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

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Structured Abstract

Objective: We conducted a systematic evidence review on the diagnostic and prognostic value of the resting ankle-brachial index (ABI) in unselected populations. This review also examined the benefit and harms of treating generally asymptomatic persons with peripheral artery disease (PAD). We conducted this review to support the U.S. Preventive Services Task Force in updating its recommendation on screening for PAD.

Data Sources: We searched MEDLINE and the Cochrane Central Registry of Controlled Trials from 1996 through September 2012 to locate relevant English-language studies. We supplemented these searches with suggestions from experts' reference lists from 62 related systematic reviews.

Study Selection: Two investigators independently reviewed 4,434 abstracts and 418 articles against the specified inclusion criteria for diagnostic accuracy studies, prognostic studies, and treatment studies. Our review focused on the utility of using the ABI as a screening or prognostic tool in asymptomatic persons. We excluded populations with symptomatic PAD or known cardiovascular disease (CVD), diabetes, or severe chronic kidney disease. We included diagnostic accuracy studies that evaluated ABI against a reference standard. We included risk prediction studies that evaluated ABI's ability to predict future coronary artery disease (CAD) or CVD events in addition to the Framingham risk score (FRS). Treatment studies were limited to trials evaluating interventions to reduce CVD or maintain lower extremity function. We excluded interventions aimed primarily at management of lower extremity symptoms.

Data Extraction: We extracted all relevant study details (pertaining to population/setting, diagnostic test or intervention, reference standard or comparator, followup and outcomes), which varied by key question. Diagnostic accuracy studies had outcomes focused on measures of test performance (i.e., sensitivity and specificity). For risk prediction studies, outcomes focused on measures of risk reclassification (i.e., number reclassified, net reclassification index [NRI]), measures of discrimination (i.e., differences in the area under the curve [AUC]), or associations of risk adjusted for FRS predictors (i.e., hazard or risk ratios). We extracted any reported outcomes for treatment trials, including adverse effects. We independently appraised all articles for quality and excluded poor-quality studies.

Data Synthesis: *Screening*: In one fair-quality study (n=306) in older Swedish adults, the sensitivity of ABI (≤0.9) was low (15% to 20%) but specificity was near 100 percent, and the positive and negative predictive values for ABI were greater than 80 percent. Other diagnostic studies of ABI were primarily conducted in persons referred for vascular testing or with symptoms.

Risk prediction: From multiple population cohort studies (18 cohorts; n=52,510), low ABI (≤0.9) was generally associated with future CAD and CVD events, independent of FRS factors. The clinical relevance of the association of a low ABI (≤0.9) and the impact on risk reclassification for CAD and CVD events, however, was less certain. A well-conducted individual patient-level meta-analysis conducted by the ABI Collaboration demonstrated that ABI results could

reclassify 10-year CAD risk for 19 percent of men and 36 percent of women when added to the FRS, across 13 population-based cohorts (n=43,919) representing a wide spectrum of persons. Five other studies (n=22,055) evaluated the additional prognostic value of ABI to the FRS using the AUC and/or NRI. In general, these studies suggest that the overall reclassification (among persons of any risk category) is low for CAD or CVD events, the NRI may be higher for older persons for total or hard CAD events (Health ABC; n=2,191), and the NRI is not significant for persons younger than age 65 years for total CVD events (ARIC; n=11,594).

Treatment: We excluded the majority of treatment trials because they focused on persons with intermittent claudication. In one good-quality trial (n=3,350), low-dose aspirin did not prevent CVD events in adults ages 50 to 75 years without known CVD who had a low ABI (≤0.9). In fact, there was a nonsignificant increase in major bleeding events. One smaller, fair-quality trial (n=355) showed that an intensive telephone counseling intervention aimed at adults with primarily asymptomatic PAD can decrease low-density lipoprotein cholesterol levels and achieve treatment goal levels (<100 mg/dL) compared with usual care.

Limitations: A general lack of evidence limited our understanding of the diagnostic test performance for screening ABI and treatment of asymptomatic PAD. The limitations in the understanding of the incremental prognostic value of ABI in CVD risk prediction are due to the differences in populations (e.g., age, sex, race/ethnicity), choice of referent group (i.e., definition of normal ABI), the definitions of composite CAD outcomes (i.e., hard vs. incident vs. total CAD) and risk categories (e.g., intermediate risk of 10% to 19%, 15% to 25%, or 5% to 20%), and measures of reclassification (e.g., number reclassified vs. NRI). These differences make comparisons between risk prediction studies difficult, which limited our ability to interpret findings.

Conclusions: There is very limited evidence examining the diagnostic accuracy of the ABI as a screening tool (one study) or examining the treatment of generally asymptomatic persons with PAD or a low ABI (two trials). However, there is a large body of evidence (18 population-based cohorts) suggesting that a low ABI is independently associated with increased CAD and CVD risk, after adjusting for FRS factors. Despite this association, the magnitude of risk reclassification of ABI in addition to FRS is still unclear and is likely small. The net reclassification may have the largest impact among persons age 65 years and older and persons at the thresholds of FRS risk categories.

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Chapter 1. Introduction

Scope and Purpose

The U.S. Preventive Services Task Force (USPSTF) will use this evidence review to update its previous recommendation on peripheral artery disease (PAD) screening. In 2005, the USPSTF recommended against routing screening for PAD based on fair-quality evidence indicating that routine screening for PAD in asymptomatic adults had little benefit (D recommendation).

Background

Disease Definition

PAD is an atherosclerotic occlusive condition in which plaque builds up in the distal arteries, constricting circulation and blood flow.[1] PAD has also been referred to previously as peripheral vascular disease or peripheral artery occlusive disease. Lower-extremity PAD refers to atherosclerosis of arteries distal to the aortic bifurcation and most commonly occurs in the legs.[2] The term PAD is also used more broadly to encompass a larger range of noncoronary arterial diseases or syndromes that are caused by the altered structure or function of arteries to the brain, visceral organs, and limbs.[3] This review limits the definition of PAD, however, to atherosclerosis of the arteries distal to the aortic bifurcation, which is synonymous with lower-extremity PAD.

Claudication is the most common symptom of lower-extremity PAD. Claudication is defined as discomfort, cramping, ache, or pain in one or both legs when walking that does not go away with continued walking and is relieved by rest. Most people with PAD, however, do not have any symptoms. Many people with PAD also have atypical manifestations of claudication or leg symptoms other than intermittent claudication, which further complicates diagnosis.[3,4] Other signs and symptoms of PAD include foot pain at rest; numbness, tingling, cyanosis, hair loss, nonhealing ulcers, or gangrene of the lower extremity; functional impairment (e.g., poor standing balance, difficulty rising from a seated position); and erectile dysfunction.[3,5,6]

PAD diagnosis relies on both anatomy and function because atherosclerosis in the relevant vessels is what leads to impaired or constricted blood flow. Guidelines do not specify the degree of stenosis or impaired blood flow that is clinically relevant. The gold standard for diagnosis is digital subtraction angiography (DSA), in which images taken before injection of contrast medium are subtracted from images taken after injection, leaving images of only the vessel itself. As an invasive procedure, DSA carries risks for nephrotoxic and hypersensitivity reactions to the contract medium, as well as for complications from arterial catheter access.[7,8] Due to these risks, less invasive angiography (i.e., magnetic resonance angiography [MRA] and multirow detector computed tomography angiography [CTA]) are used in clinical practice, although the degree to which these tests have replaced DSA as the reference standard remains unclear. The resting ankle-brachial index (ABI) is the most commonly used test to screen and detect PAD in clinical settings. The ABI is the ratio of the systolic blood pressure measured over the ankle to the

systolic blood pressure measured over the brachial artery.[9] For many epidemiological studies, an abnormal ABI of less than 0.9 is often used to define PAD. It is important to note, however, that an abnormal ABI is not diagnostic for PAD.

Prevalence and Burden of PAD

Studies on the prevalence of PAD among general populations or unselected primary care populations use a low ABI as a surrogate for PAD. As such, the true prevalence of PAD in the general population is not known. The National Health and Nutrition Examination Survey (NHANES) provides recent data on the prevalence of low ABI (≤0.9) from large, community-based sampling of the U.S. population. From 1999 to 2004, 5.9 percent of the U.S population age 40 years or older had a low ABI, which amounts to 7.1 million people.[10] Excluding individuals with known coronary artery or cerebrovascular disease, 4.7 percent of the adult U.S. population had a low ABI.[10] Similarly, another report that included data from seven U.S. population-based studies produced similar findings estimating that a total of 5.8 percent of the U.S. population age 40 years or older had a low ABI or history of lower-extremity revascularization, representing 6.8 million people.[11]

The prevalence of low ABI (≤0.9) increases with age. About 1.9 percent of individuals ages 40 to 59 years have a low ABI, 8.1 percent among those ages 60 to 74 years have a low ABI, and 17.5 percent among those age 75 years and older have a low ABI.[12] Although PAD is thought to be more common in men,[11] the prevalence of low ABI does not appear to vary significantly by sex after adjusting for age.[12-14] PAD prevalence also varies by race and ethnicity, with blacks having the highest age-adjusted prevalence of low ABI.[11-15]

Studies have estimated that the mean annual inpatient and outpatient costs attributable to PAD for Medicare beneficiaries was $1,868 per PAD patient, representing a total of $4.37 billion in 2001.[16] Placement of a vascular shunt, angioplasty, and lower-limb amputations were the most commonly performed procedures for PAD. A study of privately insured patients found the annualized PAD-related medical, hospital, outpatient, and pharmacy costs to be $5,995 per PAD patient in 1999–2003.[17] A registry of patients with known PAD or low ABI found annual hospital costs ranged from $3,780 to $6,162 (depending on severity of disease) in 2003 to 2006.[18]

Etiology and Natural History

PAD is a manifestation of systemic atherosclerosis and is considered a predictor for other cardiovascular disease (CVD) (e.g., coronary artery disease [CAD] and cerebrovascular disease) and CVD events such as myocardial infarction (MI), cerebrovascular accident (CVA), and death.[11] PAD is generally classified according to its clinical presentation:

- Asymptomatic (Rutherford Category 0; Fontaine Stage I)
- Mild claudication (Rutherford Category 1; Fontaine Stage IIa)
- Moderate claudication (Rutherford Category 2; Fontaine Stage IIb)
- Severe claudication (Rutherford Category 3; Fontaine Stage IIb)

- Ischemic rest pain (Rutherford Category 4; Fontaine Stage III)
- Minor tissue loss (Rutherford Category 5)
- Ulceration or gangrene (Rutherford Category 6; Fontaine Stage IV)

Typically, 20 to 50 percent of persons with low ABI are asymptomatic. Of these, 40 to 50 percent exhibit atypical leg pain, 10 to 35 percent have claudication, and 1 to 2 percent have critical ischemia.[3] Studies estimate that over a 5-year period, 70 to 80 percent of symptomatic persons without critical ischemia will have stable claudication, 10 to 20 percent will experience worsening claudication, and 1 to 2 percent will develop critical ischemia.[3]

