Chapter 4. Discussion

Summary of Review Findings

We have provided a summary of the evidence by KQ (**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 heterogenous literature; 3) no new small aneurysm early surgery vs. surveillance trials beyond ADAM, UKSAT, PIVOTAL, and 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 KQ

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 vs. control groups for either elective 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 heterogenous 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 smaller than 3 cm in diamter progress to larger than 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 participants 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 to surveillance (until diameter reaches 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 antihypertensive, antibiotic, and 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 ages 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 age 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 compared to the overall trial results. None of the included population-based screening trials included adults younger than age 64 years.

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 an AAA diameter of 5 cm or larger in 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 ages 65 to 74 years to 298 events per 10,000 patient-years for men age 85 years or older.[38] Two-thirds of ruptures were found in those aged 75 years or older.

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 (age ≥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 (standard deviation, 2.8), with more than 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 repair vs. 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 older than age 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 in men.[23, 30] The best available evidence is a meta-analysis of eight studies with more than 1.5 million women age 60 years or 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 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 (three 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 Atherosclerosis Risk in Communities (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=0.002 for interaction).[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 an AAA diameter 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 unlike in men, absolute diameter may not be the best predictor of rupture in women given smaller body surface area. They have proposed the aortic size index (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 in 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 to 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 the surgical threshold of 5 and 5.5 cm, respectively, compared to surveillance.[208, 209]

A recent model examined the effectiveness of screening women age 65 years or older 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 age 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 reduction in rupture and emergency repairs, and 3 percent reduction in AAA-related deaths in women ages 65 to 95 years (or 7% in women ages 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 to 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 CIs 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, and 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,[69] and rupture rates.[69] There is a dose-response relationship as greater smoking exposure is associated with higher ORs for AAA[29, 179] but 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 ages 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 to the MASS trial in which 12 percent of AAA diameters were 5.5 cm or larger 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] The study 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 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 (Vascular Quality Initiative data N=17,346; 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 vs. 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 age 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 its screening guidelines in which men ages 65 to 74 years are eligible for screening regardless of risk factors and reports between a 1 and 3 percent prevalence (2015 to 2017 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 U.S. 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 measuring 4 cm or larger, 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 measuring 3 cm or larger and 5 cm or larger, 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 data to estimate AAA prevalence in the U.S. 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 CT 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 with a mean age of 74 years, with abdominal ultrasound, CT, or MRI for other indications)[230] or 2 percent (in VA men with a mean age of 73 years during CT of abdomen and pelvis),[231] to 5.8 percent (men and women age 50 years or older during abdominal CT scans),[232] and 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 reinterpreted 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 clinicians 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 clinician 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 pre-existing imaging and then reread these images specifically for AAAs. The sensitivity of this approach has been shown to be high (97.2%).[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 to 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 KQs (KQ2, KQ4, and 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 KQs, 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 for AAA in older Caucasian men. 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 predated 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 persons who screen negative and those who 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 persons 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 persons identified with AAA to warrant the CVD risk management strategies for those at high risk for CVD events (statins, hypertension control, and smoking cessation). There is some emerging interest in exploring the potential effects of AAA screening on CVD mortality by identifying persons 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, persons identified with AAA would already be candidates for aggressive CVD risk management based on atherosclerotic cardiovascular disease predicted 10-year risk of 7.5 percent or greater 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 antibiotics, 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, and 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 Danish Cardiovascular Screening Trial, a 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 persons 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 U.S.-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 ages 65 to 75 years and 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, and 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-analysis 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 5 times the number of screenings to prevent 1 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, and persons with family history), with and without additional risk factors, making conclusions challenging.