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Screening for Peripheral Artery Disease Using the Ankle-Brachial Index: An Updated Systematic Review for the U.S. Preventive Services Task Force

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Structured Abstract

Objective: We conducted this systematic review to support the U.S. Preventive Services Task Force (USPSTF) in updating its recommendation on screening for peripheral artery disease (PAD). Our review addressed five key questions: 1) Is screening for PAD in generally asymptomatic adults with the ankle-brachial index (ABI) effective in reducing cardiovascular disease (CVD) or PAD morbidity (e.g., impaired ambulation or amputation) or mortality? 2) What is the diagnostic accuracy of the ABI as a screening test for PAD in generally asymptomatic adults? 3) What are the harms of screening for PAD with the ABI? 4) Does treatment of screen-detected or generally asymptomatic adults with PAD or an abnormal ABI lead to improved patient health outcomes? 5) What are the harms of treatment of screen-detected or generally asymptomatic adults with PAD or an abnormal ABI?

Data Sources: We searched MEDLINE, PubMed publisher-supplied records, and the Cochrane Central Register of Controlled Trials (CENTRAL) for relevant English-language literature published between January 2012 and May 2, 2017. One ongoing screening trial was published after the search date and was formally evaluated for inclusion. Additionally, we re-evaluated all studies included in the 2013 review. We supplemented our searches with reference lists from relevant existing systematic reviews, suggestions from experts, and ClinicalTrials.gov to identify ongoing trials.

Study Selection: Two researchers reviewed 4,194 titles and abstracts and 105 full-text articles applying prespecified inclusion criteria. Eligible studies included: randomized controlled or clinically controlled trials and systematic reviews on the effectiveness of PAD screening and early treatment of screen-detected PAD to prevent CVD and PAD morbidity and mortality and quality of life; observational diagnostic accuracy studies and systematic reviews on the accuracy of the ABI to diagnose PAD; and randomized or clinically controlled trials, cohort studies, observational studies, and case-control studies on the harms of screening and treatment.

Data Analysis: One investigator abstracted data into an evidence table and a second investigator confirmed these data. Two investigators independently assessed study quality using methods developed by the USPSTF. We qualitatively synthesized the data for each key question.

Results: No population-based screening trials evaluated the direct benefits or harms of ABI screening alone. We identified a total of five trials (n=5,864 total) examining indirect evidence for the effectiveness and harms of screening and treatment of screen-detected PAD. A single diagnostic accuracy study in a screen-detected older population of adults (n=306) showed that the ABI has low sensitivity (confidence intervals ranging from 7 to 34% in individual limbs) and high specificity (96 to 100%) characteristics compared with MRA gold standard imaging; false negative rates were high (>80%). Overall, data are limited but suggest that the ABI may not be a sufficiently sensitive screening test to detect PAD in generally asymptomatic adults. Two adequately powered trials (n=4,626) in asymptomatic populations with a low ABI (≤0.95 or ≤0.99) with and without diabetes showed no statistically significant effect of aspirin 100 mg daily for composite CVD outcomes (adjusted HR 1.00 [95% CI, 0.81 to 1.23] and HR 0.98 [95% CI, 0.76 to 1.26]); there were no differences seen in individual CVD outcomes or all-cause mortality compared with placebo control after 6 to 8 years of followup. There is no compelling

evidence to support a differential treatment effect by age, sex, or diabetes status. Limited evidence from one trial demonstrates a trend toward higher risk for major bleeding events with the use of aspirin; the same trial showed no effect on major GI bleeding. Two trials reported conflicting results on total or fatal hemorrhagic CVA risk with wide confidence intervals due to a rare event rate. Two exercise trials (n=932) in populations that were screen-detected or oversampled for no or atypical symptoms reported no differences in quality of life (QOL), the Walking Impairment Questionnaire (WIQ) walking distance, or symptoms at 12 and 52 weeks. No harms were reported in the exercise trials.

Limitations: Our search was limited to English-language literature. We excluded trials specifically recruiting participants from vascular laboratories for screening accuracy studies and treatment trials of symptomatic populations that would not be generalizable to screen-detected or generally asymptomatic populations. Our review protocol prioritized hard health outcomes (PAD and CVD morbidity and mortality; quality of life) and did not include changes in functional testing (e.g., 6-minute walk, lower-extremity strength), changes in the ABI, behavioral changes (e.g., physical activity levels, smoking cessation), or intermediate cardiovascular outcomes (e.g., blood pressure, lipid levels).

Conclusions: The current evidence base for screening for PAD is limited, with no direct evidence examining the effectiveness of ABI screening alone. Indirect evidence is scant and includes a single diagnostic accuracy study of the ABI in an unselected population showing poor sensitivity; two aspirin trials in screen-detected populations (with and without diabetes) with a low ABI defined as ≤ 0.95 or ≤ 0.99 show no benefit for primary composite cardiovascular outcomes. Two underpowered exercise trials in screen-detected or atypical and asymptomatic populations show no statistically significant effect on hard health outcomes.

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Chapter 1. Introduction

Condition Definition

Peripheral artery disease (PAD) is atherosclerotic occlusive disease manifesting in the lower extremities.[1] While the term PAD is also used more broadly to encompass a larger range of noncoronary arterial diseases,[2] this review limits the definition of PAD to lower-extremity PAD. Currently, United States Preventive Services Task Force (USPSTF) recommendations and associated systematic reviews on other peripheral arterial diseases include carotid artery stenosis and abdominal aortic aneurysm.[3, 4]

The resting ankle-brachial index (ABI) is the most commonly used screening and diagnostic test for PAD. It is defined as the ratio of systolic blood pressure at the ankle to the systolic blood pressure at the brachial artery.[5] While the term "abnormal ABI" is often used interchangeably with "PAD" in clinical practice and research, this review will differentiate an abnormal ABI from PAD diagnosed by a confirmatory imaging study (i.e., digital subtraction angiography [DSA], computed tomography angiography [CTA], magnetic resonance angiography [MRA], and duplex ultrasound). Terminology definitions are discussed further in the methods section of this report.

Prevalence

PAD

Studies on the prevalence of PAD among general populations or unselected primary care populations use a low ABI as a surrogate for PAD. However, since the ABI does not have 100 percent sensitivity and specificity, the true prevalence of PAD in the general population is not known.

Abnormal ABI

The definition of a low ABI varies across epidemiologic studies, with some studies using a cutoff of less than 0.9 and others using a cutoff of less than or equal to 0.9. The National Health and Nutrition Examination Survey (NHANES) identified the prevalence of a low ABI (≤0.9) from 1999 to 2004; 5.9 percent of the U.S population age 40 years or older had a low ABI, which amounts to 7.1 million people.[6] Excluding individuals with known coronary artery or cerebrovascular disease, 4.7 percent of the adult U.S. population had a low ABI.[6] NHANES population screening from 1999–2002 identified asymptomatic disease in two-thirds of U.S. adults age 40 or older with an ABI <0.9.[7] Among a self-pay vascular screening cohort of over 3.5 million individuals with a mean age of 64 years, the prevalence of a low ABI (<0.9) was 4.1 percent; 54 percent of these individuals reported no intermittent claudication.[8]

The prevalence of noncompressible arteries (ABI >1.30 or >1.40) is generally low. Among the

NHANES cohort, 3.6 percent had an ABI greater than 1.30 and 1.5 percent had an ABI greater than 1.40.[6] In other community-based cohorts, 3.9 to 5.5 percent had an ABI greater than 1.30 and 1.1 to 1.2 percent had an ABI greater than 1.4.[20-22] The prevalence of noncompressible arteries also increases with age and CVD risk factors. For example, in the United States, 6.3 percent of clinic patients who were older than age 70 years, or those ages 50 to 69 years with CVD risk factors, had an ABI greater than 1.40.[22] While the clinical implications of a high ABI (>1.30 or >1.40) are uncertain, persons with a high ABI are generally older and more likely to have CVD risk factors, particularly diabetes and hypertension.[21-23] Persons with noncompressible arteries who are suspected of having PAD usually go on to additional diagnostic testing.

The most contemporary prevalence data available are baseline data from two Danish population-based screening trials.[24, 25] The Viborg Vascular (VIVA) screening trial of Danish men ages 65 to 74 years identified a PAD prevalence of 11 percent in the screening population, where PAD was defined as an ABI <0.9 or >1.4. Two-thirds of identified patients reported no intermittent claudication.[24] The DANCAVAS screening trial of Danish men and women ages 65 to 74 years reported a PAD prevalence of 19 percent in men and 11 percent in women where PAD was defined as an ABI ≤0.9 or ≥1.4; the proportion reporting symptoms was not reported.[25]

Burden and Natural History

Burden

The global burden of PAD has been estimated to be high.[26] Research has shown that PAD is associated with substantial and statistically significant decrements in health-related quality of life as well as work-related impairments such as absenteeism.[27] While rates of PAD-related amputations have declined over time,[28] major lower-extremity amputations are associated with extremely high mortality risk, with about half of patients dying within 1 year.[29]

Clinical Presentation

PAD may be classified according to its clinical presentation using a Rutherford category or Fontaine staging ranging from asymptomatic PAD to severe disease with associated ulceration or gangrene.[30] While intermittent claudication is the classically described PAD symptom of calf pain associated with walking and relieved by rest,[31] other signs and symptoms of PAD include foot pain at rest; numbness, tingling, cyanosis, hair loss, nonhealing ulcers, or gangrene of the lower extremity; functional impairment (e.g., poor walking endurance, poor standing balance, difficulty rising from a seated position); and erectile dysfunction.[2, 30, 32] It is now understood that the majority of patients with a low ABI may not have classical symptoms of intermittent claudication but may be either asymptomatic or have atypical symptoms.[33] Atypical symptoms may include leg pain on exertion that sometimes starts at rest and exertional leg pain that does not cause the patient to stop walking (i.e., “leg pain/carry on”).

In studies of community-dwelling populations, of those identified with PAD or a low ABI, approximately 10 percent have symptoms of intermittent claudication, 60 percent are asymptomatic, and 30 percent have atypical symptoms (exertional leg symptoms other than

intermittent claudication). In studies of primary care populations, approximately 10 percent have symptoms of intermittent claudication, 30 to 60 percent are asymptomatic, and 50 percent have atypical symptoms.[33] Consistent with the large proportion of patients who are asymptomatic, an abnormal ABI is underdiagnosed; a community-based PAD detection program found that about half of people found to have an abnormal ABI in primary care were not previously diagnosed. [10]

Lower-Extremity Outcomes

The extent of atherosclerosis, acuity of limb ischemia, and ability to restore arterial circulation determine the prognosis of the lower extremity in patients with PAD.[2] For patients with chronic atherosclerosis and progression to symptoms of critical limb ischemia, for example, prognosis for viability of the affected limb is very poor unless it can be revascularized. For patients with acute occlusive events (i.e., thromboembolic occlusion with little underlying atherosclerosis), on the other hand, the prognosis for viability of the limb is related to the rapidity and completeness of revascularization before the onset of irreversible ischemic tissue damage.[2] A 2016 systematic review found that over 5 years of followup, approximately 7 percent (95% CI, 4 to 11) of patients with asymptomatic PAD developed intermittent claudication and approximately 21 percent (95% CI, 12 to 29) of patients with intermittent claudication progressed to critical limb ischemia.[34] Recent investigators have posited that patients with PAD may reduce activity levels as a means to manage symptoms, thus the perceived stability of leg symptoms in many patients may conceal objectively measured functional decline associated with PAD.[35] One cohort study demonstrated that about half of those with asymptomatic low ABI remained asymptomatic over 2 years of followup; however, asymptomatic individuals with a low ABI experienced a dramatically greater annual decline in ambulatory function as measured by the 6-minute walk test compared with those with a normal ABI (-76.8 vs. -8.67 feet).[35]

CVD Outcomes

Because PAD is a manifestation of systemic atherosclerosis, it is associated with the presence of other CVD (e.g., coronary artery disease [CAD], cerebrovascular disease) and CVD events such as myocardial infarction (MI), cerebrovascular accident (CVA), and death.[18] Both CAD and cerebrovascular disease are significantly associated with a low ABI (<0.9).[36, 37] Analysis from the ABI Collaboration individual-patient data meta-analysis of 16 cohorts demonstrated that within each Framingham risk category, those with a low ABI (≤0.90) had about double the 10-year all-cause mortality, cardiovascular mortality, and major coronary event rate compared with the overall rate in a given Framingham risk category.[38] In general, the risk of mortality due to CVD events in persons with a low ABI and/or claudication is similar to that of persons with a history of CAD or cerebrovascular disease.[5] A 2016 systematic review found that the 5-year cumulative incidence of cardiovascular mortality in asymptomatic patients with a low ABI was 9 percent (95% CI, 7 to 12) and 13 percent for patients with symptomatic low ABI (95% CI, 9 to 17); this is compared with an incidence of 5 percent (95% CI, 4 to 6) among patients with a normal ABI.[34]

The presence of PAD confers a high risk for cardiovascular events even in the absence of symptoms.[39-42] Analyses in several general population cohorts with 5 to 7 years of followup that define asymptomatic PAD by an ABI <0.9 or <0.95 suggest that risk for cardiovascular events

may be reasonably similar between symptomatic and asymptomatic PAD. An analysis of 6,880 unselected adults age 65 years or older in Germany showed that among those with PAD, the risk of a composite of all-cause death, MI, and CVA was not statistically significantly different for those with and without symptoms (HR 1.18 [95% CI, 0.92 to 1.52]).[40] However, risk of a composite outcome additionally including lower-extremity peripheral vascular events or any revascularization was statistically significantly higher in those with symptoms (HR 1.48 [95% CI, 1.21 to 1.80]). This composite outcome was driven by peripheral revascularizations, which may have been triggered by symptoms. The presence of PAD conferred high risk for cardiovascular events or all-cause mortality, regardless of symptoms, when compared with adults with no PAD (symptomatic adults HR 1.85 [95% CI, 1.57 to 2.17]; asymptomatic adults HR 1.72 [95% CI, 1.41 to 2.10]). Similarly, an analysis of a Dutch general population cohort of adults ages 40 to 78 years with over 7 years of followup suggests that compared with adults without PAD, asymptomatic PAD is associated with a much higher incidence of fatal cardiovascular disease (35.8 vs 2.3 per 1000 person-years).[41] Additionally, the prognosis for fatal and nonfatal events was similar in those with symptomatic PAD and those with asymptomatic PAD. For example, compared with those with no PAD, the hazard ratio for fatal CVD was 1.6 (95% CI, 1.0 to 2.5) for those with asymptomatic PAD and 1.5 (95% CI, 1.1 to 2.2) for those with symptomatic PAD. The Edinburgh Artery Study, which is an older study consisting of a Scottish general practice cohort of adults ages 55 to 74 years with 5 years of followup, was generally confirmatory; the relative risk for cardiovascular events was highest among adults with intermittent claudication, but confidence intervals overlapped with individuals categorized as having both major and minor symptomatic PAD.[39]

Risk Factors

In addition to increasing age, major risk factors for PAD include diabetes, smoking, hypertension, high cholesterol, obesity, and physical inactivity.[43, 44 45 11, 14, 36, 46-49] Smoking and diabetes show the strongest association with a low ABI in most multivariable analyses; smoking has odds ratios (ORs) ranging from 1.55 (95% confidence interval [CI], 1.34 to 1.79)[11] to 5.35 (95% CI, 1.77 to 16.22)[46] and diabetes has ORs ranging from 1.59 (95% CI, 1.00 to 2.51)[49] to 3.8 (95% CI, 1.6 to 9.0).[47] Among the Lifeline self-pay vascular screening cohort of over 3.5 million individuals, hypertension (OR 2.26 [95% CI, 2.23 to 2.36]), hyperlipidemia (OR 1.35 [95% CI, 1.34 to 1.37]), and sedentary lifestyle (OR 1.38 [95% CI, 1.37 to 1.39]) were all associated with an increased risk of a low ABI (<0.9) in addition to smoking status and diabetes.[50]

Rationale for Screening and Screening Strategies

There are two potential reasons to consider PAD screening. First, screening for PAD may lead to early detection and treatment of PAD before clinical presentation, which may slow the progression of atherosclerosis and resultant functional decline. Second, because PAD is considered an important manifestation of systemic atherosclerosis, screening for PAD in asymptomatic persons may lead to early CVD risk-factor modification in persons with undiagnosed atherosclerosis. In addition to its ability to detect PAD, an abnormal ABI may be useful for improving upon the calibration or discrimination of traditional risk-factor models to predict CVD and may appropriately reclassify risk in some individuals, leading to more

aggressive medical management.

DSA demonstrating 50 percent or more stenosis is used as the gold standard for evaluating the accuracy of other tests to diagnose PAD.[51] As an invasive procedure, DSA carries risks for nephrotoxic and hypersensitivity reactions to the contrast medium, as well as for complications from arterial catheter access.[52, 53] Because of these risks, less invasive angiography (i.e., MRA and CTA) is used in clinical practice for anatomic localization and estimation of degree of stenosis in patients who are candidates for revascularization[54, 55] While the resting ABI is the most commonly used test to screen and detect PAD in clinical settings and is often considered synonymous with PAD,[56] it is important to note that an abnormal ABI is not diagnostic for PAD because resting ABI is a screening test that does not have 100 percent sensitivity and specificity.