Patients with PAD have an increased risk of CVD events due to concomitant coronary and cerebrovascular disease. In general, persons with low ABI and/or claudication have similar risk of mortality due to CVD as patients with a history of CAD or cerebrovascular disease.[9] Studies estimate that 20 percent of individuals with PAD will experience a nonfatal cardiovascular event and 15 to 30 percent will die within 5 years.[3] Among patients with PAD, up to half have evidence of CAD (based on history or electrocardiography), 60 to 80 percent have serious CAD (of at least one vessel), and up to 25 percent have serious carotid artery disease (diagnosed by duplex ultrasound).[3] Both CAD and cerebrovascular disease are significantly associated with low ABI ($\leq$0.9).[19,20] A low ABI is also associated with unrecognized subclinical CVD (i.e., diagnosed by electrocardiography, echocardiography, exercise stress test, MRA, or carotid duplex ultrasound).[21-23]

The extent of atherosclerosis, acuity of limb ischemia, and ability to restore arterial circulation determine the prognosis of the lower extremity in patients with PAD.[3] For patients with chronic atherosclerosis and progression to symptoms of chronic limb ischemia, for example, prognosis of the affected limb is very poor unless it can be revascularized. For patients with acute occlusive events (i.e., thromboembolic occlusion with little underlying atherosclerosis), on the other hand, the prognosis of the limb is related to the rapidity and completeness of revascularization before the onset of irreversible ischemic tissue damage.[3]

Risk Factors

In addition to increasing age, major risk factors for PAD include diabetes, smoking, hypertension, high cholesterol, obesity, and physical inactivity.[16,24] The estimated prevalence of low ABI is about 7.6 to 9.6 percent in adults with diabetes, 5.5 percent in smokers, 6.7 to 7.6 percent in adults with hypertension, 4.6 to 5.6 percent in adults with hypercholesterolemia, and 5.3 to 5.7 percent in adults with a body mass index (BMI) over 30 kg/m^2.[15,25] Several studies in primary care or general populations have shown significant associations between most of these risk factors and low ABI in multivariable analyses.[19,26-30] Smoking and diabetes show the strongest association with low ABI in most multivariable analyses; smoking has odds ratios (ORs) ranging from 1.55 (95% confidence interval [CI], 1.34 to 1.79)[28] to 5.35 (95% CI, 1.77 to 16.22)[26] and diabetes has ORs ranging from 1.59 (95% CI, 1.00 to 2.51)[30] to 3.8 (95% CI, 1.6 to 9.0).[27] An estimated 80 percent of persons with PAD are current or former smokers, and 12 to 20 percent of persons with PAD have diabetes.[16]

Rationale for Screening

PAD is an important manifestation of systemic atherosclerosis. Therefore, screening for PAD in asymptomatic persons may lead to early CVD risk factor modification in persons with undiagnosed atherosclerosis. In addition, PAD has been underdiagnosed and undertreated compared with other types of CVD because the majority of patients with PAD do not have symptoms or have atypical symptoms.[31] Taking a patient's clinical history alone is not a sufficient screening method for PAD, as less than 10 percent of community-dwelling adults with PAD report having classic symptoms (such as intermittent claudication) and up to 48 percent report no symptoms at all.[32] Likewise, a physical examination has limited value for screening asymptomatic persons, as only a femoral bruit, a pulse abnormality, or skin changes significantly increase the likelihood ratio for low ABI (≤0.9) and all these signs indicate moderate to severe disease.[32]

In many epidemiologic surveys, population-based diagnosis and classification have used standardized questionnaires, most commonly the World Health Organization Rose questionnaire or the Edinburgh Modification of the Rose questionnaire. The Walking Impairment Questionnaire and the San Diego claudication questionnaire are more recently developed questionnaires designed to screen for PAD with greater sensitivity and specificity.[3] These questionnaires, however, only detect persons with symptoms.

The resting ABI is the most commonly used test to screen for and detect PAD in clinical settings. The ABI is the ratio of the systolic blood pressure measured over the ankle to the systolic blood pressure measured over the brachial artery.[9] The systolic blood pressure is measured after the patient has rested for 5 to 10 minutes and is in the supine position,[33] using a manual sphygmomanometer and a handheld Doppler ultrasound probe, [34] although specific techniques vary. This variation in protocols of measurement may lead to differences in the ABI values obtained.[25,35,36] Overall, the ABI is considered to have good reproducibility (variance of about 0.10).[3]

Traditionally, ABI values of 1.00 to 1.29 are considered normal. ABI values of 0.00 to 0.40 indicate severe PAD, 0.41 to 0.90 indicate mild to moderate PAD, 0.91 to 0.99 are considered borderline, and greater than 1.30 indicates noncompressible arteries.[3] Recent recommendations state that ABI values greater than 1.40 indicate noncompressible arteries and that 1.00 to 1.40 be considered normal.[6]

The prevalence of abnormal ABI in primary care varies depending on the population's age and CVD risk profile. Prevalence of low ABI (≤0.9) is as low as 2 percent, for example, among adults younger than age 60 years or populations without known CVD.[12,26] This prevalence increases dramatically, however, with older age and increased cardiovascular risk factors. For example, the prevalence of a low ABI was 29 percent in a national sample of 6,979 people who were age 70 years or older or ages 50 to 69 years with a history of smoking or diabetes.[37]

The prevalence of noncompressible arteries (ABI >1.30 or 1.40) is generally low. Among the NHANES cohort, 3.6 percent had an ABI greater than 1.30[12] and 1.5 percent had an ABI greater than 1.40.[10] In other community-based cohorts, 3.9 to 5.5 percent had an ABI greater than 1.30

and 1.1 to 1.2 percent had an ABI greater than 1.40.[38,39] The prevalence of noncompressible arteries also increases with age and CVD risk factors. For example, in the United States, 6.3 percent of clinic patients who were older than age 70 years, or those who were ages 50 to 69 years with CVD risk factors, had an ABI greater than 1.40.[40] While the clinical implications of a high ABI (>1.30 or 1.40) are uncertain, persons with a high ABI are generally older and more likely to have CVD risk factors, particularly diabetes and hypertension.[39-41] Persons with noncompressible arteries who are suspected of having PAD usually go on to additional diagnostic testing.

There are multiple other noninvasive vascular diagnostic techniques, including the toe-brachial index, segmental pressure measurements, pulse volume recordings, duplex ultrasound imaging, Doppler waveform analysis, and exercise/treadmill testing.[3] The toe-brachial index is used for patients with suspected PAD who have noncompressible arteries at the ankle. Studies have suggested segmental pressure examination and duplex ultrasound represent noninvasive methods for followup diagnostic testing in symptomatic persons with suspected PAD who have a normal (or supranormal) ABI value.[3] Other testing may be useful in the diagnostic workup, assessment of prognosis, or monitoring therapy for PAD. MRA, CTA, and invasive angiographic techniques are generally reserved for further workup of PAD in persons with symptoms for whom revascularization may be an option.

In addition to its ability to detect PAD, an abnormal ABI may be useful for predicting CVD morbidity and mortality. Like other CVD risk factors or CAD risk equivalents, ABI measurement may increase existing CVD risk assessments' discrimination or calibration. Currently, the Adult Treatment Panel (ATP) III of the National Cholesterol Education Program algorithm is the most widely used system for categorizing CAD risk in the United States.[42] This sex-specific algorithm uses the traditional Framingham risk factors (sex, age, total cholesterol, high-density lipoprotein [HDL] cholesterol, smoking status, and systolic blood pressure) to stratify individuals who do not have established atherosclerosis or diabetes into three risk categories for developing CAD events.[43] Low-risk individuals have less than a 10 percent risk of developing CAD events over 10 years, intermediate-risk individuals have a 10 to 20 percent risk, and high-risk individuals have more than a 20 percent risk.[42] While ATP III is widely used, it was developed in 2001 and will soon be updated.[44] Additionally, the ATP III focuses on predicting hard CAD events (as opposed to global CVD events). While the Framingham risk score (FRS) generally provides good discrimination for future morbidity and mortality, it is still imperfect (c-statistic can range from 0.60 to 0.80) and may not perform as well in nonblack minorities.[45-50] Other risk prediction scores have since been developed, validated, and used to predict global CVD events, including the Framingham global CVD score,[51] QRISK2,[52,53] and the Reynolds risk score.[54,55] In clinical practice, these risk prediction tools help guide the type and intensity of management of risk factor modification and will help practitioners communicate risk with patients.

Interventions/Treatment

The primary aims of treating PAD itself, or treating PAD as a manifestation of systemic atherosclerosis, are to reduce overall CVD morbidity (e.g., MI, CVA), decrease PAD morbidity (e.g., increase walking distance and quality of life by improving symptoms of intermittent

claudication and leg function, prevent or reduce limb complications, and preserve limb viability), and decrease mortality, while minimizing the harms of treatment. Treating PAD can be categorized into measures to reduce CVD risk, medical treatment of PAD symptoms (e.g., claudication), and revascularization of the lower extremities.

CVD risk reduction includes smoking cessation, cholesterol lowering, glycemic control, weight reduction, blood pressure control, and antiplatelet therapy. Medical treatment of symptoms includes pharmacologic (i.e., pentoxifylline, cilostazol) and nonpharmacologic (i.e., exercise therapy) interventions. Revascularization by angioplasty, thrombolysis, stenting, or bypass surgery is reserved for persons with severe PAD who are severely disabled by claudication or have acute or critical limb ischemia or by thrombolysis for persons with acute limb ischemia.[8,56] Because this review focuses on screening for PAD in asymptomatic persons, our review of treatment options focuses on CVD risk reduction.

Current Clinical Practice

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) practice guidelines recommend resting ABI testing for detecting PAD among patients at increased risk, including those age 65 years or older, those age 50 years or older with a history of smoking or diabetes, or those of any age with exertional leg symptoms or nonhealing wounds.[6,57] In their 2010 "Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults," the ACCF/AHA also recommended the ABI as a reasonable tool for cardiovascular risk assessment among patients at intermediate risk.[57] A survey of primary care practices across the United States, however, found that nearly 70 percent of providers reported never using ABI in their practice settings, 6 to 8 percent reported using ABI annually, while 12 to 13 percent reported using ABI weekly or monthly.[58]

Administering the ABI takes about 15 minutes in primary care practices.[3] ABI alone, however, is usually not reimbursed by health care payers, as they require documentation that might be obtained using pulse volume recordings or Doppler waveform tracings.[3]

Previous USPSTF Recommendations

In 2005, the USPSTF recommended against routine screening for PAD (D recommendation),[59,60] which was unchanged from the 1996 recommendation.[61] Previously, the USPSTF concluded that there was fair evidence that screening with ABI can detect adults with asymptomatic PAD. Screening for PAD among asymptomatic adults in the general population, however, would have few or no benefits because the prevalence of PAD in this group is low and there was little evidence that treating PAD at the asymptomatic stage improves health outcomes beyond treatment based on standard CVD risk assessment.[60]

The review to support the 2005 recommendation[62] was a targeted review that included only three studies.[63-65] The review concluded that while evidence exists to support the use of physical activity and smoking cessation to improve outcomes in early PAD (one trial), these interventions are already offered to all patients and do not necessarily offer additional benefit to persons with

screen-detected PAD.[60] This review, however, had a very limited scope. First, the review focused on outcomes of lower-extremity symptoms and function, rather than outcomes related to CAD or other CVD. The review did not examine PAD as a risk factor for CAD. Second, the review used a literature search strategy that was probably not comprehensive. A commentary in response to the 2005 USPSTF recommendation on screening for PAD stated that the evidence review did not include three large studies of the prevalence of PAD in primary care.[66] Third, the 2005 review searched from 1994 to update the 1996 recommendation. The 1996 recommendation, however, was not based on systematically reviewed evidence.[61]

Additionally, in 2009, the USPSTF found insufficient evidence to assess the balance of benefits and harms of using nontraditional risk factors, including ABI, to screen asymptomatic men and women with no history of coronary heart disease (CHD) to prevent CHD events.[67] Other nontraditional risk factors included in this recommendation were high-sensitivity C-reactive protein, leukocyte count, fasting blood glucose level, periodontal disease, carotid intima-media thickness, coronary artery calcification score on electron-beam computed tomography, homocysteine level, and lipoprotein(a) level.

