A systematic review for the screening for peripheral arterial disease in asymptomatic patients

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Background: **Peripheral arterial disease (PAD) is common and associated with significant morbidity and mortality. PAD can be detected through a noninvasive measurement of the ankle-brachial index (ABI).**
Methods: **We conducted a systematic review of several electronic bibliographic databases for studies that evaluated ABI as a screening test for PAD in asymptomatic individuals. We conducted random-effects meta-analysis, reporting pooled hazard ratios (HRs) when appropriate.**
Results: **We included 40 individual studies, 2 systematic reviews, and 1 individual-patient data meta-analysis. We found no studies comparing ABI screening with no screening in terms of patient-important outcomes (mortality, amputations). The yield of PAD screening averaged 17% (range, 1%-42%) and was 1% to 4% in lower risk populations. Patients with PAD had higher adjusted risk of all-cause mortality (HR, 2.99; 95% confidence interval, 2.16-4.12) and of cardiovascular mortality (HR, 2.35; 95% confidence interval, 1.91-2.89). Data on benefits, harms, and cost-effectiveness of screening were limited; however, ABI screening was associated with additional prognostic information and risk stratification for heart disease. The overall quality of evidence supporting screening was low.**
Conclusions: **The current available evidence demonstrates that PAD is common in patients with multiple cardiovascular risk factors and is associated with significant morbidity and mortality, but it does not support the benefit of routine ABI screening. (J Vasc Surg 2015;61:42S-53S.)**

Peripheral arterial disease (PAD) is estimated to affect 8 million Americans,[1] with prevalence that is increasing over time.[2] Between 9% and 23% of people 55 years of age and older are affected by PAD.[3,4] Notably, only 10% of these individuals have the classic symptoms of intermittent claudication, whereas 50% experience other leg symptoms and the other 40% are asymptomatic.[5,6] Persons with PAD (ankle-brachial index [ABI] <0.90) who never experience exertional leg symptoms have poorer functional performance, poorer quality of life, and more adverse calf muscle characteristics compared with persons with intermittent claudication and also compared with a sedentary, asymptomatic, age-matched group of non-PAD persons.[7]

Patients with PAD have higher 10-year cardiovascular mortality than similar age-matched controls without PAD (18.7% vs 4.4%; hazard ratio [HR], 4.2 for men and 3.5 for women), even after adjusting for traditional cardiovascular risk factors using the Framingham Risk Score.[8] The risk of cardiovascular morbidity was comparable between individuals with asymptomatic and symptomatic PAD[9] and is similar to or higher than the cardiovascular risk of secondary prevention populations.[4,10]

Risk factors associated with PAD are those classically associated with atherosclerosis and include increasing age, cigarette use, diabetes, dyslipidemia, hypertension, elevated C-reactive protein, and hyperhomocysteinemia.[11,12] Cigarette smoking, in particular, is a powerful risk factor for PAD, increasing the risk twofold to sixfold.[13,14] In two large population-based studies, >80% of patients with PAD were either current or former smokers.[15,16]

In summary, PAD is a condition with significant morbidity and mortality that can be asymptomatic and has known risk factors; all are characteristics of a condition in which effective screening strategies may be desirable. ABI measurement is a simple, noninvasive, risk-free, and inexpensive test that compares the ankle systolic blood pressure to the brachial artery systolic blood pressure. It also has desirable diagnostic performance properties (sensitivity, 70%-95%; specificity, 95%-100%[17]) that make ABI suitable as a screening test. Alternative PAD detection methods in asymptomatic individuals have significant limitations; the Rose questionnaire has poor sensitivity, and the

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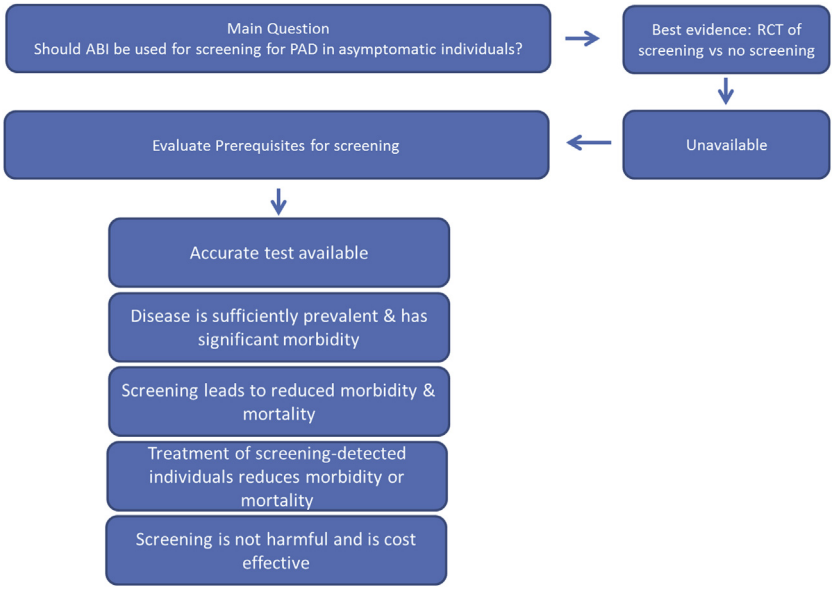

