasc Surg. 2011;41(3):324-31. PMID: 21145269. https://doi.org/10.1016/j.ejvs.2010.11.005.

PIVOTAL

Eisenstein EL, Davidson-Ray L, Edwards R, et al. Economic analysis of endovascular repair versus surveillance for patients with small abdominal aortic aneurysms. Journal of vascular surgery. 2013;58(2):302-10. PMID: 23562339. https://dx.doi.org/10.1016/j.jvs.2013.01.038.

Pharmacotherapy vs Placebo

Lindholt JS, Henneberg EW, Juul S, et al. Impaired results of a randomised double blinded clinical trial of propranolol versus placebo on the expansion rate of small abdominal aortic aneurysms. International angiology : a journal of the International Union of Angiology. 1999;18(1):52-7. PMID: 10392481.

Surgical Registries

VASCUNET

Budtz-Lilly J, Venermo M, Debus S, et al. Editor's Choice - Assessment of International Outcomes of Intact Abdominal Aortic Aneurysm Repair over 9 Years. Eur J Vasc Endovasc Surg. 2017;54(1):13-20. PMID: 28416191. https://dx.doi.org/10.1016/j.ejvs.2017.03.003

ASERNIP-S

Golledge J, Parr A, Boult M, et al. The outcome of endovascular repair of small abdominal aortic aneurysms. Ann Surg. 2007;245(2):326-33. PMID: 17245188. https://doi.org/10.1097/01.sla.0000253965.95368.52.

Appendix C. Included Studies

VSGNE
Lo RC, Bensley RP, Hamdan AD, et al. Gender differences in abdominal aortic aneurysm presentation, repair, and mortality in the Vascular Study Group of New England. Journal of vascular surgery. 2013;57(5):1261-8, 8.e1-5. PMID: 23384493. https://dx.doi.org/10.1016/j.jvs.2012.11.039

ACS NSQIP
Overbey DM, Glebova NO, Chapman BC, et al. Morbidity of endovascular abdominal aortic aneurysm repair is directly related to diameter. Journal of vascular surgery. 2017;66(4):1037-47. PMID: 28433338. https://dx.doi.org/10.1016/j.jvs.2017.01.058

EUROSTAR
Peppelenbosch N, Buth J, Harris PL, et al. Diameter of abdominal aortic aneurysm and outcome of endovascular aneurysm repair: does size matter? A report from EUROSTAR. Journal of vascular surgery. 2004;39(2):288-97. PMID: 14743127. https://doi.org/10.1016/j.jvs.2003.09.047.

Appendix D. Excluded Studies

Reason for Exclusion*
E1. Study Aim
E2. Setting **E2a.** Non-HDI country **E2b.** Screening and/or intervention is not conducted in, recruited from, or feasible for primary care
E3. Population **E3a.** Patients experience symptoms of AAA **E3b.** Patients with AAAs with an aortic diameter larger than 5.4 cm or smaller than 3.0 cm **E3c.** Patients with known or established CVD
E4. Outcome: No relevant outcomes
E5. Intervention **E5a.** Screening with physical examination, CT, or MRI **E5b.** Non-relevant treatment for small AAA
E6. Comparator: Not an included comparator (e.g., comparison of surveillance interval [KQ2], active intervention [KQ4,5])
E7. Study design: Not an included study design, which includes: KQ1,4= Case-control, cross-sectional, and cohort studies; editorials, letters, and opinions; cost studies; KQ2,3= Case-control and cross-sectional studies; editorials, letters, and opinions; cost studies
E8. Study Quality: Poor
E9. Publication type: Abstract-only, Non-English publication

*Assigned at full-text phase

1. Anonymous. Population-Based Study of Incidence of Acute Abdominal Aortic Aneurysms With Projected Impact of Screening Strategy.[Erratum for J Am Heart Assoc. 2015 Aug;4(8):e001926; PMID: 26289347]. J Am Heart Assoc. 2015;4(10):e001992. PMID: 26486168. https://dx.doi.org/10.1161/JAHA.115.001992 **KQ1E9, KQ2E9, KQ3E9,**
2. Bath MF, Sidloff D, Saratzis A, et al. Impact of abdominal aortic aneurysm screening on quality of life. British Journal of Surgery. 2018;105(3):203-8. PMID: 29405273. https://dx.doi.org/10.1002/bjs.10721 **KQ1E1, KQ2E1, KQ3E7.**
3. Baxter BT, Matsumura J, Curci J, et al. Non-invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial (N-TA(3)CT): Design of a Phase IIb, placebo-controlled, double-blind, randomized clinical trial of doxycycline for the reduction of growth of small abdominal aortic aneurysm. Contemporary clinical trials. 2016;48:91-8. PMID: 27018941. 10.1016/j.cct.2016.03.008 **KQ4E4, KQ5E4.**
4. Bergqvist D, Lindeman JH, Lindholt JS, et al. Antimicrobial treatment to impair expansion of abdominal aortic aneurysm (AAA): a systematic review of the clinical evidence. Current vascular pharmacology. 2013;11(3):288-92. PMID: 22724481. **KQ4E7, KQ5E7.**
5. Candell L, Tucker LY, Goodney P, et al. Early and delayed rupture after endovascular abdominal aortic aneurysm repair in a 10-year multicenter registry. Journal of vascular surgery. 2014;60(5):1146-52. PMID: 24957409. https://dx.doi.org/10.1016/j.jvs.2014.05.046 **KQ4E3b, KQ5E3b.**
6. Chung C, Tadros R, Torres M, et al. Evolution of gender-related differences in outcomes from two decades of endovascular aneurysm repair. Journal of vascular surgery. 2015;61(4):843-52. PMID: 25595407. https://dx.doi.org/10.1016/j.jvs.2014.11.006 **KQ4E3b, KQ5E3b.**
7. Cotter AR, Vuong K, Mustelin L, et al. Do psychological harms result from being labelled with an unexpected diagnosis of abdominal aortic aneurysm or prostate cancer through screening? A systematic review. BMJ open. 2017;7(12):e017565. PMID: 29237653. https://dx.doi.org/10.1136/bmjopen-2017-017565 **KQ1E1, KQ2E1, KQ3E7.**
8. Dahl M, Sogaard R, Frost L, et al. Effectiveness of Screening Postmenopausal Women for Cardiovascular Diseases: A Population Based, Prospective Parallel Cohort Study. European Journal of Vascular & Endovascular Surgery. 2018;55(5):721-9. PMID: 29625727. https://dx.doi.org/10.1016/j.ejvs.2018.02.034 **KQ1E7, KQ2E1, KQ3E1.**
9. Dalman RL, Xuan H, Wang W, et al. Angiotensin Receptor Blockers in Abdominal Aortic Aneurysm Management: Evidence Supporting the TEDY Trial. Journal of vascular surgery. 2016;64(2):539. PMID: 27763287. https://dx.doi.org/10.1016/j.jvs.2016.05.009 **KQ4E1, KQ5E1.**
10. Davenport DL, Xenos ES. Deep venous thrombosis after repair of nonruptured abdominal aneurysm. Journal of vascular surgery. 2013;57(3):678-83.e1. PMID: 23343666. https://dx.doi.org/10.1016/j.jvs.2012.09.048 **KQ4E3b, KQ5E3b.**
11. de Blic R, Alsac JM, Julia P, et al. Elective treatment of abdominal aortic aneurysm is reasonable in patients >85 years of age. Annals of vascular surgery. 2014;28(1):209-16. PMID: 24084274. https://dx.doi.org/10.1016/j.avsg.2013.01.022 **KQ4E3b, KQ5E3b.**

12. Deery SE, O'Donnell TFX, Bodewes TCF, et al. Early reintervention after open and endovascular abdominal aortic aneurysm repair is associated with high mortality. Journal of vascular surgery. 2018;67(2):433-40.e1. PMID: 28943011. https://dx.doi.org/10.1016/j.jvs.2017.06.104 **KQ4E1, KQ5E3b.**
13. Deery SE, Schermerhorn ML. Open versus endovascular abdominal aortic aneurysm repair in Medicare beneficiaries. Surgery. 2017;162(4):721-31. PMID: 28343694. https://dx.doi.org/10.1016/j.surg.2017.01.022 **KQ4E3b, KQ5E3b.**
14. Deery SE, Soden PA, Zettervall SL, et al. Sex differences in mortality and morbidity following repair of intact abdominal aortic aneurysms. Journal of vascular surgery. 2017;65(4):1006-13. PMID: 27986477. https://dx.doi.org/10.1016/j.jvs.2016.08.100 **KQ4E3b, KQ5E3b.**
15. Dua A, Ali F, Traudt E, et al. Utilization of the National Inpatient Sample for abdominal aortic aneurysm research. Surgery. 2017;162(4):699-706. PMID: 28237647. https://dx.doi.org/10.1016/j.surg.2016.12.036 **KQ4E1, KQ5E1.**
16. Dua A, Kuy S, Lee CJ, et al. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010. Journal of vascular surgery. 2014;59(6):1512-7. PMID: 24560865. https://dx.doi.org/10.1016/j.jvs.2014.01.007 **KQ4E7, KQ5E7.**
17. Dubois L, Novick TV, Harris JR, et al. Outcomes after endovascular abdominal aortic aneurysm repair are equivalent between genders despite anatomic differences in women. Journal of vascular surgery. 2013;57(2):382-9.e1. PMID: 23266281. https://dx.doi.org/10.1016/j.jvs.2012.09.075 **KQ4E3b, KQ5E3b.**
18. Duwayri Y, Goss J, Knechtle W, et al. The Readmission Event after Vascular Surgery: Causes and Costs. Annals of vascular surgery. 2016;36:7-12. PMID: 27321981. https://dx.doi.org/10.1016/j.avsg.2016.02.024 **KQ4E3b, KQ5E3b.**
19. Ericsson A, Holst J, Gottsater A, et al. Psychosocial consequences in men taking part in a national screening program for abdominal aortic aneurysm. J Vasc Nurs. 2017;35(4):211-20. PMID: 29153229. https://dx.doi.org/10.1016/j.jvn.2017.06.001 **KQ1E1, KQ2E1, KQ3E7.**
20. Flink BJ, Long CA, Duwayri Y, et al. Women undergoing aortic surgery are at higher risk for unplanned readmissions compared with men especially when discharged home. Journal of vascular surgery. 2016;63(6):1496-504.e1. PMID: 27106246. https://dx.doi.org/10.1016/j.jvs.2015.12.054 **KQ4E3b, KQ5E3b.**
21. Hafez H, Druce PS, Ashton HA. Abdominal aortic aneurysm development in men following a "normal" aortic ultrasound scan. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2008;36(5):553-8. PMID: 18718773. **KQ1E4, KQ2E4, KQ3E4,**
22. Hicks CW, Obeid T, Arhuidese I, et al. Abdominal aortic aneurysm repair in octogenarians is associated with higher mortality compared with nonoctogenarians. Journal of vascular surgery. 2016;64(4):956-65.e1. PMID: 27364946. https://dx.doi.org/10.1016/j.jvs.2016.03.440 **KQ4E5b, KQ5E5b.**
23. Hinterseher I, Kuffner H, Berth H, et al. Long-term quality of life of abdominal aortic aneurysm patients under surveillance or after operative treatment. Annals of vascular surgery. 2013;27(5):553-61. PMID: 23540664. **KQ4E6, KQ5E6.**
24. Hoel AW, Faerber AE, Moore KO, et al. A pilot study for long-term outcome assessment after aortic aneurysm repair using Vascular Quality Initiative data matched to Medicare claims. Journal of vascular surgery. 2017;66(3):751-9.e1. PMID: 28222989. https://dx.doi.org/10.1016/j.jvs.2016.12.100 **KQ4E3b, KQ5E3b.**
25. Hughes K, Abdulrahman H, Prendergast T, et al. Abdominal aortic aneurysm repair in nonagenarians. Annals of vascular surgery. 2015;29(2):183-8. PMID: 25461753. https://dx.doi.org/10.1016/j.avsg.2014.07.037 **KQ4E3b, KQ5E3b.**
26. Hultgren R. Commentary on "Five Year Natural History of Screening Detected Sub-Aneurysms and Abdominal Aortic Aneurysms in 70 Year Old Women and Systematic Review of Repair Rate in Women". European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2017;53(6):810. PMID: 28420552. https://dx.doi.org/10.1016/j.ejvs.2017.03.013 **KQ1E7, KQ2E7, KQ3E7,**
27. Hye RJ, Inui TS, Anthony FF, et al. A multiregional registry experience using an electronic medical record to optimize data capture for longitudinal outcomes in endovascular abdominal aortic aneurysm repair. Journal of vascular surgery. 2015;61(5):1160-6. PMID: 25725597. https://dx.doi.org/10.1016/j.jvs.2014.12.055 **KQ4E3b, KQ5E3b.**
28. Jacomelli J, Summers L, Stevenson A, et al. Update on the prevention of death from ruptured abdominal aortic aneurysm. Journal of medical screening. 2017;24(3):166-8. PMID: 28756762. https://dx.doi.org/10.1177/0969141316667409 **KQ1E4, KQ2E4, KQ3E4,**
29. Karthikesalingam A, Bahia SS, Patterson BO, et al. The shortfall in long-term survival of patients with repaired thoracic or abdominal aortic

