Annals of Internal Medicine | Review

The Ankle–Brachial Index for Peripheral Artery Disease Screening and Cardiovascular Disease Prediction Among Asymptomatic Adults: A Systematic Evidence Review for the U.S. Preventive Services Task Force

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Background: Screening for peripheral artery disease (PAD) may reduce morbidity and mortality.

Purpose: To review the evidence on the ability of the ankle–brachial index (ABI) to predict cardiovascular disease (CVD) morbidity and mortality independent of Framingham Risk Score (FRS) factors in asymptomatic adults and on the benefits and harms of treating screen-detected adults with PAD.

Data Sources: MEDLINE and the Cochrane Central Register of Controlled Trials (1996 to September 2012), clinical trial registries, reference lists, and experts.

Study Selection: English-language, population-based prognostic studies evaluating the ABI in addition to the FRS and treatment trials or studies of treatment harms in screen-detected adults with PAD.

Data Extraction: Dual quality assessment and abstraction of relevant study details.

Data Synthesis: One large meta-analysis (n = 43 919) showed that the ABI could reclassify 10-year risk for coronary artery disease (CAD), but it did not report measures of appropriate reclassification (the net reclassification improvement [NRI]). Four heterogeneous risk prediction studies showed that the magnitude of the NRI was probably small when the ABI was added to the FRS to predict CAD or CVD events. Of 2 treatment trials meeting inclusion criteria, 1 large trial (n = 3350) showed that low-dose aspirin did not prevent CVD events in persons with a screen-detected low ABI but may have increased the risk for major bleeding events.

Limitations: Most prognostic studies did not allow for calculation of a bias-corrected NRI. Evidence on treatment benefits and harms was limited to aspirin and was scant.

Conclusion: Adding the ABI to the FRS probably has limited value for predicting CAD or CVD. Treatment benefits for asymptomatic individuals with screen-detected PAD are not established.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2013;159:333-341. www.annals.org
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Lower-extremity peripheral artery disease (PAD) refers to atherosclerosis of the arteries distal to the aortic bifurcation. The ankle–brachial index (ABI), the ratio of the ankle and brachial systolic blood pressures, is often used as a surrogate marker for PAD. An ABI of 1.0 to 1.4 is generally considered normal, whereas an ABI less than 0.9 is abnormal and suggests PAD (1). An estimated 5% of U.S. persons aged 40 years or older without known cardiovascular disease (CVD) have an ABI of 0.9 or less (2). Peripheral artery disease has been underdiagnosed and undertreated, in part, because most patients do not have symptoms or have atypical symptoms (3, 4). Therefore, screening for PAD using the ABI may reduce patient morbidity and mortality through identification and treatment of PAD or other comorbid CVD (for example, coronary artery disease [CAD] or cerebrovascular disease).

In 2005, the U.S. Preventive Services Task Force (USPSTF) recommended against routine screening for PAD in primary care (D recommendation) (5, 6). It concluded that screening would have few or no benefits because there was little evidence that treatment of asymptomatic persons would improve patient outcomes beyond treatment based on standard CVD risk assessment (5, 6). In 2009, as part of a larger recommendation statement on the use of nontraditional risk factors in CAD risk prediction, the USPSTF found insufficient evidence to assess the balance of benefits and harms of the ABI for screening asymptomatic adults to prevent CAD events (I statement) (7). We undertook this systematic review to assist the USPSTF in updating these recommendations.

Currently, no randomized, controlled trials directly address the benefits and harms of screening for PAD (8). Therefore, we reviewed the evidence on the ability of the ABI to predict CVD morbidity and mortality independent of Framingham Risk Score (FRS) factors in asymptomatic adults and on the benefits and harms of treating adults with screen-detected PAD.

Methods

Our full evidence report included 6 key questions designed to evaluate the value of the ABI in screening for asymptomatic disease in the primary care population (8).

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That report addressed the direct trial evidence of ABI screening on health outcomes (question 1), the diagnostic accuracy of the ABI in asymptomatic adults (question 2), the harms of ABI screening (question 3), the predictive value of the ABI for CAD or CVD events (question 4), the benefits of treatment in screen-detected adults with PAD (question 5), and the harms of treatment in screen-detected adults with PAD (question 6). This article summarizes findings for questions 4 through 6, which represent the primary evidence considered by the USPSTF.

Detailed methods, including the analytic framework, search strategies, flow diagrams of the search and selection processes, quality assessment, and evidence tables for the full report, are available at www.uspreventiveservicestaskforce.org.

Data Sources and Searches

We searched MEDLINE and the Cochrane Central Register of Controlled Trials from 1996 through September 2012 to locate relevant English-language studies. We supplemented searches with suggestions from experts and reference lists from existing systematic reviews. We also searched ClinicalTrials.gov on 12 September 2012 for ongoing trials.

Study Selection

Two investigators independently reviewed abstracts and full-text articles for inclusion using predetermined criteria. We resolved discrepancies by consulting a third investigator. Our review focused on the value of the ABI in persons without known PAD, CAD, cerebrovascular disease, diabetes, or severe chronic kidney disease. We included population-based prospective cohort risk prediction studies that adjusted for, at a minimum, all of the FRS patient characteristics as defined by the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) (age, sex, smoking status, systolic blood pressure, total cholesterol level, and high-density lipoprotein cholesterol level) (9). We included trials that had at least 3 months of follow-up and were designed to evaluate treatment benefit in screen-detected persons or adult populations that approximated screen-detected persons (that is, those in which most adults had no symptoms or atypical symptoms not necessarily recognized as PAD). For harms, we included studies of any design except for case series or case reports. We focused on pharmacologic or lifestyle interventions primarily aimed at reducing CVD risk (for example, interventions to stop smoking, decrease cholesterol level, control blood pressure, or inhibit platelet aggregation). Interventions aimed at treating lower-extremity symptoms or function were conducted in symptomatic adults and were therefore excluded from this review. We included intermediate cardiovascular outcomes (for example, blood pressure, cholesterol level, and smoking cessation), cardiovascular or lower-extremity–related health outcomes, and serious adverse events (for example, death, serious adverse drug reactions, or unexpected medical attention).