Fig 1. Analytic framework. *PAD,* Peripheral arterial disease; *RCT,* randomized controlled trial.

lower extremity pulse palpation has limited reproducibility and low specificity.[18]

In 2013, the U.S. Preventive Services Task Force (USPSTF) considered evidence to be insufficient to recommend ABI screening in asymptomatic adults who do not have a known diagnosis of PAD, cardiovascular disease (CVD), severe chronic kidney disease, or diabetes. This rating of I or insufficient evidence was a change from their prior recommendation rating of D, which was against screening.[19] On the other hand, the American College of Cardiology and the American Heart Association joint practice guidelines recommend using ABI in patients at increased risk, including adults ≥65 years old or those ≥50 years with a history of smoking or diabetes, and in those with nonhealing wounds.[20]

Considering the lack of consistency in practice and in expert recommendations and the publication of studies since the formulation of those guidelines, the Society for Vascular Surgery commissioned an updated synthesis of the existing evidence. Hence, we conducted a systematic review of PAD screening studies.

METHODS

Study eligibility and data sources. Studies were eligible for this review if they reported on a screening program for PAD in asymptomatic individuals using ABI. Studies were included regardless of design (ie, randomized or not), language, size, or length of follow-up. Outcomes of interest were the yield of screening and the benefits and harms of screening, followed by treatment (in terms of death, amputation, development of symptoms, and quality of life). We updated an evidence report from the USPSTF[21] published in 2005 that served as a data source up to that date. A comprehensive search of several databases from 2005 to March 2010 was conducted and then updated in June 2014. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and the National Guideline Clearinghouse. The search strategy was designed and conducted by an expert reference librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to define the two concept areas, peripheral vascular disease and screening, as well as to limit the search to clinical studies. The detailed strategy is available in the Appendix. We also included relevant systematic reviews and meta-analyses. For each comparison of interest, evidence was derived from a credible systematic review if it existed; if not, individual studies were evaluated.

Data extraction and analysis. The analytic framework for this review was derived from the essential prerequisites for a screening test and incorporated the approach of the USPSTF guideline.[21] Therefore, we asked five questions and reported the results accordingly (Fig 1).

Teams of reviewers, working in duplicates, reviewed the abstracts and full-text articles and extracted descriptive, methodologic quality, and outcome data. We used dedicated software (DistillerSR, Ottawa, Canada) to conduct the online article review and data extraction procedures, the latter using piloted electronic forms. Chance-adjusted inter-reviewer agreement for study selection averaged 0.80. Relative association measures (relative risk, odds ratios, and HRs) and the associated 95% confidence intervals (CIs) were pooled across studies using a random-effects model. Heterogeneity in results across studies was assessed by the I^2 statistic.[22]

RESULTS

Literature search yielded 446 references, from which 406 were excluded (287 were not original and 119 did not report on screening in asymptomatic patients). Of note, some included studies enrolled a proportion of symptomatic patients with claudication; however, studies that did not enroll any asymptomatic patients were excluded. There were 40 eligible studies enrolling 139,830 screened individuals. Of these 40 studies, 38 reported data on screening yield, 19 reported data on the association between PAD and mortality, and 5 reported on outcomes of interventions provided to PAD patients identified through screening. We also included two systematic reviews[23,24] and one individual-patient data meta-analysis.[8]

We found no randomized controlled trials that evaluated a PAD screening program in terms of its effect on patient-important outcomes[25]; such data would be most useful to guideline developers providing recommendations about the utility of screening.

An accurate test is available

A systematic review and meta-analysis pooled four studies comprising 569 patients (922 limbs) and evaluated the diagnostic accuracy of ABI ≤0.90 for PAD diagnosis compared with angiography. The area under the curve of the summary receiver operator curve was 0.87 (standard error = 0.02), suggesting good accuracy. The diagnostic odds ratio was 15.33 (95% CI, 9.39-25.02). The pooled sensitivity and specificity of ABI ≤0.90 for PAD diagnosis were 75% and 86%, and the pooled positive likelihood ratio and negative likelihood ratio were 4.18 and 0.29, respectively.[24] Evidence summary by the American College of Cardiology and the American Heart Association also suggested that ABI <0.9 has a sensitivity ranging from 79% to 95%, with specificity >95%.[26]

The disease is sufficiently prevalent and has significant morbidity

The included studies are described in Table I. Thirty-eight studies provided a screening yield that averaged 17.2% (median, 14.7%; range, 2.1%-42%) for an abnormal ABI (defined as <0.90 in most studies). The heterogeneity of the screening yield was clearly attributable to heterogeneity in the prevalence of cardiovascular risk, reflected in the mean age and risk factors across studies. Studies that showed lower prevalence (1%-4%) enrolled lower risk patients (general population with no history of cardiac disease and a relatively younger age).[27-29] Studies showing higher prevalence enrolled patients who were older and had other risk factors, particularly diabetes[30] and history of stroke,[31] or were hospitalized.[32,33] Within high-risk patients, the more risk factors a patient had, the higher the screening yield was. For example, Khammash et al[33] studied a higher risk hospitalized population and found the prevalence of PAD to be 34% in those with diabetes vs 25% in those without diabetes.