aneurysms: retrospective case-control analysis of hospital episode statistics. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2013;46(5):533-41. PMID: 24091096. https://dx.doi.org/10.1016/j.ejvs.2013.09.008 **KQ4E3b, KQ5E3b.**

30. Khashram M, Thomson IA, Jones GT, et al. Abdominal aortic aneurysm repair in New Zealand: a validation of the Australasian Vascular Audit. ANZ J Surg. 2017;87(5):394-8. PMID: 27492991. https://dx.doi.org/10.1111/ans.13702 **KQ4E3b, KQ5E3b.**
31. Lederle FA. Does Abdominal Aortic Aneurysm Screening Save Lives? JAMA Surgery. 2016;151(8):697-8. PMID: 27119312. https://dx.doi.org/10.1001/jamasurg.2016.0044 **KQ1E7, KQ2E7, KQ3E7,**
32. Lee SY, Peacock MR, Farber A, et al. Perioperative Infections after Open Abdominal Aortic Aneurysm Repair Lead to Increased Risk of Subsequent Complications. Annals of vascular surgery. 2017;4:203-10. PMID: 28483623. https://dx.doi.org/10.1016/j.avsg.2017.04.022 **KQ4E3b, KQ5E3b.**
33. Lijftogt N, Vahl AC, Wilschut ED, et al. Adjusted Hospital Outcomes of Abdominal Aortic Aneurysm Surgery Reported in the Dutch Surgical Aneurysm Audit. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2017;53(4):520-32. PMID: 28256396. https://dx.doi.org/10.1016/j.ejvs.2016.12.037 **KQ4E3b, KQ5E3b.**
34. Lilja F, Mani K, Wanhainen A. Editor's Choice - Trend-break in Abdominal Aortic Aneurysm Repair With Decreasing Surgical Workload. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2017;53(6):811-9. PMID: 28392057. https://dx.doi.org/10.1016/j.ejvs.2017.02.031 **KQ4E3b, KQ5E3b.**
35. Lindholt JS, Vammen S, Fasting H, et al. Psychological consequences of screening for abdominal aortic aneurysm and conservative treatment of small abdominal aortic aneurysms. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2000;20(1):79-83. PMID: 10906303. https://doi.org/10.1053/ejvs.1999.1087 **KQ1E4, KQ2E4, KQ3E6,**
36. Locham S, Lee R, Nejim B, et al. Mortality after endovascular versus open repair of abdominal aortic aneurysm in the elderly. J Surg Res. 2017;215:153-9. PMID: 28688641. https://dx.doi.org/10.1016/j.jss.2017.03.061 **KQ4E3b, KQ5E3b.**
37. Loftus I, Vascular Society of Great B, Ireland. National Vascular Registry Report on surgical outcomes and implications for vascular centres (Br J Surg 2014; 101: 637-642). British Journal of Surgery. 2014;101(6):642. PMID: 24723018. **KQ4E7, KQ5E7.**
38. Makrygiannis G, Labalue P, Erpicum M, et al. Extending Abdominal Aortic Aneurysm Detection to Older Age Groups: Preliminary Results from the Liege Screening Programme. Annals of vascular surgery. 2016;36:55-63. PMID: 27364735. https://dx.doi.org/10.1016/j.avsg.2016.02.034 **KQ1E4, KQ2E4, KQ3E4,**
39. Mani K, Bjorck M, Wanhainen A. Changes in the management of infrarenal abdominal aortic aneurysm disease in Sweden. British Journal of Surgery. 2013;100(5):638-44. PMID: 23334950. https://dx.doi.org/10.1002/bjs.9046 **KQ4E3b, KQ5E3b.**
40. Matyal R, Shakil O, Hess PE, et al. Impact of gender and body surface area on outcome after abdominal aortic aneurysm repair. Am J Surg. 2015;209(2):315-23. PMID: 25457240. https://dx.doi.org/10.1016/j.amjsurg.2014.07.008 **KQ4E3b, KQ5E3b.**
41. Mayor S. Women having surgery for abdominal aortic aneurysm are nearly twice as likely to die as men. BMJ. 2017;357:j2054. PMID: 28446431. https://dx.doi.org/10.1136/bmj.j2054 **KQ4E9, KQ5E9.**
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43. Morris DR, Cunningham MA, Ahimastos AA, et al. Erratum to: 'TElmisartan in the management of abDominal aortic aneurYsm (TEDY): The study protocol for a randomized controlled trial'.[Erratum for Trials. 2015;16:274; PMID: 26081587]. Trials [Electronic Resource]. 2016;17:43. PMID: 26791257. https://dx.doi.org/10.1186/s13063-016-1183-x **KQ4E4, KQ5E4.**
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Appendix E Table 1. Methodological and Intervention Characteristics of Included One-Time Screening Studies (KQs 1 and 3)

Comparison	Author, Year Trial name	Study Quality	N Randomized	Country	Mean length of FU, y	Intervention	Control
Screening vs. no screening	Ashton, 2007[113] (Men only) & Scott, 2002[36] (Women only) Chichester	Fair	15,382 Men: 6040 Women: 9342	UK	15.0 (Men only) 10yr (Women only)	Ultrasound screening; patients with an aneurysm of 3.0–4.4 cm diameter were rescanned annually and those with an aneurysm of 4.5–5.9 cm diameter were rescanned every 3 months. This was continued until February 1994 or until the patient died, underwent surgical intervention, or declined followup.	Surveillance
	Thompson, 2012[12, 170] MASS	Good	67,770	UK	13.1	Ultrasound screening; patients with an aortic diameter of 3.0–4.4 cm were rescanned yearly. Those with an aortic diameter of 4.5–5.4 cm were rescanned at 3 month intervals. Urgent referral to a vascular surgeon was recommended for patients with aortic diameter ≥5.5 cm. QOL was assessed in patients with screen- detected AAA and those with normal scans at 1.5, 3, and 12 months (n=1,956).[12]	Surveillance
	Lindholt, 2010[147] Viborg	Good	12,639	Denmark	13	Ultrasound screening; participants with aneurysms ≥5 cm were referred to a vascular surgeon; those with AAA 3–4.9 cm were offered annual scans to check for expansion. After 5 y those with initial ectatic aorta (diameter 2.5–2.9 cm) were offered rescreening.	Surveillance
	Lindholt, 2017[146] VIVA	Fair	50,156 (Screening group n=25,078)	Denmark	4.4*	Ultrasound screening; patients with aneurysms ≥ 5 cm were referred to CT scanning and assessment by a vascular surgeon for repair. Participants were invited to one annual clinical followup, which consisted of ultrasound screening. Person identification numbers were used to search the Danish Vascular Registry for vascular procedures. ABI screening; participants with possible hypertension alone encouraged to consult with general practitioner for confirmation of diagnosis, initiation of prophylactic activities, or both. Blood total cholesterol measurement if diagnosis of AAA or PAD was confirmed with repeated ultrasonography and ABI measurement. If total serum cholesterol concentration exceeded 4.0mmol/L, participant prescribed statin therapy (40mg/day simvastatin) and aspirin (75 mg/day). All positive findings and initiated medications	Surveillance

Appendix E Table 1. Methodological and Intervention Characteristics of Included One-Time Screening Studies (KQs 1 and 3)

Comparison	Author, Year Trial name	Study Quality	N Randomized	Country	Mean length of FU, y	Intervention	Control
						communicated to general practitioner to ensure medication continuation and followup.	
	McCaul, 2016[15, 168] Western Australia	Fair	38,480	Australia	12.8*	Ultrasound screening†; QOL (SF-36, EuroQOL EQ- 5D) was assessed 12 months after screening (n=365).[168]	Surveillance
Screening harms	Lesjak, 2012[141]	Fair	NR‡	Australia	6 mo	At the time of time of screening, self-administered questionnaires were completed including the Medical Outcomes Short Form 36v 2 (MOSF36). Six months after screening, all participants who had an abnormal aortic diameter (≥2.6cm) were follow up on and completed MOSF36 questionnaires (n=53).	A random sample of men with normal scans were follow up six months after screening (n=130).
	Lucarotti, 1997[150]	Fair	NR	UK	1 mo	Men invited to screening filled out the QOL questionnaire (General Health Questionnaire; linear analogue scale) prior to screening. 1 month after initial screening, the first 61 men with diagnosed AAA (definition NR) were asked to complete the QOL assessment again (n=61).	Men invited to screening filled out the QOL questionnaire (General Health Questionnaire; linear analogue scale) prior to screening. 1 month after initial screening, the first 100 men with normal scans were asked to complete the QOL assessment again (n=100).
	Wanhainen, 2004[174]	Fair	NR	Sweden	1.0	Participants were given a QOL assessment questionnaire (SF-36) at baseline and then 12 months after screening. A cohort of participants with screen-detected AAA were followed (n=24).	Participants were given a QOL assessment questionnaire (SF-36) at baseline and 12 months after screening. A cohort of age-/

Appendix E Table 1. Methodological and Intervention Characteristics of Included One-Time Screening Studies (KQs 1 and 3)

Comparison	Author, Year Trial name	Study Quality	N Randomized	Country	Mean length of FU, y	Intervention	Control
							sex-matched controls with normal AAA scans were followed (n=45).