Resting ABI

The resting ABI, the ratio of the systolic blood pressure measured over the ankle to the systolic blood pressure measured over the brachial artery,[57] is the most commonly used screening test for PAD. The systolic blood pressure is measured after the patient has rested for 5 to 10 minutes and is in the supine position,[58] using a manual sphygmomanometer and a handheld Doppler ultrasound probe,[59] although specific techniques vary. This variation in measurement protocols (e.g., use of mean vs. highest recorded pressures; manual vs. automated devices) may lead to differences in ABI results.[60-62] AHA guidance recommends using the highest of the two ankle pressures (dorsalis pedis vs. posterior tibial) in each leg divided by the highest of the brachial pressures (right versus left).[63] Overall, the ABI is considered to have good reproducibility (variance of about 0.10).[2]

Traditionally, ABI values of 1.00 to 1.3 are considered normal. ABI values of 0.00 to 0.40 indicate severe PAD and 0.41 to 0.90 indicate mild to moderate PAD, values of 0.91 to 0.99 are considered borderline, and values greater than 1.30 indicates noncompressible arteries.[2] More recent recommendations state that ABI values greater than 1.40 indicate noncompressible arteries and that 1.00 to 1.40 should be considered normal.[32] While the ABI threshold of ≤0.90 has been widely accepted in clinical practice, the data supporting this single threshold are scant and have been based on different reference criteria in different populations.[63]

Other Noninvasive Screening or Diagnostic Modalities

Other noninvasive tools used to diagnose or screen for PAD include the postexercise ABI, toe-brachial index, duplex ultrasound, exercise treadmill testing, segmental pressure measurements, pulse volume recordings, and pulse oximetry.[64]

PAD Symptom Questionnaires

In many epidemiologic surveys, population-based diagnosis and classification have used standardized, symptom-based questionnaires, most commonly the World Health Organization Rose questionnaire or the Edinburgh Modification of the Rose questionnaire. The Walking Impairment Questionnaire and the San Diego claudication questionnaire are more recently

developed questionnaires designed for PAD patients to measure their walking limitations.[2]

Treatment Approaches

The primary aims of treating PAD as a lower extremity disease or treating PAD as a manifestation of systemic atherosclerosis, are to reduce overall CVD morbidity (e.g., MI, CVA), decrease PAD morbidity (e.g., increase walking distance and quality of life by improving symptoms of intermittent claudication and reducing walking impairment, prevent or reduce limb complications, preserve limb viability), and decrease mortality, while minimizing the harms of treatment.[56, 65] Treatment can be categorized into measures to reduce CVD risk or to improve lower-extremity dysfunction or symptoms. CVD risk reduction includes smoking cessation, cholesterol lowering, blood pressure control, and antiplatelet therapy. Medical treatment of symptoms includes pharmacologic (i.e., cilostazol) and nonpharmacologic (i.e., exercise therapy) interventions, but medications approved by the FDA for PAD are all based on trials of symptomatic patients. Revascularization by angioplasty, thrombolysis, stenting, or bypass surgery is reserved for persons with severe symptomatic PAD.[53, 66]

Current Clinical Practice in the United States

Administering the ABI takes about 15 minutes in primary care practices,[2] although it is often performed in specialty settings (e.g., radiology, vascular labs). A survey of primary care practices across the United States found that nearly 70 percent of providers reported never using the ABI in their practice settings, 6 to 8 percent reported using the ABI annually, and 12 to 13 percent reported using the ABI weekly or monthly.[67] A recent analysis of Medicare administrative data shows that noninvasive testing (the ABI, pulse volume recordings, segmental BP, bidirectional Doppler) and duplex ultrasound rates increased from 2001 to 2013 by 63 percent and 88 percent, respectively, with the greatest growth in specialty settings, although indication for testing was not specified.[68]

Professional Organization Guidelines

Based on evidence from a 2015 systematic review,[69] the Society for Vascular Surgery recommended against routine screening for lower-extremity PAD in the absence of risk factors, history, or signs or symptoms of PAD. However, the guidelines state that for asymptomatic individuals at elevated risk (i.e., those over age 70, smokers, diabetic patients, those with an abnormal pulse examination or other established CVD), screening for PAD may be reasonable if used to improve risk stratification, preventive care, and medical management.[56] Similarly, joint recommendations from the American Heart Association and American College of Cardiology Foundation in 2016 recommended against PAD screening in adults who are not at increased risk and do not have a history or physical examination findings suggestive of PAD, but stated that such screening is reasonable in patients at increased risk of PAD (defined as those 65 years or older; those ages 50 to 64 years with risk factors for atherosclerosis, to include diabetes, history of smoking, hyperlipidemia, hypertension, or family history of PAD; those younger than 50 years old with diabetes and one other risk factor for atherosclerosis; or those with known

atherosclerotic disease in another vascular bed)[65, 70] (**Table 1**).

The 2013 joint AHA/ACC guideline on assessment of cardiovascular risk stated that the use of the ABI could be considered to inform decisionmaking if a risk-based treatment decision was uncertain after quantitative risk assessment. This recommendation was based on expert opinion.[71] The American Academy of Family Physicians (AAFP) adopted the 2013 Task Force recommendation that current evidence was insufficient to assess the balance of benefits and harms of screening for PAD and CVD risk assessment with the ABI in adults.[72]

Previous USPSTF Recommendation

In 2013, the USPSTF concluded that evidence was insufficient to assess the balance of benefits and harms of screening for PAD and CVD risk assessment with the ABI in asymptomatic adults. (I statement)[73]

Chapter 2. Methods

Scope and Purpose

This report will be used by the USPSTF to update its 2013 recommendation on Screening for Peripheral Artery Disease and Cardiovascular Disease Risk Assessment with the Ankle-Brachial Index in Adults.[73] A concurrent systematic review will be used to address questions pertaining to the ability of the ABI to improve risk prediction when added to traditional CVD risk assessment.[74]

Key Questions and Analytic Framework

We developed an Analytic Framework (**Figure 1**) and five Key Questions (KQs) to guide the literature search, data abstraction, and data synthesis.

KQs

1. Is screening for PAD in generally asymptomatic adults* with the ABI effective in reducing CVD or PAD morbidity (e.g., impaired ambulation or amputation) or mortality?
   a. Does the effectiveness of screening for PAD vary by subpopulations at greater risk for PAD?
2. What is the diagnostic accuracy of the ABI as a screening test for PAD in generally asymptomatic adults*?
   a. Does the diagnostic accuracy of screening with the ABI vary by subpopulations at greater risk for PAD?
3. What are the harms of screening for PAD with the ABI?
   a. Do the harms of screening for PAD vary by subpopulations at greater risk for PAD?
4. Does treatment of screen-detected or generally asymptomatic adults* with PAD or an abnormal ABI† lead to improved patient health outcomes?
   a. Does the effectiveness of treatment vary by subpopulations at greater risk for PAD?
5. What are the harms of treatment of screen-detected or generally asymptomatic adults* with PAD or an abnormal ABI†?
   a. Do the harms of treatment vary by subpopulations at greater risk for PAD?

* Adults without lower-extremity symptoms clinically considered suspicious for PAD
† Defined as ABI of ≤0.90 or >1.40.

Review Terminology

For the purposes of this review, we will use the following terminology:

- **PAD:** Patients with confirmed PAD diagnosed by a confirmatory imaging study (e.g.,

DSA, CTA, MRA)

- **Low ABI:** Patients with a resting ABI ≤0.9*
- **Abnormal ABI:** Patients with a resting ABI ≤0.9 or >1.3*
- **Atypical lower-extremity symptoms:** Patients with lower-extremity symptoms associated with PAD other than classic intermittent claudication. Two common types of atypical symptoms are: 1) leg pain occurring with exertion and rest and 2) exertional leg pain that does not cause the patient to stop walking ("leg pain with carry on")[33]
- **Generally asymptomatic:** Patients with no lower-extremity symptoms or without symptoms clinically considered suspicious for PAD

* Some studies may use a cutoff of low or abnormal ABI of <0.9 or ≥1.3 or 1.4.

Data Sources and Searches

This review was designed as an update of the screening, diagnostic accuracy, treatment, and harms KQs of our prior systematic review.[75] As such, we evaluated all of the previously included studies from this review for potential inclusion. We then searched for new, primary, published literature from January 2012 to May 2, 2017. We searched the following databases: CENTRAL, Ovid Medline, and PubMed (publisher-supplied records only). We worked with a research librarian to develop our search strategy (**Appendix A**). One ongoing screening trial was published after the search date and was formally evaluated for inclusion. Additionally, due to an expansion in the scope of the current review to include individuals with diabetes as well as exercise or physical therapy interventions aimed at improving lower limb function, we performed a targeted search of the bibliographic database for the previous review for these terms; this database included results of a comprehensive literature search from 1996 to September 2012, as well as outside sources (**Appendix A**).

We also examined the reference lists of recent systematic reviews to identify any potential studies for inclusion.[69, 76-83] We supplemented our searches with articles identified through news and table-of-content alerts such as those produced by the USPSTF Scientific Resource Center LitWatch activity.[84] On January 24, 2017, we searched Clinicaltrials.gov for interventional studies on PAD restricted to adult and senior populations that accepted healthy volunteers. One reviewer scanned titles of the 66 records, and 10 were reviewed in more detail. When the trial description provisionally met criteria, we "matched" the record with the publication. We managed the literature search results using version X7 of EndNote® (Thomson Reuters, New York, NY), a bibliographic management software database.

Study Selection

Our review focuses on the clinical utility of the resting ABI as the primary screening modality because it is the most commonly used screening modality in clinical practice, does not require advanced technical skills or expensive equipment, and is able to detect asymptomatic individuals. Therefore, our review excluded other methods of screening (e.g., questionnaires, the exercise ABI, toe-brachial measurement, pulse oximetry, duplex ultrasound, MRA). Consistent

with the scope of the USPSTF, our review focuses on screen-detected and/or generally asymptomatic adults and thus we excluded studies whose subjects primarily had known intermittent claudication. However, PAD is frequently associated with atypical symptoms not consistent with classic intermittent claudication; two common presentations of atypical symptoms are leg pain on exertion and rest and leg pain with carry on.[33] Even trials primarily recruiting patients with atypical PAD symptoms include a heterogeneous group of individuals in terms of symptom severity: some of these patients will fall in a minimally symptomatic category expected to be detected by screening unselected populations, and others will be on the more severe end of symptom spectrum, where they would clinically present for diagnosis (not screening). Thus, for the purposes of this review, while studies of screen-detected PAD were the ideal; it was not possible to operationalize the clinically relevant concept of "generally asymptomatic" (i.e., those with no lower-extremity symptoms or without high clinical suspicion for PAD). In order to be inclusive, this review included studies with both asymptomatic participants and those with atypical symptoms. We acknowledge that even the trials of patients with atypical symptoms may not entirely represent a screen-detected group, so we examined the mean baseline ABI and WIQ scores to include trials that would be closest to a screen-detected group. We excluded studies conducted exclusively in individuals with known CVD or severe chronic kidney disease (stages 4 and 5). We excluded studies conducted in hospital or specialty settings or that recruited from these settings (i.e., vascular clinics or laboratories), as these settings typically represented populations selected for known or highly suspected PAD.

Our primary outcomes of interest are: cardiovascular morbidity (i.e., MI and CVA), PAD morbidity (e.g., ambulation impairment, amputation), mortality, health-related quality of life, diagnostic accuracy of the resting ABI, adverse outcomes related to the ABI test, and serious adverse events related to treatment. For ambulation impairment, we accepted outcomes from the Walking Impairment Questionnaire (WIQ), a validated, disease-specific questionnaire for individuals with PAD.[85] This questionnaire captures self-reported ambulatory ability for three domains: stair climbing, walking speed, and walking distance; each domain is scored from 0 to 100 where 0 represents an inability to perform the task and 100 indicates no difficulty performing the task. Research has suggested that lower WIQ stair-climbing scores are associated with higher all-cause and cardiovascular mortality among adults with PAD;[86] WIQ distance and speed scores were not associated with mortality in this study. In included studies reporting WIQ outcomes (which were exclusively exercise trials), we also abstracted and present proportions of the population with symptoms at baseline and followup. Consistent with USPSTF methods of focusing on hard health outcomes, we excluded intermediate outcomes of ambulation (e.g., 6-minute walk test, time or distance to claudication, maximum walking distance).

Included treatments were pharmacologic or lifestyle interventions primarily aimed at CVD risk reduction, such as: interventions for smoking cessation, cholesterol-lowering therapy, diet and exercise (with or without weight loss), blood pressure control, and antiplatelet therapy. Newly included in this update were exercise and physical therapy interventions aimed at improving lower limb function. Interventions aimed only at symptomatic adults or adults with critical limb ischemia were excluded. These include pharmacologic symptom management (e.g., cilostazol, prostaglandins), nonpharmacologic symptom management, and revascularization (e.g., angioplasty, thrombolytics, stenting, bypass).

For KQ 1, we considered randomized controlled trials (RCTs), controlled clinical trial (CCTs), and systematic reviews that compared ABI screening to no screening and reported cardiovascular morbidity, PAD morbidity, mortality, or health-related quality of life. For KQ 2, we considered prospectively conducted diagnostic accuracy studies and well-conducted systematic reviews of diagnostic accuracy. We excluded case-control studies in which cases were selected based on individuals having known PAD. Distorted selection of subjects in recruitment or case-control designs has repeatedly been shown to overestimate sensitivity.[87-91] A distorted selection of subjects directly affects the applicability of the study findings and threatens its validity (i.e., spectrum bias). Spectrum bias refers to the phenomenon that diagnostic test performance may change between clinical settings due to changes in the patient case-mix. For KQ 2, diagnostic accuracy studies had to compare the resting ABI with a reference standard. Because the gold standard, DSA, is an invasive test that presents known risks, it is not ethical to administer this test in asymptomatic individuals. Therefore, we considered any diagnostic test that could image the degree of atherosclerosis (e.g., MRA, CTA) or degree of impaired blood flow (e.g., duplex ultrasound) to be a reasonable diagnostic reference standard. We accepted all measures of diagnostic accuracy (e.g., sensitivity, specificity, positive or negative predictive values, positive or negative likelihood ratios). For KQ 4, we included any trial (RCT or CCT) and systematic review with at least 12 weeks of followup that compared treatment of PAD with no treatment, with placebo treatment, or with delayed treatment. Treatment trials needed to report one of the following outcomes: cardiovascular morbidity (i.e., MI or CVA), PAD morbidity (e.g., ambulation impairment, amputation), mortality, or health-related quality of life. While we included reviews, trials, cohort studies, and case-control studies for evaluation of harms (KQs 3 and 5), we excluded case series or case reports.

Comparison of 2013 Review and This Review

While this review was designed as an update of the screening, diagnostic accuracy, treatment, and harms KQs of our prior systematic review,[75] a few changes were made to the inclusion criteria used to guide study selection (**Appendix A Table 1**). One of these changes was an expansion of the eligible population to include individuals with diabetes, who are a subpopulation at higher risk for PAD. Additionally, the scope was expanded to include early treatment trials aimed at improving lower-extremity function in screen-detected or asymptomatic persons with PAD or an abnormal ABI. This type of trial was included based on feedback from experts who stated that there is some evidence of lower-extremity impairment and functional limitation in individuals who do not report classical symptoms of intermittent claudication. Finally, intermediate outcomes (e.g., blood pressure, lipid levels) were removed, and the review focused on hard patient-centered health outcomes; USPSTF methods give greater weight to evidence of an effect on health outcomes than intermediate outcomes.[84]

Quality Assessment and Data Abstraction

Two reviewers applied USPSTF design-specific criteria to assess the methodological quality of all eligible trials (**Appendix A Table 2**),[84] and QUADAS-2 was used to evaluate studies of diagnostic accuracy (**Appendix A Table 3**).[92] Articles were rated as good, fair, or poor quality.

In general, a good-quality study met all criteria well. A fair-quality study did not meet (or it was unclear whether it met) at least one criterion but also had no known important limitation that could invalidate its results. A poor-quality study had a single fatal flaw or multiple important limitations. Flaws leading to a poor-quality rating in the one poor-quality diagnostic accuracy study were concern about the blinding of results between tests and the absence of information on personnel, training, or timing of index and reference standard tests.[93] Treatment trials were rated poor if there were baseline differences between groups, high differential attrition, and no blinding of outcome assessors[94] and for a post-hoc subgroup comparison with scant reported information on the PAD subgroup of interest.[95] We excluded poor-quality studies from this review.

For all of the included studies, one reviewer extracted key elements into standardized abstraction forms and a second reviewer checked the data for accuracy. For diagnostic accuracy studies, we abstracted general characteristics of the study (e.g., author, year, sample size), recruitment setting and method, clinical and demographic characteristics of the sample (e.g., age, cardiovascular risk factors), analytic methods, and results. We abstracted similar information for treatment trials and additionally captured intervention details (e.g., pharmacotherapy dose and duration where applicable; intervention format, provider, duration, and number of sessions where applicable).

Data Synthesis and Analysis

We synthesized data separately for each KQ. The number of contributing studies was not sufficient for quantitative pooling for each one, so we summarized these data in tables and narratively.

For diagnostic accuracy studies (KQ 2), we calculated false positive rates (positive test given the absence of the disease [1 – specificity]) and false negative rates (negative test result given the presence of the disease [1 – sensitivity]) and calculated confidence intervals using the Agresti-Coull method.[96] For the aspirin treatment trials in KQ 4, there was some heterogeneity of trial-defined primary outcome measures, so we used the approach from the 2015 systematic review of aspirin for the primary prevention of cardiovascular events commissioned by the USPSTF.[97] We constructed our own fatal composite outcome (defined as fatal MI/coronary event + fatal CVA + CVD death) and nonfatal composite outcome (defined as nonfatal MI/coronary event + nonfatal CVA). When this outcome was not reported in primary studies, we combined individual component outcomes. When measures of association were not reported, we calculated these measures using the number of individuals and the numbers of events in each randomized group. For the multifactorial trial with additional randomization to antioxidants or placebo, we report results as aspirin versus no aspirin, as there was no evidence of interaction between interventions.[98]

For continuous outcomes reported in exercise trials (KQ 4), we converted standard deviations to 95% confidence intervals using the following standard calculation:

$$95\%\ CI = \text{mean difference} \pm (1.96 * SD_{\text{mean difference}} / \text{sqrt}(n))$$

We estimated the standard deviation for between-group differences using a conservative correlation coefficient (r) of 0.5.[99] We selected a conservative default correlation coefficient in the absence of a trial with a similar population reporting mean and SD changes from baseline for SF-36 and WIQ outcomes. We calculated standard deviation between-group differences using the following formula:

$$SD_{change} = \sqrt{SD^2_{baseline} + SD^2_{followup} - (2 * r * SD_{baseline} * SD_{followup})}$$

For the proportion of participants with symptoms at baseline and followup in exercise trials, we calculated between-group p-values from the test of proportions (using the prtest command in version 13.1 of Stata [Stata Corp LP, College Station, TX]).

Stata was applied for all quantitative analyses.

Grading the Strength of the Body of Evidence

We graded the strength of the overall body of evidence for each KQ. We adapted the Evidence-based Practice Center approach,[100] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[101] 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 KQs (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 is 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 KQ).

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” suggests 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 is likely to change the estimate. A grade of “insufficient” indicates that evidence is either unavailable or does not permit estimate of an effect. Two independent reviewers rated each KQ according to consistency, precision, reporting bias, and overall strength of evidence grade. We resolved discrepancies through consensus discussion involving more reviewers.

Expert Review and Public Comment

A draft research plan was posted on the USPSTF Web site for public comment from March 24 to April 20, 2016. Based on the comments it received about the research plan, the USPSTF clarified that this review will address screening in unselected populations according to USPSTF methodology and will also review the evidence for subpopulations at greater risk for PAD based on age (particularly ≥65 years), sex, race/ethnicity, diabetes, smoking, and hypertension status. Eligibility criteria for this update were expanded to include studies in adults with diabetes. The draft version of this report was reviewed by three invited experts and one USPSTF Federal Partner. Experts were selected based on their expertise on fundamental content aspects of the review (i.e., cardiovascular epidemiology, the ABI, aspirin interventions, exercise interventions) and were selected to obtain diverse informed perspectives, including guideline developers, trialists, specialists, and practicing clinicians. All expert comments were considered, and selected comments from experts were used to clarify and extend the synthesis of evidence to ensure accuracy and address scientifically relevant concerns. All comments were shared with members of the USPSTF and AHRQ.

USPSTF Involvement

We worked with three USPSTF members at key points throughout this review, particularly when determining the scope and methods and developing the Analytic Framework and KQs. After revisions reflecting the public comment period, the USPSTF members approved the final analytic framework, KQs, and inclusion and exclusion criteria. 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

Description of Included Studies

Our literature search yielded 4,194 unique citations. From these, we provisionally accepted 105 articles for review based on titles and abstracts (**Appendix A Figure 1**). After reviewing the full-text articles and performing quality rating, we included five trials that were reported in six publications.[98, 102-106] **Appendix B** contains a full list of included studies. We carried forward two trials (reported in three articles)[102-104] from the previous review[75] and added three trials.[98, 105, 106] A comparison of trials included in this systematic review and previous USPSTF evidence reviews is provided in **Table 2**.

For the 105 articles that we reviewed in full, the most common reasons for exclusion were aim (i.e., not a study of screening or treatment for PAD), population (e.g., inclusion of symptomatic patients), absence of a reference standard (for accuracy studies), and absence of relevant health outcomes. **Appendix C** contains a list of all excluded trials and their reasons for exclusion.

