JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Peripheral Artery Disease Using the Ankle-Brachial Index

Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Peripheral artery disease (PAD) is associated with a high risk for cardiovascular events and poor ambulatory function, even in the absence of symptoms. Screening for PAD with the ankle-brachial index (ABI) may identify patients in need of treatment to improve health outcomes.

OBJECTIVE To systematically review evidence for the US Preventive Services Task Force on PAD screening with the ABI, the diagnostic accuracy of the test, and the benefits and harms of treatment of screen-detected PAD.

DATA SOURCES MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials for relevant English-language studies published between January 2012 and May 2, 2017. Surveillance continued through February 7, 2018.

STUDY SELECTION Studies of unselected or generally asymptomatic adults with no known cardiovascular disease.

DATA EXTRACTION AND SYNTHESIS Independent critical appraisal and data abstraction by 2 reviewers.

MAIN OUTCOMES AND MEASURES Cardiovascular morbidity; PAD morbidity; mortality; health-related quality of life; diagnostic accuracy; and serious adverse events.

RESULTS Five studies (N = 5864 participants) were included that examined the indirect evidence for the benefits and harms of screening and treatment of screen-detected PAD. No population-based screening trials evaluated the direct benefits or harms of PAD screening with the ABI alone. A single diagnostic accuracy study of the ABI compared with magnetic resonance angiography gold-standard imaging (n = 306) found low sensitivity (7%-34%) and high specificity (96%-100%) in a screening population. Two adequately powered trials (n = 4626) in asymptomatic populations with and without diabetes with a variably defined low ABI (≤0.95 or ≤0.99) showed no statistically significant effect of aspirin (100 mg daily) for composite CVD outcomes (adjusted hazard ratio [HR], 1.00 [95% CI, 0.81-1.23] and HR, 0.98 [95% CI, 0.76-1.26]). One trial (n = 3350) demonstrated no statistically significant increase in major bleeding events with the use of aspirin (adjusted HR, 1.71 [95% CI, 0.99-2.97]) and no statistically significant increase in major gastrointestinal bleeding (relative risk, 1.13 [95% CI, 0.44-2.91]). Two exercise trials (n = 932) in screen-relevant populations reported no differences in quality of life, Walking Impairment Questionnaire walking distance, or symptoms at 12 and 52 weeks; no harms were reported.

CONCLUSIONS AND RELEVANCE There was no direct evidence and limited indirect evidence on the benefits of PAD screening with the ABI in unselected or asymptomatic populations. Available studies suggest low sensitivity and lack of beneficial effect on health outcomes, but these studies have important limitations.

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Supplemental content

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Peripheral artery disease (PAD) is associated with a high risk for cardiovascular (CVD) events and poor ambulatory function.[1,2] Because it is often asymptomatic, PAD is underdiagnosed, and as a result, those who have it may not receive appropriate treatment.[3,4] Early detection and treatment of PAD could improve health outcomes by initiating (1) risk factor modification in people with undiagnosed atherosclerosis to reduce CVD outcomes, and (2) interventions to slow functional decline of the lower extremity.

The most commonly used screening test for PAD is the ankle-brachial index (ABI), which is the ratio of the ankle and brachial systolic blood pressures. While the ABI is recommended in patients with symptoms,[5] less is known about the benefits and harms of its use for early detection and treatment in asymptomatic patients. In 2013, the US Preventive Services Task Force (USPSTF) concluded that evidence was insufficient (I statement) to assess the balance of benefits and harms of using the ABI to screen for PAD and assess CVD risk in asymptomatic adults.[6]

The aim of this systematic review was to update the evidence on the benefits and harms of screening for PAD using the ABI, including the diagnostic accuracy of the test, and the benefits and harms of treating screen-detected patients, to inform the USPSTF in updating its recommendations.

Methods

Scope of Review

This review addressed 5 key questions (KQs), shown in **Figure 1**. Additional methodological details, including a detailed description of study selection and a list of excluded studies, and additional tabular outcome data for exercise trials, are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/peripheral-artery-disease-in-adults-screening-with-the-ankle-brachial-index.

Data Sources and Searches

This review is an update of the screening, diagnostic accuracy, treatment, and harms KQs of a prior systematic review commissioned by the USPSTF.[8] All previously included studies were reviewed for potential inclusion, and Ovid MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials were searched to identify new literature published between January 2012 and May 2, 2017 (eMethods in the Supplement). Additionally, reference lists from recent systematic reviews[9-17] were examined and ClinicalTrials.gov was searched to identify relevant ongoing trials. Since May 2, 2017, ongoing surveillance through article alerts and targeted searches of journals with a high impact factor and journals relevant to the topic were conducted to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and therefore the related USPSTF recommendation. The last surveillance was conducted on February 7, 2018, and identified 1 screening trial that was formally evaluated for inclusion but that did not meet the review criteria.

Study Selection

Two reviewers independently reviewed 4194 unique citations and 105 full-text articles against a priori inclusion criteria (**Figure 2**; eTable 1 in the Supplement). This review focused on screen-detected or generally asymptomatic adults without known CVD; therefore, studies whose participants primarily had the classic PAD symptom of intermittent claudication were excluded. This review allowed studies with participants reporting atypical symptoms with higher baseline values for ABI and lower extremity function who might also be representative of a screen-detected group.[3] For each KQ, analyses were specified a priori for the following population characteristics: age, sex, race/ethnicity, smoking history, and presence of diabetes or hypertension. These are presented where available but were rarely reported. The credibility of subpopulation analyses was evaluated based on the timing of planned analyses, interaction testing for heterogeneity of treatment effect, baseline comparability, and control for confounders.[18]

The primary outcomes of interest were cardiovascular morbidity, defined as myocardial infarction (MI) and cerebrovascular accident (CVA); PAD morbidity, which included ambulation impairment (eg, as measured by the Walking Impairment Questionnaire[19] [WIQ], which is measured on a scale of 0-100), or amputation; mortality; health-related quality of life; diagnostic accuracy of the resting ABI (sensitivity, specificity, positive predictive value, negative predictive value); adverse outcomes related to the ABI test; and serious adverse events related to treatment.[20] In studies reporting WIQ outcomes, proportions of the population with symptoms at baseline and follow-up were abstracted and reported.