Other studies in average-risk patients showed prevalence of an abnormal ABI that ranged between these two extremes and was closely associated with age. Three large European cohort studies enrolling 28,000, 7454, and 6880 patients and a stratified random sample of the Women's Health Study reported the following prevalence: 17% (mean cohort age, 62 years),[34] 18% (mean cohort age, 67 years),[35] 21% (mean cohort age, 73 years),[36] and 35% (mean cohort age, 77 years).[37]

We meta-analyzed 19 studies that evaluated the association between PAD identified through screening and cardiovascular mortality and death (Table II). Pooled adjusted HR was 2.99 for all-cause mortality (95% CI, 2.16-4.12; $I^2 = 60\%$) and 2.35 for cardiovascular mortality (95% CI, 1.91-2.89; $I^2 = 76\%$). Results are depicted in Fig 2. The observed large inconsistency in results likely reflected the heterogeneity in the risk of the populations studied, suggesting a range of cardiovascular risk among patients with asymptomatic PAD.

The asymptomatic screen-detected PAD was associated with a heightened risk of cardiovascular and all-cause mortality, which is a necessary evidence, although insufficient, to infer that screening for PAD is of benefit to patients. For this, it was necessary to determine whether patient-important outcomes were improved in those who received screening and subsequent management. We could not find randomized trials that addressed this question.

Does screening for PAD lead to reduced morbidity and mortality from PAD?

None of the studies directly compared a screened population vs a nonscreened population for PAD in terms of effect on morbidity or mortality.

ABI value in cardiovascular risk prediction. One possible benefit of screening for PAD would be adding prognostic information to allow better risk stratification for heart disease. In the updated USPSTF in 2013, this paradigm was added to their evaluation of PAD screening.[19] The systematic review[23] evaluated the evidence on the ability of the ABI to predict CVD morbidity and mortality independent of Framingham Risk Score in asymptomatic adults. The review identified a large individual patient-level data meta-analysis that included data from 16 population-based cohorts (48,294 individuals). On the basis of ABI, 19% of men and 36% of women could be reclassified in terms of their Framingham Risk Score.[8]

Does treatment of people with screening-detected PAD lead to improvement in morbidity?

Five studies contributed data to this analysis (described in Table III). Fowkes et al[34] randomized 3350 patients with ABI <0.95 to 100 mg of enteric-coated aspirin or placebo and found no significant reduction in vascular events after 8.2 years of average follow-up (HR, 1.03; 95% CI, 0.84-1.27). Two observational studies evaluated the effect of statins on asymptomatic PAD. A cross-sectional study on 392 patients by McDermott et al[38] showed that patients who were taking statins had better 6-minute walk

Table I. Description of studies that reported the yield of screening for peripheral arterial disease (PAD)