*Median

[†]After screening, participants were given a letter containing the results of their scan and a copy for their primary care physician. Any follow-up investigations or referral to a surgeon were arranged by the primary care physician. No attempt was made by investigators to influence clinical management with regards to threshold for intervention or method of repair.

[ǂ]53 men completed the questionnaire (out of 516)

Abbreviations: AAA = abdominal aortic aneurysm; EQ-5D = EuroQOL-5D; MASS = Multicenter Aneurysm Screening Study; QOL = quality of life; SF-36 = Short-form 36-item Health Survey; NR = not reported.

Appendix E Table 2. Patient Characteristics of Included One-Time Screening Studies (KQs 1 and 3)

Comparison	Author, Year Trial name	Major inclusion criteria	Mean age % Female	% Current smoking	% Family history	% Diabetes	% CVD risk factors
Screening vs. no screening	Ashton, 2007[113] (Men only) & Scott, 2002[36] (Women only) Chichester	Patients ages 65–80 y	72.0* 59.2	NR	NR	NR	NR
	Thompson, 2012[170] MASS	Men ages 65–74 y	69.2 0	NR	NR	NR	NR
	Lindholt, 2010[147] Viborg	Men ages 64–73 y who lived in Viborg county	67.7 0	NR	NR	NR	NR
	Lindholt, 2017[146] VIVA	Men aged 65-74 yrs living in Central Denmark	69.0* 0	NR	NR	NR	History of, %: Stroke: 3.0 MI: 2.7 Ischemic heart disease: 6.6 Peripheral occlusive arterial disease: 1.1
	McCaul, 2016[15] Western Australia	Men aged 64–83 yrs living in Perth and surrounding towns	72.6 0	NR	NR	NR	NR
Screening harms	Lesjak, 2012[141]	Rural men aged 65-74 who attended a community-based screening for AAA.	NR 0	NR	NR	NR	NR
	Lucarotti, 1997[150]	Men born between 1925 and 1928 living in Gloucestershire and participating in the AAA screening program	NR 0	NR	NR	NR	NR
	Wanhainen, 2004[174]	Men and women ages 65– 75 y with screen-detected AAA (≥3.0 cm) along with a group	71.0 19.4	NR	NR	NR	NR

Appendix E Table 2. Patient Characteristics of Included One-Time Screening Studies (KQs 1 and 3)

Comparison	Author, Year Trial name	Major inclusion criteria	Mean age % Female	% Current smoking	% Family history	% Diabetes	% CVD risk factors
		of those with a normal scan to act as controls					

*Median

Abbreviations: AAA = abdominal aortic aneurysm; MASS = Multicenter Aneurysm Screening Study; NR = not reported.

Appendix E Table 3. Percent of Screened Population With AAA of the Specified Size

Author, Year Trial name	Total Scanned	Total AAA (prevalence), n (%)	≥5.5cm, n (%)	5.0 to 5.9cm, n (%)	4.5 to 5.4cm, n (%)	3.0 to 4.4cm, n (%)
Scott, 1995[13] Chichester	5,394 (men and women)*	218 (4.0)	19 (0.4)†	20 (0.4)†	NR	179 (3.3)†,‡
Thompson, 2012[12, 170] MASS	27,147 (men)	1,334 (4.9)	166 (0.6)	NR	223 (0.8)	944 (3.5)
Lindholt, 2010[14, 143, 147] Viborg	4,860 (men)	191 (3.9)§	24 (0.5)	NR	NR	NR
Lindholt, 2017[146] VIVA	25,078 (men)	619 (3.3)	61 (0.3)	NR	NR	558 (3.0)‖
McCaul, 2016[15, 155] Western Australia	12,203 (men)	879 (7.2)	61 (0.5)	NR	115 (0.9)¶	699 (5.7)¶

* From 5-year followup (Scott, 1995)[13]
† Estimated
‡ AAA of 3.0 to 4.0 cm.
§ N analyzed for prevalence: 4816
‖ AAA of 3.0 to 4.9 cm
¶ From 3.6-year followup (Norman, 2004)[155]

Abbreviations: AAA = abdominal aortic aneurysm; cm = centimeter; MASS = Multicenter Aneurysm Screening Study; NR = not reported.

Appendix E Table 4. Methodological and Intervention Characteristics of Included Rescreening Studies (KQ 2)

Study, Year Quality	Trial	N	N Analyzed	Country	Mean length of follow up (yrs)	Measurement technique	Rescreening intervals; number of times rescreened
D'Audiffret, 2002[121] Fair	Patients from the ADAM trial	223	223	US	5.9 Range: NR	Aortic measurements were made in both the anterior-posterior and transverse planes and the greatest diameter was recorded.	Rescreening annually after aortic diameters of 2.5–2.9 cm were identified 5 repeat scans
Deveraj, 2008[123] Fair	Patients from the Good Hope Hospital Screening Program	999	358	UK	5.4 Range: 1-14 years	Assessed anterioposterior diameter	Rescreening of abnormal aortas (2.6–2.9 cm) annually NR
Oliver-Williams, 2018[156] Good	Patients from the Gloucestershire Aneurysm Screening Study	80,150	1233	UK	7.8 Range: 2.7-11 yrs†	Maximum anteroposterior diameter assessed by measurement from the inner wall to the inner wall of the aorta.	Men with small AAA (2.4-4.4cm had annual ultrasound followup. 6 (3-11)‡ repeat scans
Lederle, 2000[138] Good	Patients from the ADAM trial	15,098	2,622	US	4 Range: NR	Assessed infrarenal and suprarenal aortic diameter	Rescreening in those found to have no AAA 4 y after initial screening 1 repeat scan
Lindholt, 2000[148] Fair	Case/control study of the Viborg Trial	6,339	248 for 2.5-2.9 group 275 Control group	Denmark	5 Range: 3-5 yrs	Infrarenal aorta was first visualized anteroposteriorly in its entire length. Its anteroposteriorly and transversely diameters were measured and recorded at their maximal sizes.	Those with aorta 2.5–2.9 cm were offered rescreening 3 to 5 y after initial screen; control group were those with no AAA
Scott, 2001[165] Fair	Cohort of 65 year-old men found to have normal aorta	1,011	649	UK	10 Range: NR	Both antero-posterior and transverse measurements of aortic diameter were taken and the maximum of the two measurements was used as the defining diameter.	Individuals with normal-sized aortas at initial scan were rescreened every 2 y. (These patients were NOT Chichester trial participants.) 5 repeat scans

Appendix E Table 4. Methodological and Intervention Characteristics of Included Rescreening Studies (KQ 2)

Study, Year Quality	Trial	N	N Analyzed	Country	Mean length of follow up (yrs)	Measurement technique	Rescreening intervals; number of times rescreened
Soderberg, 2017[167] Fair	Population based cohort of 70 year-old women	5140	2.5-2.9cm group: 33; 26 rescanned ≥3.0cm group: 19	Sweden	5 Range: NR	The maximum antero-posterior diameter was registered according to the leading edge to leading edge principle.	All women with screened detected sub-aneurysms diameter 2.5-2.9 cm were rescanned at 5 yrs. 1 repeat scan
Svensjo, 2014[169] Fair	Population based cohort of 65 year old men	3270	<2.5cm group: 2652 2.5-2.9cm group: 40 ≥3.0cm group: 44	Sweden	5 Range: 5 yrs	The maximum antero-posterior diameter of the infrarenal aorta was recorded using the leading edge to leading edge principle.	Individuals with an infrarenal aortic 2.5-2.9 cm were rescanned after 5 years. 1 repeat scan

*Median
† Duration of follow-up was calculated for each man as the time from the initial scan to death, or to most recent scan if the individual had not died.
‡ Median (i.q.r.) within

Abbreviations: AAA = abdominal aortic aneurysm; ADAM = Abdominal Aortic Aneurysm Detection and Management Study; IQR = interquartile range; NR = not reported; yrs = years

Appendix E Table 5. Baseline Characteristics of Included Rescreening Studies for Small AAA (KQ 2)

Author, Year Quality	Major inclusion criteria	Mean AAA size	Mean age % Female	% Current smoking	% Family history	% Diabetes	% CVD risk factors
D'Audiffret, 2002[121] Fair	Those with aortic diameters of 2.5–2.9 cm	2.7cm	68.4 NR	81.6*	13.9	11.2	PAD: 12.5 HTN: 49.8 Hypercholesterolemia: 17.5
Deveraj, 2008[123] Fair	Men found to have ectatic aortas (2.6–2.9 cm in diameter) at first scan with a minimum of 1-y followup	2.8cm	NR 0	NR	NR	NR	NR
Oliver-Williams, 2018[156] Good	Men ages 65–66 y at the time of original study who had aortic diameters <2.6 cm	1.7cm (initial screening in years 2010-2015) 2.1cm (initial screening in early 1990s)	65.3† 0	NR	NR	NR	NR
Lederle, 2000[138] Good	VA patients ages 50–79 y without AAA (aortic diameters of ≤3.0 cm) who were part of the ADAM trial	2.0 cm	66.0 2.4	14.6	6.0	17.6	HTN: 55.2 High Chol: 38.9 CAD: 36.6 Any atherosclerosis: 42.3
Lindholt, 2000[148] Fair	Men ages 65–73 y with either identified small AAA (2.5–2.9 cm) or those with a normal initial scan (along with 380 controls)	NR	65.6 0	NR	NR	NR	NR
Scott, 2001[165] Fair	Male patients with a normal aorta on their initial scan at age 65 y	NR	65 0	NR	NR	NR	NR
Soderberg, 2017[167] Fair	All 70 year old women identified through the National Population Registry, in two neighboring counties in Sweden. Women diagnosed with sub-aneurysmal aortas (2.5-2.9cm) were followed.	2.64 for 2.5-2.9cm group	70 100	36	21‡	NR	Coronary disease: 12 HTN: 39 Hyperlipidemia: 36 Claudication: 9
		3.52cm for ≥3.0cm group	70 100	63	5‡	NR	Coronary disease: 16 HTN: 68 Hyperlipidemia: 47 Claudication: 11

Appendix E Table 5. Baseline Characteristics of Included Rescreening Studies for Small AAA (KQ 2)

Author, Year Quality	Major inclusion criteria	Mean AAA size	Mean age % Female	% Current smoking	% Family history	% Diabetes	% CVD risk factors
Svensjo, 2014[169] Fair	2006-2007 All men 65 years identified in the National Population Registry in Uppsala county. Rescanned 2011-2012. Men with a hx of AAA repair were excluded from invitation.	1.85	70 0	NR	NR	NR	NR

* Defined as smoking history
† Median
‡ Family history defined as first degree relative

Abbreviations: AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CVD = cardiovascular disease; NR = not reported; PAD = peripheral artery disease; VA = Department of Veterans Affairs.