KQ1. Is Screening for PAD in Generally Asymptomatic Adults With the ABI Effective in Reducing CVD or PAD Morbidity or Mortality? KQ1a. Does the Effectiveness of Screening for PAD Vary by Subpopulations at Greater Risk for PAD?

No population-based randomized trials of PAD screening were identified that reported results for ABI screening alone. There are two in-progress multicomponent screening trials, one in Denmark and one in Spain, that include PAD screening as part of a combined vascular screening program.[107, 108] None of these trials tests the independent effectiveness of ABI screening. See the Discussion section for results of the Viborg Vascular (VIVA) multicomponent screening trial.[109]

KQ2. What Is the Diagnostic Accuracy of the ABI as a Screening Test for PAD in Generally Asymptomatic Adults? KQ2a. Does the Diagnostic Accuracy of Screening With the ABI Vary by Subpopulations at Greater Risk for PAD?

Summary of Results

A single diagnostic accuracy study[103, 104] in a screen-detected older population of adults (N=306) showed that the ABI has low sensitivity (7-34%) and high specificity (95-100%) characteristics compared with MRA gold standard imaging. Overall, these data are limited but suggest that the ABI may not be a sufficiently sensitive screening test to detect PAD in unselected populations.

Study Characteristics

No new trials of diagnostic accuracy in screen-detected or generally asymptomatic populations were identified. In the last review,[75] we identified one fair-quality Swedish diagnostic accuracy study (N=306) examining the accuracy of the ABI for the diagnosis of MRA-confirmed PAD.[103, 104] This study reported the sensitivity, specificity, and negative and positive predictive values of the ABI.

Population Characteristics

The study recruited older adults age 70 years at study entry from a random subset of the population-based Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) cohort study (n=1,016) (**Table 3**).[110] Nearly half (47.4%) were women, and all were white. A small number of participants had a history of CVD (6.9% with history of MI and 3.9% with history of CVA), and 10.6 percent had diabetes. One-third of participants were taking antihypertensive medications, and 7.8 percent were current smokers. Prevalence of PAD symptoms (intermittent claudication or atypical leg pain) was not reported.

Intervention Details

ABI

All measurements were performed in the supine position after 30 minutes of rest. Brachial artery systolic measurements were made with a manual sphygmomanometer using an average of three recordings. Posterior tibial artery systolic blood pressure was measured bilaterally using Doppler. The ABI was calculated for each leg by dividing the posterior tibial artery systolic pressure by the brachial artery systolic pressure. The threshold for a low ABI was <0.9.

MRA

The gold standard was whole-body MRA. This test was performed on all subjects in four anatomic locations: supra-aortic arteries and thoracic aorta, abdominal aorta, external iliac arteries continuing to the popliteal arteries, and below the ankle. Gadodiamide contrast was used, and scan time for each of the four stations was 17 s. The threshold for PAD diagnosis was ≥50% stenosis on MRA.

The mean interval between the ABI test and MRA was 16 months (range 3-24 months). Authors did not report whether the personnel performing the MRA were blinded to ABI results.

Study Quality

This publication is a substudy of a population-based screening study of 70-year-old Swedish men and women; therefore, results reflect screening accuracy in older adults who have a higher PAD prevalence. Time lag between the ABI and MRA could have resulted in a lower ABI sensitivity, but it is unlikely that substantial interim development of atherosclerotic lesions would occur;

reported sensitivity analyses by time lag showed similar sensitivity and specificity results. Lack of reporting on blinding of MRA technicians to ABI results is a study limitation.

Results

In this study, ABI recordings and interpretable MRAs were obtained in 268 right limbs and 265 left limbs from the 306 participants. The prevalence of an ABI <0.9 was 4.5 percent in the right leg and 4.2 percent in the left leg (**Table 4**). The prevalence of MRA-confirmed PAD defined as 50 percent or greater stenosis was 19.0 and 23.0 percent in the right and left legs, respectively. One-hundred percent stenosis was detected by MRA in 12.7 and 14.0 percent of right and left legs, respectively.

Based on gold standard MRA-detected stenosis of 50 percent or greater, 20 percent (95% CI, 10 to 34%) and 15 percent (95% CI, 7 to 27%) sensitivity was reported in the right and left legs, respectively. Specificity was 99 percent (95% CI, 96 to 100%) in both limbs. PPV was 83 percent (95% CI, 51 to 97%) and 82 percent (95% CI, 48 to 97%) in the right and left legs, respectively. NPV was 84 percent (95% CI, 79 to 88%) and 80 percent (95% CI, 74 to 84%) in the right and left legs, respectively.

There were no subgroup analyses to examine whether the accuracy results vary by subpopulation.

KQ3. What Are the Harms of Screening for PAD With the ABI? KQ3a. Do the Harms of Screening for PAD Vary by Subpopulations at Greater Risk for PAD?

Summary of Results

The included diagnostic accuracy study reported a high false-negative rate (>80%), reflecting the low sensitivity of ABI in screening for PAD. This single study suggests that screening ABI misses a large proportion of patients with PAD. No other studies addressing screening harms (e.g., anxiety, further diagnostic testing) were identified.

Results

The aforementioned diagnostic accuracy study provided data for the calculation of false positive and false negative rates (**Table 4**). The false positive rate is 0.9 percent (95% CI, 0.0% to 3.5%) and 1.0 percent (0.0% to 3.7%), and the false negative rate is 80.4 percent (67.4% to 89.2%) and 85.2 percent (74.0% to 92.3%) in the right and left legs, respectively. A single participant had a vasovagal attack prior to contrast injection for MRA and was excluded from the study. No other harms were reported in this trial and no additional trials were identified examining the harms of screening for PAD with the ABI.

KQ4. Does Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes? KQ4a. Does the Effectiveness of Treatment Vary by Subpopulations at Greater Risk for PAD?

Summary of Results

We included two trials of aspirin, one new[98] and one from the previous review.[102] The newly included trial exclusively recruited participants with diabetes, thus was not eligible for inclusion in the previous review excluding this population. These two trials powered for composite outcomes in asymptomatic populations with a low ABI with and without diabetes showed no statistically significant effect of aspirin for those composite CVD outcomes or individual CVD outcomes compared with placebo control after 6 to 8 years of followup. There is no compelling evidence to support a differential treatment effect by age, sex, or diabetes status.

Two new trials of exercise therapy were included;[105, 106] supervised exercise and physical therapy were an excluded intervention type in the previous review, although exercise interventions were allowed if their primary aim was to reduce CVD risk or treat CVD risk factors. These exercise trials in participants with a low ABI showed no statistically significant differences in their primary outcomes of walking distance or secondary outcomes of quality of life or self-reported symptoms (intermittent claudication or atypical). One trial was an underpowered 12-week RCT of veterans with atypical or no symptoms; the other was an adequately powered 52-week RCT that recruited participants from an Australian population-based screening trial. Overall, there is inadequate evidence to assess whether exercise interventions improve health outcomes in screen-detected populations with a low ABI.

Aspirin Trials

Study Characteristics

We identified two good-quality Scottish trials (N=4,626) examining the effectiveness of aspirin in populations with a low ABI.[98, 102] The Aspirin for Asymptomatic Atherosclerosis (AAA) trial[102] (N=3,350) was a placebo-controlled randomized trial, and the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial[98] (N=1,276) was a factorial-designed RCT of aspirin and antioxidants (**Table 5**). Primary outcomes were composite cardiovascular endpoints. Both trials included fatal and nonfatal MI and CVA in this composite; in addition, the AAA trial included revascularization in the composite, while POPADAD included above-the-ankle amputation for critical limb ischemia in its composite. A second primary endpoint in POPADAD was CVD mortality (due to MI or CVA). Other reported outcomes included fatal and nonfatal MI and CVA, angina, intermittent claudication, TIA, and all-cause mortality. Mean followup was 8.2 years in AAA, which was terminated early due to futility, and median followup was 6.7 years in POPADAD.

Population Characteristics

The AAA trial recruited men and women ages 50 to 75 years with an ABI ≤0.95 and no history of vascular disease; those recruited were from a community health registry and community volunteers. The POPADAD trial recruited men and women ages ≥40 years with an ABI ≤0.99, diabetes, and no symptomatic CVD from diabetes clinics. Mean age was 62.0 and 60.3 years in the two trials. Approximately half (55.9%) and nearly three-quarters (71.5%) of participants were female in the POPADAD and AAA trials, respectively. All participants had diabetes in the POPADAD trial and 2.6 percent had diabetes in the AAA trial. The mean ABI was 0.86 in AAA and the median ABI was 0.90 in POPADAD. Nearly one-third were current smokers in both trials. Mean HgbA1c was 8.0 in the POPADAD trial. Calculated annual CVD events in the control groups were 0.99 and 2.53 percent in the AAA and POPADAD trials, respectively, indicating that POPADAD participants had higher baseline CVD risk. All participants were asymptomatic in terms of PAD in both trials. Statin use was reported in AAA to be 4.2 percent at baseline and 25 percent at 5 years of followup. Cholesterol and blood pressure values in each trial are reported in **Table 6**.

Intervention Details

The intervention group in both trials received 100 mg daily of enteric (AAA) or nonenteric (POPADAD) coated aspirin orally. The control group in the AAA trial was placebo, and the 2x2 factorial-designed POPADAD trial also included an antioxidant tablet. The intervention groups received aspirin plus placebo or antioxidant plus placebo, compared with the control group which received two placebo tablets. Authors reported no evidence of an interaction between aspirin and antioxidants, so results below are presented for the group taking aspirin (intervention group) compared with the group not taking aspirin (control group).

Study Quality

Both trials had robust reporting, baseline comparability, adjustment for confounders, and outcome ascertainment using multiple data sources (clinic, hospital records, NHS records, death records, patient diary; outcomes adjudication committees). Additionally, both AAA and POPADAD used intent-to-treat (ITT) analyses and had minimal loss to followup (0.3% and 0.5%, respectively). AAA reported that adherence was 60 percent of patient years of followup and that the primary end point did not differ in those taking and not taking the medication at 5 years of followup. POPADAD reported that 14 percent of participants stopped taking trial drugs at 1 year and cumulatively 50 percent of participants withdrew from trial therapy at 5 years of followup.

Both AAA and POPADAD were powered for composite CVD outcomes. This was true despite the fact that the AAA event rate was 60 percent lower than expected, which was reflective of a national reduction in CVD events during the trial period.

Results

Both trials reported no difference between the aspirin and control groups in trial-defined

composite cardiovascular outcomes. In the AAA trial, the adjusted hazard ratio (HR) was 1.00 (95% CI, 0.81 to 1.23) for the primary composite outcome of initial fatal or nonfatal coronary event, CVA, or revascularization. Similarly, in the POPADAD trial the HR was 0.98 (95% CI, 0.76 to 1.26) for the primary composite outcome of death from CHD or CVA, nonfatal MI or CVA, and above-the-ankle amputation for critical leg ischemia. There was no statistically significant difference in fatal CVD events [RR 1.17 (95% CI, 0.72 to 1.89) and HR 1.23 (95% CI, 0.79 to 1.93)] or all-cause mortality [HR 0.95 (95% CI, 0.77 to 1.16) and HR 0.93 (95% CI, 0.71 to 1.24)] (**Table 7**). Examining individual CVD outcomes (e.g., MI, CVA) likewise showed no statistically significant difference between the aspirin and control groups (**Table 8**). The development of intermittent claudication and need for peripheral arterial revascularization or above-the-ankle amputation procedures were similar between the aspirin and control groups (**Table 9**).

In terms of subgroups, there was no compelling evidence to support a differential treatment effect by age or sex. Within-trial comparisons revealed overlapping confidence intervals, and the single trial (POPADAD) with heterogeneity testing for CVD outcomes by age and sex reported nonstatistically significant interaction testing (**Tables 10** and **11**).

Exercise

Study Characteristics

The two exercise trials were new to this update because supervised exercise and physical therapy was not an included intervention type in the prior review. We identified one small, fair-quality U.S. trial by Collins and colleagues (n=50)[105] and one good-quality Australian trial by Fowler and colleagues (n=882)[106] examining the effectiveness of exercise in populations with a low ABI. The U.S. RCT included participants with a low ABI (<0.9) and no intermittent claudication who were referred to a vascular lab, while the Australian trial recruited participants from the population-based, Western Australian abdominal aortic aneurysm-screening trial; participants who screened positive for PAD using either the ECQ or ABI were then randomized to the intervention or control group. Primary outcomes were the change from baseline to followup in walking ability (WIQ walking distance score[105] or ability to walk 100 to 400 yards before onset of intermittent claudication[106]). Secondary outcomes were WIQ-measured speed and stair climbing, the ABI, HgbA1c, lipid values, and PACE scores;[105] HrQOL,[105, 106] physical activity,[106] intermittent claudication based on the ECQ,[106] and smoking.[106] Outcomes were ascertained at 12[105] and 52 weeks[106] of followup.

Population Characteristics

The Collins trial recruited participants who were referred to a Veterans Administration vascular lab with an ABI of 0.5 to <0.9 and without intermittent claudication; participants were almost exclusively men (98%) (**Table 12**). The Fowler trial recruited exclusively men ages 65 to 79 years who screened positive for PAD using the ECQ and/or ABI. Mean age was 69.1 and 73.1 in the trials, respectively. The Collins trial included a majority of white participants (white 64%, black 26%, Hispanic 10%), while the Fowler trial did not report race or ethnicity. Most participants in the Collins trial had hypertension (86%); mean BP was 161/87 mm Hg in the

Fowler trial. Mean total cholesterol was 189 mg/dL in the Collins trial, with approximately 60 percent of participants having an LDL greater than 100 mg/dL and HDL less than 40 mg/dL. Cholesterol levels were not reported in the Fowler trial. The Collins trial had more participants with diabetes (40%), compared with the Fowler trial (17.2%). More than half of the Collins participants were asymptomatic for PAD (56% were asymptomatic and 44% had atypical symptoms) which was intentional as the trial researchers selected participants for asymptomatic and atypical PAD using a telephone administered San Diego Claudication Questionnaire, while the Fowler screen-detected population recruited 27.4 percent asymptomatic participants; 44.6 percent had intermittent claudication and 9.2 percent had atypical symptoms. The mean ABI was 0.74 and 0.79 in the trials, respectively. Thirty percent and 18.7 percent of participants were smokers in the two trials. Nearly one-third of participants in the Fowler trial had angina and one-quarter had history of MI.

Intervention Details

The intervention in the Collins trial included two individual, nurse-delivered components: risk-factor modification and improvement in physical activity (**Table 13**). The risk-modification component included a "recognize, identify, and manage" approach whereby a nurse completed an initial 5-minute assessment of medication adherence followed by dietary advice and metabolic goals (HbA1c, LDL cholesterol). The physical activity component used the Patient-Centered Assessment and Counseling for Exercise (PACE) protocol,[111] which included a readiness-for-change-stage assessment related to physical activity and a tailored handout identifying ways to increase physical activity; followup discussions encouraged regular physical activity. The intervention occurred during an initial, individual, face-to-face session followed by five phone visits lasting less than 30 minutes each which were conducted over 10 weeks. Control group participants were advised to continue routine care with their primary care physicians.

The intervention in the Fowler trial included a smoking cessation intervention and physical therapy (PT) referral. The initial, individual, face-to-face session included an explanation of the PAD screening test results and provision of an educational packet with information about PAD, a brochure about the community PT service, smoking-cessation information if applicable, and a copy of the letter sent to their general practitioner. Participants in the intervention group were advised to discuss PAD with their physician. General practitioners were advised to discuss smoking cessation and refer each participant to the community PT service, which then contacted each participant in the intervention group (the length of this initial session is not reported). The community PT service goal was to increase physical activity and included either weekly, 45-minute supervised sessions for 49 sessions or an individually designed, home-based physical activity program. In addition, all men were advised to walk for 30 minutes or more each day (or water therapy classes or special sessions for those with disabilities). The control group received usual care; nurses briefly disclosed results of diminished flow to lower extremities but stated there was no evidence for any intervention.

Study Quality

The Collins trial was conducted as a small, short-term feasibility study to calculate effect size and estimate power for subsequent trials, so it was not intended to be large enough to detect

differences in the primary outcome (WIQ walking distance). There were large, statistically significant baseline differences in physical functioning scores as measured by the MOS SF-36, with the intervention group having greater (better) physical functioning scores, which may bias against finding a benefit from the intervention (IG 55.0, CG 39.4; p<0.009).

The Fowler trial was powered to detect differences in walking distance (e.g., 90% power to detect a 7.9% between-group difference in the proportion of men able to walk 100–400 yards before onset of intermittent claudication).

In both trials, ITT analyses were used and followup was good to excellent (greater than 80%). The Collins trial did not report whether outcome assessors were blinded. Adherence to the physical activity component differed widely in the two trials. The 12-week Collins trial reported high adherence to the physical activity recommendation of 30 minutes three times per week (40% at baseline and 82% by the fifth [final] phone call), while adherence over the longer Fowler trial was relatively low (only 16.5% of the intervention group attended classes at the 1-year followup).

Results

QOL

Quality-of-life changes from baseline as measured by the MOS SF-36 and Rosser HrQOL instruments were similar between the intervention and control groups in both trials (**Table 14**). For example, in the Fowler trial, the MOS SF-36 component score mean differences between the exercise intervention and control groups ranged from -1.8 to 18.2 without any statistically significant differences between baseline and followup.[106] In the Collins trial, the followup HrQOL scores were nearly identical in the exercise intervention and control groups.[105]

WIQ

The Collins trial reported no difference in the primary outcome of mean walking distance score on the WIQ or walking speed but did report a statistically significantly larger improvement in the stair-climbing component of the WIQ in the intervention group compared with the control group (mean difference 15.1 [95% CI, 2.4 to 32.6]; p=0.02) (**Table 15**).

Symptoms

The Collins trial showed that neither the intervention nor control groups had statistically significant changes in the proportion of participants with symptoms (atypical symptoms or intermittent claudication) over the trial duration; there was no difference between the intervention and control groups (**Table 16**). The Fowler trial reported statistically significant improvements in symptoms in both the intervention and control groups but no difference in proportions of participants with symptoms when comparing the groups. For example, 45.6 and 43.5 percent of the intervention and control groups, respectively, had intermittent claudication at baseline; these proportions decreased to 28.5 and 30.9 percent at 52 weeks (between-group p-value of 0.50). The proportion of participants with atypical symptoms showed a similar pattern,

although it was experienced by fewer participants.

In terms of subgroups, there was no evidence to address whether a differential treatment effect exists in subpopulations at greater risk for PAD.

KQ5. What Are the Harms of Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI? KQ5a. Do the Harms of Treatment Vary by Subpopulations at Greater Risk for PAD?

Summary of Results

Limited evidence from one trial demonstrates a trend toward higher risk for major bleeding events with the use of aspirin. There was no effect on major GI bleeding in one trial. Two trials reported relative risks for total or fatal hemorrhagic CVA less than and greater than 1 with wide overlapping confidence intervals due to rare events. The two exercise trials did not report measuring harms.