Data Extraction and Quality Assessment

One investigator extracted data, and a second investigator checked the extraction. We contacted study authors by e-mail for clarification when necessary. Two investigators independently critically appraised all relevant studies using the USPSTF's design-specific criteria (10) supplemented by the National Institute for Health and Clinical Excellence methodology checklists (11), the Newcastle-Ottawa Scale (12), and criteria from Hayden and colleagues (13). In general, a good-quality study met all prespecified criteria. A fair-quality study did not meet (or it was unclear whether it met) at least 1 criterion but also had no known important limitation that could invalidate its results. A poor-quality study had a single fatal flaw or several important limitations.

Data Synthesis and Analysis

We qualitatively summarized the included evidence because the limited number, heterogeneity, and nature of our included studies did not allow for quantitative synthesis.

Most of the evidence included in our review focused on the additional value of the ABI in traditional CAD or CVD risk prediction. The FRS predicts the risk for "hard" CAD events (for example, myocardial infarction or CAD death) over 10 years. Although some of our included studies used myocardial infarction and CAD death as a composite outcome, others used total CAD or CVD events. Total CAD events typically included angina, revascularization, or both in addition to myocardial infarction and CAD death. The event rates for myocardial infarction or CAD death are two thirds to three fourths those for total CAD events (14). The definitions of composite CVD events varied but generally included cerebrovascular accidents in addition to CAD events. The ATP III's FRS defines risk categories as low (<10% ten-year risk for hard CAD events), intermediate (10% to 20% risk), or high (>20% risk). Included studies defined risk categories differently. We capture these and other important study differences in our synthesis.

In this article, we focus on the ability of the ABI to improve risk stratification (that is, risk reclassification) as opposed to its independent association with CVD outcomes (for example, hazard ratio) or its discrimination of CVD events (for example, area under the curve). Risk reclassification refers to the change in risk when a new predictor is added to an existing risk prediction model (for example, persons may be placed into a different risk category from the one they were in when the original model was used). This movement among risk categories may be displayed as a reclassification table. Although studies may report the percentage of persons who change risk categories, this does not ensure that persons were correctly recategorized (15). The net reclassification improvement (NRI)

is a summary measure of the proportion of persons appropriately reclassified and is calculated as the proportion of individuals who will have a CVD event moving to a higher category, minus those moving to a lower category, plus the proportion who will not have a CVD event moving to a lower category, minus those moving to a higher category (15–17). A generally accepted cutoff for a clinically important NRI is 0.05 (18), although it depends on the relative benefits and risks of overtreatment versus undertreatment (16). Because the NRI can be artificially inflated when calculated for subgroups (for example, intermediate-risk category), we calculated a bias-corrected NRI for these intermediate-risk groups when possible (19).

External Review

A draft of our full report was reviewed by content experts, our Agency for Healthcare Research and Quality (AHRQ) medical officer, collaborating federal institutions, and the members of the USPSTF. A revised version of the full report was subsequently posted for public comment.

Role of the Funding Source

The study was funded by AHRQ under a contract to support the work of the USPSTF. Members of the USPSTF and our AHRQ medical officer assisted in the development of the scope of this review. Approval from AHRQ was required before the manuscript could be submitted for publication, but the authors are solely responsible for its content and the decision to submit it for publication.

Results

We reviewed 4434 abstracts and 418 full-text articles from our literature searches and other sources (**Appendix Figure**, available at www.annals.org). We found 1 individual patient–level meta-analysis (20) and 14 primary cohort studies (18, 21–33) addressing risk prediction and 2 trials evaluating the benefit of treatment in asymptomatic or minimally symptomatic persons with PAD (34, 35), 1 of which also reported harms (34). No prognostic studies were excluded on the basis of quality; most studies were excluded because they did not include (at a minimum) all of the ATP III's FRS factors in multivariate models. Only 1 treatment trial that was only described in a conference abstract with limited reporting of the trial methods and results was excluded because of poor quality. Most treatment studies were excluded because they were conducted in adults with intermittent claudication (see www.uspreventiveservicestaskforce.org for detailed results).

Added Predictive Value of the ABI

We identified 1 fair-quality meta-analysis and 14 fair- to good-quality primary studies that addressed whether the ABI could predict CAD or CVD morbidity and mortality independent of FRS factors (**Table 1**). In total, included studies represented 18 unique population-based cohorts. The meta-analysis was a large individual patient–level data analysis ($n = 48\,294$) conducted by the ABI Collaboration that included data from 16 population-based cohorts (20). The 14 primary studies represented 8 unique population-based cohorts, only 2 of which (Health ABC [Health, Aging, and Body Composition] study and MESA [Multi-Ethnic Study of Atherosclerosis]) were not represented in the ABI Collaboration's meta-analyses. Across this entire body of literature ($n = 52\,510$), which represented a broad spectrum of men and women from the United States, western Europe, and Australia, a low ABI (≤ 0.9) was generally associated with future CAD and CVD events independent of FRS factors (**Appendix Table**, available at www.annals.org). These studies used different reference groups (normal ABI values), CAD or CVD outcomes, and lengths of follow-up, which limits the ability to directly compare hazard ratios and understand the consistency of the magnitude of association.

Five included studies, including the ABI Collaboration's meta-analyses, provided analyses that evaluated the ability of the ABI to reclassify CAD or CVD risk when added to the FRS (18, 20, 26, 31, 33) (**Table 1**). The ABI Collaboration's analyses ($n = 43\,919$) showed that 19% of men and 36% of women could be reclassified on the basis of their ABI (20). Four additional studies ($n = 22\,055$) that used the NRI (a measure of appropriate reclassification) found that the proportion of persons being reclassified was generally less than 0.05, a commonly accepted and clinically important threshold (18, 26, 31, 33). Direct comparison of the NRI across studies was difficult because of differences in methods, definitions of composite CAD and CVD outcomes, and definitions of risk categories. The NRI for CAD and CVD outcomes was not statistically significant in the 2 largest cohort studies (18, 33) but was clinically significant (0.079 [statistical significance not reported]) in the oldest cohort, which had higher rates of CAD events (26). Although reported NRIs for the subgroup of adults at intermediate risk for CVD events were higher than those for the overall populations, the bias-corrected NRIs were not. Therefore, the reported NRIs for intermediate-risk groups should be interpreted with caution if the bias-corrected NRI could not be calculated.