						Patients with ABI <0.9					
	Patients	*No. screened*	*ABI <0.9, No. (%)*	*Asymptomatic, %*	*Follow up, years*	*Age, years*	*Smoker, %*	*Men, %*	*DM, %*	*CAD/CVA, %*	*Mean ABI*
Cirqui,[4] 1992	General population, 40-80 years	Men, 183 Women, 225	Men, 34 (19) Women, 33 (15)	NR	10	NR	NR	NR	NR	NR	NR
Ogren,[47] 1993	General population	439	60 (14)	NR	8	68	NR	100	NR	NR	NR
Hiatt,[48] 1995	Diabetes	430	3.4%-12.1%[a]	NR		59	NR	NR	NR	NR	Men, 1.15 Women, 1.09
Kornitzer,[27] 1995	General population, 40-55 years	2023	77 (3.8)	100	10	48	60	100	7	NR	1.21
Leng,[10] 1996	General population	1952	288 (18)	NR	5	55-74	NR	NR	NR	NR	1.03
Jager,[49] 1999	General population, 50-75 years	631	79 (13)	NR	5	NR	NR	NR	NR	NR	NR
Newman,[3] 1999	General population, >65 years	5714	768 (13)	100	6	NR	25.9 current	36.4	31	NR	NR
Abbott,[50] 2000	General population	2863	181 (6)[b]	100	6.2	NR	17	100	78	NR	NR
McDermott,[37] 2000	General population, women, ≥65 years	933	328 (35)	63	5	77	NR	0	29	36	0.69
Murabito,[51] 2002	General population	3313	Men, 60 (3.9) Women, 58 (3.3)	Men, 42 Women, 13	NA	67	Men, 60 Women, 49	51	Men, 33 Women, 23	NR	NR
van der Meer,[52] 2004	General population	6389	318 (20)	NR		69	NR	NR	NR	NR	1.05
Eason,[53] 2005	General population	403	62 (15)	40		64.56	60	60	64	NR	NR
Doubeni,[54] 2006	General population	717	54 (8)	NR		76.3	72.2	40.7	14.8	NR	NR
Weatherley,[28] 2007	General population, no CVD	13,588	383 (3)	94	13.1	55.7	72.8	33	17	NR	NR
Khammash,[33] 2008	Hospital patients	200	59 (30)	92		60.1	NR	51.5	50	NR	NR
Kravos,[55] 2009	General population	107	20 (19)	NR		62.85	33.3	60	29	NR	NR
Mourad,[32] 2009	General population	2146	882 (41)	80		74.7	40.2	50.2	44.8	36.8	NR
Ramos,[29] 2009	General population	6172	277 (4)	86		56.2	48.6	47	15.1	6	NR
Hooi,[56] 2004	General population Asymptomatic Symptomatic	3649	458 (13)	70	7.2	64.2 65.4	54 60.9	48.7 65.9	21.4 18.4	50.5 47.4	0.78 0.69
Resnick,[57] 2004	General population, American Indians	4393	216 (5)	NR	8.3	59.6	73.6	62	60.2	NR	NR
Bendermacher,[35] 2007	≥1 CVD risk factor	7977	1372 (17)	100		67.6	67	49.9	45.1	34.5	NR
Sen,[30] 2009	Stroke or transient ischemic attack	102	26 (25)	100	2.1	67	35	49	31	35	
Bundó,[58] 2010	Diabetes	262	36 (14)	100	7.7	71	38.9	44.4	100	16.7	
Diehm,[36] 2009	General population Asymptomatic Symptomatic	6821	1429 (21)	59	5	73.9 73.9	51.8 66.1	40.4 53.8	34 38.3	21.2 34.9	0.79 0.85
Fowler,[40] 2002	Undergoing AAA screening	7987	882 (11)	27	1	73.1	18.7 current	100	17.15	23.95 (MI)	0.79
McDermott,[38] 2003	Undergoing ABI screening	1282	392 (31)	20		71.8	NR	62.00	31.89	59.96	0.65
McDermott,[59] 2004	General population	979	109 (11)	NR	NR	NR	NR	NR	NR	NR	1.03
Sander,[41] 2008	General population, elderly	3851	716 (19)	100	2	70.1	NR	40.7	NR	NR	NR
Parameswaran,[31] 2005	Diabetics	57	24 (42)	100		63	30 (current only)	47	100	18	NR
Fowkes,[34] 2010	General population	28,980	4914 (17)[c]	100	8.2	62	65	28.5	44	0	0.86
Vidula,[39] 2010	Patients identified by ABI screening	679	679 (100)	NR	3.7	73	NR	57.6	32.5	54.6	0.65
Mehlsen,[60] 2010	Previous cerebrovascular or cardiovascular event, ≥55 years	965	340 (35.3)	100	NR	NR	82.3	NR	NR	100	NR
Farkas,[61] 2012	Hypertensive patients, 50-75 years	21,892	3152 (14.4)	100	NR	NR	NR	NR	NR	NR	NR
Jurno,[62] 2009	Migraine patients and controls, 18-60 years	88 (50 migraine, 38 controls)	31 (35.2)	100	NR	NR	NR	NR	NR	NR	NR
Ramos,[63] 2011	Spanish population, 50-79 years	235	14 (5.8)	100	NA	69.1	59.2	59.1	28.9	NR	NR
Taylor-Piliae,[64] 2011	Healthy adults, 60-69 years	1017	22 (2.1)	100	NR	NR	23	NR	41	NR	NR
Hughes,[65] 2010	Seniors ≥55 years	324	46 (14)	100	NA	NR	NR	NR	NR	NR	NR
Vinit,[66] 2011	Internal medicine patients	97	36 (37.1)	93.8	NA	NR	NR	NR	NR	NR	NR

AAA, Abdominal aortic aneurysm; *ABI,* ankle-brachial index; *CAD,* coronary artery disease; *CVA,* cerebrovascular accident; *CVD,* cardiovascular disease; *DM,* diabetes mellitus; *MI,* myocardial infarction; *NR,* not reported or unclear.

[a]Prevalence ranging from 3.4% to 12.1% at the 1.0 and 5.0 ABI percentile cutoff points.

[b]ABI <0.80.

[c]ABI <0.95.

Table II. Mortality in peripheral arterial disease (PAD) screening studies

	All-cause mortality (95% CI)	*Cardiovascular mortality (95% CI)*
Cirqui,[4] 1992	3.1 (1.9-4.9)	5.9 (3.0-11.4)
Ogren,[47] 1993	2.4 (1.5-3.9)	2.5 (1.1-5.7)
Hiatt,[48] 1995	Men, 4.25 (2.22-8.13) Women, 4.37 (2.30-8.30)	
Kornitzer,[27] 1995	2.77 (1.38-5.54)	4.16 (1.65-10.46)
Leng,[10] 1996	1.58 (1.14-2.18)	1.85 (1.15-2.97)
Jager,[49] 1999	Men, 5.34 (2.74-10.39) Women, 5.42 (2.48-11.84)	
Newman,[3] 1999	1.62 (1.24-2.12)	2.03 (1.22-3.37)
Abbott,[50] 2000		3.3 (2.2-4.9), ABI <0.8 vs ABI >1.0 1.4 (1.0-2.0), ABI 0.8-1.0 vs ABI >1.0
McDermott,[37] 2000	3.22 (2.30-4.50)	
Murabito,[51] 2002	Men, 4.67 (2.33-9.34) Women, 2.38 (0.72-7.86)	
Hooi,[56] 2004	Asymptomatic, 1.4 (1.1-1.8) Symptomatic, 1.4 (1.0-2.0)	Asymptomatic, 1.5 (1.1-2.1) Symptomatic, 1.6 (1.0-2.5)
McDermott,[59] 2004	Men, 2.11 (0.75-5.93) Women, 10.50 (3.16-34.88)	
Resnick,[57] 2004	2.33 (1.87-2.90)	
van der Meer,[52] 2004	Men, 3.25 (2.72-3.88) Women, 3.75 (3.23-4.36)	For incident MI, 1.11 (0.81-1.54)
Bendermacher,[35] 2007		White men, 2.81 (1.77-4.45) White women, 2.05 (1.20-3.53) African American men, 4.86 (2.78-8.47) African American women, 2.34 (1.26-4.35)
Diehm,[36] 2009	Asymptomatic, 1.66 (1.38-2.0) Symptomatic, 1.89 (1.55-2.3)	Asymptomatic, 2.19 (1.59-3.01) Symptomatic, 1.83 (1.28-2.61)
Sen,[30] 2009	4.21 (1.92-9.26)	3.43 (1.43-8.21) for composite outcome (stroke, TIA, MI, death)
Bundó,[58] 2010		2.32 (1.27-4.22); fatal/nonfatal CVD
Fowkes,[34] 2010	10.20%	