Results

The two trials, AAA and POPADAD, report bleeding harms associated with 100 mg daily aspirin use (enteric coated in AAA and nonenteric coated in POPADAD) (**Table 17**). Major GI bleeding, major hemorrhage, and total hemorrhagic CVA were outcomes reported in AAA (N=3,350). Major GI bleeding requiring hospital admission was similar in the aspirin and control groups (0.5% versus 0.5%; relative risk (RR) 1.13 [95% CI, 0.44 to 2.91]). Major hemorrhage (defined as nonfatal or fatal hemorrhagic CVA, fatal or nonfatal subarachnoid/subdural hemorrhage, GI bleed requiring admission, and other bleeding requiring hospital admission) did not reach statistical significance but was higher in the aspirin group (2.0% vs. 1.2%; HR 1.71 [95% CI, 0.99 to 2.97]). There was a trend for increased total hemorrhagic CVA associated with aspirin use; however, confidence intervals were wide due to the rare event rate and crossed one (0.3% vs. 0.2%; RR 1.25 [95% CI, 0.34 to 4.65]); five hemorrhagic CVAs occurred in the aspirin group and four occurred in the control group. POPADAD reported a nonsignificant reduction in fatal hemorrhagic CVA in the aspirin group, but again, confidence intervals were wide due to rare events (0.3% versus 0.5%; RR 0.67 [95% CI, 0.11 to 3.98]); two hemorrhagic CVAs occurred in the aspirin group and three occurred in the control group. POPADAD reported gastrointestinal bleeding without indication of severity, so these results were not included.

There are no subgroup analyses published from the two included trials reporting bleeding harms associated with aspirin in subpopulations at greater risk for PAD.

Chapter 4. Discussion

Summary of Evidence

There is no direct evidence addressing the effectiveness of screening for PAD with the ABI to reduce PAD- or CVD-related morbidity or mortality. However, we are aware of three in-progress trials that include PAD screening as part of combination vascular screening, which may provide overarching direct evidence; two of these trials have anticipated publication dates in the next 1-2 years (2017-18) (**Appendix D Table 1**).[107, 112] The indirect chain of evidence presented in this review is limited. A single diagnostic accuracy study demonstrates that the ABI has poor sensitivity for detecting PAD in unselected populations. In contrast, other systematic reviews of largely symptomatic populations have reported much higher diagnostic accuracy compared with our review.[69, 76, 77, 83] For example, pooled sensitivities and specificities for an ABI ≤0.9 compared with an angiographic gold standard have been reported at 75 percent (95% CI, 71% to 79%) and 86 percent (95% CI, 83% to 90%), respectively, with significant heterogeneity.[83] The far lower sensitivity in our single included study compared with the larger literature in symptomatic populations is likely due to an expected poorer accuracy in screening populations. These populations have lower pretest probability of disease compared with symptomatic populations, as well as issues of study quality in a single study population. One recent diagnostic accuracy study comparing two algorithms for targeted screening in high-risk populations as defined per AHA guidelines[65] (>65 years; 50 to 64 years with a traditional CVD risk factor or family history of PAD; <50 years with diabetes and a traditional CVD risk factor) reported a sensitivity of 49 percent and specificity of 94 percent; this study used the TBI in place of the ABI as the diagnostic test in those with an ABI above 1.4, and was thus excluded from our review.[113] For treatment benefit, our review identified two primary prevention trials of aspirin that recruited asymptomatic individuals with a low ABI. These trials demonstrate that aspirin is not effective in reducing composite CVD morbidity or mortality over 6 to 8 years of followup. Both trials defined a low ABI using higher thresholds than in standard clinical practice (i.e., ≤0.95 or ≤0.99); the aim was to use the ABI as a nontraditional risk factor and identify a population with a higher risk for CVD events that might potentially benefit from aspirin, not to diagnose PAD in a screening population. Other systematic reviews of antiplatelet therapy have similarly reported no overall reduction in CVD events with aspirin, compared with control in populations with a low ABI.[69, 81, 82] Our review did not identify any other pharmacologic trials in screen-detected PAD populations reporting patient health outcomes; observational studies suggest both functional and mortality benefits of statins, but confidence in results is substantially limited by the nonrandomized nature of study designs.[69, 114-117] In our review, two underpowered, short-term exercise trials in participants recruited through screening or oversampling of individuals without symptoms or with atypical symptoms show no statistically significant treatment effect on quality of life or development of symptoms at 3 and 12 months of followup, with the exception of one trial showing an improvement in the stair-climbing component of the WIQ. In contrast, several systematic reviews of exercise therapy in largely symptomatic populations have concluded that exercise programs are associated with improved maximum walking distance and time, pain-free walking distance, 6-minute walk, WIQ scores, and quality of life.[69, 78-80] Consistent with this evidence, the Centers for Medicare & Medicaid Services recently approved coverage of supervised exercise therapy in beneficiaries with intermittent claudication for the treatment of

symptomatic PAD.[118]

Evidence is summarized in the Summary of Evidence (**Table 18**).

Targeting High-Prevalence Subpopulations

Overall, the evidence base addressing screening for PAD in either general or high-risk asymptomatic populations remains scant. While universal screening in primary care populations is inefficient,[119] there is much interest in targeted screening in subpopulations with higher PAD prevalence, such as older adults and patients with diabetes, hypertension, hyperlipidemia, and increased global CVD risk.[120] Screening guidance provided by several professional organizations targets these subpopulations (**Table 1**).[56, 65] In particular, older age, diabetes, and cigarette smoking have been highlighted as risk factors associated with the highest risk for PAD in high-income countries.[15] Several groups have derived models to predict prevalent PAD from population-based cohorts, and some have externally validated these models in non-U.S. populations, demonstrating reasonable sensitivity but low specificity (e.g., sensitivity 85%, specificity 47%);[37, 45, 120, 121] there remains an inadequate evidence base to apply any models in U.S. clinical practice.

The argument in favor of screening follows a logic that these high-prevalence populations can be easily identified based on established risk factors for PAD; that the ABI is relatively accurate based on studies in symptomatic patients; and that cardiovascular risk-factor modification is appropriate because CVD morbidity and mortality are high in adults with PAD regardless of symptoms.[56] Conversely, even when higher-prevalence populations are identified for screening, the missing link in the indirect evidence chain remains the effectiveness of screening in identifying individuals who are not already candidates for pharmacologic and exercise treatment based on their global CVD risk.[122] While there is a robust evidence base supporting treatment benefit in patients with intermittent claudication (exercise, statins, and cilostazol improve walking performance measures; antiplatelet agents reduce revascularization and cardiovascular and all-cause mortality),[123-127] some treatments will be recommended regardless of the ABI (exercise, statins, antiplatelet drugs) based on global CVD risk, while other treatments are only for symptomatic PAD (cilostazol).

Diabetes is a classic example of a disease where early detection is particularly desirable to halt lower-extremity disease progression because PAD outcomes (amputation and mortality) are substantially worse.[128] However, screening considerations in individuals with diabetes have added complexity as an abnormal ABI (both low and high ABI) is quite prevalent;[19, 50, 129-131] the presence of peripheral neuropathy confounds both clinical presentation and ABI accuracy;[76, 132] and most importantly, medical management of CVD risk with tight blood-pressure control, aspirin, statins, and exercise recommendations along with routine foot examination has become the standard of diabetes clinical practice guidelines.[133] It is unclear how screening for PAD would change clinical management in persons with diabetes. This logic holds for other PAD risk factors as well: since the risk factors for PAD (one manifestation of atherosclerotic disease) overlap with the major risk factors for global CVD risk,[71] it is not clear how detection of PAD would alter medical decisionmaking.[73]

Lower-Extremity Treatment Benefit in Screen-Detected Populations

On one hand, expecting unselected, generally asymptomatic populations to achieve improvements in PAD-related morbidity seems unreasonable; on the other hand, if patients unaware of symptoms because of limited activity underwent treatment, there could be potential to improve overall function, ability to ambulate, and quality of life. Supporting this theory is evidence that patients with a low ABI have worse lower-extremity function and quality of life than those with intermittent claudication, positing that perhaps those with asymptomatic PAD reduce their walking to avoid symptoms with subsequent development of muscle wasting and questioning the traditional thinking that presence of symptoms or their severity directly correlates to atherosclerotic occlusive disease severity.[134] Several observational studies of screen-detected or asymptomatic populations demonstrated that those with a low ABI have statistically significantly worse subjective and objective measures of function (6-minute walk distance, 4-meter walking velocity, 400-meter walk time, SF-36 physical functioning subscale scores, WIQ distance and speed scores) compared with those with a normal ABI.[134-139] Two notable exercise-based intervention trials in patients with PAD or a low ABI have shown improved lower-extremity functional outcomes.[140, 141] The GOALS trial demonstrated that a home-based walking program incorporating a group-mediated cognitive behavioral intervention was associated with statistically significant improvements in 6-minute walk, WIQ distance, and speed scores at 6 months, and short physical performance battery and mobility loss at 12 months.[140, 142, 143] Another trial of supervised treadmill exercise and lower-extremity resistance training with similar recruitment to the GOALS trial showed improved 6-minute walk and QOL at 6 months.[141] Both of these trials were not included in our systematic review because although the recruitment approach solicited community as well as clinical referrals with a minority of patients with classic intermittent claudication, the baseline ABIs and WIQ distance and speed scores reflect a more severe functional impairment and disease severity than would be expected in an unselected primary care population. Replication of these findings in screened populations is needed.

Use of the ABI to Improve CVD Risk Prediction and Subsequent Medical Management

Aside from lower-extremity function improvement as a potential benefit from early identification of PAD, a common argument in support of early case-finding is that the detection of PAD signals the presence of widespread atherosclerotic disease, where its detection may lead to CVD risk reclassification and intensive medical management.[38] In this case, the sensitivity and specificity of the ABI in detecting PAD is not relevant as the ABI would be used as a nontraditional CVD risk marker. This critically important question is addressed in a concurrent systematic review evaluating whether the addition of the ABI and other nontraditional risk factors to traditional cardiovascular risk assessment could improve risk prediction in terms of calibration, discrimination, and risk reclassification.[74] This systematic review identified a large body of evidence from 21 unique cohorts, including one IPD meta-analysis of 18 cohorts for the ABI as a nontraditional risk factor.[144] The extension of the Framingham risk prediction model to include the ABI in the IPD MA was performed in a development/internal validation data set of over 27,000 participants and evaluated in an external validation dataset of over 20,000

participants.

Collectively, evidence suggests that the addition of the ABI to traditional risk factors can improve risk prediction in some subpopulations. Results are more robust for discrimination and reclassification (as opposed to calibration), and point to a larger improvement in predictive accuracy for women, particularly those at intermediate risk. The ability of the ABI to improve risk prediction is particularly notable when the performance of traditional cardiovascular risk prediction models is poor (for example, in women) or when clinical action is uncertain (e.g., intermediate risk individuals). While the ABI added to traditional cardiovascular risk assessment may improve predictive accuracy in some subpopulations, the clinical impact of such changes is unknown, limiting application to clinical practice.

Limitations of the Review

Our review captured a single trial of ABI accuracy because this was the only accuracy trial in which the ABI was used in an unselected population applicable for screening. Trials using convenience samples from vascular labs were excluded as they would represent an enriched sample and such studies are subject to spectrum bias when applying them to screening populations.[87-91] We recognize that there is much broader and higher-quality literature reporting ABI accuracy, with sensitivities and specificities ranging from 17 to 100 percent and 80 to 100 percent.[56, 63] We also recognize that in clinical practice, an abnormal ABI is often considered diagnostic of PAD, and that duplex, CTA, MRA, and DSA are used for localization of stenoses for the purpose of surgical intervention rather than for confirmation of PAD. The scope of this review did not include diagnostic accuracy of other screening methods or modalities such as automated oscillometric ABI measurement methods,[145, 146] the postexercise ABI (which may be relevant in clinically "asymptomatic" populations that self-limit exertion), and the toe-brachial index.

For treatment trials, our review's requirement that the treated population could be considered an unselected population with population-based or primary care recruitment could be considered unnecessarily limiting. However, in order to develop an indirect chain of evidence in support of screening, it is critical that treatment trials are applicable to a population that reflects the screen-detected population in terms of disease severity and treatment effectiveness. The prespecified hard health outcomes abstracted in this review include CVD and PAD morbidity or mortality or quality of life with the exclusion of intermediate outcomes (behavior changes, intermediate measures of lower limb function [6-minute walk test or lower-extremity strength], the ABI, or intermediate cardiovascular risk factors). We did exclude a 12-month study of 355 adults with PAD or a low ABI that evaluated a telephone counseling intervention designed to motivate patients to request more intensive cholesterol-lowering therapy from their physician.[147] This study found that LDL-cholesterol reduction was not statistically significantly greater in the intervention compared with the usual care group (mean between-group difference of 5.1 mg/dL (95% CI, -2.9 to 13.1]). No studies of asymptomatic populations were excluded on the basis of reporting the 6-minute walk but not CVD or PAD morbidity and mortality. The included treatment trials reporting QOL most commonly used the SF-36, and none of the included studies used the Vasculo-QOL questionnaire, which is better able to discriminate between severe and

mild disease at baseline and between large and small change in disease severity after followup;[148] this reflects a limitation in the literature rather than in the review approach.[148]

Population-Based Multicomponent Screening Trials

There are three population-based screening trials that examine the effectiveness of the combination of multiple vascular screening tests on all-cause mortality and/or cardiovascular morbidity and mortality at 10 to 15 years of followup; one trial has reported results and two are in progress. The Viborg Vascular (VIVA) screening trial enrolled 50,156 men ages 65 to 74 years from 2008–2011.[109] Participants were randomized to screening versus no screening for hypertension, PAD, and abdominal aortic aneurysm (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. An interim analysis at median 4.4 years of followup reported a 0.006 (95% CI, 0.001 to 0.011) absolute decrease in all-cause mortality (hazard ratio, 0.93 [95% CI, 0.88 to0.98]) in the screened group. Based on post-hoc sensitivity analyses removing smokers or those initiating hypertensive therapy, which did not alter the results, authors hypothesize that the benefit was largely seen from preventive measures including statin and aspirin use. Applicability of such findings to the U.S. population are called into question because: 1) hypertension screening and management are standard practice and occur at a lower diagnostic threshold than used in the trial; 2) AAA screening in ever-smoking men in this age group is already recommended (although variably implemented); and 3) nearly all participants would have 10 percent or greater 10-year ASCVD risk based on age and male sex alone, they would be candidates for consideration of statins or aspirin already. Secondary analyses including cost-effectiveness analyses to isolate the effect of ABI screening are planned, but these analyses would be considered exploratory; it is unlikely that such analyses would definitively demonstrate ABI screening effectiveness given the aforementioned considerations. The second trial, the Danish Cardiovascular Screening Trial (DANCAVAS), has an estimated enrollment of 45,000 men ages 65 to 74 years who are randomized to no screening or screening including the following components: brachial and ankle blood-pressure index to detect PAD and hypertension, low-dose CT scan to detect coronary artery calcification and aortic/iliac aneurysms, telemetric assessment of heart rhythm, and measurement of cholesterol and plasma glucose levels.[107] The primary outcome of this study is overall mortality. Enrollment began in October 2014 and 10 years of followup is planned. An interim publication is planned for mid-2018.[149] The third trial, the ILERVAS project in Spain, is currently enrolling adults ages 45 to 70 years with at least one cardiovascular risk factor, recruited from primary health care centers; the planned N is 19,800.[108] The intervention group will receive multicomponent screening for subclinical arterial disease (including ABI assessment) and chronic kidney disease. Ten years of followup for cardiovascular disease is planned.

Future Research Needs

Given the paucity of included studies and the high prevalence of undetected PAD—particularly in high-risk populations—there is opportunity for future research to clarify the role of PAD screening in primary care. First, a population-based screening trial of ABI screening versus no

screening with robust subpopulation analyses ideally would answer this question definitively. The VIVA trial, as well as two ongoing trials,[107, 108] include the ABI in addition to other vascular screening tests, so it will not be possible to estimate the independent effect of the ABI. Nonetheless, population-based trials of screening ABI alone compared with no screening would represent the highest-quality evidence examining the effectiveness of screening. In the absence of direct evidence, additional studies of ABI accuracy against a duplex ultrasound gold standard in unselected populations would be useful to estimate accuracy in a population with a spectrum of disease reflective of a screened population. Exercise and statin trials specifically recruiting screen-detected populations may support screening, and inclusion of populations at clinically accepted diagnostic thresholds (i.e., <0.9) would enhance the applicability of evidence. If treatment effectiveness has been established in this population, then validated risk models would be useful to identify individuals for targeted screening in primary care.

Conclusion

The current evidence base is limited, with no direct evidence examining the effectiveness of ABI screening alone for PAD. Indirect evidence is scant and includes a single ABI accuracy study in an unselected population showing poor sensitivity; two aspirin trials in screen-detected populations (with and without diabetes) with a low ABI defined as ≤0.95 or ≤0.99 show no benefit for primary composite cardiovascular outcomes. Two underpowered exercise trials in screen-detected, atypical, or asymptomatic populations show no statistically significant effect on hard health outcomes.