Appendix E Table 6. Quality of Life Results of Included One-Time Screening Studies (KQs 1 and 3)

Comparison	Author, Year Trial name	Study Quality	N Randomized	Country	Mean length of FU, y	Instrument	Group	QoL Data
Screening vs. no screening	Ashton, 2007[113] (Men only) & Scott, 2002[36] (Women only) Chichester	Fair	15,382 Men: 6040 Women: 9342	UK	15.0 (Men only) 10yr (Women only)	--	--	--
	Thompson, 2012[12, 170] MASS	Good	67,770	UK	13.1	SF-36, HADS, EQ-5D	Surgery	3 months Physical Health, mean: 50.0‡ Mental Health, mean: 48.4‖ Depression, mean: 3.0‡ Anxiety, mean: 29.1‡ Weighted Health Index, mean: 0.85‡ 12 months Physical Health. mean: 51.1‡ Mental Health, mean: 50.6‡ Depression, mean: 3.1‡ Anxiety, mean: 28.6‡ Weighted Health Index, mean: 0.85‡
							Surveillance	3 months Physical Health, mean: 51.0‡ Mental Health, mean: 51.7‖ Depression, mean: 3.0‡ Anxiety, mean: 28.9‡ Weighted Health Index, mean: 0.83‡ 12 months Physical Health, mean: 49.8‡ Mental Health, mean: 50.1‡ Depression, mean: 3.2‡ Anxiety, mean: 29.6‡ Weighted Health Index, mean: 0.83‡
	Lindholt, 2010[147] Viborg	Good	12,639	Denmark	13	--	--	--
	Lindholt, 2017[146] VIVA	Fair	50,156 (Screening group n=25,078)	Denmark	4.4*	--	--	--

Appendix E Table 6. Quality of Life Results of Included One-Time Screening Studies (KQs 1 and 3)

Comparison	Author, Year Trial name	Study Quality	N Randomized	Country	Mean length of FU, y	Instrument	Group	QoL Data
	McCaul, 2016[15, 168] Western Australia	Fair	38,480	Australia	12.8*	MOS SF-36; HADS, EQ-5D	AAA Group	12 months Physical Functioning, mean (SD): 62.9 (27.4) ‖ Mental Health, mean (SD): 81.3 (15.9) Anxiety/Depression, mean (SD): 3.6 (3.0) Health States Score, mean (SD): 0.83 (0.18)
							CG	12 months Physical Functioning, mean (SD): 68.9 (25.8) ‖ Mental Health, mean (SD): 78.3 (17.7) Anxiety/Depression, mean (SD): 3.6 (3.2) Health States Score, mean (SD): 0.80 (0.21)
Screening harms	Lesjak, 2012[141]	Fair	NR‡	Australia	6 month	MOS SF-36, HADS	AAA Group	*Physical Functioning* Prescreening score, mean (SD): 40.4 (10.7) Postscreening score, mean (SD): 41.1 (11.7) *Mental Health* Prescreening score, mean (SD): 49.6 (11.1) Postscreening score, mean (SD): 49.8 (11.9) *Depression* Prescreening score, mean (SD): 5.1 (4.1) Postscreening score, mean (SD): 5.5 (4.6) *Anxiety* Prescreening score, mean (SD): 5.1 (3.9) Postscreening score, mean (SD): 5.9 (4.9)
							CG	*Physical Functioning* Prescreening score, mean (SD): 41.3 (11.7)

Appendix E Table 6. Quality of Life Results of Included One-Time Screening Studies (KQs 1 and 3)

Comparison	Author, Year Trial name	Study Quality	N Randomized	Country	Mean length of FU, y	Instrument	Group	QoL Data
								Postscreening score, mean (SD): 44.3 (10.2) *Mental Health* Prescreening score, mean (SD): 51.6 (10.5) Postscreening score, mean (SD): 51.8 (10.7) *Depression* Prescreening score, mean (SD): 4.2 (3.3) Postscreening score, mean (SD): 4.1 (3.6) *Anxiety* Prescreening score, mean (SD): 5.3 (3.8) Postscreening score, mean (SD): 4.8 (3.7)
	Lucarotti, 1997[150]	Fair	NR	UK	1 month	GHQ	AAA Group	Prescreening score, mean (SD): 15.71 (9.13)‡ Postscreening score, mean (SD): 14.25 (7.68)‡
							CG	Prescreening score, mean (SD): 15.51 (9.17)‡ Postscreening score, mean (SD): 14.36 (7.28)‡
	Wanhainen, 2004[174]	Fair	NR	Sweden	1.0	SF-36	AAA Group	*Physical Health Cluster* Mean score before screening: 43‡ Mean score after screening: 43‡ *Mental Health Cluster* Mean score before screening: 52‖ Mean score after screening: 49‖
							CG	*Physical Health Cluster* Mean score before screening: 46‡ Mean score after screening: 44‡ *Mental Health Cluster* Mean score before screening: 51‡ Mean score after screening: 52‡

Appendix E Table 6. Quality of Life Results of Included One-Time Screening Studies (KQs 1 and 3)

*Median
†53 men completed the questionnaire (out of 516)
ǂ Between group: p = NS
§ Within group: p = NS
‖p < 0.05

Abbreviations: AAA = abdominal aortic aneurysm; CG = Control group; EQ-5D = European Quality of Life; GHQ = General Health Questionnaire; HADS = Hospital Anxiety & Depression Scale; MASS = Multicenter Aneurysm Screening Study; MOS SF-36 = Medical Outcomes Short Form-36; NR = not reported; SD = Standard deviation; SF-36 = Short Form-36; UK = United Kingdom

Appendix E Table 7. Methodological and Intervention Characteristics of Included Treatment Studies (KQs 4 and 5)

Intervention	Study, Year	Quality	N randomized	Country	Mean followup, years	Intervention	Control
Open surgery vs. surveillance	Lederle, 2002[140] ADAM	Good	1,136	United States	4.9	Elective open surgery within 6 weeks of AAA identification	Surveillance until AAA reached 5.5 cm, enlarged by at least 0.7 cm in 6 months/1.0 cm in 1 year, or symptoms developed
	Powell, 2007[161-163] UKSAT	Good	1,090	United Kingdom	12	Elective open surgery within 3 months of AAA identification	Surveillance until AAA reached 5.5 cm, rapidly increased in diameter (>1 cm/y) or developed symptoms
EVAR vs. surveillance	Cao, 2011[118] CAESAR	Fair	360	20 European/western Asian hospitals	2.6‡	Patients received surgery via EVAR as soon as possible	Surveillance until AAA reached 5.5 cm in diameter, a rapid increase of >1 cm/year was found, or the aneurysm became symptomatic
	Ouriel, 2010[158] PIVOTAL	Fair	728	United States	1.7	Patients underwent EVAR ≤30 days of randomization	Surveillance until AAA reached 5.5 cm or enlarged ≥0.5 cm between any two 6-month assessments
Pharmacotherapy vs. placebo	Bicknell, 2016[114] AARDVARK	Good	227	United Kingdom	2	10 mg perindopril (IG1) or 5 mg amlodipine (IG2) daily for 2 years	Placebo
	Hogh 2009[132]	Good	92	Denmark	5	300 mg oral roxithromycin once daily for 28 days	Placebo
	Karlsson, 2009[133]	Fair	247	Sweden	1.5	600 mg azithromycin once daily for 3 days, followed by 600 mg once a week for 15 weeks	Placebo
	Lindholt, 1999[142]‖	Fair	54	Denmark	2	40 mg propranolol twice a day for 2 years	Placebo

Appendix E Table 7. Methodological and Intervention Characteristics of Included Treatment Studies (KQs 4 and 5)

Intervention	Study, Year	Quality	N randomized	Country	Mean followup, years	Intervention	Control
	Meijer, 2013[152]	Fair	286	The Netherlands	1.5	100 mg doxycycline daily for 18 months	Placebo
	Mosorin, 2001[153]	Fair	32	Finland	1.5	150 mg doxycycline daily for 3 months	Placebo
	PAT Investigators, 2002[164] PAT	Good	552	Canada	2.5	20 mg propranolol twice a day; increased to 40 mg after 1 week, 80 mg after 2 weeks, and 120 mg at 4 weeks. Target dose was 80–120 mg twice a day. Pts observed for mean of 2.5 years	Placebo
	Sillensen, 2015[166] AORTA	Fair	168	Multisite¶	1	40 mg pemirolast twice a day# for 52 weeks	Placebo

*No AAA-related death was found in both groups.
†This study also reported 5-y followup data on growth rate.
‡Median
§Due to a large loss to followup, efficacy data were not usable. However, these losses were due to adverse events so the harms data are included.
‖ This study is included for KQ5 (harms) only
¶ 15 sites participated from Sweden, Denmark, and the United Kingdom
#Study also reports 10 mg twice a day and 25 mg twice a day

Abbreviations: AAA = abdominal aortic aneurysm; ADAM = aAbdominal Aortic Aneurysm Detection and Management Study; AORTA: the Anti-inflammatory Oral Treatment of AAA; CAESAR = Comparison of Surveillance vs. Aortic Endografting for Small Aneurysm Repair; N = sample size; NA = not applicable; EUROSTAR = European Collaborators on Stent-Graft Techniques for aAbdominal Aortic Aneurysm Repair; PAT = Propanolol Aneurysm Trial; PIVOTAL = Positive Impact of Endovascular Options for Treating Aneurysms Early; UKSAT = UK Small Aneurysm Trial.