The ABI Collaboration provides the most evidence on risk reclassification using the ABI (20). Its analysis included the 21 433 men and 22 486 women without a history of CAD from 13 cohorts with relevant outcome data available. Most cohorts ranged in size from 1000 to 5000 persons, although the largest one (ARIC [Atherosclerosis Risk in Communities] study) included more than 14 000 persons. The mean age in these cohorts ranged from 47 to 78 years. Median duration of follow-up ranged from 3.0 to 16.7 years, and about half of the cohorts had at least 10 years of follow-up. The ABI Collaboration defined intermediate predicted risk as 10% to 19% risk for total CAD, as opposed to myocardial infarction and CAD death only, within 10 years. The largest portion of men reclassified were those who had a normal ABI, were at high risk on the

Table 1. **Characteristics of Included Risk Prediction Studies**

Cohort (Country)	Study, Year (Reference)	Quality	Sample Size, *n*	ABI Reference Group	Follow-up, *y*	Age, *y**	Women, %
ABI Collaboration (multiple)†	Fowkes et al, 2008 (20)	Fair	48 294	1.11–1.40	10	61.7	48.3
ARIC (United States)	Weatherley et al, 2007 (21)	Good	13 588	≥0.90	13.1	54.0	56.8
	Murphy et al, 2012 (18)	Good	11 594	1 SD	14	53.8	56.4
	Tsai et al, 2001 (22)	Good	14 306	≥1.20	7.2	NR	55.4
CHS (United States)	O'Hare et al, 2006 (23)	Fair	5748	1.11–1.20	11.1	73	57
Edinburgh (United Kingdom)	Lee et al, 2004 (24)	Fair	1507	>0.9	12	64.7	47.7
	Price et al, 2007 (25)	Fair	1007	>0.9	12	69.4	48.3
Health ABC (United States)§	Rodondi et al, 2010 (26)	Good	2191	1.01–1.30	8.2	73.5	55.3
	Sutton-Tyrrell et al, 2008 (27)	Good	2886	0.91–1.30	6.7	73.6	51.7
Honolulu (United States)	Abbott et al, 2000 (28)	Fair	2863	≥1.0	3–6	71–93	0
	Abbott et al, 2001 (29)	Fair	2767	≥0.9	3–6	71–93	0
Hoorn (The Netherlands)	Hanssen et al, 2012 (30)	Fair	634‖	≥0.9	17.2	64.3	51.9
MESA (United States)§	Yeboah et al, 2012 (31)	Fair	1330	1 SD	7.6	63.8	33.3
Rotterdam (The Netherlands)	van der Meer et al, 2004 (32)	Fair	6389	>1.21	9	69.3	61.9
	Kavousi et al, 2012 (33)	Good	5933	0.91–1.40	6.8	69.1	59.4

ABI = ankle–brachial index; ARIC = Atherosclerosis Risk in Communities; AUC = area under the curve; CAD = coronary artery disease; CHS = Cardiovascular Health Study; CVA = cerebrovascular accident; CVD = cardiovascular disease; Health ABC = Health, Aging, and Body Composition; HR = hazard ratio; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not reported; NRI = net reclassification improvement; OR = odds ratio; RR = risk ratio.
* Mean, median, or range.
† Includes the following cohorts: ARIC, Belgian Physical Fitness Study, CHS, Edinburgh Artery Study, Framingham Offspring Study, Health in Men Study, Honolulu Heart Program, Hoorn Study, InCHIANTI (Invecchiare in Chianti) Study, Limburg PAOD (Peripheral Arterial Occlusive Disease) Study, Men Born in 1914 Study, Rotterdam Study, San Diego Study, San Luis Valley Diabetes Study, Strong Heart Study, and Women's Health and Aging Study.
‡ Mean systolic blood pressure (mm Hg).
§ Not included in ABI Collaboration's meta-analysis.
‖ For cohort that included diabetic patients; values for nondiabetic patients not reported separately.
¶ Median ABI was 1.14.

basis of FRS alone (n = 3668), and were reclassified as having intermediate CAD risk (an observed 10-year risk of 18%) (**Table 2**). The largest portion of women reclassified were those who had an ABI of 0.91 to 1.10, were at low risk on the basis of FRS alone (n = 6192), and were reclassified as having intermediate CAD risk (an observed 10-year risk of 10%), plus those who had an ABI of 0.90 or less, were categorized as being at low risk on the basis of FRS alone (n = 1083), and were reclassified as having high CAD risk (an observed 10-year risk of 21%). The ABI Collaboration used persons with an ABI of 1.11 to 1.40 as the reference group in its analysis because it found an increased risk for CVD death even for persons with an ABI of 0.91 to 1.10. **Table 3** shows the results of reclassification based on a traditional reference group (ABI of 0.91 to 1.40).

Only 4 studies used the NRI to determine whether adding the ABI to the FRS appropriately reclassifies persons into different risk categories (18, 26, 31, 33) (**Table 4**). Two of the 4 cohorts, the Rotterdam and ARIC cohorts, were included in the ABI Collaboration meta-analyses. The Rotterdam study (n = 5933) was most similar to ATP III's FRS in its definition of the intermediate category as 10% to 20% risk and in evaluating myocardial infarction and CAD death alone (as opposed to total CAD events) (33). Participants had a median age of 69.1 years and were followed for a median of 6.8 years. Adding the ABI to the FRS did not statistically significantly change the overall reclassification (NRI, 0.006 [95% CI, −0.018 to 0.029]). Although this study also reported the NRI for the intermediate-risk group, we were unable to calculate a bias-corrected NRI given the data reported. The Health ABC study (n = 2191) likewise defined the intermediate category as 10% to 20% risk (26). This cohort was older (median age, 73.5 years) and had higher rates of CAD events (16% of participants had a CAD event over a median of 8.2 years vs. 5.8% of participants in the Rotterdam cohort). Adding the ABI to the FRS gave an overall NRI of 0.079 (CI not reported) for hard CAD events and an NRI of 0.033 (CI, 0.0004 to 0.065) for total CAD events. The reported NRI for the intermediate-risk group was higher for total CAD events (0.07 [CI, 0.029 to 0.112]); however, the recalculated bias-corrected NRI for this subgroup was no different from the overall NRI with loss of statistical significance due to fewer persons in the analysis (0.038 [CI, −0.029 to 0.105]). The ARIC study (n = 11 594) was by far the largest and youngest cohort, with a mean age of 53.8 years (18). The intermediate-risk category was defined as a 6% to 19% risk for a hard CVD event within 10 years. The overall NRI was not statistically significant for these CVD events. Finally, the MESA cohort included a subset of participants (n = 1330) from a larger cohort who were at intermediate risk, defined as having a 6% to 19% chance of having a CAD event within 10 years (31). Its analysis found that for intermediate-risk persons, adding the ABI to the FRS had an NRI of 0.036 for total CAD events and an NRI of 0.068 for total CVD events. Limitations in reported data prevented us from calculating a bias-corrected NRI. In addition, CIs were not reported and the analysis used different thresholds to define intermediate risk.