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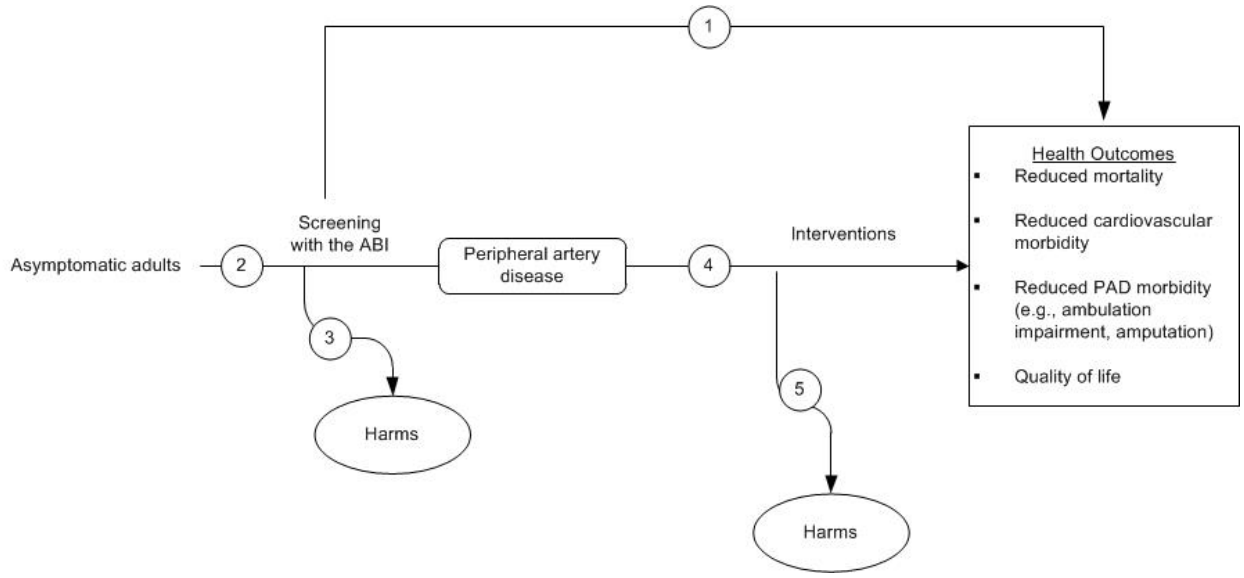
Figure 1. Analytic Framework



Abbreviations: ABI = ankle-brachial index; PAD = peripheral artery disease

Table 1. Recommendations of Other Organizations for Screening for PAD With the ABI in Individuals Without History or Physical Examination Findings Suggestive of PAD

		AHA/ACC 2016[65]	SVS 2015[56]	USPSTF 2013[73]	AAFP 2013[150]	NICE 2012[151]	ACPM 2011[152]
Asymptomatic adults with no risks	**Population**	Adults not at increased risk of PAD and without history or physical examination findings suggestive of PAD	Adults with the absence of risk factors, history, signs, or symptoms of PAD	Adults with no known diagnosis of PAD, CVD, severe CKD, or DM	Endorses USPSTF 2013	NA	Adults
	Recommendation (Grade)	No (Class III: No benefit; B-NR)*	No (2;C)†	No (I statement)‡	No (I statement)‡	NA	No (NA)
Asymptomatic adults with elevated risks	**Population**	Aged ≥65 y; Age 50-64 y with risk factors for atherosclerosis (e.g., DM, history of smoking, hyperlipidemia, hypertension) or family history of PAD; Age <50 y with DM and 1 other risk factor for atherosclerosis; known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis, or AAA)	Aged >70 y, smokers, DM; abnormal pulse examination; or other established CVD	NA	Aged >65 y; ≥50 y with history of DM, smoking, exertional leg pain, or a nonhealing extremity wound	Adults ≥18 y; symptoms suggestive of PAD **or** DM, nonhealing wounds on legs or feet or unexplained leg pain **or** considered for interventions to the leg or foot **or** need to use compression hosiery	>50 y, smokers, and DM and with clinical evidence of vascular disease
	Recommendation (Grade)	Yes, reasonable (Class IIa, B-NR)§	Yes, reasonable (2; C)†	NA	Yes (C)	Yes, suspected PAD (NA)	NA

*Class of recommendation: Class III indicates no benefit where benefit=risk (moderate strength) and level B quality of evidence (nonrandomized designs)
†Defined as weak recommendation based on low-quality or very-low-quality evidence
‡I statement is insufficient to assess the balance of benefits and harms of service
§Class of recommendation: Class IIa indicates moderate benefit where benefit >>risk (moderate strength) and level B quality of evidence (nonrandomized designs)

Abbreviations: ABI = ankle-brachial index; ACMP = American College of Preventive Medicine; AHA/ACC = American Heart Association and American College of Cardiology; CKD = chronic kidney disease; AAFP = American Academy of Family Physicians; DM = diabetes mellitus; NA = not applicable or not provided; SVS = Society for Vascular Surgery; USPSTF = United States Preventive Services Task Force; y = year(s)

Table 2. Comparison of Studies Included in Previous and Present USPSTF Reviews

USPSTF Recommendation		USPSTF Reviews and Recommendations			
		D* for routine screening	D* for routine screening	I† for screening and risk assessment with the ABI	
KQ	Study	1996[153]	2005[154]	2012[75]	Current
KQ1 Morbidity	Fowler 2002[106]		X		
KQ2 Diagnostic Accuracy	Wikstrom 2009[104]			X	X
	Wikstrom 2008[103]			X	X
	Vogt 1993[155]	X			
	Moneta 1987[156]	X			
	Strandness 1987[157]	X			
	Criqui 1985[158]	X			
	Barnes 1979[159]	X			
KQ3 Screening Harms	Wikstrom 2009[104]				X
	Wikstrom 2008[103]				X
Risk Prediction*	Hoorn 2012[160]			X	
	Kavousi 2012[161]			X	
	Murphy 2012[162]			X	
	Yeboah 2012[163]			X	
	Rodondi 2010[164]			X	
	Fowkes 2008[38]			X	
	Sutton-Tyrrell 2008[165]			X	
	Price 2007[166]			X	
	Weatherley 2007[167]			X	
	O'Hare 2006[20]			X	
	Lee 2004[168]			X	
	Van der Meer 2004[169]			X	
	Abbott 2001[170]			X	
	Abbott 2000[171]			X	
	Tsai 2001[172]			X	
	Vogt 1993[155]	X			
KQ4 Treatment Benefit	McDermott 2011[147]			X	
	Fowkes 2010[102]			X	X
	Belch 2008[98]				X
	Collins 2007[105]				X
	McDermott 2003[114]		X		
	Fowler 2002[106]				X
	Tornwall 1997[173]		X		
KQ5 Treatment Harms	Fowkes 2010[102]			X	X
	Belch 2008[98]				X

*A D Recommendation is defined as: "The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits."
† An I Statement is defined as: "The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined."

Abbreviations: ABI = ankle-brachial index; KQ = key question; USPSTF = United States Preventive Service Task Force

Table 3. Study and Participant Characteristics for KQ2: What Is the Diagnostic Accuracy of the ABI as a Screening Test for PAD in Generally Asymptomatic Adults?

Study name Author, Year	Quality	Country	N Analyzed	Recruitment setting and method	ABI cutoff	Reference standard	Mean age, years	% Women	% White	% Risk factor
PIVUS Wikstrom, 2008[103] Wikstrom, 2009[104]	Fair	Sweden	306 (analyzed as 268* right and 265* left limbs)	Community; Population-based	<0.9	MRA	70	47.4	100†	Current smoker: 7.8 Hx MI: 6.9 Hx CVA: 3.9 HTN meds: 33 Hx DM: 10.6

*Number for whom ABI recordings and assessable MRA examinations were obtained
†Assumed

Abbreviations: ABI = ankle-brachial index; DM = diabetes mellitus; HTN meds = anti-hypertensive medications; Hx = history; KQ = key question; MI = myocardial infarction; MRA = magnetic resonance angiography; N = sample size; PAD = peripheral artery disease; PIVUS = Prospective Investigation of the Vasculature in Uppsala Seniors

Table 4. Results for KQ2: What Is the Diagnostic Accuracy of the ABI as a Screening Test for PAD in Generally Asymptomatic Adults?

Study name Author, Year	% with ABI <0.9	% Stenosis on MRA	% Sensitivity/Specificity (95% CI)	% PPV/NPV (95% CI)	FPR/FNR (95% CI)
PIVUS Wikstrom, 2008[103] Wikstrom, 2009[104]	*Right leg* 12/268=4.5% *Left leg* 11/265=4.2%	≥ 50% stenosis *Right leg* 51/268 =19.0% *Left leg* 61/265= 23.0%	*Right leg* Sensitivity: 20 (10 to 34) Specificity: 99 (96 to 100) *Left leg* Sensitivity: 15 (7 to 27) Specificity: 99 (96 to 100)	*Right leg* PPV: 83 (51 to 97) NPV: 84 (79 to 88) *Left leg* PPV: 82 (48 to 97) NPV: 80 (74 to 84)	*Right leg* FPR: 0.9% (0.0% to 3.5%) FNR: 80.4% (67.4% to 89.2%) *Left leg* FPR: 1.0% (0.0% to 3.7%) FNR: 85.2% (74.0% to 92.3%)
		100% stenosis *Right leg* 34/268 =12.7% *Left leg* 37/265=14.0%	*Right leg* Sensitivity: 24 (11 to 42) Specificity: 98 (95 to 99) *Left leg* Sensitivity: 16 (7 to 33) Specificity: 98 (95 to 99)	*Right leg* PPV: 67 (35 to 89) NPV: 90 (85 to 93) *Left leg* PPV: 55 (25 to 82) NPV: 88 (83 to 91)	Not calculated

Abbreviations: ABI = ankle-brachial index; CI = confidence interval; FNR = false negative rate; FPR= false positive rate; KQ = key question; MRA = magnetic resonance angiography; NPV = negative predictive value; PAD = peripheral artery disease; PIVUS = Prospective Investigation of the Vasculature in Uppsala Seniors; PPV = positive predictive value

Table 5. Methodological and Intervention Characteristics for Included Aspirin Studies for KQ4: Does Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes?

Trial name Author, Year	N	Study design	Inclusion	Recruitment	ASA dose & formulation	ASA duration & mean followup	Primary endpoint	Secondary endpoints	Adherence & crossover
AAA Fowkes, 2010[102]	3,350	RCT	Men and women ages 50-75 years with no history of vascular disease and an ABI ≤0.95	Community health registry and community volunteer	100 mg daily, tablet, enteric coated	8.2 years*	Composite outcome: initial fatal or nonfatal coronary event or CVA or revascularization	1) All initial vascular events, defined as a composite outcome: primary end point event or angina, intermittent claudication, or TIA; 2) all-cause mortality	Participants adhered to study medication for 60% of p-y of F/U. Effect on primary end point did not differ between those taking and not taking medication at 5 years
POPADAD Belch, 2008[98]	1,276	2x2 RCT, Antioxidant	Men and women age ≥40 years with diabetes, no symptomatic CVD, and an ABI ≤0.99	Diabetes clinics	100 mg daily, tablet, not enteric coated	6.7 years†	2 composite end points: 1) death from CHD or CVA, nonfatal MI or CVA, above ankle amputation for critical limb ischemia; 2) death from CHD or CVA	All-cause mortality; nonfatal MI; and occurrence of other individual vascular events	At 1 year, 14% of participants stopped taking trial drugs; at 5 years, 50% (cumulative) of patients withdrew from trial therapy

*Terminated early
†Median

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle-brachial index; ASA = aspirin; CHD = coronary heart disease; CVA = cerebrovascular accident; F/U = followup; MI = myocardial infarction; N = number; PAD = peripheral arterial disease; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RCT = randomized controlled trial; p-y = patient years; TIA = transient ischemic attack

Table 6. Participant Characteristics for Included Aspirin Studies for KQ4: Does Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes?**

Trial name Author, Year	Quality	Country	N	Age, years (mean)	% Female	SBP/DBP, mm Hg (mean)*	TC, mg/dL (mean)	LDL, mg/dL	HDL, mg/dL	% with DM†	% with Low ABI	% Asymptomatic	ABI (mean)	% Current smokers	Annual risk of CVD events (%)‡
AAA Fowkes, 2010[102]	Good	Scotland	3,350	62.0	71.5	148/84	238§	NR	NR	2.6	100.00 with an ABI ≤0.95‖	100.0	0.86	33.0	0.99
POPADAD Belch, 2008[98]	Good	Scotland	1,276	60.3	55.9	145/79	213.3 ¶	120¶	47¶	100.0	100.0 with an ABI ≤0.99#	100.0	0.90‖	31.1	2.53

* Percent with hypertension not reported in either trial. In AAA, 15.2% were treated with a diuretic, 6.4% were treated with a nitrate or calcium channel blocker, 6.2% were treated with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, and 9.8% were treated with a beta blocker. Hypertension treatment was not reported in POPADAD.
†Mean fasting plasma glucose not reported; mean HbA1c was 8.0% in POPADAD and was not reported in AAA
‡Data are from Berger 2011 meta-analysis;[174] calculated as percent with cardiovascular events in control group/years followup
§4.2% were on lipid-lowering treatment at baseline and 25% were treated at 5 years; use of lipid-lowing treatment was not reported in POPADAD.
‖ Referred to as low ABI (not PAD)
¶ Median
# Referred to as asymptomatic PAD
** Mean CVD risk score was not reported in either trial; no participants in either trial had prior CVD. Median body mass index in POPADAD was 29.2 and was not reported in AAA.

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle-brachial index; CVD = cardiovascular disease; DBP = diastolic blood pressure; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; N = number; NR = not reported; PAD = peripheral arterial disease; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; SBP = systolic blood pressure; TC = total cholesterol

Table 7. Composite and Mortality Outcomes for Included Aspirin Studies for KQ4: Does Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes?

Outcome	Trial name Author, Year	Mean F/U, years	IG N Analyzed	IG N Events (%)	CG N Analyzed	CG N Events (%)	IG vs. CG HR (95% CI)
Primary Composite CVD Outcome*	AAA Fowkes, 2010[102]	8.2	1,675	181 (10.8%)	1,675	176 (10.5%)	1.00 (0.81 to 1.23)†
	POPADAD Belch, 2008[98]	6.7‡	638	116 (18.2%)	638	117 (18.3%)	0.98 (0.76 to 1.26)
Composite Fatal Coronary Events + CVA + CVD Death	AAA Fowkes, 2010[102]	8.2	1,675	35 (2.1%)§	1,675	30 (1.8%)§	1.17 (0.72 to 1.89)§‖
	POPADAD Belch, 2008[98]	6.7‡	638	43 (6.7%)	638	35 (5.5%)	1.23 (0.79 to 1.93)
Composite Nonfatal MI + CVA	AAA Fowkes, 2010[102]	8.2	1,675	99 (5.9%)§	1,675	106 (6.3%)§	0.93 (0.72 to 1.22)§‖
	POPADAD Belch, 2008[98]	6.7‡	638	84 (13.2%)§	638	97 (15.2%)§	0.87 (0.66 to 1.14)§‖
All-Cause Mortality	AAA Fowkes, 2010[102]	8.2	1,675	176 (10.5%)	1,675	186 (11.1%)	0.95 (0.77 to 1.16)
	POPADAD Belch, 2008[98]	6.7‡	638	94 (14.7%)	638	101 (15.8%)	0.93 (0.71 to 1.24)

* Defined in AAA as: initial fatal or nonfatal coronary event or CVA or revascularization; defined in POPADAD as death from CHD or CVA, nonfatal MI or CVA, above ankle amputation for critical limb ischemia

† HR adjusted for baseline age, ankle-brachial index, cholesterol, systolic blood pressure, smoking, and socioeconomic status; unadjusted HR 1.03 (95% CI, 0.84 to 1.27)

‡ Median

§ Calculated

‖ RR

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis Trial; Adj = adjusted; CG = control group; CI = confidence interval; CVA = cerebrovascular accident; CVD = cardiovascular disease; HR = hazard ratio; IG = intervention group; MI = myocardial infarction; N = sample size; NR = not reported; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RR = relative risk

Table 8. Myocardial Infarction and Cerebrovascular Accident Outcomes for Included Aspirin Studies for KQ4: Does Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes?

Outcome	Trial name Author, Year	Mean F/U, yrs	IG N Analyzed	IG N Events (%)	CG N Analyzed	CG N Events (%)	IG vs. CG HR (95% CI)
Nonfatal MI + coronary death	AAA Fowkes, 2010[102]	8.2	1,675	90 (5.4%)*	1,675	86 (5.1%)*	1.05 (0.78 to 1.40)*†
	POPADAD Belch, 2008[98]	6.7‡	638	90 (14.1%)*	638	82 (12.9%)*	1.10 (0.83 to 1.45)*†
Fatal coronary event	AAA Fowkes, 2010[102]	8.2	1,675	28 (1.7%)	1,675	18 (1.1%)	1.56 (0.86 to 2.80)*†
	POPADAD Belch, 2008[98]	6.7‡	638	35 (5.5%)	638	26 (4.1%)	1.35 (0.81 to 2.25)
Nonfatal MI	AAA Fowkes, 2010[102]	8.2	1,675	62 (3.7%)	1,675	68 (4.1%)	0.91 (0.65 to 1.28)*†
	POPADAD Belch, 2008[98]	6.7‡	638	55 (8.6%)	638	56 (8.8%)	0.98 (0.68 to 1.43)
Total CVA	AAA Fowkes, 2010[102]	8.2	1,675	44 (2.6%)*	1,675	50 (3.0%)*	0.88 (0.59 to 1.31)*†
	POPADAD Belch, 2008[98]	6.7‡	638	37 (5.8%)*	638	50 (7.8%)*	0.74 (0.49 to 1.12)*†
Fatal CVA	AAA Fowkes, 2010[102]	8.2	1,675	7 (0.4%)	1,675	12 (0.7%)	0.58 (0.23 to 1.48)*†
	POPADAD Belch, 2008[98]	6.7‡	638	8 (1.3%)	638	9 (1.4%)	0.89 (0.34 to 2.30)
Nonfatal CVA	AAA Fowkes, 2010[102]	8.2	1,675	37 (2.2%)	1,675	38 (2.3%)	0.97 (0.62 to 1.52)*†
	POPADAD Belch, 2008[98]	6.7‡	638	29 (4.6%)	638	41 (6.4%)	0.71 (0.44 to 1.14)
Total ischemic CVA	AAA Fowkes, 2010[102]	8.2	1,675	30 (1.8%)*	1,675	37 (2.2%)*	0.81 (0.50 to 1.31)*†
Fatal ischemic CVA	AAA Fowkes, 2010[102]	8.2	1,675	2 (0.1%)	1,675	7 (0.4%)	0.29 (0.06 to 1.37)*†
	POPADAD Belch, 2008[98]	6.7‡	638	3 (0.5%)	638	5 (0.8%)	0.60 (0.14 to 2.50)*†
Nonfatal ischemic CVA	AAA Fowkes, 2010[102]	8.2	1,675	28 (1.7%)	1,675	30 (1.8%)	0.93 (0.56 to 1.56)*†

* Calculated.
† RR
‡ Median.

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis Trial; CG = control group; CI = confidence interval; CVA = cerebrovascular accident; HR = hazard ratio; IG = intervention group; N = population; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RR = relative risk

Table 9. PAD-Specific Outcomes for Included Aspirin Studies for KQ4: Does Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes?

Trial name Author, Year	Mean F/U, years	Outcome	IG N Analyzed	IG N Events (%)	CG N Analyzed	CG N Events (%)	IG vs. CG HR (95% CI)
AAA Fowkes, 2010[102]	8.2	Development of IC	1,675	53 (3.2%)	1,675	53 (3.2%)	1.00 (1.00 to 1.00)*†
POPADAD Belch, 2008[98]	6.7‡	Development of IC	638	97 (15.2%)	638	107 (16.8%)	0.89 (0.68 to 1.18)
AAA Fowkes, 2010[102]	8.2	Peripheral revascularization	1,675	23 (1.4%)	1,675	20 (1.2%)	1.15 (0.63 to 2.09)*†
POPADAD Belch, 2008[98]	6.7‡	Peripheral arterial bypass surgery	638	7 (1.1%)	638	5 (0.8%)	1.41 (0.45 to 4.43)
POPADAD Belch, 2008[98]	6.7‡	Peripheral arterial angioplasty	638	11 (1.7%)	638	13 (2.0%)	0.85 (0.38 to 1.89)
POPADAD Belch, 2008[98]	6.7‡	Above ankle amputation for critical limb ischemia	638	11 (1.7%)	638	9 (1.4%)	1.23 (0.51 to 2.97)

* Calculated
† RR
‡ Median

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis Trial; CG = control group; CI = confidence interval; HR = hazard ratio; IC = intermittent claudication; IG = intervention group; N = population; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RR = relative risk.

Table 10. Age Subgroup Analyses for Reported Outcomes in Included Aspirin Studies for KQ4: Does Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes?

Trial name Author, Year	Mean F/U, years	Type of analysis	Outcome	Age, years	IG N Analyzed	IG N Events (%)	CG N analyzed	CG N Events (%)	IG vs. CG HR (95% CI)	P-Value for interaction
AAA Fowkes, 2010[102]	8.2	A priori	Primary composite: Initial fatal or nonfatal coronary event, CVA or revascularization	<62	NR	57 per 1,000 p-y (95% CI): 8.6 (6.5 to 11.2)	NR	70 per 1,000 p-y (95% CI): 10.2 (8.0 to 12.9)	0.85 (0.60 to 1.20)	NR
				≥62	NR	124 per 1,000 p-y (95% CI): 18.8 (15.6 to 22.4)	NR	106 per 1,000 p-y (95% CI): 16.6 (13.6 to 20.1)	1.13 (0.87 to 1.47)	
POPADAD Belch, 2008[98]	6.7*	Specification unclear	Fatal Coronary Events + Fatal CVA	<60	297	10 (3.4%)	315	10 (3.2%)	1.07 (0.44 to 2.56)	0.44
				≥60	341	33 (9.7%)	323	25 (7.7%)	1.24 (0.74 to 2.09)	
POPADAD Belch, 2008[98]	6.7*	Specification unclear	Primary composite: death from CHD or CVA, nonfatal MI or CVA, or above ankle amputation for critical limb ischemia	<60	297	38 (12.8%)	315	36 (11.4%)	1.11 (0.70 to 1.75)	0.77
				≥60	341	78 (22.9%)	323	81 (25.1%)	0.89 (0.65 to 1.21)	

* Median.