Our evidence review, therefore, addresses overall net benefit of screening for PAD in unselected populations or in generally asymptomatic populations.

Chapter 2. Methods

This review is not simply an update of the previous review because it includes broader CVD outcomes than the previous review in support of the 2005 USPSTF recommendation statement. Our current review specifically focuses on: 1) resting ABI test as the only screening modality; 2) the diagnostic performance of ABI testing in primary care populations, unselected populations, and/or asymptomatic populations; 3) the predictive value of ABI testing in primary care or unselected populations for major CVD outcomes; and 4) the treatment of patients with asymptomatic or minimally symptomatic PAD impacting both general CVD morbidity and PAD-specific (lower extremity) morbidity.

Development of Work Plan

We prepared a draft work plan (from August to October 2011) that three external expert reviewers subsequently reviewed in October and November 2011. We presented the revised draft plan to the three USPSTF leads in December 2011. We presented this revised plan to stakeholders in Webinar format and portions of the plan (analytic framework, key questions [KQs], and inclusion criteria) were posted for public comment for 4 weeks in December 2011 and January 2012. We made minor revisions based on feedback garnered during this process and submitted a final version of our work plan in February 2012.

Analytic Framework and KQs

Using the USPSTF's methods,[68] we developed an analytic framework (**Figure 1**) and six KQs to guide our literature search. These KQs include:

KQ 1. Is screening generally asymptomatic adults for PAD using ABI effective in reducing CVD morbidity (e.g., MI, CVA), morbidity from PAD (e.g., amputation, impaired ambulation, impaired function), or mortality (e.g., CVD specific, overall)?

a. Does the effectiveness of screening for PAD vary by subgroup (i.e., age [especially for age 65 years and older], sex, race, risk factors)?

KQ 2. In generally asymptomatic adults, what is the diagnostic accuracy (e.g., sensitivity, specificity, positive and negative predictive value) of ABI as a screening test for PAD?

a. Does the diagnostic accuracy of ABI screening vary by subgroup (i.e., age [especially for age 65 years and older], sex, race, risk factors)?

KQ 3. What are the harms of screening (e.g., diagnostic inaccuracy [overdiagnosis], harms of additional testing)?

a. Do the harms of screening vary by subgroup (i.e., age [especially for age 65 years and

older], sex, race, risk factors)?

KQ 4. Does ABI in generally asymptomatic adults accurately predict CVD morbidity (e.g., MI, CVA) and mortality independent of traditional risk factors?

a. What is the prevalence of a normal and abnormal ABI among low-, intermediate-, and high-risk adults?

b. At what frequency does the use of ABI significantly change the risk of CVD morbidity or mortality based on traditional risk factors alone (e.g., from intermediate risk to low or high risk)?

c. What is the accuracy of risk reclassification of CVD morbidity or mortality (in addition to traditional risk factors)?

KQ 5. Does treatment of asymptomatic or minimally symptomatic adults with PAD lead to improvement in patient outcomes beyond the benefits of treatment in symptomatic adults, or beyond the benefits of treatment of adults with known CVD risk factors (i.e., smoking, hypertension, hyperlipidemia)?

a. Does the effectiveness of treatment vary by subgroup (i.e., age [especially for age 65 years and older], sex, race, risk factors)?

KQ 6. What are the harms of treatment of screen-detected PAD?

a. Do the harms of treatment vary by subgroup (i.e., age [especially for age 65 years and older], sex, race, risk factors)?

Data Sources and Searches

We searched MEDLINE and the Cochrane Central Registry of Controlled Trials from 1996 through September 2012 to locate relevant English-language studies for all KQs (**Appendix A**). We supplemented our searches with suggestions from experts and reference lists from 62 recent relevant existing systematic reviews (**Appendix B**). We also searched ClinicalTrials.gov on September 12, 2012 for relevant ongoing trials (**Appendix C**).

Study Selection

Two investigators independently reviewed 4,434 abstracts and 418 full-text articles (**Appendix D**) against the specified inclusion criteria (**Appendix E**). We resolved discrepancies by consultation with a third investigator. We list the studies we excluded at the full-text phase (i.e., based on exclusion criteria or for poor quality) in **Appendix F**.

Our review focuses on the clinical utility of resting ABI as the primary screening modality

because it is the most commonly used and is able to detect asymptomatic persons. Therefore, our review excluded other methods of screening (e.g., questionnaires, exercise ABI, toe pressure measurement, pulse oximetry, duplex ultrasound, MRA). Our review also focuses on generally asymptomatic adults, which may include populations with atypical symptoms or minor symptoms not recognized as PAD. We excluded studies whose subjects primarily had known intermittent claudication. We also excluded studies conducted exclusively in persons with known CVD, diabetes, or severe chronic kidney disease (stage 4 and 5). We excluded studies conducted in hospital or specialty settings (i.e., vascular clinics or laboratories), as these settings typically represented populations selected for known or highly suspected PAD. Because we focus on largely asymptomatic persons, our primary outcomes of interest are CVD events and risk factor reduction, rather than lower-extremity symptoms. If studies that met our inclusion criteria also reported PAD-specific outcomes (e.g., limb function, ambulation, amputation), however, we considered these outcomes. Likewise, our included treatments focused on pharmacologic or lifestyle interventions primarily aimed at CVD risk reduction (e.g., smoking cessation, cholesterol lowering, blood pressure control, and antiplatelet therapy). Therefore, we excluded interventions aimed primarily at management of lower-extremity symptoms or functioning (e.g., cilostazol, supervised exercise training or physical therapy, revascularization).

For KQ 1, we considered any trial (randomized, controlled trial [RCT] or controlled clinical trial [CCT]) or systematic review that compared ABI screening to no screening reporting any outcome of interest (i.e., CVD or PAD-specific morbidity or mortality). For KQ 2, we considered prospectively conducted diagnostic accuracy studies or well-conducted systematic reviews of diagnostic accuracy. We excluded case-control studies in which cases were selected based on having known PAD. Distorted selection of subjects in recruitment or case-control designs has repeatedly been shown to overestimate sensitivity.[69-73] A distorted selection of subjects directly affects the applicability of the study findings and threatens its validity (i.e., spectrum bias). Spectrum bias refers to the phenomenon that the diagnostic test performance may change between clinical settings due to changes in patient case-mix. For KQ 2, diagnostic accuracy studies had to compare ABI with a reference standard. Because the gold standard, DSA, is an invasive test that presents known risks, it is not ethical to administer this test in asymptomatic persons. Therefore, we considered any diagnostic test that could image the degree of atherosclerosis (e.g., MRA, CTA) or degree of impaired blood flow (e.g., duplex ultrasound) to be a reasonable diagnostic reference standard. We accepted all measures of diagnostic accuracy (e.g., sensitivity, specificity, positive or negative predictive values, positive or negative likelihood ratios). For KQ 4, we considered prospective longitudinal cohort studies or systematic reviews of risk prediction. Included risk prediction studies had to assess ABI in addition to existing FRS factors, as defined in ATP III (i.e., age, sex, smoking status, systolic blood pressure, total cholesterol, and HDL cholesterol).[43] While studies could adjust for additional known risk factors, we excluded studies that did not consider all existing FRS factors as a minimum. For KQ 5, we included any trial (RCT or CCT) or systematic review with at least 12 weeks of followup that compared treatment of PAD with no treatment, with placebo treatment, or with delayed treatment. Again, we considered any outcome of interest (i.e., CVD or PAD-specific morbidity or mortality). While we included reviews, trials, cohort studies, and case-control studies for KQs 3 and 6, we excluded case series or case reports.

Data Extraction and Quality Assessment

For screening studies, we extracted details about each study's location, recruitment, inclusion/exclusion criteria, participant characteristics, reference standard, test performance characteristics, and adverse events. For risk prediction studies, we extracted details about each study's location, recruitment, inclusion/exclusion criteria, participant characteristics, technique for measuring ABI, adequacy and length of followup, method for ascertaining outcomes, inclusion of prognostic factors other than ABI, analytic approach, and outcomes. Outcomes included relative event outcomes (e.g., hazard ratio [HR], relative risk [RR], or OR) or measures of risk reclassification. Measures of discrimination or risk reclassification included differences in the area under the curve (AUC) or c-statistic, percent reclassified (i.e., from a reclassification table), and net reclassification improvement (NRI) (**Table 1**).

Risk reclassification refers to the change in risk when a new predictor is added to an existing risk prediction model (i.e., subjects may be placed into a different risk category than the one they were in when the original model was used). This movement between risk categories may be displayed as a reclassification table. This table shows the number (and percent) of subjects in each risk category using the original model versus the number (and percent) of subjects in each risk category using the model with the new predictor. While studies may report the percent of subjects who change risk categories, this does not ensure subjects were correctly recategorized.[74] Subjects who will have an outcome event should move to a higher risk category, while subjects who will not have an event should move to a lower risk category. For subjects who will have an event, movement to a higher risk category is improved classification, while movement to a lower risk category is worse (incorrect) classification; likewise, for subjects who will not have an event, movement to a lower risk category is improved classification, while movement to a higher risk category is worse classification.[74-76] The NRI quantifies this as (proportion of subjects who will have an event moving higher minus proportion of subjects who will have an event moving lower) + (proportion of subjects who will not have an event moving lower minus proportion of subjects who will not have an event moving higher).[75]Another way to think of the NRI is the sum of the improvement in sensitivity and the improvement in specificity.[75]

In a risk reclassification table, those cells representing no change in risk category between prediction models lie on a diagonal; the other cells represent a change in risk between the original model and the new model. If the original and new prediction models were the same, the numbers in the cells representing change would be symmetric about the cells representing no change. The number of subjects who will have an event moving to a higher risk category would equal the number moving to a lower risk category and the number of subjects who will not have an event moving to a lower risk category would equal the number moving to a higher risk category. If an NRI were calculated for the entire table, it would be zero.[77] However, an NRI might be calculated only for certain risk categories, as defined by the original model. Only those cells lying in certain rows of the risk reclassification table would be used, and some of the symmetric cells from the reclassification table would be excluded. An NRI could be calculated; if it were positive, it would imply improvement, even though the models were identical. Therefore, an NRI for any subset of risk categories will be artificially inflated by this expected NRI simply because some of the symmetrically distributed cells are excluded. A corrected NRI may be calculated by subtracting the expected NRI from the apparent NRI.[77] For risk prediction

studies reporting NRI for subgroups (i.e., intermediate-risk groups), we calculated a corrected NRI for the intermediate risk category where data were available to do so.