Table 1—Continued

White, %	Hypertension, %	Tobacco Users, %	Diabetes Mellitus, %	ABI <0.9, %	Outcome	Outcome Measure
NR	NR	NR	NR	7.7	CAD and CVD	HR, AUC, and proportion reclassified
73.8	33.2	25.8	8.7	2.8	CAD	HR
75.8	33.4	25.7	0	2.3	CVD	HR, AUC, and NRI
73.8	24.4	25.7	9.4	2.9	CVA only	HR
85	47.1	10.1	7.4	13.8	CVD	HR
NR	145‡	25.7	9.4	16.3	CAD and CVD	RR and AUC
NR	146‡	NR	3.9	18.7	CVD	OR and AUC
58.9	46.1	10.1	13.3	NR	CAD	HR, AUC, and NRI
59.4	49.9	10.1	14.6	13.3	CAD and CVD	RR
0	NR	NR	NR	NR	CAD	RR
0	52.4	7.3	27.0	11.6	CVA only	RR
NR	39.1	NR	24.8	10.4	CVA only	RR
35.7	38.2	16.5	0	NR¶	CAD and CVD	RR, AUC, and NRI
NR	29.4	21.5	10.1	NR	CAD	HR
NR	23.5	17.5	12.9	14	CAD	HR, AUC, and NRI

Benefits and Harms of Treatment of Asymptomatic Adults With PAD

We identified 2 trials evaluating treatment in screen-detected adults, asymptomatic adults, or adults with atypical leg symptoms (34, 35); only 1 of these reported harms (34). We did not find any additional studies explicitly evaluating harms of treatment in generally asymptomatic adults with PAD. The good-quality study ($n = 3350$), the Aspirin for Asymptomatic Atherosclerosis trial, assessed whether low-dose aspirin reduced CVD morbidity and mortality among participants with a screen-detected low ABI (34). Participants with an ABI of 0.95 or less who were not taking aspirin and did not have existing CVD were randomly assigned to receive aspirin, 100 mg/d, or placebo. Participants' mean age was 62 years; 71.5% were women, and about one third were current smokers. About one third of participants were receiving antihypertensive medication, and mean systolic blood pressure was 148 mm Hg. Only about 4% were receiving lipid-lowering medication; the mean total cholesterol level was about 6.2 mmol/L (239 mg/dL). After a mean follow-up of 8.2 years, CVD events (fatal or nonfatal myocardial infarction, cerebrovascular accident, or revascularization) did not differ between the aspirin and placebo groups (hazard ratio, 1.03 [CI, 0.84 to 1.27]). Furthermore, there was no statistically significant difference in any of the individual components of the composite outcome, in any secondary end point, or for any subgroup (including the subgroup with ABI ≤0.90). Persons randomly assigned to aspirin may have had an increased risk (hazard ratio, 1.71 [CI, 0.99 to 2.97]) for major bleeding (hemorrhagic stroke, subarachnoid or subdural hemorrhage, gastrointestinal ulcer requiring hospitalization for control, retinal hemorrhage, or severe anemia) compared with those receiving placebo, although the lower 95% CI estimate crossed 1.0.

The second trial, a fair-quality treatment trial ($n = 355$), assessed whether a telephone intervention promoting the use of lipid-lowering medication improved low-density lipoprotein cholesterol level in persons with PAD and a

Table 2. **Risk Reclassification of ABI When Added to FRS in the ABI Collaboration Cohorts*, by Sex**

FRS Risk Category†	Total		ABI ≤0.90		ABI, 0.91–1.10		ABI, 1.11–1.40		ABI >1.40	
	Patients, *n* (%)	Total 10-y Predicted CAD Risk, %	Patients, *n* (%)	Total 10-y Predicted CAD Risk, %	Patients, *n* (%)	Total 10-y Predicted CAD Risk, %	Patients, *n* (%)	Total 10-y Predicted CAD Risk, %	Patients, *n* (%)	Total 10-y Predicted CAD Risk, %
Men										
Low	5643 (26.3)	5	76 (0.4)	8	1076 (5.0)	5	4255 (19.9)	4	236 (1.1)	5
Intermediate	7392 (34.5)	13	245 (1.1)	16	2069 (9.7)	12	4815 (22.5)	12	263 (1.2)	8‡
High	8398 (39.2)	23	1149 (5.4)	40	3406 (15.9)	21	3668 (17.1)	18‡	175 (0.8)	14‡
Women										
Low	15 505 (69.0)	11	1083 (4.8)	21‡	6192 (27.5)	10‡	7909 (35.2)	9	321 (1.4)	11‡
Intermediate	5563 (24.7)	13	558 (2.5)	25‡	2429 (10.8)	12	2433 (10.8)	11	143 (0.6)	13
High	1418 (6.3)	27	200 (0.9)	44	598 (2.7)	21	577 (2.6)	22	43 (0.2)	34

ABI = ankle–brachial index; CAD = coronary artery disease; FRS = Framingham Risk Score.
* See reference 20.
† Patients at low, intermediate, and high risk have a 10-y risk for hard CAD events of <10%, 10% to 20%, and >20%, respectively.
‡ Risk category changed from that predicted by the FRS when the ABI was included.