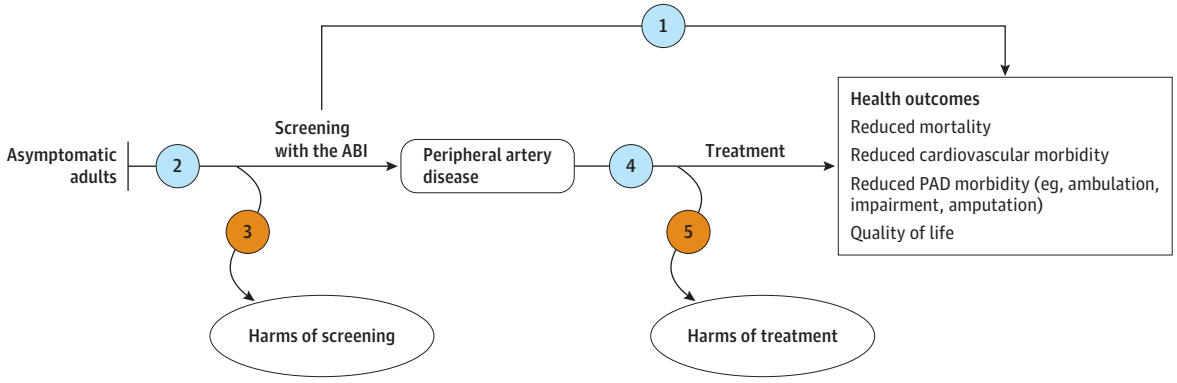
For treatment KQs (KQ4 and KQ5), pharmacologic or lifestyle interventions aimed at reducing CVD risk were included. New in this update were exercise and physical therapy interventions aimed at improving lower limb function.

For KQ1, randomized clinical trials (RCTs), nonrandomized controlled intervention studies, and systematic reviews that compared screening using the resting ABI with no screening and reported a primary outcome were eligible. For KQ2, prospectively conducted diagnostic accuracy studies and well-conducted systematic reviews of diagnostic accuracy were eligible. Case-control studies were excluded because selection of participants in this study design has been shown to overestimate sensitivity and result in spectrum bias.[21-25] For KQ2, diagnostic accuracy studies had to compare the resting ABI with a reference standard (ie, any diagnostic test that could image the degree of atherosclerosis or degree of impaired blood flow). For KQ4, any trial or systematic review with at least 12 weeks of follow-up that compared treatment of PAD with no treatment, with placebo treatment, or with delayed treatment was eligible. For evaluation of harms (KQ3 and KQ5), trials, cohort studies, and case-control studies were included; case series or case reports were excluded.

Data Extraction and Quality Assessment

Included studies were critically appraised by 2 independent reviewers using predefined criteria,[7,26] with disagreements resolved by a third reviewer (eTable 2 in the Supplement). Articles were rated as good, fair, or poor quality. In general, a good-quality study met all criteria. A fair-quality study did not meet, or it was unclear whether it met, at least 1 criterion but had no known important limitations that could invalidate its results. A poor-quality study had a single fatal flaw or multiple important

Figure 1. Analytic Framework



Key questions

1 Is screening for PAD in generally asymptomatic adults with the ABI effective in reducing CVD or PAD morbidity (eg, 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?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate to interventions and outcomes. Further details are available from the USPSTF procedure manual.[7] ABI indicates ankle-brachial index; PAD, peripheral artery disease.

limitations. Poor-quality studies were excluded because of substantial concerns about the validity of results for the KQ being addressed. One reviewer abstracted descriptive and outcome data from each study into standardized evidence tables; a second checked for accuracy and completeness.

Data Synthesis and Analysis

Data were synthesized separately for each KQ. The number of contributing studies was not sufficient for quantitative pooling for any KQ, so data are summarized narratively and in tables. For diagnostic accuracy studies (KQ2), 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]) were calculated; confidence intervals were calculated using the Agresti-Coull method.[27] For treatment trials (KQ4), standard deviations for continuous outcomes were converted to 95% CIs. For dichotomous outcomes, measures of association and between-group *P* values were calculated where not reported with 1- and 2-sample tests of proportions at the 5% significance level (2-sided test). Stata version 13.1 (StataCorp) was used for all quantitative analyses. Calculation methods are described further in the full report.