The AUC—specifically, the area under the receiver operating characteristic curve—represents a model's ability to discriminate between subjects who will and will not have an event.[78] The AUC is the probability that a model will assign a higher risk for an event to a randomly selected subject who will have an event than to a randomly selected subject who will not have an event.[74, 79,80] The range of the AUC is 0.5 (no discriminatory ability) to 1 (perfect discrimination).[76] For prognostic models, the AUC is typically 0.6 to 0.85.[80] When a new predictor is added to a model, the improvement in the model's ability to discriminate may be measured by the difference between the AUC for the model with the new predictor and the AUC for the original model.[74] An increase in the AUC of 0.025 is considered clinically relevant.[81]

For treatment trials, we extracted details about each study's location, recruitment, inclusion/exclusion criteria, patient characteristics, experimental and comparison intervention(s), internal validity, retention, method for ascertaining outcomes, analytic approach, outcomes, and adverse effects. A second reviewer verified all extracted data. We contacted study authors by email for clarification, when necessary.

At least two reviewers independently critically appraised articles meeting inclusion criteria using the USPSTF's design-specific quality criteria,[82] supplemented with the National Institute for Health and Clinical Excellence (NICE) methodology checklists,[83] Quality Assessment of Diagnostic Accuracy Studies (for studies of diagnostic accuracy [KQ 2]),[84,85] and the Newcastle-Ottawa Scale[86] and Hayden criteria[87] (for prediction studies [KQ 4]). Articles were rated as good, fair, or poor quality. In general, a good-quality study met all criteria well. A fair-quality study did not meet (or it was unclear whether it met) at least one criterion but also had no known important limitation that could invalidate its results. A poor-quality study had a single fatal flaw or multiple important limitations. The most common flaws leading to poor-quality ratings among studies about diagnostic accuracy were having an inappropriate reference standard, a biased spectrum of subjects, or verification bias. The most common flaw leading to poor-quality ratings among studies about prognosis was lack of relevant outcomes. However, the majority of prognostic studies were excluded because they did not include all the ATP III FRS factors in multivariable models and therefore did not meet our inclusion criteria. For treatment trials, we excluded the majority of studies because they were conducted in persons with intermittent claudication. We excluded poor-quality studies from this review.

Synthesis and Analysis

We did not conduct any quantitative analyses for any of the KQs due to the low volume, heterogeneity, and nature of our included studies. We found no studies for KQ 1. For KQs 2 and 3, we included only one study and therefore describe the results of this single study along with our quality and applicability assessment. For KQ 4, we included 14 studies representing eight different cohorts and one large individual patient-level data meta-analysis. The meta-analysis included all but two of the cohorts represented in the 14 other studies. Given the available information, we were unable to attempt further quantitative syntheses. Instead, we qualitatively

synthesized data from this pooled analysis, comparing and contrasting its results with findings from individual studies by outcomes, focusing primarily on measures of risk reclassification and secondarily on measures of association (HR and RR) adjusted for FRS factors (i.e., age, sex, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol).[43] We use summary tables to display differences between important study characteristics and outcomes across included studies. For KQs 5 and 6, we included only two treatment studies that were quite different from one another. Therefore, we summarize the results of these studies in the context of their quality and applicability.

For each KQ, we summarize the overall body of evidence, commenting on several domains, including quality of findings (including risk of bias), applicability of findings, consistency of findings (including possible clinical heterogeneity explaining inconsistencies), magnitude of findings, and precision around the magnitude of findings.[82]

USPSTF Involvement

We worked with three USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and KQs, to address methodological decisions on applicable evidence, and to resolve issues around scope for the final evidence synthesis. The Agency for Healthcare Research and Quality (AHRQ) funded this work under a contract to support the work of the USPSTF. AHRQ staff provided oversight for the project, reviewed the draft report, and assisted in external review of the draft evidence synthesis.

Chapter 3. Results

Our review presents all new evidence that was generated since the 2005 systematic review to support the previous USPSTF recommendation (**Table 2**). The previous review included only three studies, none of which were included in our review; we excluded two studies because they focused primarily on persons with symptomatic PAD[63,64] and one study because it was a cross-sectional study evaluating treatment.[65] We excluded studies from the 1996 review due to general lack of relevance or study design considerations.

KQ 1. Is Screening Generally Asymptomatic Adults for PAD Using ABI Effective in Reducing CVD Morbidity and Mortality?

We found no studies that directly assessed the impact of screening unselected adults (or generally asymptomatic adults) with ABI on CVD or PAD health outcomes.

KQ 2. What Is the Diagnostic Accuracy of ABI as a Screening Test for PAD in Generally Asymptomatic Adults?

We found one fair-quality study (described in two articles) that estimated the test performance of ABI screening for PAD in a generally asymptomatic population that was representative of patients in primary care (**Table 3**).[88] We excluded two poor-quality studies because they used a suboptimal reference standard (central augmentation index) or because this standard was not applied to a reasonable portion of the sample.[89,90] We included one diagnostic accuracy study that involved 306 individuals randomly recruited from a larger population-based cohort study called the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) (n=1,016).[88] Participants in this study were 70-year-old (at the time of study recruitment) men and women (equally distributed) without contraindications for an MRA (e.g., without a cardiac pacemaker, prosthetic valves, intracranial clips, or claustrophobia). Approximately 8 percent of participants were smokers, 7 percent had a history of MI, 4 percent had a history of CVA, 11 percent had diabetes, and 33 percent were on medications for hypertension.

This study used whole-body MRA to detect at least 50 percent stenosis or total occlusion (100% stenosis) in the pelvic or lower extremity arteries as its reference standard for diagnosing PAD. While this was a well-conducted study, the mean interval between ABI and MRA was 16 months (range, 3 to 24 months) and it is unclear whether the ABI and MRA (reference standard) were interpreted independently. While using at least 50 percent stenosis as a definition for PAD is reasonable, it is unclear whether this is the optimal or universally accepted threshold for the diagnosis. Furthermore, ABI testing in this study was conducted after subjects had rested supine for 30 minutes, which may not be applicable in primary care.

About 4 percent of persons in this trial had an ABI of less than 0.9 (used as the cutoff for low

ABI). An ABI of less than 0.9 was 15 (95% CI, 7 to 27) to 20 percent (95% CI, 10 to 34) sensitive for at least 50 percent stenosis but 99 percent (95% CI, 96 to 100) specific. Although an ABI of less than 0.9 had very low sensitivity for detecting at least 50 percent stenosis by MRA, the positive and negative predictive values were reasonable: 82 (95% CI, 48 to 97) to 83 percent (95% CI, 51 to 97) and 80 (95% CI, 70 to 84) to 84 percent (95% CI, 79 to 88), respectively. Given the sample size of only 306 persons, only 4 percent of whom had a low ABI, the CIs around these estimates are quite wide.

We are unable to comment on whether and how the diagnostic accuracy of ABI varies by age, sex, race/ethnicity, or CVD risk factors based on this single study that was conducted in 70-year-old Swedish men and women.

KQ 3. What Are the Harms of Screening With ABI?

We found no studies that directly addressed the harms of screening with ABI. In the only study that estimated the test performance of ABI in a population relevant to primary care screening, one person had a vasovagal episode before contrast for the reference MRA was administered; no other harms were reported.[88]

Since the ABI test is noninvasive, the harms associated with this test should be minimal. While there are potential harms from false-positive test results leading to unnecessary diagnostic testing or overdiagnosis, the diagnostic workup for an abnormal ABI in generally asymptomatic persons is also noninvasive and can be done without radiation (e.g., using duplex ultrasound or MRA). Therefore, the harms of false-positive test results and subsequent diagnostic testing should be low. Another potential harm is from false-negative testing leading to a missed diagnosis, as the sensitivity was quite low. The clinical importance of such missed diagnoses is unclear because these asymptomatic persons would not be detected without screening.

KQ 4. Does ABI Accurately Predict CVD Morbidity and Mortality Independent of Traditional Risk Factors?

Summary of Overall Findings

We included one fair-quality systematic review and 14 fair- to good-quality studies that addressed whether ABI could predict CAD or CVD morbidity and mortality independent of the FRS factors (**Table 4**). We included studies that demonstrated the additional prognostic value of ABI to age, sex, smoking status, systolic blood pressure, total cholesterol, and HDL cholesterol. Most evidence for this KQ comes from one large, individual patient-level meta-analysis from the ABI Collaboration.[46] This meta-analysis (n=48,294) included 16 international population-based cohorts relevant to primary care: Atherosclerosis Risk in Communities (ARIC) Study, Belgian Physical Fitness Study, Cardiovascular Health Study (CHS), Edinburgh Artery Study (EAS), Framingham Offspring Study, Health in Men Study, Honolulu Heart Program, Hoorn Study, InCHIANTI Study, Limburg Peripheral Arterial Occlusive Disease (PAOD) Study, Men Born in 1914 Study, Rotterdam Study, San Diego Study, San Luis Valley Diabetes Study, Strong Heart

Study, and the Women's Health and Aging Study. The other 14 studies included in our review represent eight unique cohorts (ARIC, CHS, EAS, Health ABC, Honolulu Heart Program, Hoorn study, Multi-Ethnic Study of Atherosclerosis [MESA], and Rotterdam Study), only two of which (Health ABC; n=2,191 and MESA; n=1,330) are not represented in the ABI Collaboration. We excluded many of the cohorts that were included in the ABI Collaboration meta-analysis because the individual articles did not include all the FRS factors in their multivariable models. Since the ABI Collaboration had access to patient-level data, however, they were able to include these cohorts in their analyses.

Overall, low ABI (≤0.9) is generally associated with future CAD and CVD events, independent of FRS factors. This result is based on a large number of persons (n=52,510) across 18 different population-based cohorts, representative of a wide age range of adults of both sexes. The clinical relevance of this association (i.e., the degree to which it can reclassify CAD or CVD risk beyond FRS), however, is still uncertain. In general, the body of evidence can be divided into pragmatic studies (i.e., "Does ABI reclassify risk?") and explanatory studies (i.e., "Can ABI reclassify risk?"). The ABI Collaboration meta-analysis provides by far the largest body of evidence. This pragmatic study demonstrates that ABI can reclassify both men and women based on their 10-year risk of total CAD events (CAD death, MI, and angina). This reclassification analysis included 13 population-based cohort studies reporting adequate information.[46] While this analysis showed that 19 percent of men and 36 percent of women could be reclassified based on their ABI, several issues limit the interpretation of their findings. First, the study does not report the NRI, which limits our understanding of what proportion of persons have been appropriately reclassified and limiting the comparison of their findings to other studies included in this review (**Table 1**). Second, the ABI Collaboration reclassification table is based on risk of total CAD events (CAD death, MI, or angina), as opposed to hard CAD events (CAD death or MI only), which was the outcome used in the ATP III FRS algorithm (**Table 5**). Third, the reclassification of most men is based on relatively small absolute changes in risk (e.g., the change in 10-year risk for high-risk men with normal ABI changed from 23% to 18%) (**Table 6a**). Such absolute changes in risk, which currently result in risk reclassification, may not be clinically important if imprecision around these measurement of risk exists or if different definitions of risk categories (e.g., total vs. hard CAD events, CAD vs. CVD events, different treatment thresholds) are applied.