Appendix E Table 8. Patient Characteristics of Included Treatment Studies (KQs 4 and 5)

Intervention	Study, Year	Major inclusion criteria	Mean age % Female	AAA diameter at baseline, cm	% Current smoking	% Family history	% CVD risk factors
Open surgery vs. surveillance	Lederle, 2002[140] ADAM	Patients ages 50–79 years with AAA 4.0– 5.4 cm identified via CT within the previous 12 weeks	68.1 0.8	4.7	39.2	12.9	Coronary disease: 41.9 Cerebrovascular disease: 12.4 Hypertension: 56.4
	Powell, 2007[161-163] UKSAT	Patients ages 60–76 years with asymptomatic, small AAA (4.0–5.5 cm)	69.3 17.5	4.6	37.1	NR	Hypertension: 39 Probable ischemic heart disease: 14
EVAR vs. surveillance	Cao, 2011[118] CAESAR	Patients ages 50–79 years; nonsymptomatic AAA 4.1–5.4 cm in diameter measured by CT within the previous 3 months	68.9 4.2	4.7	55.3	NR	Coronary disease: 39.2 Hypertension: 75.3
	Ouriel, 2010[158] PIVOTAL	Patients ages 40–90 yrears with AAA between 4.0 and 5.0 cm found by CT performed ≤3 months prior; eligible for EVAR	70.5 13.4	4.4	91.0	23.5	MI: 31.3 CHF: 6.2 CAD: 55.4 PVD: 28.2 Hypertension: 77.8
Pharmacotherapy vs. surveillance	Hogh 2009[132]	AAA ≥3.0 cm detected by ultrasound the day of study entry; exclusively men	72.5 0	3.8	59.5	NR	NR
	Karlsson, 2009[133]	Patents aged ≤80 years with AAA 3.5–4.9 cm	71† 18.5	NR	40	14	MI: 31.0 Stroke: 14.1 Hypertension: 62.5
	Lindholt, 1999[142]	Men with AAA 3.0–4.9 cm	69.2 0	3.4	NR	NR	NR
	Meijer, 2013[152]	Aneurysm diameter 3.5-5.0 cm, or a larger aneurysm unfit for repair, or declined repair.	70.0 18.2	4.3	35.0	25.2	History of CVD: 52.1
	Mosorin, 2001[153]	Aneurysm diameter perpendicular to the aortic axis of ≥3.0 cm in size or a ratio of infrarenal to suprarenal aortic diameter of ≥1.2 and a diameter <5.5 cm; followup of at least 6 months with 2 or	68.4 9.4	3.3	35.4	NR	Hypertension: 40.2

Appendix E Table 8. Patient Characteristics of Included Treatment Studies (KQs 4 and 5)

Intervention	Study, Year	Major inclusion criteria	Mean age % Female	AAA diameter at baseline, cm	% Current smoking	% Family history	% CVD risk factors
		more ultrasound examinations					
	PAT Investigators, 2002[164] PAT	Asymptomatic small AAA (3.0–5.0 cm; some centers only, 3.0–4.5 cm) measured by ultrasound; no contraindications to study drug	68.9 16	3.8	34.7	NR	Angina: 14.8 Heart failure: 2.0 Claudication: 19.2 Hyperlipidemia: 33.6 Hypertension: 35.8 MI: 16.9 Stroke: 6.3
	Bicknell, 2016[114] AARDVARK	Men or women aged ≥ 55 years, with AAA 3.0-5.4 cm, and an SBP < 150 mmHg	71.3 5.8	4.0	25.0	NR	Hypertension: 0
	Sillensen, 2015[166] AORTA	Patients aged ≥ 50 years with AAA 3.9-4.9 cm	70.9 8.9	4.4	41.1	NR	History of cardiac disorders: IG: 38.0 CG: 42.0

*Defined as angina, MI, arrhythmia, or heart failure
†Median
‡Mean

Abbreviations: AAA = abdominal aortic aneurysm; ADAM = Abdominal Aortic Aneurysm Detection and Management Study; AORTA: the Anti-inflammatory Oral Treatment of AAA; CAD = coronary artery disease; CAESAR = Comparison of Surveillance Versus Aortic Endografting for Small Aneurysm Repair; CHF = congestive heart failure; CT = computed tomography; CVD = cardiovascular disease; EUROSTAR = European Collaborators on Stent-Graft Techniques for Abdominal Aortic Aneurysm Repair; EVAR = endovascular aneurysm repair; MI = myocardial infarction; NR = not reported; PAT = Propranolol Aneurysm Trial; PIVOTAL = Positive Impact of Endovascular Options for Treating Aneurysms Early; PVD = peripheral vascular disease; UKSAT = UK Small Aneurysm Trial.

Appendix E Table 9. Methodological Characteristics of Included Registry Studies (KQ5)

Author, Year Quality	Registry	Country	Recruitment	Mean followup, years	Surgical technique(s) included	Population Characteristics in patients with small AAA	N (%) of Small AAA	Definition of small AAA
Budtz-Lilly, 2017[116] Fair	Vascunet	International*	Data on primary intact AAA repairs were collected from vascular registries for the time period of 2005-2013. Data on small AAA <5.5cm available for 2010-2013 time period. It was estimated that coverage of participating registries was >90% for the majority, 80% in Norway, and 62% in Australia.	NR	EVAR, open	Mean age (range): NR % Female: NR % smokers: NR	12,610 (25.6)	< 5.5 cm
Golledge, 2007[129] Fair	ASERNIP-S	Australia	Surgeries performed from November 1999 to May 2001 were recorded in the registry. Participation by vascular surgeons was initially enforced. An audit cross checking Health Insurance Commission data found >90% of procedures were included.	3.2 (Median)	EVAR	Mean age (range): 75 (NR) % Female: 15.9 % current smokers: 11.0	478 (49.7)	≤ 5.5 cm
Lo, 2013[149] Fair	VSGNE	US	Voluntary collaboration among vascular surgeons, cardiologists, and radiologists from 30 academic and community hospitals in New England. The data are validated periodically to ensure that all procedures are	1.0	EVAR, open	Mean age (range): 71 (NR) % Female: 26.2 % smokers (past or current): 88.5	1336 (37.1)	< 5.5 cm

Appendix E Table 9. Methodological Characteristics of Included Registry Studies (KQ5)

Author, Year Quality	Registry	Country	Recruitment	Mean followup, years	Surgical technique(s) included	Population Characteristics in patients with small AAA	N (%) of Small AAA	Definition of small AAA
			included in the registry. This publication analyzed 2003-2011 data.					
Overbey, 2017[159] Fair	ACS NSQIP	US	A nationally validated, risk adjusted dataset comprising major surgical procedures and 30-day outcomes. Data are collected from medical charts by a trained Surgical Clinical Reviewer. This article is analysis of 2011-2015 data.	NR	EVAR, open	Mean age (range):72.3 (NR) % Female: 21.9 % current smokers: 33.6	5,126 (51.1)	Smallest quartile: 3.5-5 cm Second quartile: 5.01-5.5 cm
Peppelenbosch, 2004[160] Fair	EUROSTAR	International†	110 European institutions participate in the registry. Patient data is recorded on case record forms and submitted. Only elective treatments are tracked. This article is an analysis of 1997-2002 data.	1.7	EVAR	Mean age (range): 69.7 (43-94) % Female: 7.0 % smokers: NR	1962 (44.7)	4.0-5.4 cm

* Eleven countries: Australia, Denmark, Hungary, Iceland, New Zealand, Norway, Sweden, Switzerland, United Kingdom, Finland (Helsinki region only), Germany †Austria, Belgium, Denmark, United Kingdom, France, Germany, Greece, Israel, Italy, Luxembourg, Monaco, the Netherlands, Norway, Poland, Spain, Sweden, Switzerland

Abbreviations: AAA = abdominal aortic aneurysm; CAD = coronary artery disease; cm = centimeter; CT = computed tomography; CVD = cardiovascular disease; EUROSTAR = European Collaborators on Stent-Graft Techniques for Abdominal Aortic Aneurysm Repair; EVAR = endovascular aneurysm repair; MI = myocardial infarction; NR = not reported; PAT = Propranolol Aneurysm Trial; PIVOTAL = Positive Impact of Endovascular Options for Treating Aneurysms Early; PVD = peripheral vascular disease; US = United States.

Appendix E Table 10. Quality of Life Results in Studies of Treatment for Small AAA (KQs 4 and 5)

Intervention	Study	QOL screening	Time period	Treatment Group	N Analyzed	QOL scores, mean (SD)¶	Mean difference (95% CI), p-value
Open surgery vs. surveillance	Forbes 1998[127] UKSAT	MOS subscale*	Baseline	IG	480	Physical function: 64.2 (30.7) Mental health: 80.2 (17.2)	Physical function: -2.3 (-6.0 to 1.5); NR Mental health: 0.7 (-1.5 to 2.8); NR
				CG	512	Physical function: 66.5 (29.3) Mental health: 79.5 (17.0)	
			12 months post-randomization	IG	429	Physical function: 62.1 (29.9) Mental health: 81.7 (17.9) *Mean difference from BL:* Physical function: -3.5 (-6.1 to -0.8) Mental health: 0 (-1.5 to 1.5)	Physical function: 1.7 (-2.3 to 5.7) Mental health: 2.1 (-0.4 to 4.5)
				CG	436	Physical function: 60.3 (30.2) Mental health: 79.6 (18.6) *Mean difference from BL:* Physical function: -6.2 (-8.8 to -3.7) Mental health: 0 (1.7 to 1.8)	
EVAR vs. surveillance	De Rango 2011[122] CAESAR	SF-36*	Baseline through 6 months post-randomization	IG	173	*Mean difference (95% CI) from BL:* Overall QOL: 4.6 (2.3 to 7) Physical functioning: -0.6 (-3.7 to 2.4) Mental health: 5.2 (2.8 to 7.5)	*IG vs. CG* Overall QOL: 5.4 (2.1 to 8.8); p=0.002 Physical function: 3.8 (0.5 to 7.2); p=0.02 Mental health: 6.0 (2.7 to 9.3); p=0.0005
				CG	166	*Mean difference (95% CI) from BL:* Overall QOL: -0.8 (-3.2 to 1.6) Physical functioning: -4.3 (-7.3 to -1.2) Mental health: -0.8 (-3.2 to 1.5)	
			Baseline through end of followup§	IG	173	*Mean difference (95% CI) from BL:* Overall QOL: 4.6 (2.3 to 7) Physical functioning: -0.6 (-3.7 to 2.4) Mental health: 5.2 (2.8 to 7.5)	*IG vs. CG* Overall QOL: 2.4 (-1.7 to 6.6); p=0.25 Physical function: 1.5 (-2.6 to 5.5); p=0.48 Mental health: 2.0 (-2.4 to 6.4); p=0.38
				CG	166	*Mean difference (95% CI) from BL:* Overall QOL: -6.3 (-9.3 to -3.4)‖ Physical functioning: -8.2 (-12.0 to -4.4) Mental health: 4.8 (-7.9 to -1.7)‖	
	Eisenstein, 2013[124] PIVOTAL	EQ-5D#	Baseline	IG	351	*Utility score: 0.805 (0.1)*** *Visual analog scale: 77.8 (14)*	NR
				CG	350	*Utility score: 0.783 (0.2)*** *Visual analog scale: 78.2 (15)*	
			24 month post BL	IG	205	*Utility score: 0.797 (0.2)*** *Visual analog scale: 76.2 (17)*	
				CG	197	*Utility score: 0.817 (0.2)*** *Visual analog scale: 76.5 (18)*	