ABI, Ankle-brachial index; *CI,* confidence interval; *CVD,* cardiovascular disease; *MI,* myocardial infarction; *TIA,* transient ischemic attack.

performance, faster walking velocity, and higher summary performance scores. Vidula et al[39] performed a prospective observational study on a group of 579 asymptomatic and symptomatic individuals with PAD. They determined that after a mean follow-up of 3.7 years, baseline statin use was associated with a lower all-cause mortality (HR, 0.51; 95% CI, 0.30-0.86) and a lower CVD mortality (HR, 0.36; 95% CI, 0.14-0.89) compared with nonstatin users.[39] Inference from these two studies is limited considering the lack of randomization, the lack of outcome reporting stratified by the presence of symptoms, and the fact that the estimates of benefit from statin therapy are double or triple the benefits observed in randomized trials of statins in at-risk patients.

Two studies described lifestyle change interventions. Fowler et al[40] randomized 882 men with early PAD identified through population-based screening with the Edinburgh Claudication Questionnaire and ABI to a community-based intervention titled "stop smoking and keep walking" or to usual care. About 27% of these patients were asymptomatic. Postal follow-up at 12 months demonstrated that more men allocated to the intervention group had improved their maximum walking distance (23% vs 15%; $P = .008$) and reported walking more than three times per week for recreation (34% vs 25%; $P = .01$). Sander et al[41] reported improvement in cardiovascular risk factors (blood pressure, weight, lipids, and diabetes control) in a cohort identified by ABI screening after 2 years of a community-based intervention. Last, one trial enrolled 355 patients with average ABI of 0.68 who were mostly asymptomatic. The results demonstrated that telephone counseling helped PAD patients request more intensive cholesterol-lowering therapy from their physician and to achieve greater reduction of low-density lipoprotein cholesterol (compared with an attention control arm that received only health information).[42]

Screening is not harmful and is cost-effective?

The ABI test is a noninvasive physical examination maneuver and is—by itself—harmless. Because most experts recommend against invasive testing after a positive screening test result, harms of screening to asymptomatic patients may come about from pharmacologic interventions provided to patients identified through screening (ie, adverse effects of antiplatelet agents, cholesterol-lowering agents, cilostazol). Fowkes et al[34] randomized asymptomatic PAD patients to aspirin vs placebo and found a nonsignificant increase in major hemorrhage requiring admission to a hospital (2.5 per 1000 person-years in the aspirin group and 1.5 per 1000 person-years in the placebo group; HR, 1.71; 95% CI, 0.99-2.97). Among patients at high cardiovascular risk, some of these