Four other selected cohorts were used in studies creating explanatory models designed to determine whether ABI can accurately reclassify CAD or CVD risk (using the NRI) when added to the FRS model (**Table 7**).[47-49,91] Two of these studies are represented in the ABI Collaboration.[49,91] NRIs ranged from 0.006 (for hard CAD)[49] to 0.079 (for hard CAD).[47] The Health ABC and the Rotterdam cohorts reported NRIs for all persons and those at intermediate FRS risk and demonstrated that the NRI was higher in the intermediate-risk group. In another fair-quality cohort study, the NRI for intermediate-risk persons (MESA; n=1,330) was smaller (0.036 for CAD outcomes and 0.068 for CVD outcomes). This cohort, however, was younger than the Health ABC and Rotterdam cohorts and used a different threshold for defining intermediate risk (>5% to <20%, rather than 10% to <20%).[48] In all of these studies, however, the calculation of the NRI for the intermediate-risk group is inflated. Given limitations in reported data, we could only calculate a corrected NRI for the Health ABC and ARIC cohorts. The corrected NRI for the Health ABC cohort was similar to the overall NRI (0.038 [95% CI,

-0.029 to 0.105] vs. 0.033 [95% CI, 0.0004 to 0.065], respectively). There was no statistically significant net reclassification of risk for future CVD events in a large cohort of persons younger than age 65 years (ARIC; n=11,594).[91] Direct comparisons across studies' findings are difficult due to differences in their methods, definitions of composite CAD and CVD outcomes, and definitions of risk categories. While differences prevent us from determining the consistency of findings across different studies, results suggest that the overall NRI is relatively small, although it may be higher among older persons (Health ABC; n=2,191).[47]

Detailed Findings for Risk Prediction of CAD

CAD Risk Reclassification of ABI, in Addition to FRS

The current ATP III algorithm focuses on 10-year hard CAD risk (as defined by CAD death or MI). Risk categories for hard CAD events (CAD death or MI) are defined as: low, which represents less than 10 percent 10-year CAD risk; intermediate, representing 10 to 20 percent risk; and high, representing greater than 20 percent risk. Previous FRS, however, used total CAD events (CAD death, MI, or angina). Generally the estimates for hard CAD are about two thirds to three fourths of those for total CAD. Therefore, the risk categories for total CAD events are defined as: low, representing less than 15 percent 10-year CAD risk; intermediate, representing 15 to 25 percent risk; and high, which represents greater than 25 percent risk (**Table 5**).[42]

The vast majority of evidence comes from the ABI Collaboration review, an individual patient-level meta-analysis of population-based cohorts in which participants had no history of CAD and baseline ABI and followup data on CAD outcomes (including MI, CAD, and overall death) were available. This meta-analysis included 16 population-based cohorts (n=48,294) from the United States, Western Europe, and Australia (**Table 8**). Most cohorts included 1,000 to 5,000 persons, although the largest study (ARIC) included over 14,000 persons. The mean age within the cohorts ranged from 47 to 78 years. Eleven cohorts included both men and women, four included only men (Belgian Physical Fitness Study, Health in Men Study, Honolulu Heart Program, and Men Born in 1914 Study), and one included only women (Women's Health and Aging Study). Most cohorts were predominantly white, with the exception of ARIC (about 25% black), the Honolulu Heart Study (100% Japanese American), San Luis Valley Diabetes Study (about 40% Latino), and the Strong Heart Study (100% Native American). The median duration of followup ranged from 3.0 to 16.7 years, with nine of the 16 studies having more than 10 years of followup data.

This study reports the reclassification from FRS categories when ABI was added for both men and women from the 13 (of the 16) cohorts that had relevant outcomes available. In these cohorts, 5.5 percent in the low-risk category, 6.2 percent in the intermediate-risk category, and 13.7 percent in the high-risk category had a low ABI (≤0.9) (**Table 9**). High ABI (>1.40) was much less common, with an overall rate of 2.7 percent (1,181/43,919). In most cohorts, women had a lower average ABI and a higher percent of low ABI in each FRS category.

Using an ABI of 1.11 to 1.40 as normal (as opposed to the traditional 0.91 to 1.40), 19 percent of men and 36 percent of women were reclassified when ABI was added to the FRS (**Table 6a**). The ABI Collaboration investigators used this referent group (ABI of 1.11 to 1.40) because they

found an inverse J-shaped relationship between ABI and mortality and CVD mortality, in which all ABI groups (<0.90, 0.91 to 1.10, and >1.40) had an elevated mortality risk compared with the lowest-risk group (1.11 to 1.40). For men, the greatest percent of reclassification was among those who were initially classified as high risk (23% over 10 years) with a normal ABI (1.11 to 1.40) and were subsequently reclassified as being at intermediate risk (18% over 10 years) (**Table 6a**). Women who were initially at low or intermediate risk (11% or 13% over 10 years, respectively) who had a low ABI (≤0.9) were subsequently reclassified as being at high risk (21% and 25% over 10 years, respectively) (**Table 6a**). If the normal range of ABI was defined as 0.91 to 1.40 (the more traditional definition), the proportion reclassified would appear larger for men (35%) and smaller for women (7.3%) (**Table 6b**). In this scenario, the greatest percent of reclassification remains the same; that is, among men at high risk with normal ABI and among women at low to intermediate risk with low ABI.

These results should be interpreted with caution, however, regardless of the range of ABI used as the referent category. First, the reclassification table only illustrates the movement of individuals across categories of risk, but does not comment on the appropriateness of the reclassification. This analysis was conducted before 2008 and, therefore, did not use more recent measures of risk reclassification, such as the NRI. Without the NRI or the ability to calculate the NRI based on the data presented, the true clinical meaning of this movement is not clear and it is difficult to compare the results with the other studies we included. Second, the ABI Collaboration reclassification table examines the risk of total CAD events (CAD death, MI, and angina); however, the risk categories they use are based on hard CAD events (CAD death and MI only). If the investigators applied a modified categorization of risk (**Table 5**), most change in risk would not result in actual risk reclassification. Third, changes in risk that do result in risk reclassification may represent small absolute changes of risk (for example, a change from 23% 10-year risk using FRS alone to 18% 10-year risk among men with a normal ABI). Therefore, the clinical significance (risk reclassification) is highly dependent on accepted definitions of risk strata as well as the precision around these estimates of 10-year risk. The true clinical impact of these changes is unclear without CIs around these changes in percentages of risk. The precision around these risk estimates depends on how many individuals contributed to the 10-year followup, the number of individuals in each risk category (for example, there were only 175 men at high risk by FRS with an ABI of >1.40), and the variability in event rates. While most cohorts had at least 10 years of followup data, authors presented no sensitivity analysis comparing cohorts with at least 10 years of followup data with cohorts with shorter followup data. Length of study followup (i.e., if <10 years) may be important if the risk for CAD events over the 10 years were not constant. From the results of the ABI Collaboration, we know that a normal or abnormal ABI can reclassify risk, but the clinical impact is still uncertain given these limitations. Finally, the risk reclassification is based on ATP III, which will be updated in early 2013.[92] If the practice paradigm should shift to treatment at lower risk, the ABI may not add any value to FRS. Nonetheless, the data from the ABI Collaboration remain the largest body of evidence to date on the added value of ABI to the current approach for CAD risk prediction.

Three explanatory studies suggest that ABI can help reclassify individuals' 10-year CAD risk when added to the FRS (**Table 10**).[47-49] One additional study, an analysis of EAS, reports the difference in AUC for fatal MI only (**Table 10**).[50] Given this noncomparable outcome and that EAS is included in the ABI Collaboration, this study is not discussed in any detail. The first

U.S.-based cohort, Health ABC, was one of two cohorts not included in the ABI Collaboration.[47] In this good-quality study (n=2,191), participants were older (mean age, 73.5 years [range, 70 to 79 years]) and likely sicker, as evidenced by the fact that a high proportion of individuals had outcomes (**Table 4** and **Table 10**). Participants were followed for a median of 8.2 years. In this cohort, CAD risk was based on either hard CAD events (MI or death from MI) or total CAD events (hard events plus hospitalization due to angina or coronary revascularization). For total CAD events, the NRI of adding ABI to FRS and diabetes was 0.033 (95% CI, 0.0004 to 0.065); among the intermediate-risk group, the NRI was 0.07 (95% CI, 0.029 to 0.112) (**Table 10**). Our calculated corrected NRI for the intermediate-risk group was 0.038 (95% CI, -0.029 to 0.105), however, which is similar to the overall NRI. For hard CAD events, the NRI was higher than for total events (**Table 10**). In the Health ABC cohort, 8.8 percent of participants were reclassified when the ABI was added to the FRS. This study appears to have used the same risk categories for both the total and hard CAD analyses.

The second U.S.-based cohort, MESA, was the other cohort not included in the ABI Collaboration.[48] This fair-quality analysis focused on a subsample (n=1,330 of 6,814) of MESA participants who were at intermediate risk for incident CAD based on the FRS. The authors defined incident CAD as MI, death from CAD, resuscitated cardiac arrest, or angina (definite or probable followed by revascularization). The authors defined intermediate risk as estimated 10-year CAD risk of greater than 5 to less than 20 percent, as opposed to the traditional 10 to 19 percent risk for hard CAD or 15 to 25 percent risk for total CAD. Participants were younger (mean age, 63.8 years) than those in Health ABC (mean age, 73.5 years) (**Table 4**). Only 33 percent of participants were women and 36 percent were white. Participants were followed for a median of 7.6 years. As a result, CAD risk was redefined based on 7.5-year risk (e.g., intermediate risk of 2.0% to 15.4%). For incident CAD, the NRI was 0.036 among intermediate-risk participants. This is slightly lower than the NRI seen in Health ABC, although within its 95 percent CI. We were unable to calculate a corrected NRI for the MESA cohort, since the full reclassification table was not presented.

The third cohort, the Rotterdam study from the Netherlands, was included in the ABI Collaboration.[49] This good-quality study (n=5,933) included slightly younger (mean age, 69 years) and apparently healthier participants, with a lower rate of CAD events than the Health ABC cohort (**Table 4** and **Table 10**). Approximately 60 percent of participants were women, and presumably most were white Dutch. Participants had a median of 6.8 years followup. CAD risk was based on hard CAD events (CAD death or MI). This study used an ABI of 0.91 to 1.40 as the referent group. The NRI for all participants was not statistically significant (0.006 [95% CI, -0.018 to 0.029]) when ABI was added to the FRS. The NRI was higher for participants at intermediate risk (0.073 [95% CI, 0.029 to 0.117]) (**Table 10**). Again, we were unable to calculate a corrected NRI for the intermediate-risk group due to limited data published. While men had greater changes than women, neither sex had statistically significant changes.