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis Trial; CG = control group; CI = confidence interval; CHD = coronary heart disease; CVA = cerebrovascular accident; HR = hazard ratio; IG = intervention group; MI = myocardial infarction; NR = not reported; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; p-y: person-years

Table 11. Sex Subgroup Analyses for Reported Outcomes in Included Aspirin Studies for KQ4: Does Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes?

Trial name Author, Year	Mean F/U, years	Type of analysis	Outcome	Sex	IG N Analyzed	IG N Events (%)	CG N Analyzed	CG N Events (%)	IG vs. CG HR (95% CI)	P-Value for interaction
AAA Fowkes, 2010[102]	8.2	A priori	Primary composite: initial (earliest) fatal or nonfatal coronary event or CVA or revascularization	Men	481	96 (20.0%)	473	83 (17.5%)	1.15 (0.86 to 1.54)*†	NR
				Women	1,194	85 (7.1%)	1,202	93 (7.7%)	0.92 (0.68 to 1.23)*†	NR
POPADAD Belch, 2008[98]	6.7‡	Specification unclear	Fatal coronary events + fatal CVA + CVD death	Men	286	26 (9.1%)	277	19 (6.9%)	1.33 (0.73 to 2.40)	0.68
				Women	352	17 (4.8%)	361	16 (4.4%)	1.09 (0.55 to 2.16)	
POPADAD Belch, 2008[98]	6.7‡	Specification unclear	Primary Composite: death from CHD or CVA, nonfatal MI or CVA, or above ankle amputation for critical limb ischemia	Men	286	68 (23.8%)	277	62 (22.4%)	1.04 (0.74 to 1.47)	0.54
				Women	352	48 (13.6%)	361	55 (15.2%)	0.89 (0.60 to 1.31)	

* Calculated
† RR
‡ Median

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis Trial; CG = control group; CI = confidence interval; CHD = coronary heart disease; CVA = cerebrovascular accident; RR = Relative Risk; HR = hazard ratio; IG = intervention group; MI = myocardial infarction; NR = not reported; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; p-y: person-years

Table 12. Participant Characteristics for Included Exercise Studies for KQ4: Does Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes?*

Study name Author, Year	Quality	Country	N	Population description Recruitment method/setting	Mean Age, years (range)	% Female	Race/ Ethnicity, %	% HTN (mean SBP/DBP) BP Meds	TC, mg/dL (mean)	LDL-C, mg/dL (mean)	HDL-C, mg/dL (mean)	% DM	% Symptoms	ABI (mean)	% Smoking
Collins, 2007[105]	Fair	U.S.	50	Patients with PAD based on an ABI of 0.50 to <0.9 and without symptoms of IC Patients referred to vascular lab	69.1 (range NR)	2	White: 64 Black: 26 Hispanic: 10	86 (NR) Use of ACEI: 56 Use of BB: 34	188.6 † 10% >240 mg/dL	117.6† 60% >100 mg/dL	36.8* 62% <40 mg/dL	40	None: 56 Atypical: 44 IC: 0	0.74	30
Western Australia Trial of Screening for Abdominal Aortic Aneurysms Fowler, 2002[106]	Good	Australia	882	Men aged 65-79 who screened positive for PAD using the ECQ and ABI Population-based screening using the ECQ and ABI (the ABI conducted in 2 of 3 clinics)	73.1 (65-79)	0	NR	NR (160.6/86.9) Meds NR	NR†	NR†	NR*	17.2	None: 27.4 Atypical: 9.2 IC: 44.6	0.79	18.7

* Mean CVD risk score was not reported in either trial. In the Fowler trial, 32.4% of the population had a history of angina, 24.0% had a history of MI, and 12.8% had a history of CVA. Mean body mass index in the Fowler trial was 26.4 and was not reported in the Collins trial.
† Use of lipid-lowering treatment is not reported

Abbreviations: ABI = ankle-brachial index; ACE = angiotensin-converting enzyme inhibitor; BB = beta blocker; BMI=body mass index; BP = blood pressure; CVA = cerebrovascular accident; CVD = cardiovascular disease; ECQ = Edinburgh Claudication Questionnaire; HDL-C = high-density lipoprotein cholesterol; HTN = hypertension; IC = intermittent claudication; LDL-C = low-density lipoprotein cholesterol; mg/dL= milligrams per deciliter; MI = myocardial infarction; NR = not reported; PAD = peripheral artery disease; TC = total cholesterol

Table 13. Intervention Details for Included Exercise Studies for KQ4: Does Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes?

Author, Year	IG Description	CG Description	Format	Delivered by	Duration, weeks	# Sessions	Session length, min
Collins, 2007[105]	Advice to continue routine care with primary care physician, plus 2 intervention components: risk factor modification and improvement in physical activity (PA). Risk factor modification: "Recognize, identify, and manage" (RIM) approach used to assess risk factors. During initial 5-minute assessment, nurse used RIM to assess medication adherence. Nurse then assessed dietary needs specific to risk-factor profile, advised about HbA1c and LDL-C goals, and counseled on reading food labels, increasing fiber, and reducing calories. Participants were asked to share examples of appropriate behavior change related to their specific risk factors PA: PACE protocol, which included PA assessment of stage of readiness to change and handout tailored to help patient identify ways to increase PA based on stage of change, followed by "extensive discussion" with nurse to encourage regular PA	Usual care: patients advised to continue routine care with their primary care physician	Individual, in-person with phone F/U Unsupervised PA	Nurse	12	6 (Initial session + 5 F/U phone visits)	Initial session: NR F/U sessions: <30
Fowler, 2002[106]	"Stop smoking and keep walking" Intervention components included: 1) education, 2) letter to GP recommending smoking cessation, and 3) referral to a community PT intervention. Participants told that "your ABI or ECQ test showed a reduced blood flow to the muscles in your leg or legs caused by partial blockage of the arteries and this often results in pain on walking." Participants provided with educational package including information on PAD, a brochure on the community PT service, information on smoking cessation (if applicable), and a copy of the letter from the clinic to their GP, and were advised to consult GP about management. GP sent a package of written materials about smoking cessation, notes on obtaining optimal results from nicotine replacement products, and a fact sheet on PAD. GP asked to discuss smoking and to refer each man with early PAD to community PT service. The community PT contacted each referred man within approximately three weeks of screening exam. The community PT intervention offered options to increase PA either independently or through an organized program. Participants could attend a weekly mixed-gender group session as part of the established program, a men-only session, or a home-based PA program devised specifically for him by the senior PT. Additionally, all men in IG advised by PT to walk for ≥30 minutes/day. In certain cases, men were	Usual care: patients told by nurse at screening clinic that "the blood flow to your feet and legs is lower than normal. This is not uncommon for men of your age but there is presently no evidence to suggest you should do anything about it at this time." ABI and ECQ results were not mentioned in letters to the patient or GP regarding results of the AAA screening.	Individual initial session with print materials, PA was participants' choice of individual home-based PA or weekly group sessions	Nurse, GP, PT	52	For participants choosing group format: 51 (initial session with nurse, initial session with PT + 49 supervised PA sessions [52 weeks-3 week lead time])* For participants choosing home-based PA: 2 (initial session with nurse, initial session with PT)	Initial session with nurse: NR Initial session with PT NR Group PA sessions: 45

Table 13. Intervention Details for Included Exercise Studies for KQ4: Does Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes?

Author, Year	IG Description	CG Description	Format	Delivered by	Duration, weeks	# Sessions	Session length, min
	referred to hydrotherapy classes or special exercise sessions for those with disabilities.						

* Based on Table 4, 16.5% of IG reported being in exercise group at 12 months

Abbreviations: AAA = abdominal aortic aneurysm; ECQ = Edinburgh Claudication Questionnaire; F/U = followup; GP = general practitioner; HbA1c = glycated hemoglobin; LDL-C = low-density lipoprotein cholesterol; NR = not reported; PA = physical activity; PACE = Physician-based Assessment and Counseling for Exercise; PAD = peripheral artery disease; PT = physical therapy/physical therapist

Table 14. Quality of Life Outcomes in Included Exercise Studies for KQ4: Does Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes?

Author, Year Quality	F/U, Wks	Outcome/Instrument (except where noted, 0-100, where higher score indicates better function)	IG N*	IG Mean (SD) baseline	IG Mean (SD) F/U†	IG Mean change (95% CI)‡	CG N*	CG Mean (SD) baseline	CG Mean (SD) F/U†	CG Mean change (95% CI)‡	Between-group difference Mean (95% CI)§
Collins, 2007[105] Fair	12	MOS SF-36: Physical functioning	23	55.0 (18.5)	64.1 (25.3)	9.1 (-0.2 to 18.4)	25	39.4 (22.4)	45.4 (28.3)	6.0 (-4.1 to 16.1)	3.1 (-10.6 to 16.8); p>0.20
		MOS SF-36: Role-physical	23	36.0 (36.1)	52.2 (41.9)	16.2 (0.1 to 32.3)	25	35.0 (42.7)	33.0 (38.7)	-2.0 (-18.0 to 14.0)	18.2 (-4.5 to 40.9); p=0.11
		MOS SF-36: Bodily pain	23	40.9 (19.1)	49.0 (27.3)	8.1 (-1.8 to 18.0)	25	54.2 (28.2)	61.4 (29.0)	7.2 (-4.0 to 18.4)	0.9 (-14.1 to 15.9); p>0.20
		MOS SF-36: General health	23	55.4 (19.0)	56.3 (22.5)	0.9 (-7.7 to 9.5)	25	55.7 (23.8)	48.2 (19.1)	-7.5 (-16.1 to 1.1)	8.4 (-3.7 to 20.5); p=0.15
		MOS SF-36: Vitality	23	46.5 (18.9)	51.1 (23.6)	4.6 (-4.2 to 13.4)	25	45.9 (22.2)	41.8 (24.0)	-4.1 (-13.2 to 5.0)	8.7 (-4.0 to 21.4); p=0.12
		MOS SF-36: Social functioning	23	76.5 (24.3)	77.7 (26.4)	1.2 (-9.2 to 11.6)	25	75.0 (23.4)	78.0 (28.5)	3.0 (-7.3 to 13.3)	-1.8 (-16.4 to 12.8); p>0.20
		MOS SF-36: Role-emotional	23	45.3 (42.9)	65.2 (44.4)	19.9 (2.1 to 37.7)	25	53.3 (44.1)	70.7 (37.7)	17.4 (1.2 to 33.6)	2.5 (-21.6 to 26.6); p>0.20
		MOS SF-36: Mental health	23	71.2 (17.4)	76.5 (17.7)	5.3 (-1.9 to 12.5)	25	75.8 (17.1)	76.7 (14.8)	0.9 (-5.4 to 7.2)	4.4 (-5.1 to 13.9); p>0.20
Fowler, 2002[106] Good	52	Health-related quality of life; Rosser instrument (-1.2 to 1.0; higher indicates better)	361‖	NR	0.83 (0.13)	NR	336‖	NR	0.84 (0.14)	NR	p=0.13

* N analyzed at followup

† Adjusted for baseline values

‡ Calculated

§ Study reported p-values. Calculated between-group mean difference and 95% CI (see methods for more detail).

‖ N analyzed unclear from outcomes table; this is the number of participants returning a complete questionnaire

Abbreviations: CG = control group; CI = confidence interval; F/U = followup; IG = intervention group; MOS SF-36 = Medical Outcomes Study Short-Form Health Survey; NR = not reported; SD = standard deviation

Table 15. Walking Impairment Questionnaire Outcomes in Included Exercise Studies for KQ4: Does Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes?

Author, Year Quality	FU, Wks	Outcome (Range: 0-100, where higher score indicates better function)[175]	IG N*	IG Mean (SD) baseline	IG Mean (SD) F/U†	IG Mean change (95% CI) ‡	CG N*	CG Mean (SD) baseline	CG Mean (SD) F/U†	CG Mean change (95% CI) ‡	Between-group difference Mean (95% CI) §
Collins, 2007[105] Fair	12	WIQ: Walking distance	23	43.2 (28.2)	62.3 (33.0)	19.1 (6.5 to 31.7)	25	30.9 (34.2)	40.1 (35.7)	9.2 (-4.5 to 22.9)	9.9 (-8.7 to 28.5); p=0.18
		WIQ: Walking speed	23	40.5 (24.9)	41.4 (21.4)	0.9 (-8.6 to 10.4)	25	33.1 (31.4)	28.3 (24.5)	-4.8 (-16.0 to 6.4)	5.7 (-9.0 to 20.4); p=0.09
		WIQ: Stair climbing	23	43.7 (30.7)	61.2 (32.8)	17.5 (4.5 to 30.5)	25	37.8 (29.8)	40.2 (30.2)	2.4 (-9.4 to 14.2)	15.1 (2.4 to 32.6); p=0.02

* N analyzed at followup
† Adjusted for baseline values
‡ Calculated
§ Study reported p-values. Calculated between group mean difference and 95% CI (see methods for more detail).

Abbreviations: CG = control group; CI = confidence interval; F/U = followup; IG = intervention group; MOS SF-36 = Medical Outcomes Study Short-Form Health Survey; NR = not reported; SD = standard deviation; WIQ = Walking Impairment Questionnaire

Table 16. Proportion of Participants With Symptoms at Baseline and Followup in Exercise Studies Included for KQ4: Does Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes?

Outcome	Author, Year	FU, Wks	IG Baseline	IG F/U	IG Change p-value*	CG Baseline	CG F/U	CG Change p-value*	Calculated between-group difference, p-value*
N (%) with atypical symptoms	Collins, 2007[105]	12	12/25 (48.0)	12/23 (52.2)	0.69	10/25 (40.0)	9/25 (36.0)	0.68	0.26
	Fowler, 2002[106]	52	35/441 (7.9)†	7/347 (2.0)†	<0.001	46/441 (10.4)†	13/327 (4.0)†	<0.001	0.13
N (%) with IC	Collins, 2007[105]	12	0/25 (0.0)	1/23 (4.3)	Not calculable	0/25 (0.0)	1/25 (4.0)	Not calculable	0.95
	Fowler, 2002[106]	52	201/441 (45.6)‡	99/347 (28.5)‡	<0.001	192/441 (43.5)‡	101/327 (30.9)‡	<0.001	0.50

* p-value calculated from test of proportions

† Edinburgh Claudication Questionnaire Atypical IC Grade 1 and Grade 2 combined

‡ Edinburgh Claudication Questionnaire Definite IC Grade 1 and Grade 2 combined

Abbreviations: CG = control group; CI = confidence interval; F/U = followup; IG = intervention group; NR = not reported

Table 17. Harms in Included Aspirin Studies for KQ5: What Are the Harms of Treatment of Screen-Detected or Generally Asymptomatic Adults With PAD or an Abnormal ABI?

Trial name Author, Year	Mean F/U, years	Outcome	IG N Analyzed	IG N Events (%)	CG N Analyzed	CG N Events (%)	IG vs. CG HR (95% CI)
AAA Fowkes, 2010[102]	8.2	Major Hemorrhage*	1,675	34 (2.0%)	1,675	20 (1.2%)	1.71 (0.99 to 2.97)
	8.2	Major GI Bleeding†	1,675	9 (0.5%)‡	1,675	8 (0.5%)‡	1.13 (0.44 to 2.91)‡§
	8.2	Total Hemorrhagic CVA	1,675	5 (0.3%)‡	1,675	4 (0.2%)‡	1.25 (0.34 to 4.65)‡§
	8.2	Fatal Hemorrhagic CVA	1,675	3 (0.2%)	1,675	3 (0.2%)	1.00 (0.20 to 4.95)‡§
	8.2	Nonfatal Hemorrhagic CVA	1,675	2 (0.1%)	1,675	1 (0.1%)	2.00 (0.18 to 22.04)‡§
	8.2	Intracranial Bleeding‖	1,675	6 (0.4%)‡§	1,675	3 (0.2%)‡§	2.00 (0.50 to 7.98)‡§
POPADAD Belch, 2008[98]	6.7¶	Fatal Hemorrhagic CVA	638	2 (0.3%)	638	3 (0.5%)	0.67 (0.11 to 3.98)‡§

* Defined as nonfatal or fatal hemorrhagic CVA, fatal or nonfatal subarachnoid/subdural hemorrhage, GI bleed requiring admission, and other bleeding requiring hospital admission

† Defined as requiring admission to hospital to control bleeding; admission only to investigate bleeding not included

‡ Calculated.

§ RR

‖ Defined as fatal or nonfatal subarachnoid/subdural hemorrhage

¶ Median

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis Trial; CG = control group; CI = confidence interval; CVA = cerebrovascular accident; GI = gastrointestinal; IG = intervention group; n = population; NR = not reported; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RR = relative risk; HR = Hazard Ratio

Table 18. Summary of Evidence

KQ	No. of studies (k), No. of participants randomized (n)	Outcome	No. of trials (k), number of participants analyzed (n)	Summary of findings by outcome	Consistency/ Precision	Reporting bias	EPC assessment of strength of evidence	Study quality	Body of evidence limitations	Applicability
KQ1: Direct evidence for screening	k=0	Morbidity or mortality	0	NA				NA		
KQ2: Diagnostic accuracy	k=1 (0 new), n=307	Sensitivity, specificity, PPV, NPV	k=1, n=306	The ABI has low sensitivity (7-34%) and high specificity (96-100%) compared to MRA gold standard imaging	Consistency-NA (single study) Imprecise	Not detected	Insufficient	1 Fair	Single study, not clear if MRA interpreters were blind to ABI results; harms (aside from FP and FN) not reported other than single vasovagal episode	Screening population of older adults (age 70) in Sweden. The low sensitivity reported in this single study is well below the sensitivities reported in symptomatic populations.
KQ3: Harms	k=1 (0 new), n=307	Harms	k=1, n=306	The ABI has a high false negative rate (>80%) reflecting the low sensitivity in screening for PAD.	Consistency-NA (single study) Imprecise	Not detected	Insufficient	1 Fair		
KQ4: Treatment benefit	Aspirin k=2 (1 new), n=4,626	CVD composite, ACM, individual CVD outcomes	k=2, n=4,626	Aspirin 100 mg daily showed no effect on **CVD composite events** in the two trials: Adj HR (95% CI): 1.00 (0.81 to 1.23) HR (95% CI): 0.98 (0.76 to 1.26) No effect on **ACM**: HR (95% CI): 0.95 (0.77 to 1.16) HR (95% CI): 0.93 (0.71 to 1.24) No statistically significant difference in **individual CVD outcomes** including: MI, CVA, development of intermittent	Reasonably consistent Imprecise	Not detected	Low-to-Moderate	2 Good	Studies designed to detect differences in CVD composites but not individual CVD outcomes.	Two Scottish trials in asymptomatic patients with a low ABI defined as ≤0.95 and ≤0.99 (thresholds not typically used to define an abnormal ABI in clinical practice). 1 trial exclusively in patients with diabetes. Populations at intermediate to high CVD risk.