Table 3. **Risk Reclassification of ABI When Added to FRS in the ABI Collaboration Cohorts* Using a Traditional Reference Group, by Sex**

FRS Risk Category†	ABI, 0.91–1.40	
	Patients, *n* (%)	Total 10-y Predicted CAD Risk, %
Men		
Low	5331 (24.9)	4
Intermediate	6884 (32.1)	12
High	7074 (33.0)	19‡
Women		
Low	14 101 (62.7)	9
Intermediate	4862 (21.6)	11
High	1175 (5.2)	21

ABI = ankle–brachial index; CAD = coronary artery disease; FRS = Framingham Risk Score.
*See reference 20.
† Patients at low, intermediate, and high risk have a 10-y risk for hard CAD events of <10%, 10% to 20%, and >20%, respectively.
‡ Risk category changed from that predicted by the FRS when the ABI was included.

low-density lipoprotein cholesterol level of 1.8 mmol/L (70 mg/dL) or greater (35). Most patients had no or atypical symptoms (20.3% and 54.5%, respectively). The mean age was 70.5 years, 40.6% were women, and the mean low-density lipoprotein cholesterol level was 2.7 mmol/L (103 mg/dL). About two thirds of participants were already receiving cholesterol-lowering drugs, and about one fourth were current smokers. After 12 months, 21.6% of patients randomly assigned to receive counseling every 6 weeks met their low-density lipoprotein cholesterol level goal (<2.6 mmol/L [<100 mg/dL]) versus 9.0% of patients in the attention control group ($P = 0.003$).

Discussion

To our knowledge, our review includes all new evidence presented since the USPSTF made its D recommendation on screening for PAD in 2005 and its I statement on the ABI as a nontraditional risk factor in CAD assessment in 2009. Despite the accrual of new evidence, we found limited evidence to support the added value of the ABI in current CAD or CVD risk prediction, as well as limited trial evidence for treatment of CVD in persons with asymptomatic or minimally symptomatic PAD.

Although the ABI Collaboration's individual patient–level meta-analysis showed that the ABI can reclassify the 10-year CAD risk when added to the FRS, 4 subsequent risk prediction studies showed that the appropriate risk reclassification for CAD or CVD events was small. Despite difficulties in establishing consistency of findings due to differences in populations, definitions of risk categories, definitions of composite outcomes, and measures of reclassification definitions, we conclude the following. First, the

Table 4. **Summary of NRI Results for Risk Prediction Studies**

Cohort	Study, Year (Reference)	Sample Size, *n*	Mean Age, *y*	Intermediate Risk Definition	NRI for CAD Outcomes		NRI for CVD Outcomes	
					Total Events	Hard Events	Total Events	Hard Events
Rotterdam*	Kavousi et al, 2012 (33)	5933	69.1	10-y risk for CAD: 10%–20%	NR	All: 0.006 (95% CI, −0.018 to 0.029) Intermediate: 0.073 (CI, 0.029 to 0.117) Intermediate (bias-corrected): not calculable	NR	NR
Health ABC*	Rodondi et al, 2010 (26)	2191	73.5	7.5-y risk for CAD: 7.5%–15%	All: 0.033 (CI, 0.0004 to 0.065) Intermediate: 0.07 (CI, 0.029 to 0.112) Intermediate (bias-corrected): 0.038 (CI, −0.029 to 0.105)	All: 0.079† Intermediate: 0.193† Intermediate (bias-corrected): not calculable	NR	NR
ARIC	Murphy et al, 2012 (18)	11 594	53.8	10-y risk for CVD: 6%–19%	NR	NR	NR	All: 0.008† ($P = 0.50$) Intermediate: NR
MESA	Yeboah et al, 2012 (31)	1330	63.8	7.5-y risk for CAD: 2.0%–15.4% 7.5-y risk for CVD: 3.4%–21.1%	All: NR Intermediate: 0.036† Intermediate (bias-corrected): not calculable	NR	All: NR Intermediate: 0.068† Intermediate (bias-corrected): not calculable	NR

ARIC = Atherosclerosis Risk in Communities; CAD = coronary artery disease; CVD = cardiovascular disease; Health ABC = Health, Aging, and Body Composition; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not reported; NRI = net reclassification improvement.
* Included but adjusted for persons with diabetes mellitus.
† 95% CI not reported.

overall magnitude for appropriate risk reclassification across all risk categories is probably clinically unimportant. Second, measures of NRI for intermediate-risk subgroups, in the absence of bias-corrected measures of NRI, are probably overestimates. Third, the benefit of reclassification using the ABI may be higher, and clinically important, in older populations or those with higher CAD or CVD event rates. Fourth, the value of the ABI in risk reclassification may be minimal or nonexistent in adults younger than 65 years. Fifth, because changes in risk estimates are small, the ABI may be most useful for patients who are near the thresholds for different risk categories or near boundaries that affect clinical decision making. Finally, although the NRI captures the appropriate risk reclassification, these changes in classification are clinically important only if they affect treatment decisions. Clinicians may be reluctant to withhold therapy on the basis of lower risk estimates (for example, men at high CAD risk with a normal ABI reclassified as intermediate risk) but might add therapy on the basis of higher risk estimates (for example, women at low CAD risk with an abnormal ABI reclassified as high risk).

Most PAD treatment trials are conducted in persons with intermittent claudication or clinically established PAD (36). Direct trial evidence in asymptomatic persons with low ABI shows that low-dose aspirin probably does not benefit screen-detected persons with low ABI without known CVD or diabetes and may cause increased major bleeding (34). The findings of a lack of any major benefits in screen-detected persons are consistent with trial evidence in those with clinically established PAD, which showed no statistically significant benefit for aspirin on total CVD events (36).