In general, these three cohorts showed a small or nonsignificant NRI for the ABI in addition to the FRS alone. One of these cohorts was included in the ABI Collaboration. These explanatory models refit a regression model with all of the FRS factors (and other risk factors) to determine whether ABI can improve upon the existing prognostic model. In the case of oversimplified regressions (which assume that factors have simple linear relations and no interactions), the

incremental prognostic value estimated may be higher than in actual practice. We had difficulty making comparisons between studies because of differences in populations (e.g., age, sex, race/ethnicity), choice of referent group (i.e., definition of normal ABI), definitions of composite CAD outcomes (i.e., hard vs. incident vs. total CAD) and risk categories (e.g., intermediate risk of 10% to 19%, 15% to 25%, or 5% to 20%), and measures of reclassification (i.e., number reclassified vs. NRI).

Risk Association of CAD and ABI, Independent of FRS

In addition to, and sometimes as a precursor to, demonstrating risk reclassification, the included studies also report the association of ABI and future CAD events after adjusting for (at least) the FRS factors (**Table 10**). The ABI Collaboration showed a significant increase for major CAD events for an ABI of 0.90 or less (compared with an ABI of 1.11 to 1.40) after adjusting for FRS factors (HR, 2.16 [95% CI, 1.76 to 2.66] for men and HR, 2.49 [95% CI, 1.84 to 3.36] for women). Adjusted results were not given for an ABI of >1.40. Unadjusted HRs for a high ABI, however, were not statistically significant for major CAD events. After adjusting for FRS factors, the Health ABC, MESA, and Rotterdam cohorts all suggest an independent association of low ABI with CAD events. These results are not consistently reported for high ABI values. Among the Health ABC cohort, the adjusted HR was 1.57 (95% CI, 1.14 to 2.18) for an ABI of 0.9 or less and 2.89 (95% CI, 1.47 to 5.58) for an ABI greater than 1.40 (compared with an ABI of 1.01 to 1.30).[47] In another report from the Health ABC cohort, the adjusted RR was 1.41 (95% CI, 1.11 to 1.81) for an ABI of 0.9 or less and 1.50 (95% CI, 1.01 to 2.23) for an ABI greater than 1.40 (compared with an ABI of 0.91 to 1.30).[93] In the MESA cohort, the adjusted HR for ABI was 0.79 (95% CI, 0.66 to 0.95) per one standard deviation change in ABI.[48] While there was a trend of an association of ABI with CAD events in the Rotterdam cohort, the adjusted HR was not statistically significant (1.3 [95% CI, 1.0 to 1.7]) for an ABI of 0.9 or less (compared with an ABI of 0.91 to 1.40).[49] While the Rotterdam cohort included subjects with history of CVA, the MESA and Health ABC cohorts did not. Neither of these reports from the MESA or Rotterdam cohorts report HR for an ABI of greater than 1.30 or 1.40.

Three other included studies reported the independent HR or RR for CAD outcomes by ABI, after adjusting for FRS factors. These studies, however, did not present risk reclassification data.[50,94,95] The largest cohort study, ARIC (n=13,588), was conducted in the United States.[94] This good-quality study included participants ages 45 to 64 years (mean age, 54 years), about half of whom were women and a quarter of whom were black (**Table 4**). This study showed that ABI was consistently associated with future CAD events, after adjusting for FRS factors. HRs ranged from 1.11 to 1.25 for each 0.10 decrease in ABI measurement (**Table 10**). One cohort, EAS (n=1,507), included patients in Scotland ages 55 to 74 years (mean age, 65 years). Approximately half of participants were women, and presumably most patients were white British. This fair-quality study showed no statistically significant difference in relative risk at 12-years followup for fatal or nonfatal MI among participants with an ABI of 0.9 or less versus participants with an ABI of greater than 0.9 (RR, 1.10 [95% CI, 0.78 to 1.54]).[50] Unlike other analyses, this analysis used RR at 12 years, rather than HR over time. The RR does not account for differences in earlier events, so there may be no significant differences in event rates by year 12 even, though HRs might be statistically significantly different. Finally, the Honolulu Heart Study (n=2,863) was conducted among older men (ages 71 to 93 years) of Japanese descent.[95]

This study had much shorter followup (3 to 6 years) than other cohorts and found that an ABI of less than 0.8 was independently associated with CAD compared with an ABI of 1.0 or more, after adjusting for FRS factors (RR, 2.7 [95% CI, 1.6 to 4.5]).

While these studies included differences in populations and choice of ABI categories and referent groups, they collectively show that a low ABI (≤0.9) is generally independently associated with future CAD risk after adjusting for FRS factors across large age groups, among men and women, and in blacks, whites, and Asians.

Detailed Findings for Risk Prediction of Overall CVD Risk

CVD Risk Reclassification of ABI, in Addition to FRS

While the current ATP III algorithm focuses on 10-year CAD risk, the field is moving toward global CVD risk prediction. This risk prediction generally includes morbidity and mortality from cerebrovascular disease and PAD (in some cases). Three of our included studies reported CVD risk reclassification (NRI) or discrimination (AUC) with ABI using an explanatory model.[48,91,96] The largest single cohort, ARIC (n=11,594), included participants ages 45 to 64 years (mean age, 54 years), nearly half of whom were men and about a quarter were black (**Table 4**). This good-quality study, conducted in the United States, showed no statistically significant reclassification based on NRI and AUC for hard CVD events (CVD death, MI, or CVA) (**Table 11**).[91] The EAS (n=1,507), conducted in Scotland, included patients ages 55 to 74 years (mean age, 65 years) (**Table 4**).[96] In this cohort, the AUC for MI or CVA was statistically significantly higher (p=0.02) for FRS plus ABI (AUC, 0.64 [95% CI, 0.59 to 0.69]) compared with FRS alone (AUC, 0.61 [95% CI, 0.56 to 0.67]) (**Table 11**). The third study, conducted in the United States, presented risk reclassification among a subsample of intermediate-risk participants from the MESA cohort (n=1,330).[48] This subsample included participants with a mean age of 63.8 years, about one third of whom were women and one third were white (**Table 4**). Incident CVD in this study included incident CAD (see description in above section) and CVA or CVD death. This fair-quality study showed an NRI of 0.068 for incident CVD with ABI in addition to FRS among intermediate-risk participants, and a higher AUC (0.650 [95% CI not reported]) versus the FRS alone (0.623 [95% CI not reported]) (**Table 11**). We were unable to calculate a bias-corrected NRI for these intermediate-risk persons due to limitations in the reported data.

Generally, there are fewer data available about whether ABI can reclassify CVD than CAD risk. This result is not surprising, however, as the FRS was developed to predict CAD risk. Limited data suggest that ABI can reclassify CVD risk in addition to FRS, but not necessarily in adults younger than age 65 years. Comparisons across studies, however, are complicated by differences in populations, definitions of CVD composite outcomes, and definitions of risk categories.

Risk Association of CVD and ABI, Independent of FRS

The majority of studies do not address risk reclassification of CVD events. Instead, these studies focus on the independent risk association of ABI and future CVD events adjusting for (at least) the FRS factors (**Table 11**).[46] The ABI Collaboration showed a significant increase between total CVD mortality (from CAD or CVA) and an ABI of 0.90 or less relative to an ABI of 1.11 to

1.40 after adjusting for FRS factors (HR, 2.92 [95% CI, 2.31 to 3.70] for men and HR, 2.97 [95% CI, 2.02 to 4.35] for women) (**Table 11**).[46] While adjusted HRs are not given for an ABI of greater than 1.40, unadjusted HRs for a high ABI are not statistically significant for CVD mortality. Seven other included studies from six cohorts report the independent association of ABI and total CVD outcomes after accounting for FRS factors.[38,48,50,91,93,96,97] Only two of these studies represent cohorts not included in the ABI Collaboration meta-analysis.[48,93] The largest single cohort, ARIC (n=11,594), included participants ages 45 to 64 years (mean age, 54 years), nearly half of whom were men and about a quarter were black (**Table 4**). This good-quality study, conducted in the United States, showed a significant association per standard deviation in ABI, after adjustment for FRS (HR, 0.849 [95% CI, 0.79 to 0.91]) for hard CVD events (CVD death, MI, or CVA) (**Table 11**).[91] The CHS cohort (n=5,748) is an older population (age 65 years or older [mean age, 73 years]) from the United States (**Table 4**).[38] In this cohort, with about 10 years followup, HRs for a low ABI (≤0.9) were consistently and statistically significantly greater than those of the referent group (1.11 to 1.20) for combined CVD events (MI, CVA, angina, coronary or lower-extremity revascularization, or amputation) and CVD mortality, after adjusting for FRS factors (**Table 11**). HRs were not statistically significant for a high ABI (>1.30 or 1.40) for combined CVD events or CVD mortality. The EAS (n=1,507), conducted in Scotland, included patients ages 55 to 74 years (mean age, 65 years) (**Table 4**). With 12 years followup, this fair-quality study showed no statistically significant difference in relative risk for an ABI of 0.9 or less (vs. >0.9) and any CVD event (CVD death, MI, CVA) or CVD mortality (**Table 11**).[50] In another report from EAS, the OR for an ABI of 0.9 or less (compared with an ABI of >0.9) for MI or CVA was 1.70 (95% CI, 1.07 to2.70) at 12 years followup, after adjusting for FRS factors.[96] The Health ABC cohort (n=2,886), not represented in the ABI Collaboration meta-analysis, was a cohort of older adults in the United States (mean age, 74 years) (**Table 4**).[93] Over a mean followup of 6.7 years, low ABI (≤0.9) was associated with CVD death (RR, 2.18 [95% CI, 1.57 to 3.02]) compared with an ABI of 0.91 to 1.31, after adjusting for FRS factors (**Table 11**). The Hoorn study (n=624) was a fair-quality cohort study conducted in the Netherlands in adults ages 50 to 75 years that had similar findings. Over a median of 17.2 years of followup, this study found that a low ABI (<0.9) was associated with a nonsignificant trend for future CVD death in those without diabetes mellitus (n=469; RR, 1.95 [95% CI, 0.88 to4.33]).[97] The final study, also not included in the ABI Collaboration meta-analysis, used a subsample from the MESA cohort (n=1,330), representing a diverse group of participants at intermediate risk of CAD events.[48] This study also demonstrated a statistically significant association for ABI with incident CVD (HR per standard deviation change in ABI, 0.81 [95% CI, 0.68 to 0.95]).

These explanatory studies examining the risk association of ABI and future CVD events vary widely in the populations studied, length of followup, definition of CVD composite outcomes, and choice of ABI referent groups. Collectively, however, these studies show that a low ABI is generally independently associated with future CVD events and/or CVD mortality across large range of participants, after adjusting for numerous predictors, including the FRS factors.