Appendix E Table 10. Quality of Life Results in Studies of Treatment for Small AAA (KQs 4 and 5)

Intervention	Study	QOL screening	Time period	Treatment Group	N Analyzed	QOL scores, mean (SD)¶	Mean difference (95% CI), p-value
Pharmacotherapy vs. surveillance	Lindholt 1999[142]	ScreenQL*†	Baseline through 2 y	IG	30	NR	Overall QOL: -5.83 (6.2)‡; p=0.05 Emotional domain: -0.35 (2.1)‡; p=0.59 Health perception: -1.39 (2.98)‡; p=0.13
				CG	24	NR	Overall QOL: -1.70 (5.5)‡; p=0.07 Emotional domain: 0.00 (2.0)‡; p=0.69 Health perception: -0.38 (2.10)‡; p=0.30
	PAT Investigators, 2002[164] PAT	SF-36*	Baseline	IG	276	Physical function: 70.8 (23.9) Mental health: 78.9 (17.3)	Physical function: p=0.11 Mental health: p=0.45
				CG	272	Physical function: 74.1 (24.0) Mental health: 77.8 (17.9)	
			1 month post-randomization	IG	276	Physical function: 68.9 (18.9) Mental health: 78.9 (17.6)	Physical function: p=0.006 Mental health: p=0.58
				CG	272	Physical function: 74.4 (23.8) Mental health: 78.3 (17.5)	

*Lower score denotes poorer status.
†A validated generic and global QOL questionnaire with 24 items evaluating 6 categories: general QOL, emotional health, physical health, psychosomatic distress, social and family functions, and marriage.
‡Mean (SD); change from BL in each group, not IG vs. CG.
§Mean, 3 y from BL (SD, 1.2 y).
‖p<0.01.
¶Only summary scores reported here. For complete subscales please see full text.
Utility score uses responses to the five dimensions (Mobility, Self-care, Usual activity, Pain/discomfort, Anxious/depressed) to compute a value on a scale of -0.54 to 1.00; higher utility score indicates a better quality of life and a negative value indicates a health state worse than death that can be used to quality-adjust study patient survival time. The final EQ-5D element, visual analog score (VAS), provides a one-question assessment of an individual's quality of life and ranges from 0-100, with a higher score indicating a better quality of life.
** Utility score N Analyzed by group and FU: Baseline IG n = 348, CG n = 349; 24month post baseline IG n = 203, CG n = 191

Abbreviations: BL = baseline; CAESAR = Comparison of Surveillance Versus Aortic Endografting for Small Aneurysm Repair; CG = control group; EVAR = endovascular aneurysm repair; IG = intervention group; MOS = Medical Outcomes Study; NR = not reported; PAT = Propanolol Aneurysm Trial; QOL = quality of life; SF-36 = Short-Form 36-Item Health Survey; UKSAT = UK Small Aneurysm Trial.

Appendix F Table 1. Mortality Data for Age Subpopulation in One-Time Screening Trials (KQ1a)

Author, Year Trial name Quality	Mean Followup, yrs	Age Description	Group	N Analyzed	All-cause mortality, n (%)*	HR (95% CI)	AAA-related mortality, n (%)*	HR (95% CI)	30 day mortality, n (%)*	30 day mortality for elective repairs, n (%)*	30 day mortality for emergency repairs, n (%)*
Lindholt, 2010[147] Viborg Good	13	≤65 yrs	IG	2742	NR	NA	6 (0.2)	0.36 (0.14-0.93)	NR	NR	NR
			CG	2687	NR		16 (0.6)		NR	NR	NR
		66-73 yrs	IG	3591	NR	NA	13 (0.4)	0.33 (0.18-0.62)	NR	NR	NR
			CG	3619	NR		39 (1.1)		NR	NR	NR
		64-73 yrs Main trial results (see Table 2)	IG	-	-	-	19 (0.3)	0.34 (0.20-0.57)	-	-	-
			CG	-	-	-	55 (0.9)		-	-	-
McCaul, 2016[15] Western Australia Fair	12.8	65-74 yrs	IG	13266	5456 (41.1)	NR†	48 (0.4)	0.92 (0.62-1.36) †	14 (3.7)‡	6 (1.6)§	8 (57.1)‖
			CG	13239	5501 (41.6)		52 (0.4)		21 (6.9)‡	11 (4.0)§	10 (37.0)‖
		64-83 yrs Main trial results (see Table 2)	IG	19,249	9739 (50.6)	NR†	90 (0.46)	0.91 (0.68-1.21)†	34 (6.0)#	18 (3.4)**	16 (61.5)††
			CG	19,231	9832 (51.1)		98 (0.51)		36 (7.9)#	17 (4.1)**	19 (43.2)††

*P value for interaction NR

†Rate ratio (95% CI). Rate ratios reported as AAA-related and non-AAA deaths, not available for ACM.

‡ N analyzed, IG: 382, CG: 303

§ N analyzed for IG: 368, CG: 276

‖ N analyzed for IG: 14, CG: 27

N analyzed for IG: 562, CG: 458

** N Analyzed for IG: 536, CG: 414

†† N Analyzed for IG: 26, CG: 44

Abbreviations: AAA = abdominal aortic aneurysm; CG = control group; CI = confidence intervals; HR = hazard ratio; IG = intervention group; N = population size; n = sample size; NA = not applicable; NR = not reported; yrs = years

Appendix F Table 2. All-Cause and AAA-Related Mortality Data for Smoking Subpopulation in One-Time Screening Trials (KQ1a)*

Author, Year Trial name Quality	Age	Outcome	Never Smoked, n (%)	Ever Smoked, n (%)	OR (95%CI)	P value for interaction
McCaul, 2016[15] Western Australia Fair	64-83 years (screened)	AAA Mortality	4 (0.11)	28 (0.3)	2.95 (1.04 - 8.43)	NR
		All-cause Mortality	1,310 (36.2)	4,072 (47.4)	1.59 (1.47 - 1.72)	
	Age 65-74 years (screened)	AAA Mortality	1 (0.04)	15 (0.2)	6.31 (0.83 - 47.81)	
		All-cause Mortality	707 (26.7)	2,502 (39.7)	1.81 (1.63 - 2.00)	

* These outcomes reflect rates in the screened group; there was no outcome reporting by smoking status in the unscreened group for comparison. This subgroup analysis does not address whether screening has a differential benefit in smokers.

Abbreviations: AAA = abdominal aortic aneurysm; CG = control group; CI = confidence intervals; IG = intervention group; N = population size; n = sample size; NA = not applicable; NR = not reported; OR = odds ratio

Appendix F Table 3. AAA Prevalence, Rupture, and Surgery Data for Age Subpopulations in One-Time Screening Trials (KQ3a)

Author, Year Trial name Quality	Mean Followup, yrs	Description	Group	N Analyzed	AAA Prevalence, n (%)	AAA Rupture, n (%)	HR (95% CI) for AAA Rupture	All AAA Procedures, n (%)	Elective Surgery, n (%)	Emergency Surgery, n (%)	P value for interaction	HR (95% CI) for Emergency Surgery
McCaul, 2016[15] Western Australia Fair	12.8	65-74 yrs	IG	13266	785.6 (6.6)	NR	NR	382 (2.9)	368 (2.77)	14 (0.11)*	NR	NR
			CG	13239	NR	NR		303 (2.3)	276 (2.08)	27 (0.20)*		
		64-83 yrs Main trial results (see Table 1)	IG	19,249	879 (7.2)†	72‡	NR	562 (2.9)	536 (2.78)§	26 (0.14)*	NR	NR
			CG	19,231	NR	99		458 (2.4)	414 (2.15)	44 (0.23)*	NR	

* Total surgery for rupture
† N analyzed for prevalence: 12,203
‡ p=0.04
§ p<0.001

Abbreviations: AAA = abdominal aortic aneurysm; CG = control group; CI = confidence intervals; HR = hazard ratio; IG = intervention group; N = population size; n = sample size; NA = not applicable; NR = not reported; yrs = years

Appendix F Table 4. AAA Diameter, Rupture, and Surgery Data for Smoking Subpopulations in One-Time Screening Trials (KQ3a)

Author, Year Trial name Quality	Age	Outcome	Never Smoked, n (%)	Ever Smoked, n (%)	OR (95%CI)	P value for interaction
McCaul, 2016[15] Western Australia Fair	64-83 yrs	AAA diameter ≥3.0 cm	117 (3.24)	758 (8.83)	2.90 (2.37 to 3.53)	NR
		AAA Elective Operations	45 (1.24)	360 (4.19)	3.47 (2.54 to 4.75)	
		AAA Ruptures	2 (0.06)	16 (0.19)	3.37 (0.78 to 14.68)	
	Age 65-74 yrs	AAA diameter ≥3.0 cm	55 (2.08)	496 (7.87)	4.03 (3.04 to 5.34)	
		AAA Elective Operations	26 (0.98)	253 (4.01)	4.22 (2.81 to 6.33)	
		AAA Ruptures	1 (0.04)	11 (0.17)	4.63 (0.60 to 35.85)	

Abbreviations: AAA = abdominal aortic aneurysm; CG = control group; CI = confidence intervals; IG = intervention group; N = population size; n = sample size; NA = not applicable; NR = not reported; OR = odds ratio; yrs = years

Appendix F Table 5. All-Cause and AAA Mortality Data for Age Subpopulations in Open Versus Surveillance Trials (KQ4a)

Study, Year Quality	Mean Followup, years	Description	Treatment group	N subgroup	All-cause mortality, n (%)	HR (95% CI)	P value for interaction	AAA-related mortality, n (%)	HR (95% CI)
Lederle, 2002[140]	4.9	50-59 yrs	IG	47	8 (17.0)	1.02 (0.38-2.73)*	NR	NR	NR
			CG	51	8 (15.7)			NR	
ADAM		60-69 yrs	IG	251	61 (24.3)	1.34 (0.93-1.93)*			
			CG	279	55 (19.7)			NR	NR
Good		70-79 yrs	IG	271	74 (27.3)	1.10 (0.78-1.55)*		NR	NR
			CG	237	59 (24.9)			NR	NR
Powell, 2007[161-163]	12	60-66 yrs	IG	176	89 (50.6)	0.73 (0.55-0.99)	0.152	NR	NA
			CG	171	102 (59.6)			NR	
UKSAT		67-71 yrs	IG	191	120 (62.8)	0.86 (0.66-1.11)		NR	NA
			CG	190	125 (65.8)			NR	
Good		72-76 yrs	IG	196	153 (78.1)	1.08 (0.79-1.38)†		NR	NA
			CG	166	125 (75.3)			NR	

*Relative risk

† Primary adj made for age, sex, initial AAA diameter, smoking status, mean of left and right ankle brachial pressure indices, forced expiratory volume in 1s and aspirin use.