Many experts believe that the benefits of treating symptomatic persons with PAD can and should be extrapolated to asymptomatic persons because CVD events are similar in these groups. The getABI (German Epidemiological Trial on Ankle Brachial Index) cohort was a large, well-conducted prospective study of unselected persons aged 65 years or older not included in the ABI Collaboration (37). It included a subgroup comparison of CAD and CVD risk in symptomatic persons ($n = 593$) versus asymptomatic persons ($n = 836$) with ABIs less than 0.9. In this cohort, having a low ABI was associated with an elevated risk for CVD events, with no statistically significant difference between symptomatic and asymptomatic persons. In addition, a secondary analysis of the Heart Outcomes Prevention Evaluation randomized trial of ramipril versus placebo in persons with known CVD found no heterogeneity of outcome effects when comparing asymptomatic participants with decreasing levels of ABI and participants with symptomatic PAD (38).

Interventions (for example, antiplatelet therapy, statins, or angiotensin-converting enzyme inhibitors) that are effective in CVD risk reduction in symptomatic persons with PAD may be applicable to those without symptoms. The effectiveness of treating persons with symptomatic PAD was beyond the scope of this review. However, many persons with PAD who were included in major CVD treatment trials had comorbid CAD, diabetes, or both and should therefore already be receiving therapies for CVD risk reduction (38–43). Our review had several other limitations due to the targeted inclusion criteria. We included only English-language studies, although we were not made aware of non–English-language studies through expert suggestions. Our review focused on the additional risk discrimination that the ABI adds to ATP III's FRS. Although the FRS is the most commonly used risk prediction tool in the United States, it is not the only tool and will soon be updated with the release of ATP IV. Prognostic studies examining the additional value of the ABI to other risk tools showed similarly small, clinically insignificant NRIs (44, 45).

Although the evidence base we reviewed was limited, screening and risk prediction using the ABI is an active field of research. The Viborg Vascular screening trial, which is currently under way, is a population-based screening trial that is randomly assigning 50 000 men aged 65 to 74 years to screening for PAD and abdominal aortic aneurysm versus no screening. Primary outcome data, including all-cause and CVD mortality, should be available in late 2018 (46). In the near future, the ABI Collaboration will publish a reanalysis of its data using the NRI that will probably address most of the limitations we discuss in our review (Fowkes G. Personal communication.). In addition, ATP IV is expected to be released soon and will probably change the current definition of CAD or CVD risk as well as treatment thresholds (47). Therefore, our understanding of the value of screening with the ABI will change as new data are published, new risk prediction tools are developed, and standards continue to evolve around the clinical practice of CVD risk prediction and treatment.

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Note: AHRQ staff provided oversight for the project and assisted in external review of the draft evidence synthesis. USPSTF liaisons helped to resolve issues around the scope of the review but were not involved in the conduct of the review.

Disclaimer: The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by AHRQ or the U.S. Department of Health and Human Services.

Acknowledgment: The authors thank Daphne Plaut, MLS, for conducting the literature searches; Kevin Lutz, MFA, for his editorial support; Caitlyn Senger, MPH, and Clara Soh, MPA, for their assistance in conducting the evidence review; Tracy Wolff, MD, MPH, and Aileen Buckler, MD, MPH, for their assistance at AHRQ; Timothy Wilt, MD, MPH, Al Siu, MD, MSPH, Kirsten Bibbins-Domingo, MD, PhD, and Jessica Herzstein, MD, for their work as our USPSTF leads; and Josh Beckman, MD, MS, Nancy Cook, ScD, Gerry Fowkes, PhD, David Goff, MD, PhD, and Al Hirsch, MD, our expert reviewers, for their review of our full evidence report.

Financial Support: This review was conducted by the Kaiser Permanente Research Affiliates Evidence-based Practice Center under contract to AHRQ (contract HHSA 290-2007-10057-I, task order 13).

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-0658.

Requests for Single Reprints: Reprints are available from the AHRQ Web site (www.ahrq.gov).

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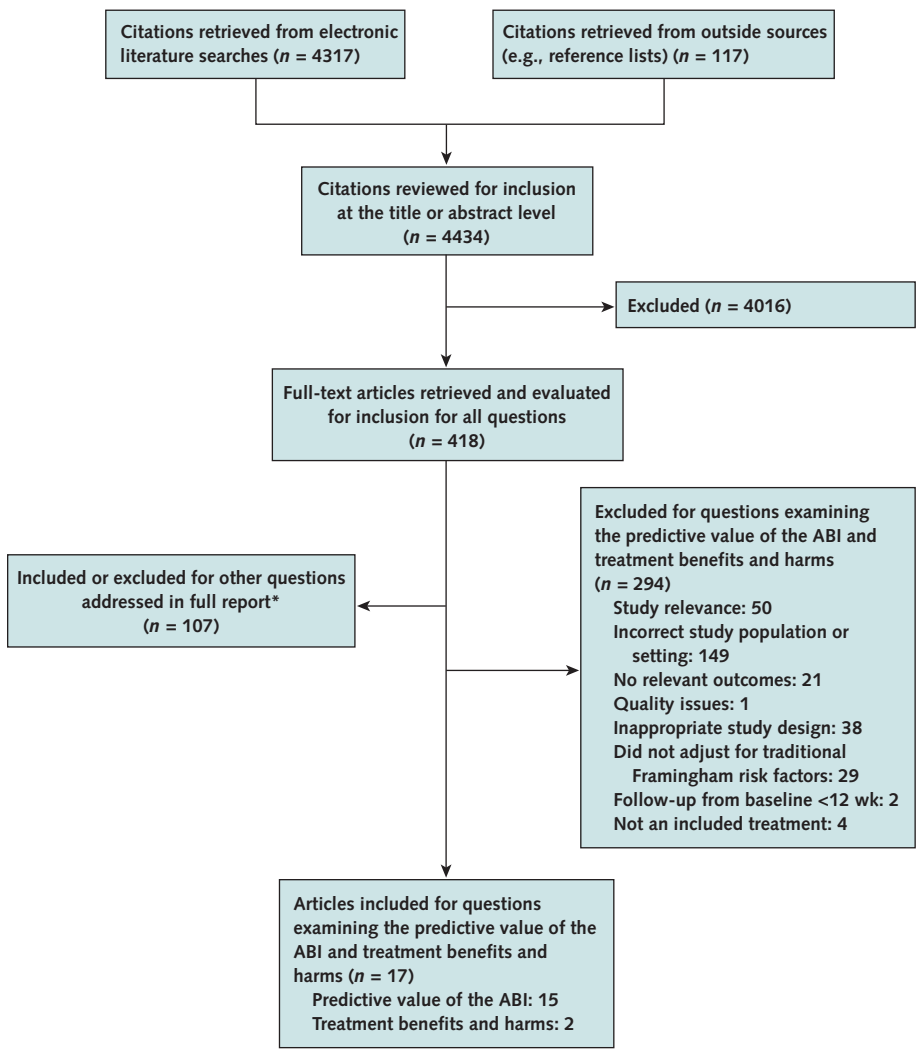
Appendix Figure. **Summary of evidence search and selection.**



ABI = ankle–brachial index.
* Available at www.uspreventiveservicestaskforce.org.