Detailed Findings for Risk Prediction of CVA Alone

Risk Association of CVA and ABI, Independent of FRS

Four studies report on cerebrovascular outcomes separately from composite CVD outcomes

(**Table 12**).[50,93,98,99] The largest cohort, ARIC (n=14,306), included participants ages 45 to 64 years, nearly half of whom were men and about a quarter were black (**Table 4**). This good-quality study, conducted in the United States, found no statistically significant association between ischemic CVA and low ABI after adjusting for FRS factors (**Table 12**).[98] Overall, however, the proportion of patients who had a CVA was low (1.4% [206/14,306]). One cohort from Scotland, EAS (n=1,507), included slightly older patients (ages 55 to 74 years) (**Table 4**). This study also found a statistically nonsignificant association of low ABI and CVA after adjusting for FRS factors, even though the proportion having a CVA was much higher (8.5% [128/1,507]).[50] Two smaller U.S.-based cohorts (Health ABC[93] [n=2,886] and the Honolulu Heart Study[99] [n=2,767]) were conducted in older adults (age 70 years or older) who had higher prevalence of hypertension (about 50%) and diabetes (14.6% and 27%). These two studies found statistically significant associations between low ABI and CVA after adjusting for FRS factors (**Table 4** and **Table 12**), but not high ABI (>1.30).[93,99]

While there are some differences between how studies were conducted (e.g., length of followup), the ABI category used as the referent group, and the definition of CVA (hemorrhagic vs. ischemic), the differences in population characteristics likely explain differences in findings.

Differences in Risk Prediction by Age, Sex, and Race/Ethnicity

The prevalence of low ABI increases with age.[12] While differences in how studies were conducted and other population characteristics prevent us from arriving at definitive conclusions, the independent value of ABI (after adjusting for FRS) appears to be less robust for predicting future CAD, CVA, and total CVD outcome events among persons ages 45 to 64 years than among older persons, based on a single large cohort (ARIC).[91,94,98]

The distribution and prevalence of low ABI also appears to differ between men and women. Although this relationship is not consistent across cohorts, it appears that women have a lower mean ABI than men (**Table 8**). Few included studies provide direct comparison of risk reclassification or risks of ABI for CAD events between men and women. In the ABI Collaboration, women with low or intermediate risk of CAD events based on FRS factors had higher prevalence of low ABI than men with low or intermediate risk (**Table 9**), with greater risk reclassification for women than men.[46] In the Rotterdam cohort (n=5,933), however, reclassification was higher for men than women, although the sex-specific NRIs were not statistically significant.[49] In both the ARIC and Rotterdam cohorts, men had slightly higher adjusted HRs for low ABI and future CAD events than women.[49,94]

There is little direct evidence addressing these differences by race/ethnicity. The largest cohort, ARIC, was conducted in the United States and included about 25 percent blacks. This cohort had slightly higher adjusted HRs for low ABI and future CAD events than whites.[94] The MESA cohort included a diverse sample of participants, but did not report ethnic-specific results for reclassification.[48] The Honolulu Heart Study was conducted entirely in older (older than age 70 years) men of Japanese ancestry.[95,99] In this cohort, low ABI was consistently associated with future CAD and CVA events after adjusting for traditional FRS factors. The Strong Heart Study (included in the ABI Collaboration analyses) was a cohort of Native American men and women, with a mean age of 56 years. The unadjusted HR for total mortality with ABI (compared with an

ABI of 1.11 to 1.40) was not statistically significant for men or women.

KQ 5. Does the Treatment of Generally Asymptomatic Persons With PAD Lead to Improved Patient Outcomes Beyond the Benefit of Treatment in Symptomatic Adults or Adults With Known CVD Risk Factors?

We found only two trials that examined the benefit of treatment in asymptomatic persons with low ABI or PAD (**Table 13**). We included trials in which the majority of patients either had no symptoms or no typical symptoms (i.e., no intermittent claudication). We excluded seven trials for quality and 77 studies because the majority of patients had intermittent claudication. No trials examined the benefit of earlier (asymptomatic) versus later (symptomatic) treatment of PAD. Included trials examined very different interventions and, as such, we discuss these trials separately.

The Aspirin for Asymptomatic Atherosclerosis (AAA) trial was a large, good-quality RCT (n=3,350) designed to determine whether persons in the general population with low ABI detected by screening would benefit from aspirin therapy (100 mg/day) (**Table 13**).[100] This trial was conducted in Scotland and included adults ages 50 to 75 years without known CVD who had a screening ABI of 0.95 or less. Of 28,980 persons screened, only 1.7 percent (4,914) had an ABI of 0.95 or less. This population's mean ABI was 0.86. Among these patients, the mean age was 62 years, 71.5 percent of participants were women, mean systolic blood pressure was about 148 mm Hg, mean total cholesterol was about 239 mg/dL, and about a third were current smokers. After a mean followup of 8.2 years, there was no significant difference in CVD events (MI, CVA, or revascularization) between those who received aspirin versus placebo (HR, 1.03 [95% CI, 0.84 to 1.27]) (**Table 14**) and no difference in CVD events for the subgroup with an ABI of 0.9 or less (HR, 1.02 [95% CI, 0.80 to 1.29]). There were no significant differences in secondary outcomes (CVD events plus angina, intermittent claudication, or transient ischemic attack) or all-cause mortality. At 5 years, there was only about 15 percent crossover (e.g., persons taking aspirin outside of the trial by prescription or self-prescription). Authors also reported results per protocol, which showed no differences in outcomes between those actually taking aspirin versus those not taking aspirin. Although this was a well-conducted trial, it was powered to identify a 25 percent reduction in the primary outcome. As such, they might not have been able to identify smaller benefits. Additionally, the population was a relatively well community-derived sample that may not be fully representative of a clinic-based population.

The second trial is a small, fair-quality RCT (n=355) designed to determine whether an intensive telephone counseling intervention could improve lipid control in patients with PAD and high LDL cholesterol levels (**Table 13**).[101] This trial was conducted at two academic centers in the United States and used mixed recruitment methods to identify adult participants with known PAD and an LDL level of greater than 70 mg/dL. The majority of patients had no or atypical symptoms (20.3% and 54.5%, respectively), and the minority of patients had intermittent claudication (15.2%).[102] The mean ABI in this sample of patients was only 0.68 and the mean LDL level was 103 mg/dL. The mean age was 70.5 years, 40.6 percent were women, the mean

total cholesterol level was 183 mg/dL, about two thirds were taking cholesterol-lowering drugs, and about one fourth were current smokers. In this trial, persons in the intervention group received eight telephone calls every 6 weeks (total of 200 minutes) focusing on the importance of lowering LDL cholesterol, adherence to medication, communicating with their treating physician about needing more intensive therapy, and increasing walking activity; in addition, study staff sent a letter to the treating physician after each call. This trial compared the intervention group with two different control groups—an attention control with telephone calls on general PAD information and a usual care control (no calls). At 12 months, persons in the intervention group had a greater change in LDL cholesterol (-18.4 mg/dL) compared with the attention control (-6.8 mg/dL; p=0.010), but not with the usual care group (-11.1 mg/dL; p=0.208) (**Table 14**). A greater proportion of persons in the intervention group achieved LDL levels of less than 100 mg/dL (21.6%) compared with the attention control (9.0%; p=0.003) and the usual care group (9.1%; p=0.018).

KQ 6. What Are the Harms of Treatment in Generally Asymptomatic Persons With PAD?

We found only one trial that directly examined the harms of treatment in asymptomatic persons with PAD. This trial was the good-quality AAA (n=3,350), which examined the effectiveness of low-dose aspirin in screen-detected persons with low ABI.[100] In this trial (described in KQ 5), persons randomized to aspirin had a nonsignificant trend for increased major bleeding (requiring hospital admission) over a mean of 8.2 years followup compared with persons randomized to placebo (HR, 1.71 [95% CI, 0.99 to 2.97]) (**Table 14**).

Chapter 4. Discussion

Summary of Review Findings

Our review presents new evidence published since the USPSTF's 2005 recommendation on screening for PAD and 2009 recommendation on ABI as a nontraditional risk factor in CAD risk assessment. The majority of evidence we found (18 population-based cohorts) addresses the additional value of ABI to FRS factors in CAD and CVD risk prediction, which was not considered as part of the 2005 and 2009 recommendations. We found very limited evidence to inform the diagnostic accuracy of ABI to detect PAD in primary care (one diagnostic accuracy study) or to treat persons with screen-detected low ABI or largely asymptomatic persons with PAD (two treatment trials) (**Table 15**).

ABI for CAD or CVD Risk Prediction

Data from multiple population cohort studies (18 cohorts) show that low ABI (≤0.9) is generally associated with future CAD and CVD events, independent of FRS factors. Overall, we found no clear and consistent association of high ABI (>1.30 or 1.40) and future CAD or CVD events. However, the clinical relevance of the association of low ABI (≤0.9) and the impact on risk reclassification for CAD and CVD events is still uncertain (**Table 15**). Currently, classifying risk of CAD or CVD into low, intermediate, and high categories is clinically important to communicate risk and guide therapies to reduce CVD risk (e.g., statins). We recognize that CVD risk prediction is a rapidly evolving field. Nonetheless, our review focuses on the current state of evidence most applicable to current practice in the United States. Our included evidence for this KQ addresses two related, yet distinct, clinical questions: 1) should clinicians consider ABI measurement in asymptomatic persons to help clarify CAD or CVD risk, in addition to using the FRS? and 2) should ABI be added to existing risk assessment tools, such as the FRS, to help clarify the risk of CAD or CVD?

The ABI Collaboration's individual patient-level meta-analysis, by far the largest body of evidence, was a pragmatic study that addressed the first question and considered whether clinicians should consider ABI measurement after calculating the FRS to help clarify CAD risk.[46] Across 13 population-based cohorts (n=43,919), the ABI Collaboration analyses demonstrate that 19 percent of men and 36 percent of women could be reclassified based on their ABI results when added to the FRS. We cannot determine whether the direction of reclassification is correct, however, because the study does not report NRI, which distinguishes reclassification separately according to whether patients suffered an event. Second, the ABI Collaboration reclassification analysis is based on the 10-year risk of total CAD (CAD death, MI, and angina), as opposed to hard CAD events (CAD death and MI only) that were used in the ATP III FRS algorithm. This difference in composite outcomes may be clinically important because the absolute change in risk (e.g., the change in the 10-year risk for high-risk men with normal ABI changed from 23% to 18%) that currently results in risk reclassification may not be clinically important if the measurements of risk are imprecise (i.e., CIs cross thresholds of risk categories) or if definitions based on total versus hard CAD events are applied.

Four included studies are explanatory models designed to answer the second question regarding whether ABI should be added to the FRS to help improve CAD or CVD risk prediction.[47-49,91] In general, these studies (n=22,055) suggest that: 1) the risk reclassification is small for CAD and CVD events, 2) the NRI may be larger for older persons for total or hard CAD events (Health ABC; n=2,191),[47] and 3) the NRI is not significant for persons younger than age 65 years for total CVD events (ARIC; n=11,594).[91] Due to limitations in the regression models, the apparent incremental prognostic value of ABI in these studies may be higher than if the Framingham investigators were to develop a new risk score that included ABI and all of the ATP III factors.