Results

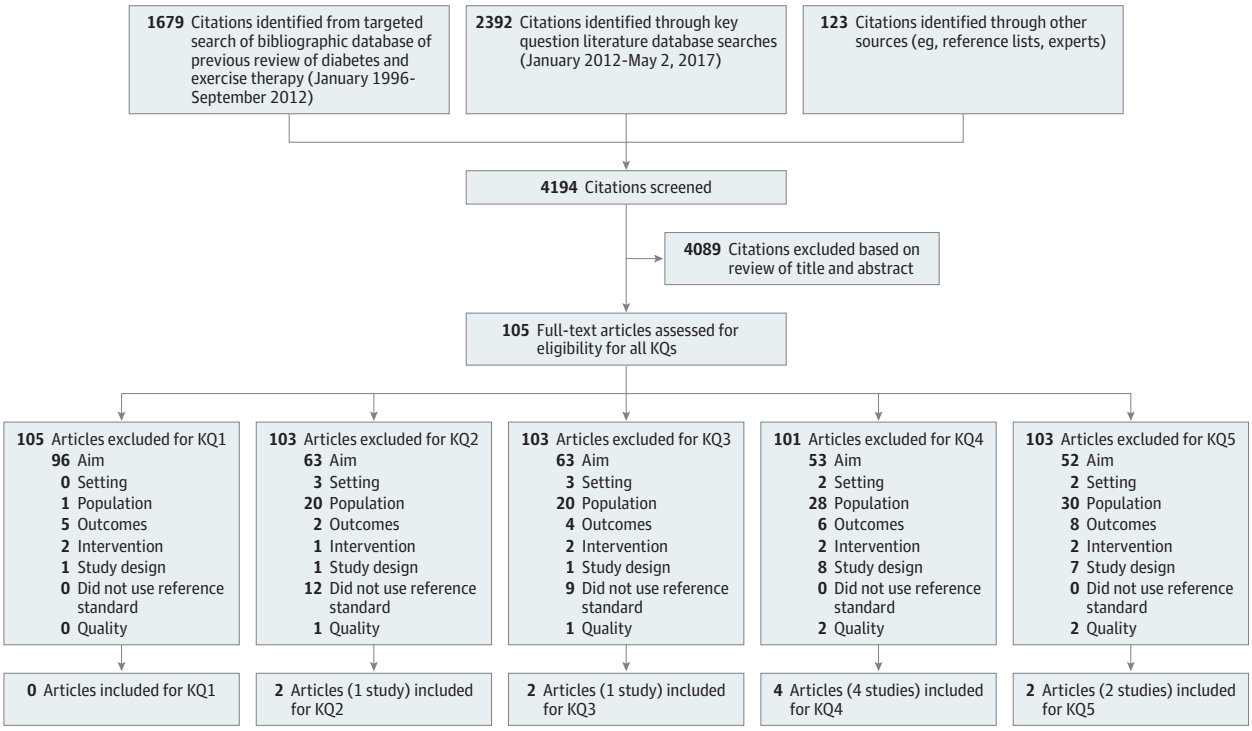
Five studies (N = 5864) met the inclusion criteria for this review (Figure 2). No direct evidence for PAD screening was identified for KQ1. One study included in the previous USPSTF systematic review evaluated the diagnostic accuracy of the ABI for KQ2 and KQ3.[28] Four trials addressed treatment benefits and harms in screen-relevant populations for KQ4 and KQ5.[29-32]

Benefits of Screening

Key Question 1. Is screening for PAD in generally asymptomatic adults with the ABI effective in reducing CVD or PAD morbidity (eg, impaired ambulation or amputation) or mortality?

No population-based randomized trials of ABI screening alone were identified. Three multicomponent screening trials are in progress, 2 in Denmark (ISRCTN12157806, NCT00662480)

Figure 2. Literature Search Flow Diagram



In total, the current review included 6 articles (5 studies); studies may appear in more than 1 key question (KQ). Reasons for exclusion: Aim: study aim not relevant. Setting: study not conducted in a country relevant to US practice or was conducted or recruited from hospital or specialty settings such as vascular clinics or laboratories that typically represented populations selected for known or highly suspected peripheral artery disease (PAD). Population: study not conducted in unselected or community-dwelling generally asymptomatic adults (KQ1, KQ2, and KQ3) or study was not conducted in screen-detected or generally asymptomatic adults with PAD or abnormal ankle-brachial index (ABI) (KQ4 and KQ5). Outcomes: study did not report required outcomes. Intervention: intervention was out of scope. Design: study did not use an included design. Did not use reference standard: for KQ2 and KQ3, the ABI was not compared with an eligible reference standard. Quality: study was poor quality.

and 1 in Spain (NCT03228459), that include PAD screening with the ABI as part of a combined vascular screening program.[33-35] None of these trials test the independent effectiveness of ABI screening.

Accuracy of Screening

Key Question 2. What is the diagnostic accuracy of the ABI as a screening test for PAD in generally asymptomatic adults?

Evidence for the diagnostic accuracy of the ABI as a screening test for PAD in asymptomatic adults is limited to 1 older fair-quality study published in 2008 that showed low sensitivity and high specificity. That study of 306 older adults in Sweden used whole-body magnetic resonance angiography (MRA) as the reference standard to confirm the presence of PAD.[28,36] The study recruited adults aged 70 years at study entry from a random subset of the population-based Prospective Investigation of the Vasculature in Uppsala Seniors cohort study (n = 1016).[37] Forty-seven percent of participants were women, 6.9% had experienced a previous MI, 3.9% had experienced a previous CVA, and 10.6% had diabetes. About 8% were current smokers.

The ABI was calculated for each leg by dividing the manual sphygmomanometer readings of posterior tibial artery systolic pressure by the mean of 3 brachial artery systolic pressures. A low ABI was defined as less than 0.9, and accuracy was calculated based on the whole-body MRA gold standard, with PAD diagnosis defined as 50% or greater stenosis.

The prevalence of an ABI less than 0.9 was 4.5% in the right leg and 4.2% in the left leg (**Table 1**). The prevalence of MRA-confirmed PAD defined as 50% or greater stenosis was 19.0% in the right leg and 23.0% in the left leg.

Sensitivity was 20% (95% CI, 10%-34%) in the right leg and 15% (95% CI, 7%-27%) in the left leg. Specificity was 99% (95% CI, 96%-100%) in both legs. Positive predictive value was 83% (95% CI, 51%-97%) in the right leg and 82% (95% CI, 48%-97%) in the left leg. Negative predictive value was 84% (95% CI, 79%-88%) in the right leg and 80% (95% CI, 74%-84%) in the left leg.

Harms of Screening

Key Question 3. What are the harms of screening for PAD with the ABI?