Appendix Table. **Summary of Results for Risk Prediction Studies Reporting Outcomes of Independent Association of ABI and CVD Morbidity and Mortality Independent of FRS and/or Measures of Discrimination of ABI Compared With FRS**

Cohort	Study, Year (Reference)	Reference Standard	Outcomes of Independent Association	Outcomes of Discrimination
ABI Collaboration	Fowkes et al, 2008 (20)	ABI of 1.11–1.40	HR* of ABI ≤0.90 for major coronary events Men: 2.16 (95% CI, 1.76 to 2.66) Women: 2.49 (CI, 1.84 to 3.36) HR* of ABI ≤0.90 for CAD or CVA death Men: 2.92 (CI, 2.31 to 3.70) Women: 2.97 (CI, 2.02 to 4.35)	AUC for major coronary events by predictors, among men FRS + DM: 0.646 FRS + DM + ABI: 0.655 AUC for major coronary events by predictors, among women FRS + DM: 0.605 FRS + DM + ABI: 0.658
ARIC	Weatherley et al, 2007 (21)	Per 0.10-point decrease in ABI	HR† for CAD event (definite CAD death, definite or probable hospitalization for MI, or unrecognized MI) White men: 1.15 (CI, 1.08 to 1.24) White women: 1.11 (CI, 1.01 to 1.23) Black men: 1.25 (CI, 1.11 to 1.41) Black women: 1.20 (CI, 1.07 to 1.34)	NR
ARIC	Murphy et al, 2012 (18)	Per 1-SD increase in ABI	HR‡ for hard CVD events (MI, cardiovascular death, or CVA): 0.849 (CI, 0.79 to 0.91)	AUC for hard CVD events Model FRS: 0.756 (CI, 0.739 to 0.773) Model FRS + ABI: 0.758 (CI, 0.741 to 0.775) $P = 0.23$
ARIC	Tsai et al, 2001 (22)	ABI >1.20	HR§ for nonhemorrhagic CVA ABI ≤0.80: 1.93 (CI, 0.78 to 4.78) ABI of 0.81–0.90: 1.45 (CI, 0.56 to 3.76) ABI of 0.91–1.00: 1.23 (CI, 0.67 to 2.26) ABI of 1.01–1.10: 1.46 (CI, 0.94 to 2.25) ABI of 1.11–1.20: 1.18 (CI, 0.77 to 1.79)	NR
CHS	O'Hare et al, 2006 (23)	ABI of 1.11–1.20	HR‖ for cardiovascular events (MI, CVA, angina, angioplasty, CABG, or lower-extremity amputation/revascularization) ABI ≤0.60: 1.60 (CI, 1.09 to 2.34) ABI of 0.61–0.70: 1.57 (CI, 1.07 to 2.20) ABI of 0.71–0.80: 1.63 (CI, 1.16 to 2.28) ABI of 0.81–0.90: 1.72 (CI, 1.35 to 2.20) ABI of 0.91–1.00: 1.37 (CI, 1.13 to 1.64) ABI of 1.01–1.10: 1.08 (CI, 0.93 to 1.25) ABI of 1.21–1.30: 0.90 (CI, 0.74 to 1.10) ABI of 1.31–1.40: 0.97 (CI, 0.68 to 1.40) ABI >1.40: 1.00 (CI, 0.57 to 1.74) HR‖ for CVD death ABI ≤0.60: 2.13 (CI, 1.49 to 3.05) ABI of 0.61–0.70: 2.31 (CI, 1.56 to 3.42) ABI of 0.71–0.80: 2.01 (CI, 1.43 to 2.81) ABI of 0.81–0.90: 2.37 (CI, 1.77 to 3.16) ABI of 0.91–1.00: 1.60 (CI, 1.25 to 2.05) ABI of 1.01–1.10: 1.05 (CI, 0.85 to 1.30) ABI of 1.21–1.30: 0.95 (CI, 0.71 to 1.26) ABI of 1.31–1.40: 1.33 (CI, 0.83 to 2.13) ABI >1.40: 1.76 (CI, 0.97 to 3.18)	NR
Edinburgh Artery Study	Lee et al, 2004 (24)	ABI >0.9	RR¶ for fatal and nonfatal MI (ABI ≤0.90): 1.10 (CI, 0.78 to 1.54) RR¶ for nonfatal MI or CVA and CVD death (ABI ≤0.90): 1.06 (CI, 0.81 to 1.39) RR¶ for nonfatal CVA (ABI ≤0.90): 1.29 (CI, 0.77 to 2.19) RR¶ for fatal and nonfatal CVA (ABI ≤0.90): 1.05 (CI, 0.67 to 1.65)	AUC for fatal MI by predictors (P value for increase in predictive value) Age + sex + DM + prevalent CVD + FRS predictors: 0.77 ($P \leq 0.001$) Age + sex + DM + prevalent CVD + FRS predictors + ABI: 0.78 ($P \leq 0.01$)
Edinburgh Artery Study	Price et al, 2007 (25)	ABI >0.9	OR* for MI or CVA (ABI ≤0.9): 1.70 (CI, 1.07 to 2.70)	AUC for MI or CVA Model FRS + DM: 0.61 (CI, 0.56 to 0.67) Model FRS + DM + ABI: 0.64 (CI, 0.59 to 0.69) (P for difference = 0.02)
Health ABC**	Rodondi et al, 2010 (26)	ABI of 1.01–1.30	HR* for total CAD events (nonfatal MI, coronary death, angina, or revascularization) ABI ≤0.90: 1.57 (CI, 1.14 to 2.18) ABI of 0.91–1.00: 1.05 (CI, 0.73 to 1.49) ABI of 1.31–1.40: 1.29 (CI, 0.75 to 2.23) ABI >1.4: 2.89 (CI, 1.47 to 5.68)	AUC for total CAD events, by predictors FRS + DM: 0.631 FRS + DM + ABI: 0.650