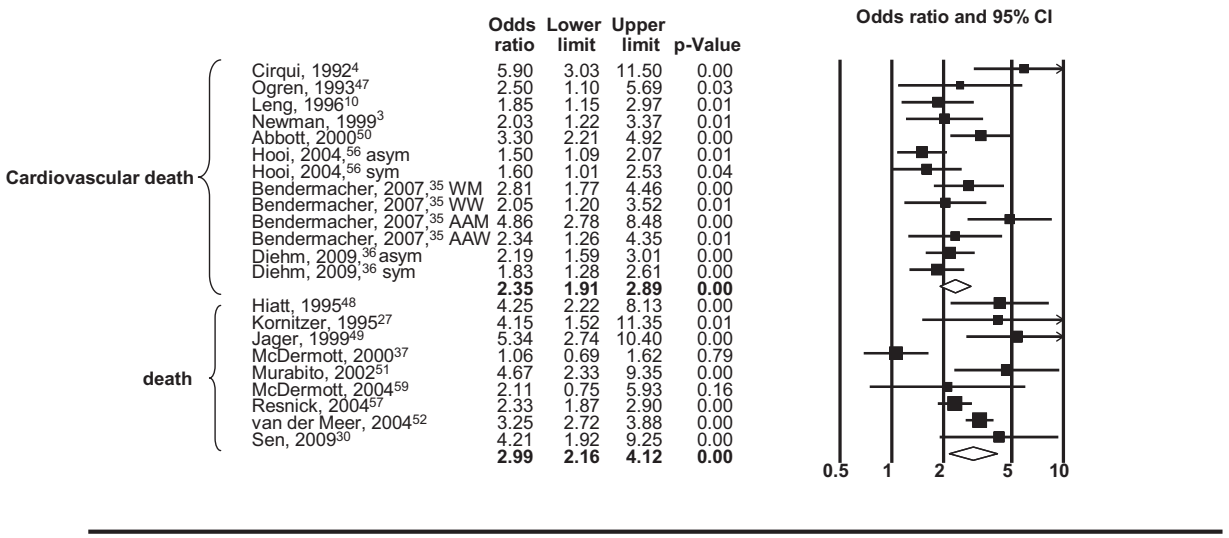

Fig 2. Meta-analysis of relative association measures of peripheral arterial disease (PAD) and death and cardiovascular mortality. *AAM,* African American men; *AAW,* African American women; *asym,* asymptomatic; *CI,* confidence interval; *sym,* symptomatic; *WM,* white men; *WW,* white women.

interventions will be desirable regardless of whether the patient had a positive ABI, and thus the harms of screening for PAD would result when low-risk patients receive these treatments, exposing them to more potential harm than benefit. Again, we found no studies comparing harms of treatment in patients with PAD detected through ABI screening.

We did not identify reliable studies of cost-effectiveness. Reliable cost-effectiveness and economic inferences require a trial comparing a screening strategy to no screening strategy, which was not available at the time of conducting this review.

The overall quality of evidence supporting screening

The quality of evidence (ie, confidence in estimates) of the five domains or questions pertinent to screening is summarized in Fig 3. Overall, the quality is low.

DISCUSSION

Main findings. We conducted a systematic review of studies that evaluated screening of asymptomatic individuals for PAD with ABI. An important finding was that there were no randomized trials that compared screening with ABI to unscreened control groups and demonstrated the effect on patient-important outcomes, such as amputation, mortality, or quality of life. Therefore, evidence to support decision-making about screening had to be derived from other data, such as test characteristics and the disease prevalence, morbidity, and mortality.

We found that the yield of screening was highly dependent on the prevalence of cardiovascular risk factors in the population screened (eg, age, gender, and smoking status). Whereas screened-positive individuals experienced higher mortality risk than the general population and the screening test is noninvasive, inexpensive, and safe, we found evidence of no benefit of medical treatment for patients with asymptomatic PAD identified through ABI screening. The Heart Protection Study Collaborative Group[43] demonstrated a significant reduction in vascular events in patients with PAD (relative risk, 0.78; 95% CI, 0.71-0.85); however, this cohort had symptomatic PAD (claudication, prior revascularization, amputation, or aneurysm repair) and therefore was excluded from this analysis. We found no evidence to support a subgroup effect that identified a clinical characteristic in a population that would benefit from screening. We also did not find evidence for cost-effectiveness or downstream harms. Screening seems to add prognostic information that can help with cardiovascular risk stratification.

Strengths and limitations. The strengths of this study include the comprehensive search strategies and the bias protection measures undertaken by the reviewers (ie, reviewing the literature by independent pairs and following a priori established protocol). The limitations stem from the sparse data and unavailability of rigorous studies to support or to refute the utility of screening.

Implications for practice and research. Only a small percentage of patients with PAD require lower extremity arterial intervention, and the risk of a cardiovascular ischemic event in these patients far outweighs the risk of an ischemic limb event.[44] Thus, although screening for PAD may not be beneficial in reducing the risk of symptomatic PAD or other patient-important outcomes, it may help identify those who need aggressive preventive

Table III. Outcomes of interventional studies

	Intervention	*No. control*	*No. treatment*	*Outcome and follow-up*
Fowler,[40] 2002	A combined community-based intervention of cessation of smoking (where applicable) and increased physical activity (walking)	441	441	After 1 year, more men allocated to the intervention group had improved their maximum walking distance (23% vs 15%; $\chi^2 = 9.74$; $df = 2$; $P = .008$). In addition, more men in the intervention group reported walking more than three times per week for recreation (34% vs 25%; $P = .01$).
McDermott,[38] 2003	Statin use at baseline vs not	215	177	A summary performance score combined performance in walking speed, standing balance, and time for five repeated chair rises into an ordinal score ranging from 0 to 12 (12 = best). Participants taking statins had better 6-minute walk performance (1276 vs 1218 feet; $P = .045$), faster walking velocity (0.93 vs 0.89 m/s; $P = .006$), and a higher summary performance score (10.2 vs 9.4; $P < .001$) than participants not taking statins.
Fowkes,[34] 2010	Aspirin vs not	1675	1675	After a mean follow-up of 8.2 years, the primary end point (a composite of initial fatal or nonfatal coronary event or stroke or revascularization) did not significantly differ between groups (13.7 events per 1000 person-years in the aspirin group vs 13.3 in the placebo group; HR, 1.03; 95% CI, 0.84-1.27). There was no significant difference in all-cause mortality between groups (176 vs 186 deaths, respectively; HR, 0.95; 95% CI, 0.77-1.16). An initial event of major hemorrhage requiring admission to the hospital occurred in 34 participants (2.5 per 1000 person-years) in the aspirin group and 20 (1.5 per 1000 person-years) in the placebo group (HR, 1.71; 95% CI, 0.99-2.97).
Vidula,[39] 2010	Statin use at baseline vs not	437	242	The mean follow-up was 3.7 years. Statin use was associated with lower all-cause mortality (HR, 0.51; 95% CI, 0.30-0.86; $P = .012$) and CVD mortality (HR, 0.36; 95% CI, 0.14-0.89; $P = .027$) compared with statin nonuse.
Sander,[41] 2008	Antihypertensives or antiplatelets vs control	716	716	Improved CV risk factors (blood pressure, weight, lipids, and diabetes control) in a cohort identified by screening ABI