Evidence for the harms of screening for PAD with the ABI was limited to false-positive and false-negative rates in the aforementioned diagnostic accuracy study[28,36] (Table 1). The false-positive rate was 0.9% (95% CI, 0.0%-3.5%) in the right leg and 1.0% (95% CI, 0.0%-3.7%) in the left leg; the false-negative rate was 80.4% (95% CI, 67.4%-89.2%) in the right leg and 85.2% (95% CI,

Table 1. Diagnostic Accuracy of the ABI as a Screening Test for PAD in Generally Asymptomatic Adults (Key Question 2)[a]

	No. With ABI <0.9/Total No. (%)	No. With Stenosis on MRA/Total No. (%)	% (95% CI)					
			Sensitivity	Specificity	PPV	NPV	FPR	FNR
≥50% Stenosis								
Right leg	12/268 (4.5)	51/268 (19.0)	20 (10-34)	99 (96-100)	83 (51-97)	84 (79-88)	0.9 (0.0-3.5)	80.4 (67.4-89.2)
Left leg	11/265 (4.2)	61/265 (23.0)	15 (7-27)	99 (96-100)	82 (48-97)	80 (74-84)	1.0 (0.0-3.7)	85.2 (74.0-92.3)
>100% Stenosis								
Right leg	12/268 (4.5)	34/268 (12.7)	24 (11-42)	98 (95-99)	67 (35-89)	90 (85-93)	NA[b]	NA[b]
Left leg	11/265 (4.2)	37/265 (14.0)	16 (7-33)	98 (95-99)	55 (25-82)	88 (83-91)	NA[b]	NA[b]

Abbreviations: ABI, ankle-brachial index; FNR, false-negative rate; FPR, false-positive rate; MRA, magnetic resonance angiography; NA, not available; NPV, negative predictive value; PAD, peripheral artery disease; PPV, positive predictive value.

[a] Sources: Wikström et al,[28] 2008 and Wikström et al,[36] 2009 (N = 306).

[b] Not calculated, as 100% stenosis was not used as a diagnostic threshold.

74.0%-92.3%) in the left leg. A single participant had a vasovagal attack before contrast injection for MRA and was excluded from the study, but this adverse event was not attributed to the ABI. No other harms were reported in this study, nor were there any additional trials examining the downstream harms of screening for PAD with the ABI, such as diagnostic testing or procedures.

Benefits of Treatment

Key Question 4. Does treatment of screen-detected or generally asymptomatic adults with PAD or an abnormal ABI lead to improved patient health outcomes?

The evidence for treatment of screen-detected or generally asymptomatic adults with an abnormal ABI to improve health outcomes consists of 2 large RCTs of aspirin[29,30] and 2 RCTs of exercise.[31,32]

Aspirin

Two good-quality trials (n = 4626), both conducted in Scotland, examined the effectiveness of aspirin in populations with a low ABI.[29,30] The Aspirin for Asymptomatic Atherosclerosis (AAA) trial[30] (n = 3350) was a placebo-controlled RCT, and the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial[29] (n = 1276) was a factorial-designed RCT of aspirin and antioxidants vs placebo. Primary outcomes in both trials were composite cardiovascular end points; secondary outcomes were fatal and nonfatal MI and CVA, angina, intermittent claudication, transient ischemic attack, and all-cause mortality. Both trials were powered for composite outcomes. Mean follow-up was 8.2 years in the AAA trial, which was terminated early because of futility, and 6.7 years in the POPADAD trial.

Although both trials recruited asymptomatic populations with no history of CVD, they studied different populations. The AAA trial recruited men and women from the community aged 50 to 75 years (mean, 62.0 years) with an ABI of 0.95 or less. The POPADAD trial recruited from diabetes clinics and included men and women 40 years and older (mean, 60.3 years) with an ABI of 0.99 or less and diabetes. Of the participants, 55.9% and 71.5% were women in the POPADAD and AAA trials, respectively. All participants in the POPADAD trial had diabetes, with a mean glycated hemoglobin level of 8.0%; 2.6% of participants in the AAA trial had diabetes. Nonetheless, ABI values were similar in both trials, with a mean of 0.86 in the AAA trial and a median of 0.90 in the POPADAD trial. In AAA and POPADAD, 33% and 31% of participants, respectively, were current smokers. Calculated annual CVD events in the control groups were 0.99% in the AAA trial and 2.53% in the POPADAD trial, indicating that POPADAD participants had higher baseline CVD risk.[38] Statin use was reported in the AAA trial to be 4.2% at baseline and 25% at 5 years of follow-up.

Intervention groups in both trials received 100 mg of oral aspirin daily; aspirin was enteric coated in the AAA trial. Control groups in both trials received placebo, and the 2 × 2 factorial-designed POPADAD trial additionally randomized to antioxidant tablet vs placebo. Authors reported no evidence of an interaction between aspirin and antioxidants, so results were analyzed for the group taking aspirin compared with the group not taking aspirin.

Both trials showed no difference between the aspirin and control groups in trial-defined composite cardiovascular outcomes, fatal CVD events, or all-cause mortality (**Table 2**). The examination of individual CVD outcomes such as MI and CVA likewise showed no statistically significant difference between the aspirin and control groups (eTable 3 in the Supplement). There was also no difference in the development of intermittent claudication and need for peripheral arterial revascularization or above-the-ankle amputation procedures (eTable 3 in the Supplement). Subgroup credibility ratings did not support a differential treatment effect by age or sex. Within-trial comparisons revealed overlapping confidence intervals, and POPADAD—the single trial with heterogeneity testing for CVD outcomes by age and sex—reported nonstatistically significant interaction testing (eTable 4 and eTable 5 in the Supplement).