Continued on following page

Appendix Table—**Continued**

Cohort	Study, Year (Reference)	Reference Standard	Outcomes of Independent Association	Outcomes of Discrimination
Health ABC**	Sutton-Tyrrell et al, 2008 (27)	ABI of 0.91–1.30	RR†† for total CAD events (coronary death, hospitalization for acute MI, or angina) ABI ≤0.9: 1.41 (CI, 1.11 to 1.81) ABI ≥1.3: 1.50 (CI, 1.01 to 2.23) RR†† for cardiovascular death (death due to atherosclerotic cardiovascular disease or CVA) ABI ≤0.9: 2.18 (CI, 1.57 to 3.02) ABI ≥1.3: 1.32 (CI, 0.66 to 2.63) RR†† for all CVAs ABI ≤0.9: 1.67 (CI, 1.13 to 2.45) ABI ≥1.3: 0.78 (CI, 0.31 to 1.93)	NR
Honolulu Heart Program	Abbott et al, 2000 (28)	ABI ≥1.0	RR‡‡ for nonfatal MI, CAD death, or sudden death ABI <0.8: 2.7 (CI, 1.6 to 4.5) ABI of 0.8 to <1.0: 1.3 (CI, 0.9 to 1.9)	NR
Honolulu Heart Program	Abbott et al, 2001 (29)	ABI ≥0.9	HR§§ for all CVAs (ABI <0.9): 2.0 (CI, 1.1 to 3.5) HR§§ for thromboembolic CVA (ABI <0.9): 1.9 (CI, 1.0 to 3.7) HR§§ for hemorrhagic CVA (ABI <0.9): 3.3 (CI, 1.2 to 9.4)	NR
Hoorn	Hanssen et al, 2012 (30)	ABI ≥0.9	RR‖‖ for CVD death among persons without DM (ABI <0.9): 1.95 (CI, 0.88 to 4.33)	NR
MESA**	Yeboah et al, 2012 (31)	Per 1-SD increase in ABI	HR¶¶ for CAD events (MI, CAD death, resuscitated cardiac arrest, or angina with revascularization): 0.79 (CI, 0.66 to 0.95) HR¶¶ for CVD events (CAD death, MI resuscitated cardiac arrest, angina with revascularization, CVA, or CVD death): 0.81 (CI, 0.68 to 0.95)	For CAD events AUC for FRS alone: 0.623 AUC for FRS + ABI: 0.650 For CVD events AUC for FRS alone: 0.623 (CI, NR) AUC for FRS + ABI: 0.650 (CI, NR)
Rotterdam	Kavousi et al, 2012 (33)	ABI of 0.91–1.40	HR*** for nonfatal MI, fatal MI, or fatal CAD (ABI ≤0.90) Overall: 1.3 (CI, 1.0 to 1.7) Men: 1.6 (CI, 1.1 to 2.2) Women: 1.1 (CI, 0.7 to 1.6)	AUC for nonfatal MI, fatal MI, or fatal CAD with FRS predictors: 0.73 (CI, 0.71 to 0.75) Change in AUC when PAD was added as a predictor Overall: 0.00 (CI, 0.00 to 0.00) Men: 0.01 (CI, 0.00 to 0.01) Women: 0.00 (CI, 0.00 to 0.00)
Rotterdam	van der Meer et al, 2004 (32)	ABI ≥1.21	HR††† for fatal or nonfatal incident MI ABI <0.97: 1.59 (CI, 1.05 to 2.39) ABI of 0.97–1.10: 1.55 (CI, 1.04 to 2.31) ABI of 1.10–1.21: 1.12 (CI, 0.74 to 1.70)	NR

ABI = ankle–brachial index; ARIC = Atherosclerosis Risk in Communities; AUC = area under the curve; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHS = Cardiovascular Health Study; CVA = cerebrovascular accident; CVD = cardiovascular disease; DM = diabetes mellitus; FRS = Framingham Risk Score; Health ABC = Health, Aging, and Body Composition; HR = hazard ratio; MESA = Multi-Ethnic Study of Atherosclerosis; MI = myocardial infarction; NR = not reported; OR = odds ratio; PAD = peripheral artery disease; RR = relative risk.

* Also adjusted for diabetes.

† Also adjusted for center, low-density lipoprotein cholesterol level, and diabetes.

‡ Also adjusted for race and low-density lipoprotein cholesterol level.

§ Also adjusted for diabetes, prevalent CAD, low-density lipoprotein cholesterol level, antihypertensive medication use, and pack-years of smoking.

‖ Also adjusted for race, diabetes, prevalent CVD (CAD, CVA, or congestive heart failure), low-density lipoprotein cholesterol level, triglyceride use, diastolic blood pressure, antihypertensive medication use, creatinine level, body mass index, and C-reactive protein level.

¶ Also adjusted for diabetes and prevalent CAD.

** Not in ABI Collaboration.

†† Also adjusted for race, site, prevalent CVD, diabetes, body mass index, physical activity, and triglyceride use.

‡‡ Also adjusted for diabetes, alcohol intake, fibrinogen level, body mass index, distance walked per day, and past smoking.

§§ Also adjusted for diabetes, fibrinogen level, distance walked per day, and atrial fibrillation.

‖‖ Also adjusted for triglyceride use, albuminuria, estimated glomerular filtration rate, waist circumference, history of CVD, and impaired glucose metabolism.

¶¶ Also adjusted for race/ethnicity, body mass index, blood pressure medication use, and statin use.

*** Also adjusted for treatment of hypertension and diabetes.

††† Also adjusted for diabetes; diastolic blood pressure; body mass index; and use of aspirin, antihypertensive medications, and cholesterol-lowering medications.