Abbreviations: AAA = abdominal aortic aneurysm; ADAM = Abdominal aortic aneurysm Detection and Management study; CG = control group; CI = confidence interval; HR = hazard ratio; IG = intervention group; N = population size; n = sample size; NR = not reported; RR = relative risk; UKSAT = the UK Small Aneurysm Trial

Appendix F Table 6. All-Cause and AAA Mortality Data for Sex Subpopulations in Open Versus Surveillance Trials (KQ4a)

Study, Year Quality	Mean Followup, years	Description	Treatment group	N subgroup	All-cause mortality, n (%)	HR (95% CI)	P value for interaction	AAA-related mortality, n (%)	HR (95% CI)
Powell, 2007[161-163]	12	Men	IG	468	299 (63.8)	0.90 (0.76-1.06)*	0.756	NR	NR
			CG	434	284 (65.4)			NR	
		Women	IG	95	63 (66.3)	0.89 (0.62-1.28)		NR	NR
UKSAT			CG	93	68 (73.1)			NR	
Good									

***** Primary adj made for age, sex, initial AAA diameter, smoking status, mean of left and right ankle brachial pressure indices, forced expiratory volume in 1s and aspirin use.

Abbreviations: AAA = abdominal aortic aneurysm; CG = control group; CI = confidence interval; HR = hazard ratio; IG = intervention group; N = population size; n = sample size; NR = not reported; RR = relative risk; UKSAT = the UK Small Aneurysm Trial

Appendix F Table 7. All-Cause Mortality Data for Smoking Subpopulations in Open Versus Surveillance Trials (KQ4a)

Study, Year Quality	Mean Followup, years	Description	N subgroup	All-cause mortality, n (%)	HR (95% CI)†, ‡	P value for interaction
Powell, 2007[161-163] UKSAT Good	10*	Current Smoker (at BL)	404	204 (50.5)	1.25 (1.03-1.53)	NR
		Former Smoker	620	259 (41.8)	1.00	
		Never Smoker	64	32 (50.0)	1.30 (0.88-1.92)	

*Data are from Powell 2002[161]

† HRs and P values determined by Cox proportional hazards regression analysis and adjusted for baseline age, sex, smoking status, aneurysm diameter, average of left and right ABI, FEV, and use or nonuse of aspirin.

‡ This subgroup analysis reports ACM HRs by smoking status in the entire study population. It does not provide outcomes by IG and CG in smokers and nonsmokers so does not provide comparisons to determine if there is a differential treatment effect of early surgery by smoking status.

Abbreviations: AAA = abdominal aortic aneurysm; ACM = all-cause mortality; CG = control group; CI = confidence interval; HR = hazard ratio; IG = intervention group; N = population size; n = sample size; NR = not reported; RR = relative risk; UKSAT = the UK Small Aneurysm Trial

Appendix G Box 1. Overall summary (Contextual Question 2):

- Major risk factors confirmed to be: older age, male sex, smoking, family history.
- Older adults have higher prevalence and risk of rupture but also higher surgical mortality and competing causes of mortality compared to younger adults. Screening is only rational for surgical candidates. Validated surgical prognostic models are available for decision-making although some issues around predictive accuracy have been raised.
- Women have lower prevalence, higher rupture risk at same diameter but at older age than men. Women have higher surgical morbidity and mortality compared to men. While women female smokers have prevalence approaching that of men in the trials, their surgical morbidity and mortality remain higher than men. A 2018 DA estimated NNIS for 65-70 year old women 1800-3900 (compared to 700 for men).
- With declining prevalence of AAA, male smokers and those with family history have AAA prevalence that approach that of men in the landmark screening trials. There is no available evidence to suggest that smokers or those with family history have different surgical outcomes.

Overall risk by demographic characteristics and smoking status: Large cohort studies and contemporary trial

These cohorts and one contemporary screening trial confirm that older age, male sex, smoking and family history are the strongest risk factors for AAA development.

Lifetime AAA prevalence from contemporary US cohort for age, sex, smoking, race[30]
ARIC Cohort: This cohort reported women have half to one-third the prevalence of AAA as men. Female current smokers have a similar risk as male former smokers. This study is a prospective, community cohort of 15,792 individuals recruited in the U.S. between 1987-1989 and followed through 2013. It reported an overall lifetime risk of developing a clinically significant AAA was 5.6% (95% CI 4.8-6.1). Risk was higher for men (8.2%), whites (6.5%), current smokers (10.5%) and those in the top 2 tertiles of smoking pack-years (9.0% and 11.1%). There was a gradient effect identified for the length of smoking years.

AAA prevalence risk from US self-referred, self-pay screening cohort[29, 179]
Life Line Screening Cohort: A self-referred, retrospective cohort of 3.1 million participants was analyzed to assess risk factors for developing AAA (US, 2003-2008). This population was fairly young (20% <50 yrs), 65% female, and predominantly white (87%). This analysis confirmed that male, smoking, increasing age, family history, and cardiovascular disease are factors that increase risk for developing AAAs. Protective factors were frequent exercise and consumption of nuts, fruits and vegetables. Smoking cessation also reduced risk. This pattern of risk factors mirrors the analysis done on this same dataset examining predictors of large AAA (size ≥5.0cm)

Risk factors in contemporary Danish screening population[22]
VIVA trial: The VIVA trial is a contemporary RCT in Denmark which randomizes male participants aged 65-74 yrs to screening for AAA, PAD, and hypertension or to usual practice of no systematic screening. 18,749 men attended screening and AAA was identified in 619 men (3.3%). Current smoking and family history were strong risk factors for identification of AAA. Current smoker n=258/619 OR 3.25 (2.76 - 3.84). First-degree relative with AAA n=41/619 OR 2.45 (1.76 - 3.41).

Prevalence

Women

The best available evidence estimating AAA prevalence in women is derived from a new meta-analysis by the SWANN collaborative. There is an additional large UK Lifeline cohort that was published subsequent to the meta-analysis.

AAA prevalence in women from meta-analysis of screening cohorts[23]

Overall pooled prevalence of AAA > 3.0 cm estimated to be 0.74% (95% CI 0.53, 1.03) with a higher prevalence in ever-smokers 1.34% (95% CI 0.82, 2.19) and a lower prevalence in never smoking women of 0.28% (95% CI 0.09, 0.93). These estimates are far lower than reported prevalence in men. This is a systematic review and meta-analysis of eight cohort studies (population-based, self-referral, and physician-initiated screening) of AAA screening of 1.5 million women age 60 years and older in Ireland, Italy, Norway, Sweden, UK, US. The range of prevalence reported in these studies was 0.31 to 1.46%.

AAA prevalence in UK self-referred, self-pay screening cohort[247]

Life Line Screening Cohort: The first 50,000 women self-referring and self-paying to attend the Life Line Screening program in the UK and Ireland (2012-2013) were included. The prevalence of AAA in women 66 to 85 yrs was 0.29% (72/25,170). The prevalence in nonsmoking women was 0.26%. In women younger than 66 years of age, the prevalence was 0.02%. In women 66-85 years with a 40-pack year history of smoking, prevalence was 2.14% but there were few women in this category (3/140) so this estimate lacks precision.

Smokers

With declining overall prevalence of AAA over the past 2 decades, one VA study suggests that contemporary male smokers have similar AAA prevalence to those of participants in the 4 landmark screening trials.

AAA prevalence male smokers in a contemporary cohort[212]

This study shows that the prevalence of male ever smokers reaches the prevalence seen in the major screening trials even though overall prevalence is decreasing. A regional VA health care network identified male smokers 65 to 75 yrs of age who had smoked at least 100 cigarettes in their lifetime and screened them for AAA between 2007 and 2011 (n=8,751). The prevalence of for any aneurysm ≥ 3.0 cm was 7.2% with 77.9% of the aneurysms identified measuring between 3.0 – 4.4 cm.

Family history

New evidence from a contemporary Danish screening trial reports that men with a family history of AAA have prevalence similar to those of participants in the 4 landmark screening trials.

AAA prevalence in those with a family history

Reported estimates of prevalence of AAA in those with a family history vary widely and are obtained using a variety of methodology.

The prevalence of AAA in 65 to 74 year old men with at least one first-degree relative with AAA was 6.7%.[217] This is double the prevalence of those without a family history reported in VIVA (3.0%) and having a female relative with the disease had a higher association with AAA risk (OR 4.32 if female first degree relative; OR 1.61 if male relative). The screened arm of the Danish VIVA trial is the only analysis we identified estimating the prevalence of familial AAA based on

population-based screening (N=18,614 screened; 569 with a positive family history based on a questionnaire).

The prevalence of AAA in women with a positive family history in the Life Line Screening cohort (self-referred, self-pay US), was reported to be 1%.[11] This is still much lower than the prevalence of men in the screening trials.

AAA Rupture risk for subgroups

An IPDMA and large UK population cohort demonstrate that older adults, women, current smokers and those with high MAP have higher risk of rupture when controlled for other risk factors.

Small AAA rupture risk from meta-analysis of international studies[69]
Women and current smokers have the highest risk of rupture when controlling for the diameter of the AAA. Individuals under surveillance for small AAAs (n=15,475; k=18; Australia, Canada, Denmark, Norway, Spain, UK, US) were monitored for AAA growth and rupture. The influence of risk factors on rupture was evaluated in an individual patient meta-analysis. Authors found higher rupture rates for women (HR 3.76 [95% CI 2.58, 5.47]), current smokers (HR 2.02 [95% CI 1.33, 3.06]), and those with higher mean arterial blood pressure HR 1.32 [95% CI 1.11, 1.56]).

Large UK population cohort AAA rupture risk[38]
The Oxford Vascular Study was a prospective, population-based cohort in the UK (n=92,728, 2002-2014) that looked at the effect of patient characteristics on acute AAA events (AAA rupture or the symptomatic AAA). Men accounted for 72.8% of the acute events and incidence per 100,000 population per year greatly increased with age although current smokers incurred events at younger ages than ex-smokers or never-smokers. Wide confidence intervals make comparing rates in current female smokers and past male smokers difficult.

Operative mortality and complications

Women

A new meta-analysis reports consistent evidence showing that women have higher post-operative complication rates following EVAR and open repair.

A systematic review (k= 8, n=19,247)[202] found women had higher 30-day mortality compared to men in both EVAR and open repairs. Women had higher 30-day mortality (2.31%) than men (1.37%) after EVAR procedures OR 1.67 (95%CI 1.38, 2.04) and open repair (5.37% vs 2.82%) OR 1.76 (95% CI 1.35, 2.30).

Age

A new meta-analysis reports consistent evidence showing that octagenarians have higher post-operative complication rates following EVAR compared to younger adults.

Meta-analysis comparing surgical outcomes in ≥80 yr olds to <80 yr olds[180]
A systematic review and meta-analysis (k=9, n=25,723) of surgical outcomes in EVAR procedures in patients ≥ 80 yrs compared to younger patients. Octogenarians had a higher 30-day mortality (3.7% vs 1.7%; OR 2.372 [1.992, 2.825]) and a higher rate of 30-day endoleak (25.83% vs 21.31%; OR 1.281 [1.183, 1.388]). Although, octogenarians had higher harms, the authors state that the absolute rates are acceptable.