Exercise

Two trials examined the effectiveness of exercise in populations with low ABI: a good-quality Australian trial by Fowler et al (n = 882)[32] and a small, fair-quality US pilot study by Collins et al (n = 50).[31] The first trial recruited participants from the population-based Western Australian abdominal aortic aneurysm screening trial, while the US pilot RCT included participants with a low ABI, defined as less than 0.9, and no intermittent claudication who were referred to a Veterans Administration vascular

Table 2. Composite and Mortality Outcomes for Aspirin in Participants With Low Ankle-Brachial Index (Key Question 4)

Outcome	Trial	No. With the Event/Total No. (%)		HR (95% CI)
		Intervention	Control	
Primary composite CVD outcome[a]	AAA[b]	181/1675 (10.8)	176/1675 (10.5)	1.00 (0.81-1.23)[d]
	POPADAD[c]	116/638 (18.2)	117/638 (18.3)	0.98 (0.76-1.26)
Composite fatal coronary events + CVA + CVD death	AAA[b]	35/1675 (2.1)[e]	30/1675 (1.8)[e]	1.17 (0.72-1.89)[e,f]
	POPADAD[c]	43/638 (6.7)	35/638 (5.5)	1.23 (0.79-1.93)
Composite nonfatal MI + CVA	AAA[b]	99/1675 (5.9)[e]	106/1675 (6.3)[e]	0.93 (0.72-1.22)[e,f]
	POPADAD[c]	84 (13.2)[e]	97 (15.2)[e]	0.87 (0.66-1.14)[e,f]
All-cause mortality	AAA[b]	176/1675 (10.5)	186/1675 (11.1)	0.95 (0.77-1.16)
	POPADAD[c]	94/638 (14.7)	101/638 (15.8)	0.93 (0.71-1.24)

Abbreviations: AAA, Aspirin for Asymptomatic Atherosclerosis trial; CVA, cerebrovascular accident; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; POPADAD, Prevention of Progression of Arterial Disease and Diabetes.

[a] Defined in the AAA trial as initial fatal or nonfatal coronary event or CVA or revascularization; defined in the POPADAD trial as death from coronary heart disease or CVA, nonfatal MI or CVA, or above-ankle amputation for critical limb ischemia.

[b] Fowkes et al,[30] 2010 (N = 3350).

[c] Belch et al,[29] 2008 (N = 1276).

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

[e] Calculated.

[f] Relative risk.

laboratory. Primary outcomes were the change from baseline to follow-up at 12[31] and 52 weeks[32] in walking ability; this was defined in the trial by Fowler et al[32] as the ability to walk 91.4 to 365.8 m before onset of intermittent claudication and in the trial by Collins et al[31] as the WIQ walking distance score. Because the trial by Collins et al was designed as a small, short-term feasibility study, it was not powered for its primary outcome.

Compared with the populations in the aspirin trials, participants in the exercise trials were more frequently men, older, more symptomatic, and had lower ABI. Both trials were exclusively or almost exclusively conducted among men. Mean age was 73.1 years in the trial by Fowler et al and 69.1 years in the trial by Collins et al. Because the trial by Fowler et al recruited participants who screened positive for PAD via either the ABI or the Edinburgh Claudication Questionnaire, about 44% of the population had intermittent claudication; atypical symptoms were present in about 9% of the population, and the remainder were asymptomatic. Fifty-six percent of participants in the trial by Collins et al were asymptomatic for PAD, and the remaining 44% had atypical symptoms. Mean ABI was 0.79 in the trial by Fowler et al and 0.74 in the trial by Collins et al.

The interventions in the 2 trials were somewhat heterogeneous with respect to format and intensity; each trial included lifestyle messages in addition to exercise. Intervention details are provided in eTable 6 in the Supplement. The intervention in the trial by Fowler et al included a smoking cessation intervention and physical therapy referral. The 52-week intervention began with an individual face-to-face session including explanation of the PAD screening test results and provision of an educational packet about PAD, a brochure about the community physical therapy service, smoking cessation information if applicable, and a copy of the letter sent to the patient's general practitioner. The community physical therapy service goal was to increase physical activity and included 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. In the control group, nurses disclosed results of diminished flow to the lower extremities but told participants that "there is presently no evidence to suggest you do anything about it at this time."

The intervention in the trial by Collins et al included 2 components delivered individually by a nurse: risk factor modification and counseling to improve physical activity. The 12-week intervention started with a face-to-face session followed by 5 telephone visits, each lasting less than 30 minutes. The control group was advised to continue routine care with primary care physicians. Adherence to the physical activity component differed widely between the 2 trials: it was relatively low in the longer trial by Fowler et al (16.5% at 1 year of follow-up) and high in the 12-week trial by Collins et al related to the physical activity recommendation of 30 minutes 3 times per week (40% at baseline and 82% by the final telephone call).

The variability of outcome measures reported in the 2 trials precludes definitive conclusions, but generally, evidence suggests that exercise-based treatment of screen-detected PAD may have limited effectiveness. Neither trial showed statistically significant between-group differences in self-reported quality of life, as measured by the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), used in the trial by Collins et al, or the Rosser Health-related Quality of Life instrument, used in the trial by Fowler et al. Only the trial by Collins et al reported eligible ambulation impairment outcomes, showing no difference in the primary outcome of mean walking distance score on the WIQ or walking speed. However, a statistically significant larger improvement was found for the intervention group for the stair-climbing component of the WIQ compared with the control group (mean difference, 15.1 [95% CI, 2.4 to 32.6]; $P = .02$). Neither trial showed statistically significant between-group differences for the proportion of participants experiencing symptoms between baseline and follow-up. However, in the trial by Fowler et al, the proportion of participants experiencing atypical symptoms and intermittent claudication decreased in both the intervention and the control groups. Symptom patterns in the trial by Collins et al were more inconsistent, possibly because of a very small sample.

Harms of Treatment

Key Question 5. What are the harms of treatment of screen-detected or generally asymptomatic adults with PAD or an abnormal ABI?

Evidence for the harms of treatment are limited to the 2 trials of aspirin and suggest that aspirin may be associated with increased major bleeding, although rare events and wide confidence intervals preclude definitive conclusions from these studies alone. Both the AAA and the POPADAD trials reported bleeding harms associated with use of 100 mg of aspirin daily. Major gastrointestinal bleeding requiring hospital admission was similar in the aspirin and control groups (0.5% vs 0.5%; relative risk [RR], 1.13 [95% CI, 0.44-2.91]).[30] Major hemorrhage (defined as nonfatal or fatal hemorrhagic CVA, fatal or nonfatal subarachnoid or subdural hemorrhage, gastrointestinal bleeding requiring admission, and other bleeding requiring hospital admission) in the AAA trial was higher in the aspirin group but did not reach statistical significance (2.0% vs 1.2%; HR, 1.71 [95% CI, 0.99-2.97]).[30] Five hemorrhagic CVAs occurred in the aspirin group and 4 in the control group; confidence intervals were wide, because of the rare event rate (0.3% vs 0.2%; RR, 1.25 [95% CI, 0.34-4.65]). The POPADAD trial reported a nonsignificant reduction in fatal hemorrhagic CVA in the aspirin group, but again, confidence intervals were wide because of rare events (2 events [0.3%] vs 3 events [0.5%]; RR, 0.67 [95% CI, 0.11-3.98]).