ABI, Ankle-brachial index; *CI,* confidence interval; *CV,* cardiovascular; *CVD,* cardiovascular disease; *HR,* hazard ratio.

measures for cardiovascular and cerebrovascular risk reduction. The meta-analysis by Fowkes et al[8] demonstrated that a low ABI (<0.90) was associated with approximately twice the 10-year total mortality, cardiovascular mortality, and major coronary event rate compared with the overall rate in each Framingham Risk Score category. Inclusion of the ABI in cardiovascular risk stratification resulted in reclassification of the risk category and modification of treatment in approximately 19% of men and 36% of women. To this extent, a positive ABI may have a similar impact on overall cardiovascular risk estimates as the elicitation of a family history of premature cardiovascular events in a first-degree relative. A positive ABI leads to important changes in risk estimates, particularly among individuals with a 5% to 20% 10-year cardiovascular risk estimated by traditional risk factors. However, the available evidence does not support the inference that ABI screening leads to net benefit, particularly in asymptomatic low-risk patients. The accompanying clinical practice guidelines by the Society for Vascular Surgery provide the clinical context of our findings and offer practice recommendations.

Future trials focusing on the benefits of interventions in low-risk asymptomatic patients with an abnormal ABI would be useful. Thus, high-quality evidence of the effect of ABI screening on morbidity and mortality in patients

Fig 3. Results and quality of evidence. The quality of evidence is rated as high (⊕⊕⊕⊕), moderate (⊕⊕⊕O), low (⊕⊕OO), and very low (⊕OOO). *ABI,* Ankle-brachial index; *CV,* cardiovascular; *FRS,* Framingham Risk Score.

with low or intermediate cardiovascular risk may be obtainable. However, trials in low-risk populations will require large samples and are likely to yield small absolute benefits that may not trump the undesirable features of such treatments in terms of harms, burdens, and costs. Furthermore, lifestyle interventions may be more favorably assessed. As patients' risk increases, whether or not they have PAD, patients will find interventions for which there is strong evidence that their use reduces the risk of cardiovascular events highly desirable,[45] rendering a trial in these populations unnecessary and potentially unethical. Studies on individuals with noncompressible ankle arteries are important because the implications of elevated ABIs are not fully understood and they represent potential false negatives. The Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated that both a low and a high ABI (<1.0 and ≥ 1.4) were associated with increased cardiac risk in persons free of known CVD, independent of standard and novel risk factors.[46] Other surrogate outcomes, such as smoking cessation and compliance with an exercise program, may not be adequate end points to gauge efficacy of screening and interventions. This is mainly because it requires strict monitoring and consistent reliability. It is also important to emphasize that screening may increase awareness and patient compliance.

CONCLUSIONS

The current available evidence demonstrates that the yield of the ABI screening test in asymptomatic individuals depends on the prevalence of traditional risk factors. A positive ABI increases the 10-year cardiovascular risk estimates in these individuals. No high-quality evidence, however, supports patient-important benefits from screening of low-risk asymptomatic individuals or from aggressively treating those with an abnormal ABI. High-risk individuals may not need ABI screening as they have sufficient reasons to receive aggressive cardiovascular risk reduction.

AUTHOR CONTRIBUTIONS

Conception and design: MM, MC, VM
Analysis and interpretation: MM, MC, VM, FA
Data collection: FA, AW, RM, TE, AR, ML, LP
Writing the article: MM, MC, VM, RM
Critical revision of the article: MM, MC, VM, RM, FA, TE, AW, AR, ML, LP
Final approval of the article: MM, MC, VM, RM, FA, TE, AW, AR, ML, LP
Statistical analysis: MM, FA
Obtained funding: MM
Overall responsibility: MM
AW and FA contributed equally to this study.