Family History

A retrospective review of a large US surgical registry did not indicate that individuals with a family history have worse surgical outcomes than individuals without a family history.

Vascular Quality Initiative registry comparing surgical outcomes for those with and without a family history of AAA. [248]

Surgical outcomes were compared for patients with or without a family history of AAA in the VQI registry from 2003-2017. 1997 individuals were identified to have a family history and 18,815 were without a family history. Procedures included open repair and EVAR. No differences were identified in postoperative complications (p=0.510), 30-day mortality (p=0.177), or long-term mortality (p=0.259).

Current Clinical Practice: Surgical Threshold

New data from national registries demonstrate that AAA repair thresholds are lower in clinical practice for both men and women in the US compared to the UK; the US has lower AAA related deaths compared to the UK.

UK v US comparative data of contemporary surgical practice comparing surgical approaches and threshold for intervention in men and women[104]

It is much more common for men and women in the US to undergo repair prior to reaching the indicated surgical thresholds of 5.5 cm for men (39.21% vs 8.82%) and 5.0 cm for women (17.19% vs. 4.72%) compared to the UK. A review of registry data in England and US was undertaken to identify the frequency of AAA repair along with the aortic diameter at the time of repair (2005-2012; n=29,300 in England; n=278,921 in US). Repairs in the US were undertaken at a smaller diameter (5.83 cm vs 6.37 cm, p<0.001) although AAA-related death and hospitalization due to AAA rupture were more common in England.

Outcomes Table for Screening Women

A new decision-analysis with CEA reports that screening women is not cost effective and estimates NNIS of 3,900 to prevent 1 AAA death in women.

Decision-analysis of screening women (outcomes table)[210]

A decision analysis assessing AAA screening in women. If women were screened at age 65 years, 3,900 women would need to be invited to be screened to prevent one AAA-related death with an overdiagnosis rate of 33%. A second strategy of screening women at age 70 years would require 1,800 invitations to screen to prevent one AAA-death with an overdiagnosis rate of 55%. Uncertainty around the AAA prevalence in women makes it difficult to accurately estimate the effects of screening.

Appendix G Table 1. Odds Ratios of Risk Factors Associated With Developing AAAs (Based On Adjusted Multivariate Analyses)

Factors associated with AAA	Any AAA ≥ 3 cm[29]	Any AAA ≥ 5 cm[179]
Male sex (vs. female sex)	5.71	7.70
Female sex (vs. male sex)	NR	NR
Age (vs. < 55 yrs)		
55-59	2.76	3.20
60-64	5.35	8.10
65-69	9.41	13.20
70-74	14.46	20.70
75-79	20.43	32.0
≥ 80	28.37	53.10
Hispanic/Black/Asian (vs. White)	0.69 to 0.72	0.70
Family history of AAA	3.80	3.20
Smoking: years (<10 yrs, 10 to 35 yrs or >35 yrs) + PPD (≤0.5, 0.5 to 1, >1)	2.61 to 12.13	2.60 to14.50
Smoking cessation (5 to 10 yrs, >10 yrs)	0.42-0.87	0.50-0.80
Diabetes	0.75	0.70
CVD morbidities	1.1 to 1.7	1.10 to 1.70

Abbreviations: AAA = abdominal aortic aneurysm; cm = centimeter; CVD = cardiovascular disease; NR = Not reported; PPD = packs per day; Vs = versus; Yrs = years

Appendix H. Ongoing Studies

Trial identifier	Study name	Location	Participants, n	Intervention	Outcome measures	Status Aug 2018
NCT01756833	Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial (N-TA^3CT) Michael Terrin	US	Men and women aged 55 years and older N=261	Doxycycline 100mg po bid for 2 years vs Placebo	AAA growth	Active, expected completion 2019 Protocol published 2016
NCT01683084	Study of the Effectiveness of Telmisartan in Slowing the Progression of Abdominal Aortic Aneurysms (TEDY) (Ronald L Dalman)	US	Adults 50 to 85 years N=22	Telmisartan 40mg daily for 24mo vs Placebo	Rate of AAA growth, AAA diameter, AAA biomarkers, QoL	Completed 2016. No result publication found Protocol published 2015
NCT02717481	Using US to Evaluate Aortic Aneurysm Size Based on 3D Co-registration to Previous CT Scan (Diana Gaitini)	Israel	Men and women aged 18+ diagnosed w/ AAA or following invasive repair N=120	Ultrasound	Primary: Exact and reliable evaluation of the aneurysm size Secondary: The size difference between systolic and diastolic aneurysm; Aneurysm neck size and changes following an invasive procedure to repair it (EVAR); Evaluation of the pressure on the aneurysmal wall	Not yet recruiting, expected completion 2018
NCT01205945	The Effect of Abdominal Aortic Aneurysm Screening on Mortality in Asian Population (Jin Hyun Joh)	S Korea	Men and women aged 50-85 w/ CVD risk factors, family history AAA N=12000	Ultrasound	Benefits of screening older population	Ongoing, estimated completion 2017. No publications found.
NCT02345590	Eplerenone in the Management of Abdominal Aortic Aneurysms (Leah Isles)	Australia	Men and women aged 60-90 w/ AAA 30-49mm N=172	Eplerenone 25mg/day vs placebo	AAA maximum orthogonal diameter	Ongoing, estimated completion 2019
NCT02229006	Sodium Fluoride Imaging of Abdominal Aortic Aneurysms (SoFIA3) (Rachael O Forsythe)	UK	Men and women 50+ in MA3RS study w/ AAA >40mm N=100	Radiation: 18F-NaF PET-CT	Primary: Change in AAA anteroposterior diameter at 6 & 12 months measured w/ CTA Secondary: Co-localisation of 18F-NaF with USPIO uptake on MRI scanning	Completed 2017. No publications found.

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Trial identifier	Study name	Location	Participants, n	Intervention	Outcome measures	Status Aug 2018
NCT02604303	A Prospective Analysis on the Expansion Rates of Abdominal Aortic Aneurysms (Eugene S Lee)	US	Veteran men and women 21+ screened for AAA by VA N=200	Observational using screening	Primary Aortic Expansion Rate measured w/ ultrasound Secondary: RhoA levels	Ongoing, expected completion Nov 2018
NCT02070653	The Efficacy of Ticagrelor on Abdominal Aortic Aneurysm (AAA) Expansion (TicAAA) (Anders Wanhainen)	Sweden	Men and women 50-85yo w/ AAA 35-49mm N=145	Ticagrelor 180mg/day vs placebo	Primary: AAA volume growth measured w/ MRI Secondary: AAA diameter growth measured w/ ultrasound and MRI; need for surgery; rupture	Completed 2018. No publications found.
NCT02548546	Estimation of Biomechanical Aortic Wall Properties in Healthy and Aneurysmal Aortas Using Novel Imaging Techniques (Houssam Farres)	US	Men and women aged 21+ w/ AAA ≥1.5x normal diameter N=30	Surveillance vs open repair vs EVAR	Primary: ECHO imaging Secondary: ECG-gated MRA Imaging	Ongoing (recruiting), expected completion Aug 2018.
NCT02225756	Cyclosporine A in Patients With Small Diameter Abdominal Aortic Aneurysms (ACA4) (Eric Allaire)	France	Men w/ AAA 30-49mm, women w/ AAA 25-44mm 50-85yo N=360	Cyclosporine vs placebo	Primary: AAA diameter evolution on CT-scanner 12 months after treatment interruption Secondary: AAA diameter evolution on duplex-scanner 12 months after treatment interruption; all cause CV mortality/morbidity	Ongoing (recruiting), expected completion Sep 2018
NCT02022436	Evaluation of Predictors of Aortic Aneurysm Growth and Rupture (Rabih Chaer)	US	Men and women aged 21+ diagnosed w/ AAA N=148	Contrast ultrasound	Primary: Time to Growth and/or Rupture of abdominal aortic aneurysm Secondary: AAA-biomarkers	Ongoing (recruiting), expected completion Jul 2020
NCT02179801	Screening Cardiovascular Patients for Aortic aNeurysms (SCAN) (Hans-Henning Eckstein, Karl-Ludwig Laugwitz)	Germany	Men any age w/ 1 or more risk factors for AAA & coronary artery intervention N=1000	Ultrasound screening	Primary: Prevalence of AAA Secondary: Prevalence of AAA in the cohort requiring treatment; Correlation of risk factors for AAA with risk factors for CAD; Distribution of risk factors	Ongoing (recruiting), expected completion Apr 2018. No publications found.

Appendix H. Ongoing Studies

Trial identifier	Study name	Location	Participants, n	Intervention	Outcome measures	Status Aug 2018
NCT02846883	Safety and Efficacy of Allogeneic MSCs in Promoting T-regulatory Cells in Patients With Small Abdominal Aortic Aneurysms (VIVAAA) (Michael Patrick Murphy, Richard L. Roudebush)	US	Men and women aged 40-80 diagnosed w/ AAA 35-45mm	Intravenous infusion of 1 or 3 million allogeneic MSCs/kg vs placebo	Primary: Incidence of treatment related adverse events at 12 months Secondary: Changes in inflammatory AAA-biomarkers; change in aortic inflammation measured by 18-FDG PET/CT	Ongoing (recruiting), expected completion 2021
ISRCTN10945166	Abdominal aortic aneurysm screening by ultrasonography in primary care (Ana Claveria)	Spain	Men 65-74yo N=3348	Screening	Primary: impact of early diagnosis on overall/CV mortality w/ incidental AAA Secondary: CV mortality; surgery for AAA; type of hospital discharge	Ongoing, expected completion 2021
NCT01420991	Brain and Abdominal Aneurysm Study (BAAS) (James Meschia)	US	Men and women aged 18+ diagnosed w/ intracranial aneurysm N=81	Opportunistic screening	Primary: prevalence of AAA Secondary: Functional outcomes at 30 days	Ongoing, expected completion 2024
NCT00662480	Randomized Preventive Vascular Screening Trial of 65-74 Year Old Men in the Central Region of Denmark (VIVA)	Denmark	40,000	Screening for hypertension, lower limb atherosclerosis and abdominal aortic aneurysm	ACM, Cardiovascular events	Active, expected completion Dec 2023 Median (4.4yr) results published in 2017[146]
ISRCTN12157806	The Danish Cardiovascular Screening Trial (DANCAVAS) (Jes Lindholt)	Denmark	45,000	Large population-based randomized clinical multicenter trial testing combo cardiovascular screening in men aged 65-74 year old	ACM, Costs & cost effectiveness after 3,5 and 10yrs to assess possible health and/or societal benefits of the screening; Nationwide registry-based information on health care consumption	Ongoing, expected completion Jan 2026 Protocol published 2015