Discussion

An overall summary of the evidence is presented in **Table 3**. No population-based screening trials address the effectiveness of ABI screening for PAD as a single intervention to reduce PAD- or CVD-related morbidity or mortality. The indirect chain of evidence linking screening with the ABI in generally asymptomatic adults to improved health outcomes is limited (Figure 1). A single diagnostic accuracy study demonstrates that the ABI has poor sensitivity for detecting PAD in unselected populations; that same study was included in the previous review for the USPSTF. Evidence for treatment benefit consists of 2 trials of aspirin and 2 trials of exercise; 1 of the aspirin trials[29] and both exercise trials[31,32] are newly included in this updated review for the USPSTF. The 2 aspirin trials demonstrated that aspirin is not effective in reducing composite CVD morbidity or mortality over 6 to 8 years of follow-up and also demonstrated an increased bleeding risk that was not statistically significant. However, both trials defined low ABI with higher thresholds than used in clinical practice because their aim was to use the ABI as a nontraditional risk factor to identify a high CVD risk population that might benefit from aspirin, not to screen for clinical PAD; as such, a sizable proportion of the study population would not have met the clinical threshold of ABI less than 0.9. The 2 exercise trials similarly showed limited effectiveness across most outcome measures; statistically significant improvement was seen for the stair-climbing component of the WIQ only, reported in 1 trial.

The poor sensitivity of the ABI identified in the 1 included diagnostic accuracy study contrasts with evidence in symptomatic populations. Other systematic reviews of largely symptomatic populations have reported much higher diagnostic accuracy.[9-11,17] For example, pooled sensitivities and specificities for ABI 0.9 or less compared with an angiographic reference standard have been reported at 75% (95% CI, 71%-79%) and 86% (95% CI, 83%-90%), respectively, with significant heterogeneity.[17] The far lower sensitivity and higher specificity in the single included study compared with the larger literature involving symptomatic populations is likely owing to a combination of factors: an expected poorer accuracy in screening populations compared with symptomatic populations (spectrum effect)[39]; different methods for calculating the ABI; and limitations of study quality in a single, small population sample. One recent diagnostic accuracy study not meeting the review's inclusion criteria reported a sensitivity of 49% and specificity of 94% for targeted screening in high-risk populations as defined per American Heart Association guidelines[5] (patients aged >65 years or >50 years with the presence of diabetes or currently smoking; patients with exertional leg pain), using color duplex as the reference standard.[40]

Similarly, the finding of limited effectiveness of exercise interventions in the present review differ from the findings of several systematic reviews in largely symptomatic populations. The literature centered on symptomatic populations has 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.[9,12-14] Expecting unselected populations to achieve improvements in ambulation may not be reasonable if they are not reporting symptoms; however, if patients are unaware of symptoms because they have limited their activity levels, treatment could potentially improve ambulation and quality of life. Several observational studies of screen-detected or asymptomatic populations do show that those with a low ABI have statistically significant worse measures of function than those with a normal ABI, including 6-minute walk distance, 4-m walking velocity, 400-m walk time, SF-36 physical functioning subscale scores, and WIQ distance and speed scores.[41-46] Two exercise-based intervention trials in patients with PAD or a low ABI showed improved lower-extremity functional outcomes but were not included in this review because 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, screen-detected primary care population.[47,48] Replication of these findings in screened populations is needed.

Other systematic reviews of antiplatelet therapy have similarly reported no overall reduction in CVD events with aspirin compared with control in populations with low ABI.[9,15,16] Findings of bleeding risk associated with aspirin use should be considered in the context of the broader literature about aspirin use for CVD primary prevention.[49] The present 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.[9,50-53] An RCT of statin therapy in individuals with an abnormal ABI may be of uncertain value because many of these individuals may qualify for statin therapy based on 10-year risk alone—data from a 2008 large, individual participant data meta-analysis suggest that 95% of men and 41% of women with an ABI of 0.9 or less would already be above a 10% Framingham Risk Score 10-year risk threshold.[1]