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APPENDIX (UPDATED THROUGH JUNE 2014)

EMBASE, Ovid MEDLINE, CDSR

#	*Searches*	*Results*
1	exp Peripheral Vascular Diseases/	629314
2	exp Peripheral Vascular Diseases/pc	45067
3	peripheral vascular disease/or blackfoot disease/or cold limb/or erythromelalgia/or glomus tumor/or hand arm vibration syndrome/or peripheral blood vessel malformation/or raynaud phenomenon/or telangiectasia/	36498
4	peripheral vascular disease/pc or blackfoot disease/pc or cold limb/pc or erythromelalgia/pc or glomus tumor/pc or hand arm vibration syndrome/pc or peripheral blood vessel malformation/pc or raynaud phenomenon/pc or telangiectasia/pc	609
5	peripheral vascular disease*.mp.	23397
6	peripheral arteriopath*.mp.	384
7	peripheral blood vessel disease*.mp.	4
8	peripheral vascular disorder*.mp.	268
9	peripheral vessel disease*.mp.	43
10	blackfoot disease*.mp.	356
11	cold limb*.mp.	184
12	erythromelalgia*.mp.	968
13	glomus tumor*.mp.	3213
14	hand arm vibration syndrome*.mp.	511
15	peripheral blood vessel malformation*.mp.	21
16	(Raynaud* adj2 (phenomenon or disease* or disorder*)).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, tx, kw, ct]	11871
17	telangiectasia*.mp.	17497
18	blue toe syndrome*.mp.	199
19	Livedo Reticularis*.mp.	1749
20	Phlebitis*.mp.	8160
21	Postphlebitic Syndrome.mp.	838
22	Thrombophlebitis.mp.	26068
23	CREST Syndrome*.mp.	878
24	peripheral angiopath*.mp.	62
25	peripheral arterial disease*.mp.	7234
26	exp intermittent claudication/	9845
27	exp intermittent claudication/pc	115
28	angina cruris.mp.	2
29	angiosclerotica intermittens.mp.	1
30	claudicatio intermittens.mp.	356
31	intermittent claudicatio*.mp.	11368
32	leg ischemia*.mp.	3244
33	or/28-32	14331
34	or/5-25	97452
35	from 1 keep 590464-629314	38851
36	3 or 34 or 26 or 33 or 35	110446
37	exp Mass Screening/	147540
38	mass screening.mp.	77773
39	health screening.mp.	3139
40	multiphasic screening.mp.	1113
41	population screening.mp.	3291
42	anonymous testing.mp.	610
43	or/37-42	153262
44	36 and 43	504
45	from 2 keep 41630-45067	3438
46	4 or 27 or 44 or 45	4337
47	exp controlled study/	3095468
48	exp evidence based medicine/	349360
49	evidence-based.mp.	116683
50	meta analysis/	61026
51	meta-analys$.mp.	96173
52	exp "systematic review"/	31296
53	systematic review$.mp.	66258
54	exp Guideline/or exp Practice Guideline/	182604
55	guideline$.ti.	61308
56	case series.mp.	37978
57	((clinical or control* or randomized) adj2 (study or studies or trial or trials)).mp.	5003663

(*Continued on next page*)

Continued.

#	*Searches*	*Results*
58	clinical trial/	1023727
59	or/47-58	5299826
60	46 and 59	1490
61	from 46 keep 579-4333	3755
62	limit 61 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial) [Limit not valid in EMBASE, CDSR; records were retained]	1135
63	60 or 62	1729
64	limit 63 to (editorial or letter or news) [Limit not valid in EMBASE,CDSR; records were retained]	73
65	63 not 64	1656
66	remove duplicates from 65	1634
67	limit 66 to english language [Limit not valid in CDSR; records were retained]	1379
68	limit 67 to yr="2005-Current"	220

Scopus

1	TITLE-ABS-KEY ("peripheral vascular disease" OR "peripheral arteriopath*" OR "peripheral blood vessel disease" OR "peripheral vascular disorder" OR "peripheral vessel disease" OR "blackfoot disease" OR "cold limb" OR "erythromelalgia*" OR "glomus tumor" OR "hand arm vibration syndrome" OR "peripheral blood vessel malformation" OR "Raynaud? phenomenon" OR "Raynaud? disease" OR "Raynaud? disorder" OR "telangiectasia*" OR "blue toe syndrome" OR "Livedo Reticularis*" OR "Phlebitis*" OR "Postphlebitic Syndrome" OR "Thrombophlebitis" OR "CREST Syndrome" OR "peripheral angiopath*" OR "peripheral arterial disease" OR "intermittent claudicatio*" OR "angina cruris" OR "angiosclerotica intermittens" OR "claudicatio intermittens" OR "leg ischemia")
2	TITLE-ABS-KEY ("mass screening" OR "health screening" OR "multiphasic screening" OR "population screening" OR "anonymous testing")
3	TITLE-ABS-KEY ((evidence W/1 based) OR (meta W/1 analys*) OR "systematic review" OR guideline OR "case series" OR (control* W/2 stud*) OR (control* W/2 trial*) OR (randomized W/2 stud*) OR (randomized W/2 trial*) OR (clinical W/2 stud*) OR (clinical W/2 trial*))
4	PMID (0*) OR PMID (1*) OR PMID (2*) OR PMID (3*) OR PMID (4*) OR PMID (5*) OR PMID (6*) OR PMID (7*) OR PMID (8*) OR PMID (9*)
5	(1 and 2 and 3) and not 4

National Guidelines Clearinghouse

Searched for these keywords individually limited to the "screening" guideline category.

Peripheral
Blackfoot
cold limb
Erythromelalgia
glomus
hand arm vibration
Raynaud
Telangiectasia
Blue toe
Livedo Reticularis
Phlebitis
Postphlebitic Syndrome
Thrombophlebitis
CREST Syndrome
intermittent claudication
leg ischemia
angina cruris
angiosclerotica intermittens
claudicatio intermittens
intermittent claudication