Table 18. Summary of Evidence

KQ	No. of studies (k), No. of participants randomized (n)	Outcome	No. of trials (k), number of participants analyzed (n)	Summary of findings by outcome	Consistency/ Precision	Reporting bias	EPC assessment of strength of evidence	Study quality	Body of evidence limitations	Applicability
				claudication and need for peripheral arterial revascularization or above the ankle amputation procedures						
	Exercise k=2 (2 new), n=932	Quality of Life	k=2, n=745	No difference in quality of life changes from baseline (as measured by MOS SF-36 and Rosser HrQOL questionnaire)	Reasonably consistent Imprecise	Not detected	Insufficient	1 Good, 1 Fair	One feasibility trial in almost exclusively men was short (12 weeks) and underpowered (n=50) to detect difference in primary or secondary outcomes. Second trial (N=882) powered to detect walking ability before onset of symptoms	Unclear whether population representative of screen-detected population; included participants almost 100% male
		WIQ	k=1; n=48	No difference in WIQ score change from baseline for distance or speed components; statistically significant improvement in stair climbing component in IG compared to CG	NA	Not detected	Insufficient	1 Fair		
		Proportion of participants with symptoms	k=2, n=722	No change in proportion of participants who develop IC or atypical symptoms	Reasonably consistent Imprecise	Not detected	Insufficient	1 Good, 1 Fair		
KQ4a: Treatment benefit by subgroup	Aspirin k=2 (1 new), n=4,626	CVD composite, individual CVD outcomes, fatal CVD events, ACM	k=2, n=4,626	No compelling evidence to support a differential treatment effect by age, sex, or diabetes status. Within trial comparisons	Inconsistent (age) Reasonably consistent (sex) Imprecise (age, sex)	Not detected	Insufficient	2 Good	Only 1 trial performed interaction testing by age, sex and unclear if a priori planned analysis. Other trial	Both Scottish trials in asymptomatic patients with a low ABI defined as ≤0.95 and ≤0.99 (thresholds not

Table 18. Summary of Evidence

KQ	No. of studies (k), No. of participants randomized (n)	Outcome	No. of trials (k), number of participants analyzed (n)	Summary of findings by outcome	Consistency/ Precision	Reporting bias	EPC assessment of strength of evidence	Study quality	Body of evidence limitations	Applicability
				revealed overlapping CIs and the single trial (POPADAD) reporting heterogeneity testing for CVD outcomes by age and sex reported nonstatistically significant interaction testing. Results exclusively in participants with diabetes (POPADAD) showing similar outcomes to those almost exclusively without diabetes (AAA)					prespecified subgroup analysis but did not perform interaction testing. No available data for within-group comparisons by diabetes status. CIs wide and overlapping across subgroups analyzed.	typically used to define an abnormal ABI in clinical practice). One trial exclusively in patients with diabetes. Populations at intermediate to high CVD risk.
	Exercise: k=0	-	-	No exercise trials examine the differential treatment effect by subpopulation.	-	-	-	-	-	-
KQ5: Treatment harms	Aspirin k=2 (1 new), n=4,626	Major GI bleeding requiring admission	k=1, n=3,350	Major GI bleeding requiring hospital admission was similar in one reporting trial (AAA) of 100 mg enteric coated aspirin at 8.2 year followup: 0.5% versus 0.5%; RR (95% CI): 1.13 (0.44 to 2.91)). Limited evidence from this trial	Consistency-NA (single study) Imprecise	Not detected	Low	1 Good	Rare events, wide CIs	Asymptomatic patients with a low ABI defined as ≤0.95 with intermediate CVD risk

Table 18. Summary of Evidence

KQ	No. of studies (k), No. of participants randomized (n)	Outcome	No. of trials (k), number of participants analyzed (n)	Summary of findings by outcome	Consistency/ Precision	Reporting bias	EPC assessment of strength of evidence	Study quality	Body of evidence limitations	Applicability
				demonstrates a trend towards higher risk for major bleeding events with the use of aspirin. Two trials reported conflicting results on total or fatal hemorrhagic CVA risk with wide confidence intervals due to rare event rate.						
		Major hemorrhage (defined as nonfatal or fatal hemorrhagic CVA, fatal or nonfatal subarachnoid subdural hemorrhage, GI bleed requiring admission, and other bleeding requiring hospital admission)	K=1, n=3,350	Major hemorrhage did not reach statistical significance but was slightly higher in the aspirin group: 2.0% vs. 1.2%; HR (95% CI): 1.71 (0.99 to 2.97)	Consistency-NA (single study) Imprecise	Not detected	Low	1 Good	Single trial, relatively rare event with wide CIs	
		Hemorrhagic CVA	k=2, n=4,626	Trend of higher risk for total hemorrhagic CVA with aspirin in AAA (0.3% v 0.2%; RR 1.25 (95% CI, 0.34 to 4.65) and a	Inconsistent, Imprecise	Not detected	Low/ insufficient	2 Good	Somewhat conflicting results when comparing total and fatal hemorrhagic across 2 trials	

Table 18. Summary of Evidence

KQ	No. of studies (k), No. of participants randomized (n)	Outcome	No. of trials (k), number of participants analyzed (n)	Summary of findings by outcome	Consistency/ Precision	Reporting bias	EPC assessment of strength of evidence	Study quality	Body of evidence limitations	Applicability
				lower risk for fatal hemorrhagic CVA in POPADAD (0.3% vs. 0.5%; RR 0.67 [95% CI, 0.11 to 3.98]) but CIs were wide due to rare events					which recruited different populations (diabetic and nondiabetic trials)	
	Exercise	-	No trials reporting harms	-	-	-	No evidence	-	-	-

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis Trial; ACM = all-cause mortality; Adj = adjusted; CG = control group; CI = confidence interval; CVA = cerebrovascular accident; CVD = cardiovascular disease; EPC = Evidence-based Practice Center; GI = gastrointestinal; HR = hazard ratio; IG = intervention group; KQ = key question; MI = myocardial infarction; NA = not applicable; NPV: negative predictive value; NR = not reported; PPV = positive predictive value; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RR = relative risk

Literature Search Strategies for Primary Literature

Key:
/ = MeSH subject heading
$ = truncation
* = truncation
? = wildcard
ab = word in abstract
adj# = adjacent within x number of words
ae = adverse effects
kw = keyword
near/# = adjacent within x number of words
ti = word in title

CENTRAL

#1 ((peripheral next arter*) near/2 disease*):ti,ab,kw
#2 (lower next (limb or extremity) near/2 disease*):ti,ab,kw
#3 (leg next artery next disease*):ti,ab,kw
#4 (ankle near/1 (brachial or arm) near/4 (index* or indices or ratio or gradient or pressure)):ti,ab,kw
#5 (ankle next (index* or indices)):ti,ab,kw
#6 ABPI:ti,ab,kw
#7 #1 or #2 or #3 or #4 or #5 or #6 Publication Year from 2012 to May 2, 2017, in Trials

MEDLINE (via Ovid)

Screening

Database: Ovid MEDLINE(R) Epub Ahead of Print <May 2, 2017>, Ovid MEDLINE(R) <1946 to May Week 1 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 2, 2017>, Ovid MEDLINE(R) Daily Update <May 2, 2017>

1 Peripheral Arterial Disease/
2 Arterial Occlusive Diseases/
3 Peripheral Vascular Diseases/
4 peripheral arter$ disease$.ti,ab.
5 peripheral arter$ occlusive disease$.ti,ab.
6 (lower adj (limb or extremity) adj2 disease$).ti,ab.
7 leg artery disease$.ti,ab.
8 or/1-7
9 Ankle Brachial Index/
10 (brachial adj1 ankle adj4 (ratio$ or index$ or indices or gradient$ or pressure)).ti,ab.
11 (arm adj1 ankle adj4 (ratio$ or index$ or indices or gradient$ or pressure)).ti,ab.
12 (ankle adj (index$ or indices)).ti,ab.
13 Ankle/bs [Blood Supply]
14 Brachial Artery/ph, pp, us [Physiology, Physiopathology, Ultrasonography]
15 Blood pressure/
16 Ankle/
17 15 and 16
18 9 or 10 or 11 or 12 or 13 or 14 or 17
19 Mass Screening/
20 screen$.ti,ab.
21 (detect$ or predict$ or diagnos$ or identif$).ti.

22 or/19-21
23 8 and 18 and 22
24 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/
25 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
26 Random$.ti,ab.
27 control groups/ or double-blind method/ or single-blind method/
28 clinical trial$.ti,ab.
29 controlled trial$.ti,ab.
30 meta analy$.ti,ab.
31 or/24-30
32 23 and 31
33 "Sensitivity and Specificity"/
34 "Predictive Value of Tests"/
35 ROC Curve/
36 False Negative Reactions/
37 False Positive Reactions/
38 Diagnostic Errors/
39 "Reproducibility of Results"/
40 Reference Values/
41 Reference Standards/
42 Observer Variation/
43 Receiver operat$.ti,ab.
44 ROC curve$.ti,ab.
45 sensitivit$.ti,ab.
46 specificit$.ti,ab.
47 predictive value.ti,ab.
48 accuracy.ti,ab.
49 false positive$.ti,ab.
50 false negative$.ti,ab.
51 miss rate$.ti,ab.
52 error rate$.ti,ab.
53 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52
54 18 and 53
55 32 or 54
56 limit 55 to (english language and yr="2012 -Current")
57 remove duplicates from 56

Treatment

Database: Ovid MEDLINE(R) Epub Ahead of Print <May 2, 2017>, Ovid MEDLINE(R) <1946 to May Week 1 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 2, 2017>, Ovid MEDLINE(R) Daily Update <June 21, 2016>

1 Peripheral Arterial Disease/
2 Arterial Occlusive Diseases/
3 Peripheral Vascular Diseases/
4 peripheral arter$ disease$.ti,ab.
5 peripheral arter$ occlusive disease$.ti,ab.
6 (lower adj (limb or extremity) adj2 disease$).ti,ab.
7 leg artery disease$.ti,ab.

8 or/1-7
9 ((abnormal$ or low) adj4 (brachial adj1 ankle adj4 (ratio$ or index$ or indices or gradient$ or pressure))).ti,ab.
10 ((abnormal$ or low) adj4 (arm adj1 ankle adj4 (ratio$ or index$ or indices or gradient$ or pressure))).ti,ab.
11 ((abnormal$ or low) adj4 (ankle index$ or ankle indices)).ti,ab.
12 ((abnormal$ or low) adj ABI).ti,ab.
13 or/9-12
14 "tobacco use cessation"/ or smoking cessation/
15 smoking cessation.ti,ab.
16 Hypercholesterolemia/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]
17 Hyperlipidemias/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]
18 Anticholesteremic Agents/
19 (lower$ adj3 cholesterol).ti,ab.
20 (reduc$ adj3 cholesterol).ti,ab.
21 Diabetes Mellitus/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]
22 Diabetes Mellitus, Type 2/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]
23 Hypoglycemic Agents/
24 Hemoglobin A, Glycosylated/
25 Blood Glucose/an, me [Analysis, Metabolism]
26 Glycemic Index/
27 glycemic control$.ti,ab.
28 glycaemic control$.ti,ab.
29 glucose control$.ti,ab.
30 body weight changes/ or weight loss/
31 weight loss.ti,ab.
32 Hypertension/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]
33 Antihypertensive Agents/
34 blood pressure control$.ti,ab.
35 (hypertension adj2 control$).ti,ab.
36 Platelet Aggregation Inhibitors/
37 Blood Platelets/de [Drug Effects]
38 ((anti platelet or antiplatelet) adj2 (therapy or treatment$)).ti,ab.
39 physical activit$.ti,ab.
40 Exercise/
41 exercis$.ti.
42 Physical Fitness/
43 Walking/
44 walking.ti.
45 treadmill.ti,ab.
46 Resistance Training/
47 Motor Activity/
48 Physical Therapy Modalities/
49 Exercise Therapy/
50 Exercise Movement Techniques/
51 physical therap$.ti,ab.

52 physiotherapy$.ti,ab.
53 or/14-52
54 (8 or 13) and 53
55 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/
56 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
57 Random$.ti,ab.
58 control groups/ or double-blind method/ or single-blind method/
59 clinical trial$.ti,ab.
60 controlled trial$.ti,ab.
61 meta analy$.ti,ab.
62 or/55-61
63 54 and 62
64 "Drug-Related Side Effects and Adverse Reactions"/
65 harm$.ti,ab.
66 toxicity.ti,ab.
67 complication$.ti,ab.
68 (adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
69 adverse effects.fs.
70 toxicity.fs.
71 mortality.fs.
72 Safety/
73 safety.ti,ab.
74 product surveillance, postmarketing/
75 side effect$.ti,ab.
76 Emergency Service, Hospital/
77 Hospitalization/
78 (unexpected$ adj3 (emergency or hospital$ or medical attention)).ti,ab.
79 or/64-78
80 54 and 79
81 63 or 80
82 limit 81 to (english language and yr="2012 -Current")
83 remove duplicates from 82

PUBMED, publisher-supplied records

#7 Search (((#6) AND publisher[sb]) AND English[Language]) AND ("2012/01/01"[Date - Publication] : "3000"[Date - Publication])
#6 Search #1 OR #4 OR #5
#5 Search (ankle[tiab] AND (brachial[tiab] OR arm[tiab]) AND (index*[tiab] OR indices[tiab] OR ratio*[tiab] OR gradient*[tiab] OR pressure[tiab]) OR ankle index*[tiab])
#4 Search #2 AND #3
#3 Search ((control[tiab] OR controls[tiab] OR controlled[tiab] OR controled[tiab]) AND (trial[tiab] OR trials[tiab])) OR clinical trial[tiab] OR clinical trials[tiab] OR random*[tiab] OR systematic review[sb] OR metaanaly*[tiab] OR meta analysis[tiab]
#2 Search (peripheral artery disease [tiab] OR peripheral arterial disease [tiab] OR lower extremity disease[tiab] OR leg artery disease[tiab] OR abnormal ABI[tiab] OR low ABI[tiab]) AND (cholesterol[tiab] OR smoking[tiab] OR glycemic[tiab] OR glycaemic[tiab] OR glucose[tiab] OR weight loss[tiab] OR blood pressure[tiab] OR hypertension[tiab] OR anti hypertensive[tiab] OR antihypertensive[tiab] anti platelet[tiab] OR antiplatelet[tiab] OR physical activit*[tiab] OR exercis*[tiab] OR walking[tiab] OR treadmill[tiab] OR physical therap*[tiab])

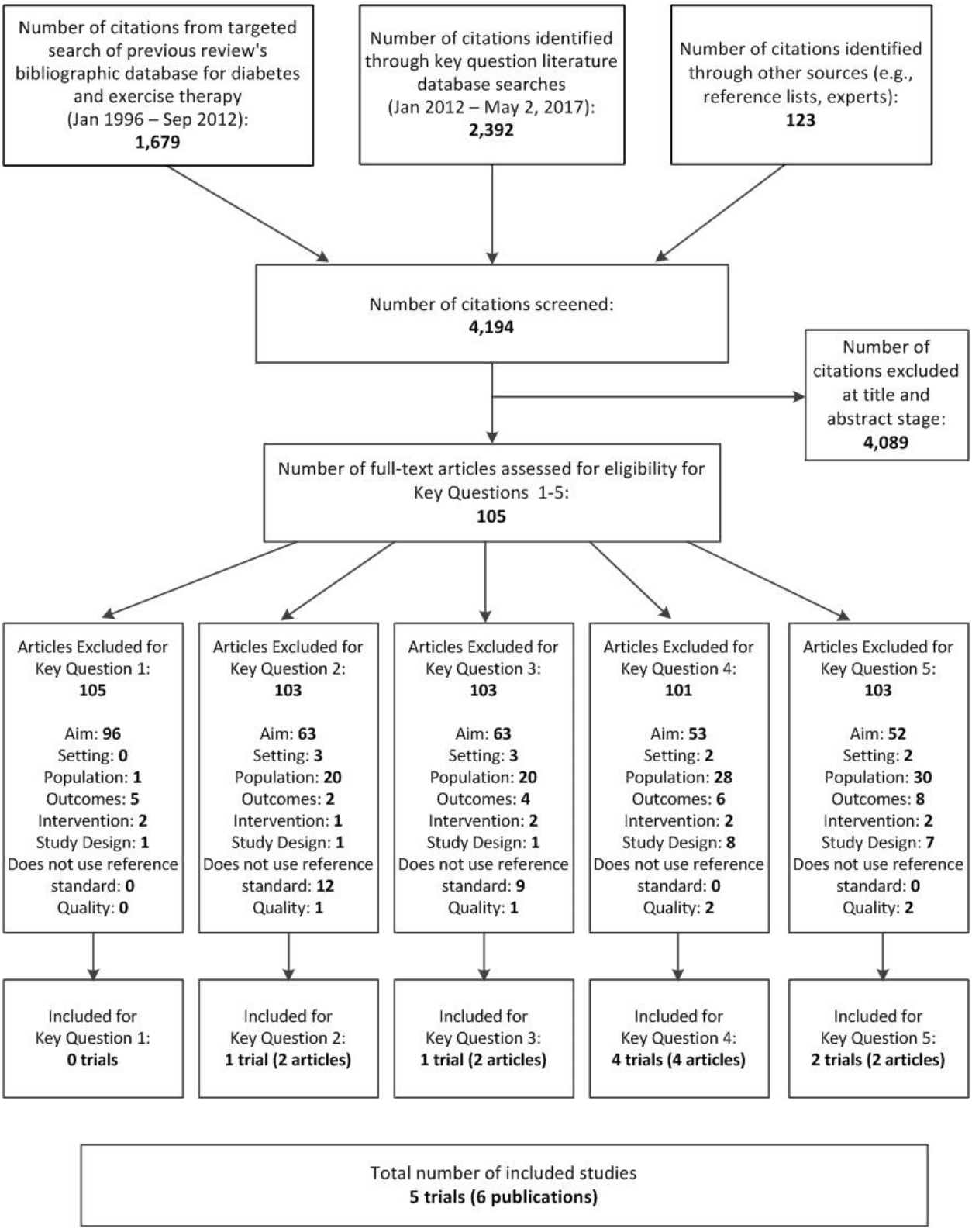
Appendix A. Detailed Methods

#1 Search (peripheral artery disease[tiab] OR peripheral arterial disease[tiab] OR lower extremity disease[tiab] OR leg artery disease[tiab]) AND screen*[tiab]

Terms used in targeted search of previous Reference Manager bibliographic database for diabetes and exercise or physical therapy

Connector	Field	Parameter	Results
	All Non-Indexed Fields	diab	1020
OR	Keywords	diab*	1066
OR	All Non-Indexed Fields	abnormal glucose	1069
OR	All Non-Indexed Fields	impaired glucose	1072
OR	All Non-Indexed Fields	uncontrolled glucose	1072
OR	All Non-Indexed Fields	insulin resistance	1112
OR	All Non-Indexed Fields	prediab	1112
OR	All Non-Indexed Fields	exercise	1527
OR	All Non-Indexed Fields	walking	1753
OR	All Non-Indexed Fields	physical activity	1775
OR	All Non-Indexed Fields	physical therap	1781
OR	All Non-Indexed Fields	motor activity	1781
OR	Keywords	Exercise Therapy	1784
OR	Keywords	Physical Activity	1784
OR	Keywords	Physical Therapy Modalities	1785