Table 3. Summary of Evidence by Key Question

Total No. of Studies and Design, No. of Participants Randomized	Outcome	No. of Trials (No. of Participants Analyzed)	Summary of Findings by Outcome	Consistency and Precision	Reporting Bias	Study Quality	Body of Evidence Limitations	Applicability
KQ1: Effectiveness of Screening								
0 studies	Morbidity or mortality	0	NA	NA	NA	NA	NA	NA
KQ2: Diagnostic Accuracy of Screening								
1 Prospective diagnostic accuracy study, n = 307 (0/1 trials identified in update)	Sensitivity, specificity, PPV, NPV	1 (n = 306)[a]	ABI has low sensitivity (7%-34%) and high specificity (96%-100%) vs MRA gold standard imaging	Consistency NA (single study) Imprecise	Not detected	Fair	Single study, not clear if MRA interpreters were blinded to ABI results; harms (aside from false positives and false negatives) not reported other than single vasovagal episode	Screening population of older adults (70 y) in Sweden The low sensitivity reported in this single study is well below the sensitivities reported in symptomatic populations
KQ3: Harms of Screening								
1 Prospective diagnostic accuracy study, n = 307 (0/1 trials identified in update)	Harms	1 (n = 306)[a]	ABI has high false-negative rate (>80%) reflecting low sensitivity in screening for PAD	Consistency NA (single study) Imprecise	Not detected	Fair	Single study, not clear if MRA interpreters were blinded to ABI results; harms (aside from false positives and false negatives) not reported other than single vasovagal episode	Screening population of older adults (70 y) in Sweden The low sensitivity reported in this single study is well below the sensitivities reported in symptomatic populations
KQ4: Benefits of Treatment								
Aspirin 2 RCTs, n = 4626 (1/2 trials identified in update)	CVD composite, ACM, individual CVD outcomes	2 (n = 4626)	Aspirin (100 mg daily) showed no effect on CVD composite events in the 2 trials: adjusted HR, 1.00 (95% CI, 0.81-1.23) and HR, 0.98 (95% CI, 0.76-1.26) No effect on ACM: HR, 0.95 (95% CI, 0.77-1.16) and HR, 0.93 (95% CI, 0.71-1.24) No statistically significant difference in individual CVD outcomes including MI, CVA, development of intermittent claudication, and need for peripheral arterial revascularization or above-ankle amputation procedures	Reasonably consistent Imprecise	Not detected	Good	Studies designed to detect differences in CVD composites but not individual CVD outcomes	Two Scottish trials in asymptomatic patients with low ABI defined as ≤0.95 and ≤0.99 (thresholds not typically used to define abnormal ABI in clinical practice) One trial exclusively in patients with diabetes. Populations at intermediate to high CVD risk
Exercise 2 RCTs, n = 932 (2/2 trials identified in update)	Quality of Life	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	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; participants almost 100% men
	WIQ	1 (n = 48)	No difference in WIQ score change from baseline for distance or speed components; statistically significant improvement in stair climbing component in intervention group vs control group	NA	Not detected	Fair		
	Proportion of participants with symptoms	2 (n = 722)	No change in proportion of participants who developed intermittent claudication or atypical symptoms	Reasonably consistent Imprecise	Not detected	1 Good, 1 fair		

(continued)

Table 3. Summary of Evidence by Key Question (continued)

Total No. of Studies and Design, No. of Participants Randomized	Outcome	No. of Trials (No. of Participants Analyzed)	Summary of Findings by Outcome	Consistency and Precision	Reporting Bias	Study Quality	Body of Evidence Limitations	Applicability
KQ4a: Benefits of Treatment by Subpopulation								
Aspirin 2 RCTs, n = 4626 (1/2 trials identified in update)	CVD composite, individual CVD outcomes, fatal CVD events, ACM	2 (n = 4626)	No compelling evidence to support differential treatment effect by age, sex, or diabetes status Within-trial comparisons revealed overlapping CIs; 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 outcomes similar to those almost exclusively without diabetes (AAA)	Inconsistent (age) Reasonably consistent (sex) Imprecise (age, sex)	Not detected	Good	Only 1 trial performed interaction testing by age and sex; unclear if a priori planned analysis Other trial 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	Both Scottish trials in asymptomatic patients with low ABI defined as ≤0.95 and ≤0.99 (thresholds not typically used to define abnormal ABI in clinical practice) One trial exclusively in patients with diabetes Populations at intermediate to high CVD risk
Exercise 0 studies	NA	NA	No exercise trials examine the differential treatment effect by subpopulation	NA	NA	NA	NA	NA
KQ5: Harms of Treatment								
Aspirin 2 RCTs, n = 4626 (1/2 trials identified in update)	Major GI bleeding requiring admission	1 (n = 3350)	Major GI bleeding requiring hospital admission was similar in 1 reporting trial (AAA) of aspirin (100 mg, enteric coated) at 8.2 y of follow-up: 0.5% vs 0.5%; RR, 1.13 (95% CI, 0.44-2.91) Limited evidence from this trial demonstrates a higher risk for major bleeding events with the use of aspirin but was not statistically significant Two trials reported conflicting results on total or fatal hemorrhagic CVA risk with wide CIs attributable to rare event rate	Consistency NA (single study) Imprecise	Not detected	Good	Rare events, wide CIs	Asymptomatic patients with low ABI defined as ≤0.95 with intermediate CVD risk
	Major hemorrhage (defined as nonfatal or fatal hemorrhagic CVA, fatal or nonfatal subarachnoid/subdural hemorrhage, GI bleeding requiring admission, and other bleeding requiring hospital admission)	1 (n = 3350)	Major hemorrhage did not reach statistical significance but was slightly higher in the aspirin group: 2.0% vs 1.2%; HR, 1.71 (95% CI, 0.99-2.97)	Consistency NA (single study) Imprecise	Not detected	Good	Single trial, relatively rare event with wide CIs	
	Hemorrhagic CVA	2 (n = 4626)	Nonsignificant higher risk for total hemorrhagic CVA with aspirin in AAA (0.3% vs 0.2%; RR, 1.25 [95% CI, 0.34-4.65]) and a lower risk for fatal hemorrhagic CVA in POPADAD (0.3% vs 0.5%; RR, 0.67 [95% CI, 0.11-3.98]), but CIs were wide because of rare events	Inconsistent, Imprecise	Not detected	Good	Somewhat conflicting results when comparing total and fatal hemorrhagic CVA across 2 trials that recruited different populations (with and without diabetes)	
Exercise 0 studies	NA	No trials reporting harms	NA	NA	NA	Good	NA	NA

Abbreviations: AAA, Aspirin for Asymptomatic Atherosclerosis Trial; ABI, ankle-brachial index; ACM, all-cause mortality; CVA, cerebrovascular accident; CVD, cardiovascular disease; EPC, Evidence-based Practice Center; GI, gastrointestinal; HR, hazard ratio; HrQOL, health-related quality of life; KQ, key question; MI, myocardial infarction; MOS SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; MRA, magnetic resonance angiography; NA, not applicable; PAD, peripheral artery disease; POPADAD, Prevention of Progression of Arterial Disease and Diabetes; RCT, randomized clinical trial; RR, relative risk; WIQ, Walking Impairment Questionnaire.

[a] Of 307 participants randomized, only 306 were analyzed (1 participant did not complete gold standard test).

Table 4. Recommendations for Screening for PAD With ABI in Individuals Without History or Physical Examination Findings Suggestive of PAD

	USPSTF 2018	ESC 2017[54]	AHA/ACC 2016[5]	SVS 2015[55]	AAFP 2017[56]	NICE 2012[57]	ACPM 2011[58]
Population for which screening is recommended	Insufficient evidence for asymptomatic adults	Aged >65 y; Aged <65 y classified at high CVD risk according to ESC guidelines; aged >50 y with family history; known atherosclerotic disease (CAD, any PAD), AAA, CKD, heart failure	Aged ≥65 y Aged 50-64 y with risk factors for atherosclerosis (eg, DM, history of smoking, hyperlipidemia, hypertension) or family history of PAD Aged <50 y with DM and 1 other risk factor for atherosclerosis; known atherosclerotic disease in another vascular bed (eg, coronary, carotid, subclavian, renal, mesenteric artery stenosis, or AAA)	Aged >70 y, smokers, DM; abnormal pulse examination; or other established CVD	Insufficient	Adults with symptoms suggestive of PAD; have DM, nonhealing wounds on legs or feet, or unexplained leg pain; are being considered for interventions to the leg or foot; need to use compression hosiery	Clinicians should be alert to symptoms in those at increased risk (>50 y, smokers, and those with DM) and evaluate patients with clinical evidence of vascular disease

Abbreviations: AAA, abdominal aortic aneurysm; ABI, ankle-brachial index; ACPM, American College of Preventive Medicine; AHA/ACC, American Heart Association/American College of Cardiology; AAFP, American Academy of Family Physicians; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; ESC, European Society of Cardiology; NR, not reported; PAD, peripheral artery disease; SVS, Society for Vascular Surgery; USPSTF, US Preventive Services Task Force.

Some organizations recommend screening for PAD with the ABI in populations above certain ages or with various risk factors (**Table 4**).[5,55-58] The rationale is that high-prevalence populations, such as those at older age, with diabetes, and who smoke cigarettes, can be easily identified based on established risk factors for PAD[59]; 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.[55] Conversely, even when higher-prevalence populations with high CVD risk 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 lifestyle and pharmacologic treatment based on their global CVD risk.[60]

Three population-based screening trials are testing the effectiveness of combined multiple vascular screening tests on all-cause mortality, cardiovascular morbidity and mortality, or both at 10 to 15 years of follow-up. However, none of these trials isolates the independent effectiveness of ABI screening. The Viborg Vascular (VIVA) screening trial enrolled 50 156 men aged 65 to 74 years and randomized to screening vs no screening for hypertension, PAD, and abdominal aortic aneurysm; the intervention included subsequent counseling for physical activity, smoking cessation, and a low-fat diet, as well as cholesterol testing with aspirin and statin therapy prescribed to those meeting a total cholesterol threshold value.[61] An interim analysis at a median of 4.4 years of follow-up reported an absolute risk reduction of 0.006 (95% CI, 0.001-0.011) in all-cause mortality in the screened group (HR, 0.93 [95% CI, 0.88-0.98]) and a reduction in PAD-specific hospital days (HR, 0.81 [95% CI, 0.76-0.87]). The authors hypothesized that the all-cause mortality benefit was largely seen from preventive measures including statin and aspirin use; these conclusions were based on sensitivity analyses that removed smokers or those initiating hypertensive therapy, which did not change the main results. Applicability of such findings in the context of current treatment thresholds for pharmacotherapy based on global CVD risk[62-64]is uncertain, as nearly all participants would have a 10% or greater 10-year CVD risk based on age and male sex alone[65] and thus would already be candidates for consideration of statins or aspirin. Secondary analyses, including cost-effectiveness analyses to estimate the independent effect of ABI screening, are planned, but it is unlikely that such analyses will definitively demonstrate ABI screening effectiveness given the aforementioned considerations.

Two other large, in-progress multicomponent screening trials (ISRCTN12157806, NCT03228459) using population-based or primary care–based recruitment include the ABI as part of the multicomponent screening intervention and will report primary outcomes of all-cause mortality and CVD events at 10 years of follow-up.[34,35,66] As with the VIVA trial, the multicomponent nature of these trials will likely preclude definitive conclusions about the effect of ABI screening alone.

Limitations

This evidence report has several limitations. To be consistent with the scope of the USPSTF, the review excluded symptomatic individuals for both diagnostic accuracy and treatment questions. However, the varied clinical presentation of PAD and the recognition that severity of leg symptoms may not directly correspond to atherosclerotic burden are problematic in identifying a screening-relevant population. The scope of this review did not include diagnostic accuracy of other screening methods or modalities, such as automated oscillometric ABI measurement methods[67,68]; the post-exercise ABI, which may be relevant in clinically "asymptomatic" populations who self-limit exertion; and the toe-brachial index.

For treatment trials, the narrow population requirement could be considered unnecessarily limiting. However, to develop an indirect chain of evidence in support of screening, it is critical that treatment trials be applicable to a population that reflects the screen-detected population in terms of disease severity and

treatment effectiveness. The prespecified health outcomes required in this review include CVD and PAD morbidity or mortality or quality of life, with the exclusion of intermediate outcomes such as behavior changes, ABI changes, intermediate cardiovascular risk factors, or intermediate measures of lower limb function to include the 6-minute walk test or lower-extremity strength. No treatment trials were excluded from this review on the basis of reporting 6-minute walk outcomes.

Conclusions

There was no direct evidence and limited indirect evidence on the benefits of PAD screening with the ABI in unselected or asymptomatic populations. Available studies suggest low sensitivity and lack of beneficial effect on health outcomes, but these studies have important limitations.

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Author Contributions: Dr Guirguis-Blake had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Guirguis-Blake, Evans, Lin.
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