Appendix A Figure 1. Literature Flow Diagram



Appendix A Table 1. Inclusion and Exclusion Criteria

	Included	Excluded
Population	**KQs 1–3:** Unselected or community-dwelling, generally asymptomatic adults* **KQs 4, 5:** Screen-detected or generally asymptomatic adults with PAD or an abnormal ABI† A priori subpopulations at greater risk for PAD will be examined based on the following factors: age (particularly ≥65 years), sex, race/ethnicity, diabetes, smoking, and hypertension status	Symptomatic adults; study populations consisting exclusively of adults with known CVD or severe chronic kidney disease (stages 4 and 5)
Setting	Primary care and outpatient settings (i.e., ambulatory care)	Vascular surgery clinics (KQs 1, 2); hospital/inpatient settings
Disease/ Condition	Lower-extremity PAD secondary to atherosclerosis‡	Other anatomic locations for vascular disease (e.g., coronary artery stenosis, abdominal aortic aneurysm)
Screening	Resting ABI	History taking, physical examination, questionnaires, digital subtraction arteriography (DSA), duplex ultrasonography, magnetic resonance angiography (MRA), computed tomographic angiography (CTA), toe pressure measurement, treadmill testing (exercise ABI), pulse oximetry, near-infrared spectroscopy, and all invasive diagnostic testing
Treatment or management interventions	Pharmacologic or lifestyle interventions primarily aimed at CVD reduction: interventions for smoking cessation, cholesterol-lowering therapy, diet and exercise (with or without weight loss), blood pressure control, and antiplatelet therapy Exercise or physical therapy interventions aimed at improving lower limb function	Vitamins or nutritional or herbal supplements Interventions aimed only at symptomatic adults or adults with critical limb ischemia: pharmacologic symptom management (pentoxyfylline, cilostazol, prostaglandins), nonpharmacologic symptom management, and revascularization (angioplasty, thrombolytics, stenting, bypass)
Comparisons	**KQ 1:** No screening **KQ 2:** Reference standard (DSA, diagnostic imaging of atherosclerosis [e.g., MRA, CTA]) or degree of impaired blood flow (e.g., duplex ultrasonography) **KQ 4:** True control group (receives placebo, no intervention, or usual care); intervention/treatment at later or symptomatic stage of disease (vs. earlier or asymptomatic stage)	
Outcomes	**KQ 1:** Cardiovascular morbidity (myocardial infarction, cerebrovascular accident), PAD morbidity (ambulation impairment, amputation) or mortality (all-cause, PAD-related, or CVD-related), and health-related quality of life **KQ 2:** Sensitivity, specificity, positive and negative predictive value for PAD, and incidence or prevalence **KQ 4:** Patient health outcomes (listed above for KQ 1)	Surrogate markers for atherosclerosis, including imaging (e.g., carotid intima-media thickness) or biochemical markers (e.g., high-sensitivity C-reactive protein) Patient satisfaction Cost-related outcomes (for screening and treatment) Intermediate cardiovascular outcomes (e.g., blood pressure, cholesterol); behavior changes (e.g., smoking cessation, physical activity level); and intermediate measures of lower limb function (e.g., 6-minute walking test, lower-extremity strength) Change in ABI

Appendix A Table 1. Inclusion and Exclusion Criteria

	Included	Excluded
Harms	**KQ 3:** Adverse outcomes related to ABI test (diagnostic inaccuracy) or harms of subsequent testing **KQ 5:** Serious adverse events (e.g., death, serious adverse drug reactions) and unexpected medical attention (e.g., emergency department visits, hospitalizations)	Patient satisfaction
Study designs	**KQs 1, 4:** Good-quality systematic reviews and randomized or clinically controlled trials **KQ 2:** Good-quality systematic reviews and diagnostic accuracy studies **KQs 3, 5:** Good-quality systematic reviews, randomized or clinically controlled trials, and cohort or case-control studies	Poor-quality studies based on established design-specific quality criteria **KQ 2:** Case-control studies of diagnostic accuracy **KQ 4:** Studies with less than 3 months of followup
Countries	Economically developed countries, defined as member countries of the Organisation for Economic Co-operation and Development (2015): Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, and United States	Studies performed in countries with populations not similar to the United States Countries that are not a member of the Organisation for Economic Co-operation and Development
Language	English only	Non-English languages

* Adults without lower extremity symptoms or with vague symptoms not attributed to PAD.
† Defined as an ABI of ≤0.90 or >1.40.
‡ The condition definition for PAD would ideally be confirmed by diagnostic imaging (MRA, CTA, or DSA); however, the review will include trials that recruit participants with an abnormal ABI.

Abbreviations: ABI = ankle-brachial index; CTA = computed tomographic angiography; CVD = cardiovascular disease; DSA = digital subtraction arteriography; MRA = magnetic resonance angiography; PAD = peripheral artery disease

Appendix A Table 2. USPSTF and QUADAS-2 Quality Rating Criteria

USPSTF quality rating criteria for trials[84]
• Initial assembly of comparable groups • Employs adequate randomization, including first concealment and whether potential confounders were distributed equally among groups • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to followup or overall high loss to followup • Measurements: equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered • Intention-to-treat analysis
Quality criteria from QUADAS-2[92]
• Were tests clearly described (or referenced)? • Domain 1: Patient Selection (Could the selection of patients have introduced bias?)* o Was the spectrum of patients representative of the patients who will receive the test in primary care? o Was the selection process clearly defined? o Are there concerns that the included patients and setting do not match the review question? • Domain 2: Index Test (Could the conduct or interpretation of the index test have introduced bias?) o Was the index test interpreted without knowledge of the reference standard results? o If a threshold was used, was it prespecified? o Are there concerns that the index test, its conduct, or its interpretation differ from the review question? • Domain 3: Reference Standard (Could the conduct or interpretation of the reference standard have introduced bias?) o Is the reference standard acceptable for correctly classifying the target condition? o Was the reference standard interpreted without knowledge of the index test results? o Are there concerns that the target condition as defined by the reference standard does not match the review question? o Did the whole or partial selection of patients receive the reference standard? • Domain 4: Flow and Timing (Could the patient flow have introduced bias?) o Was there an appropriate interval between the index test and reference standard? o Did all patients receive the same reference standard? o Were all patients included in the analysis?

* Domain 1 questions minimally adapted

Appendix B. Included Studies

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

1. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ. 2008;337:a1840. PMID: 18927173. https://doi.org/10.1136/bmj.a1840
2. Collins TC, Johnson SL, Souchek J. Unsupervised walking therapy and atherosclerotic risk-factor management for patients with peripheral arterial disease: a pilot trial. Ann Behav Med. 2007;33(3):318-24. PMID: 17600459. https://doi.org/10.1080/08836610701360181
3. Fowkes FG, Price JF, Stewart MC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA. 2010;303(9):841-8. PMID: 20197530. https://doi.org/10.1001/jama.2010.221
4. Fowler B, Jamrozik K, Norman P, et al. Improving maximum walking distance in early peripheral arterial disease: randomised controlled trial. Aust J Physiother. 2002;48(4):269-75. PMID: 12443521.
5. Wikstrom J, Hansen T, Johansson L, et al. Ankle brachial index <0.9 underestimates the prevalence of peripheral artery occlusive disease assessed with whole-body magnetic resonance angiography in the elderly. Acta Radiol. 2008;49(2):143-9. PMID: 18300136. https://doi.org/10.1080/02841850701732957
    a) Wikstrom J, Hansen T, Johansson L, et al. Lower extremity artery stenosis distribution in an unselected elderly population and its relation to a reduced ankle-brachial index. J Vasc Surg. 2009;50(2):330-4. PMID: 19446989. https://doi.org/10.1016/j.jvs.2009.03.008

Appendix C. Excluded Studies

Reason for Exclusion	
E1.	Aim
E2.	Population
E2a.	Patients with symptomatic PAD
E2b.	Exclusively persons with known CVD
E3.	Outcomes
E4.	Poor quality
*E4c.	Poor quality: Does not use reference standard
E5.	Setting (hospital, inpatient, long-term care, vascular clinics)
E6.	Not an included study design
*E6a.	Study design: case control (applies to KQ2 only)
†E6b.	Study design: followup from baseline < 3 months (12 weeks)
E7.	Intervention
*E7a.	Not a study of the ABI
†E7b.	Not an included treatment
†E7c.	Comparative effectiveness

* Screening-specific exclusion codes

† Treatment-specific exclusion codes

Abbreviations: ABI = ankle-brachial index; CVD = cardiovascular disease; PAD = peripheral artery disease

1. Aerden D, Massaad D, von KK, et al. The ankle--brachial index and the diabetic foot: a troublesome marriage. Ann Vasc Surg. 2011;25(6):770-7. PMID: 21514102. **KQ1E1, KQ2E2, KQ3E2, KQ4E1, KQ5E1.**
2. Alavi A, Sibbald RG, Nabavizadeh R, et al. Audible handheld Doppler ultrasound determines reliable and inexpensive exclusion of significant peripheral arterial disease. Vascular. 2015;23(6):622-9. PMID: 25628222. **KQ1E1, KQ2E4c, KQ3E1, KQ4E1, KQ5E1.**
3. Allen J, Oates CP, Henderson J, et al. Comparison of lower limb arterial assessments using color-duplex ultrasound and ankle/brachial pressure index measurements. Angiology. 1996;47(3):225-32. PMID: 8638864. **KQ1E1, KQ2E2, KQ3E2, KQ4E1, KQ5E1.**
4. Alnaeb ME, Crabtree VP, Boutin A, et al. Prospective assessment of lower-extremity peripheral arterial disease in diabetic patients using a novel automated optical device. Angiology. 2007;58(5):579-85. PMID: 18024941. **KQ1E1, KQ2E2, KQ3E2, KQ4E1, KQ5E1.**
5. Aronow WS, Nayak D, Woodworth S, et al. Effect of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. Am J Cardiol. 2003;92(6):711-2. PMID: 12972114. **KQ1E1, KQ2E1, KQ3E1, KQ4E2a, KQ5E2a.**
6. Aubert CE, Cluzel P, Kemel S, et al. Influence of peripheral vascular calcification on efficiency of screening tests for peripheral arterial occlusive disease in diabetes--a cross-sectional study. Diabet Med. 2014;31(2):192-9. PMID: 23952656. **KQ1E1, KQ2E2, KQ3E2, KQ4E1, KQ5E1.**
7. Auteri A, Angaroni A, Borgatti E, et al. Triflusal in the treatment of patients with chronic peripheral arteriopathy: multicentre double-blind clinical study vs placebo. Int J Clin Pharmacol Res. 1995;15(2):57-63. PMID: 8593974. **KQ1E1, KQ2E1, KQ3E1, KQ4E2a, KQ5E2a.**
8. Baltic A, Baljic R, Radjo I, et al. Health Effects of the Programmed Physical Activities on Lipid Profile in Peripheral Arterial Disease of the Lower Extremities. Med Arh. 2015;69(5):311-4. PMID: 26622083. **KQ1E1, KQ2E1, KQ3E1, KQ4E5, KQ5E5.**
9. Barone Gibbs B, Dobrosielski DA, Althouse AD, et al. The effect of exercise training on ankle-brachial index in type 2 diabetes. Atherosclerosis. 2013;230(1):125-30. PMID: 23958264. **KQ1E1, KQ2E1, KQ3E1, KQ4E3, KQ5E3.**
10. Burton NW, Ademi Z, Best S, et al. Efficacy of brief behavioral counselling by allied health professionals to promote physical activity in people with peripheral arterial disease (BIPP): study protocol for a multi-center randomized controlled trial. BMC Public Health. 2016;16(1):1148. PMID: 27829449. **KQ1E1, KQ2E1, KQ3E1, KQ4E2, KQ5E2.**

11. Campens L, Backer T, Simoens S, et al. Accuracy of oscillometric determination of the anklebrachial index as screening method for peripheral artery disease. Acta cardiologica. 2012;67(1):136-7. PMID: None. **KQ1E1, KQ2E4c, KQ3E4c, KQ4E1, KQ5E1.**
12. Catalano M, Born G, Peto R. Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial. J Intern Med. 2007;261(3):276-84. PMID: 17305650. **KQ1E1, KQ2E1, KQ3E1, KQ4E2a, KQ5E2a.**
13. Clairotte C, Retout S, Potier L, et al. Automated ankle-brachial pressure index measurement by clinical staff for peripheral arterial disease diagnosis in nondiabetic and diabetic patients. Diabetes Care. 2009;32(7):1231-6. PMID: 19366974. **KQ1E1, KQ2E2, KQ3E2, KQ4E1, KQ5E1.**
14. Coe ER. Screening for peripheral arterial disease in a rural community health setting. J Vasc Nurs. 2014;32(4):137-8. PMID: 25455318. **KQ1E1, KQ2E4c, KQ3E4c, KQ4E1, KQ5E1.**
15. Collins EG, O'Connell S, McBurney C, et al. Comparison of walking with poles and traditional walking for peripheral arterial disease rehabilitation. J Cardiopulm Rehabil Prev. 2012;32(4):210-8. PMID: 22595894. **KQ1E1, KQ2E1, KQ3E1, KQ4E7c, KQ5E7c.**
16. Collins T, editor. Home-based walking therapy improves walking ability and quality of life in patients with diabetes mellitus and peripheral arterial disease. 33rd Annual Meeting of the Society of General Internal Medicine; 2010 Apr 28-May 1; Minneapolis, MN (US). PREVDB Targeted Search: J Gen Intern Med; ABSTRACT ONLY. **KQ1E1, KQ2E1, KQ3E1, KQ4E2a, KQ5E2a.**
17. Collins TC, Krueger PN, Kroll TL, et al. Face-to-face interaction compared with video watching on use of physical activity in peripheral arterial disease: a pilot trial. Angiology. 2009;60:21-30. PMID: 18586757. **KQ1E1, KQ2E1, KQ3E1, KQ4E7c, KQ5E7c.**
18. Collins TC, Lunos S, Carlson T, et al. Effects of a home-based walking intervention on mobility and quality of life in people with diabetes and peripheral arterial disease: a randomized controlled trial. Diabetes Care. 2011;34(10):2174-9. PMID: 21873560. **KQ1E1, KQ2E1, KQ3E1, KQ4E2a, KQ5E2a.**
19. Dedes H, Figoni SF, Kalioundji G, et al. Prospective Trial of Calf Ergometry Training on Walking Ability in Peripheral Arterial Disease. Phys Med Rehab. 2010;2(9 (Suppl 1)):S26. PMID: None. **KQ1E1, KQ2E1, KQ3E1, KQ4E2a, KQ5E2a.**
20. Domanchuk K, Ferrucci L, Guralnik JM, et al. Progenitor cell release plus exercise to improve functional performance in peripheral artery disease: the PROPEL Study. Contemp Clin Trials. 2013;36(2):502-9. PMID: 24080099. **KQ1E1, KQ2E1, KQ3E1, KQ4E3, KQ5E3.**
21. Elam MB, Hunninghake DB, Davis KB, et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: A randomized trial. Arterial Disease Multiple Intervention Trial. JAMA. 2000;284(10):1263-70. PMID: 10979113. **KQ1E1, KQ2E1, KQ3E1, KQ4E3, KQ5E2a.**
22. Esteghamati A, Aflatoonian M, Rad MV, et al. Association of osteoprotegerin with peripheral artery disease in patients with type 2 diabetes. Arch Cardiovasc Dis. 2015;108(8-9):412-9. PMID: 26184866. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1.**
23. Feigelson HS, Criqui MH, Fronek A, et al. Screening for peripheral arterial disease: the sensitivity, specificity, and predictive value of noninvasive tests in a defined population. Am J Epidemiol. 1994;140(6):526-34. PMID: 8067346. **KQ1E1, KQ2E4c, KQ3E4c, KQ4E1, KQ5E1.**
24. Fowler B, Jamrozik K, Norman P, et al. Prevalence of peripheral arterial disease: persistence of excess risk in former smokers. Aust N Z J Public Health. 2002;26(3):219-24. PMID: 12141616. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1.**
25. Franz RW, Garwick T, Haldeman K. Initial results of a 12-week, institution-based, supervised exercise rehabilitation program for the management of peripheral arterial disease. Vascular. 2010;18(6):325-35. PMID: 20979920. **KQ1E1, KQ2E1, KQ3E1, KQ4E2a, KQ5E2a.**
26. Girleanu I, Alexandrescu DM, Petris A, et al. Barriers of antiaggregant treatment. Rev Med Chir Soc Med Nat Iasi. 2014;118(2):333-8. PMID: 25076696. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E2.**

27. Gouveri E, Papanas N, Marakomichelakis G, et al. Post-exercise ankle-brachial index is not an indispensable tool for the detection of peripheral arterial disease in an epidemiological survey. A post-hoc analysis of the Athens Study. International angiology : a journal of the International Union of Angiology. 2013;32(5):518-25. PMID: 23903312. **KQ1E1, KQ2E4c, KQ3E4c, KQ4E1, KQ5E1.**
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Appendix D. Ongoing Studies

Study Reference Trial Identifier	Study Name	Location	Estimated N	Description	2017 Status
ISRCTN12157806	The Danish Cardiovascular Screening Trial (DANCAVAS)	Denmark	45,000 (men)	Population-based, randomized trial to evaluate the health benefits and cost-effectiveness of using noncontrast computer tomography scans (to measure coronary artery calcification (CAC) and identify aortic/iliac aneurysms) and measurements of the ankle-brachial blood pressure index (ABI) as part of a multifocal screening and intervention program for CVD in men aged 65 to 74 years.	Ongoing: Est Interim Publication Date 2018; Completion Date Jan 2026
NR (Protocol) (project page)	Randomized intervention study to assess the prevalence of subclinical vascular disease and hidden kidney disease and its impact on morbidity and mortality: The ILERVAS project	Spain	19,800	Adults 45 to 70 years without previous history of CVD and with ≥1 CVD risk factor will be randomly selected from the primary health care centers across the province of Lérida. The following baseline tests will be given to the intervention group in a mobile screening unit: artery ultrasound (carotid, femoral, transcranial and abdominal aorta); the ABI; spirometry; determination of advanced glycation end products; dried blood spot and urine spot tests.	Ongoing: Est Data Collection Completion Date 2017; Followup through 2025
ACTRN 12614000592640 (Protocol)	Effect of a brief behavioural counselling intervention on physical activity behaviour in people with peripheral artery disease.	Australia	200	Multicenter RCT in four cities across Australia; participants (N = 200) will be recruited from specialist vascular clinics, general practitioners and research databases. This trial will assess the efficacy of a brief behavioral counselling intervention delivered by allied health professionals to improve physical activity in persons with PAD.	Ongoing: Est Data Collection Completion Date NR
NCT01321086	Motivational Interviewing (MI) for African Americans With Peripheral Arterial Disease (PAD)	U.S.	174	Clinical research trial to determine the role of motivational interviewing on promoting home-based walking therapy to improve walking ability in African Americans with PAD (ABI <0.995). Quality of life, measured with the SF-12 and VascQOL questionnaires, is a prespecified secondary outcome.	Completed Nov 2016; not yet published
NCT00537225	Multifactor Risk Reduction for Optimal Management of PAD (VIGOR2)	U.S.	300	To examine effectiveness of a long-term multifactor CVD risk reduction program (HEAR2T) vs. enhanced standard care on walking and quality of life in patients with PAD.	Ongoing: Est Completion Date Jun 2018
NCT02622282	Text Messaging to Promote Walking Among Latino Adults at Risk for Peripheral Arterial Disease	U.S.	69	The purpose of this study is to learn about the impact of text messaging on physical activity in persons with risk factors for PAD. Quality of life is a prespecified secondary outcome.	Completed Dec 2016; not yet published

Abbreviations: Est = estimated; Jan = January; Jul = July; Jun = June, Nov=November, Dec=December; PAD = peripheral artery disease; RCT = randomized controlled trial; Sept = September; U.S. = United States