Unfortunately, making meaningful comparisons across studies is very difficult due to differences in populations, (e.g., age, sex, race/ethnicity), differences in choice of referent group (i.e., definition of normal ABI), differences in the definitions of composite CAD and CVD outcomes (e.g., hard vs. total CAD) and risk categories (e.g., intermediate risk of 10% to 19%, 15% to 25%, or 5% to 20%), and differences in measures of reclassification (i.e., percent reclassified, NRI, difference in AUC). These differences, however, reflect the real-world practice of CVD risk prediction. Despite difficulties in establishing consistency of findings due to differences in methods, we can posit that: 1) the magnitude for appropriate risk reclassification across all risk categories is likely small (at best); 2) because changes in magnitude of risk are likely small, ABI may be most useful for patients who are near the thresholds for different risk categories or near boundaries that affect clinical decisionmaking;[92] and 3) the value of ABI for risk reclassification may be less or nonexistent for adults younger than age 65 years. Based on these conclusions, screening ABI (i.e., not in symptomatic persons) should be conducted in targeted populations, as opposed to unselected adults (as with universal screening). For a more detailed discussion of targeted screening, see a later section.

Our review focused only on the additional value of ABI to the FRS, as defined by ATP III. Therefore, we excluded publications from eight cohorts that did not adjust for all the FRS factors: the Belgian Physical Fitness,[103] Framingham,[104] getABI,[105,106] Limburg PAOD,[107] Men Born in 1914,[108] NHANES,[10] Casas Artery,[109] and SHEP[110] studies. Four of these eight cohorts were included in the ABI Collaboration meta-analysis, as the ABI Collaboration investigators had access to patient-level data and were able to conduct de novo analyses. The findings from the four cohort studies not included in the ABI Collaboration were consistent with the findings from studies included in our review (i.e., consistent risk association of low ABI and future CAD or CVD morbidity and/or mortality, as well as all-cause mortality). The getABI cohort was a large (n=6,880) well-conducted prospective study of unselected persons age 65 years or older. This cohort was not included in the ABI Collaboration.[105] This study included a subgroup comparison of CAD and CVD risk in symptomatic persons (n=593) versus asymptomatic persons (n=836) with an ABI of less than 0.9. In this cohort, having a low ABI was associated with an elevated risk for CVD events and mortality. There was no significant difference between risk of CVD events and mortality in symptomatic persons with a low ABI.

Our review found four new studies that addressed risk reclassification published since 2006, the final search year for the previous review conducted for the USPSTF on screening for intermediate risk factors for CAD.[47-49,91] While this previous review found only three cohort studies that suggested that ABI was predictive of some CVD events, the overall strength of evidence was poor.[111] We found no other reviews that addressed the reclassification of CAD or

CVD risk using ABI, other than the ABI Collaboration meta-analysis included in our review. The ACCF/AHA 2010 "Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults" recommended ABI as a reasonable tool for cardiovascular risk assessment among persons at intermediate risk (Class IIa, Level B),[57] primarily citing the ABI Collaboration meta-analysis.[46] In our summary of this meta-analysis, however, the greatest reclassification was among high-risk men with normal ABI and low- or intermediate-risk women with low ABI. Therefore, ABI is helpful for intermediate-risk women but not necessarily intermediate-risk men, based solely on the ABI Collaboration findings.

Our review focuses on the additional risk discrimination of ABI to the FRS, as defined by ATP III. This risk classification algorithm will be updated in early 2013.[92] This new algorithm will likely focus on the risk for global CVD events, rather than CAD-specific risk. If the updated algorithm and recommendations change the definition of risk categories (i.e., intermediate risk) or shift the practice paradigm to lower thresholds of treatment (e.g., statins or lower LDL goals for lower-risk individuals), the value of ABI will most certainly change, and possibly render this algorithm less clinically important.

ABI to Detect PAD in Primary Care

Based on one small, fair-quality study (n=306) in older Swedish adults, it appears that the sensitivity of ABI (≤0.9) is low (15% to 20%) but the specificity near 100 percent. The positive and negative predictive values for ABI were adequate (i.e., >80%) (**Table 15**).[88] Other diagnostic studies of ABI were mainly conducted in persons referred for vascular testing or with symptoms. The 2012 NICE guidelines on lower limb PAD explicitly do not address screening for asymptomatic PAD; however, they do recommend using ABI as part of the diagnostic evaluation in persons with suspected PAD (e.g., having intermittent claudication, leg ulcers, common foot problems, or cardiovascular risk factors).[112] These guidelines included five studies of diagnostic accuracy in persons with suspected PAD, using an imaging reference standard. The guidelines found that sensitivity and specificity for an ABI of less than 0.9 ranged from 71 to 89 percent and 42 to 93 percent, respectively. The five studies used different diagnostic reference standards in different populations, with different ABI protocols (e.g., manual Doppler or oscillometric blood pressure). Another recent review of eight diagnostic accuracy studies also found that the sensitivity and specificity of ABI ranged from 61 to 95 percent and 56 to 90 percent, respectively.[113] Both of these reviews focus on the test performance of ABI conducted in symptomatic patients or specialized populations (e.g., inpatients). As a result, the estimates of test performance may not apply to screening in primarily asymptomatic persons or unselected populations.

While we found no evidence that explicitly evaluates the harms of ABI testing, we do not hypothesize any major harms, given that the test itself and subsequent diagnostic testing in persons without symptoms are noninvasive. Draft NICE guidelines also found no specific evidence for harms and state that ABI is a noninvasive test with no recognized harms with correct equipment use.[112] Lack of appropriate training in how to conduct ABI testing, however, may result in misdiagnosis.

Treatment of Persons With Screen-Detected Low ABI or Asymptomatic PAD

There is very sparse evidence addressing asymptomatic or minimally symptomatic (e.g., with atypical symptoms or mild intermittent claudication) persons with low ABI or PAD. Based on one large, good-quality trial (n=3,350), low-dose aspirin does not prevent CVD events in adults ages 50 to 75 years without known CVD who have a low ABI (≤0.9). In fact, low-dose aspirin may increase major bleeding events. One smaller trial showed that an intensive telephone counseling intervention aimed at adults with primarily asymptomatic PAD can decrease LDL levels and achieve treatment goal levels (<100 mg/dL) compared with an attention control.

The vast majority of treatment research is conducted in symptomatic persons with PAD. Expert-based guidelines by the ACCF/AHA and the Trans-Atlantic Inter-Society Consensus (TASC) II are generally in agreement on their recommendations on the management of PAD, other than a few key differences in the grading of, and language used for, these recommendations.[3,8] Both of these groups agree on aggressive medical management of PAD and aggressive management of the diseases (i.e., diabetes) or CVD risk factors (i.e., smoking, increased lipids, hypertension) contributing to PAD. These treatment guidelines, however, largely focus on treatment of symptomatic PAD, citing literature in persons with symptomatic disease. Therefore, we did not include this evidence in our review. In 2012, NICE issued evidence-based treatment guidance that focuses exclusively on exercise therapy, naftidrofuryl oxalate, and revascularization in persons with intermittent claudication or critical limb ischemia and pain management in critical limb ischemia.[112] In October 2012, a draft report of a comprehensive review of "Treatment Strategies for Patients With PAD" was posted for public comment through AHRQ's Effective Health Care program.[114] This report focused on treatment of persons with intermittent claudication or critical limb ischemia. This report also assessed the effectiveness of antiplatelet therapy for asymptomatic persons with PAD and found the same evidence and came to the same conclusion as our review.

ABI in Clinical Practice

The ABI measurement followed rigorous protocols in the diagnostic and prognostic studies included in our review. As with any intervention or testing, the real-world performance of ABI may be less than ideal. The implementation of ABI as a screening practice in primary care represents challenges around opportunity costs of screening, as well as reproducibility. The ABI may take up to 15 minutes to measure and likely cannot be conducted as part of the primary care visit.[3] In the diagnostic study, ABI testing required a minimum of 30 minutes of rest before the ABI was measured.[88] In the prognostic population-based cohort studies, the resting time before ABI was measured varied. Although the ABI is considered to have good reproducibility,[3] measuring it correctly requires training. Without proper training, results can vary substantially, which can impact its test performance. Ideally, ankle pressure is measured over two sites on each leg—one of which is the posterior tibial artery, the other being the dorsalis pedis artery or the anterior tibial artery. The value used for the ankle measurement could be the higher, the lower, or the mean of the two arterial pressures. Similarly, arm pressure is ideally measured over the right and left arms; the value used could be the mean or the higher of the right and left pressures.[25,35,36,115] While ABIs are calculated separately for each leg, a single ABI—usually, the lower of the

two leg values—might be used to reflect a patient's general health.[115,116] The technique chosen can affect the prevalence of a low ABI (≤0.9),[25,35,36,115] as well as the association of a low ABI with CVD risk factors,[25,35,115] prevalent CVD,[36,115] and subclinical atherosclerosis.[35]

The handheld Doppler ultrasound should be used to measure systolic pressure. Other methods, such as an oscillometric (automated) device,[34,117] a stethoscope,[118] or palpation[119] should not be substituted, as these methods have lower test performance when compared with the handheld Doppler ultrasound. Both the recent AHA scientific statement on the measurement of ABI and the NICE guidelines explicitly recommend that the ABI be conducted manually with a Doppler probe in preference to an automated system.[112,116]

Protocols for conducting ABI measurement vary across guidelines, research, and practice. Both the ACCF and AHA, for example, recommend using the *higher* of the systolic pressures from the ipsilateral dorsalis pedis and posterior tibial arteries, divided by the *higher* of the systolic pressures from the right and left brachial arteries.[3,116] NHANES, on the other hand, used the *mean* of the systolic pressures from the ipsilateral dorsalis pedis and posterior tibial arteries, divided by the *mean* of the systolic pressures from the right and left brachial arteries.[25] Most protocols for ABI measurement in our included studies used a manual device, an average of pressures, and measurement from the posterior tibial artery. There was variation, however, in the number of times the blood pressure was measured (e.g., PIVUS took the average of three brachial measurements, while EAS took a single posterior tibial measurement), the choice of measurement used (e.g., MESA used the higher of dorsalis pedis or posterior tibial pressures), the location of ankle measurement (e.g., MESA measured dorsalis pedis and posterior tibial pressures), and the choice of manual versus automated devices (e.g., ARIC used an oscillometric blood pressure device).

Currently in the United States, ABI alone does not have a billing code for reimbursement.[120] As such, reimbursement requires additional testing (i.e., Doppler waveform recording and analysis, volume plethysmography, or transcutaneous oxygen tension measurements), so implementation of ABI in clinical practice would require specialized equipment.

Targeted Screening

As mentioned earlier, certain subgroups may derive a higher benefit from screening than a general population, suggesting that targeted (as opposed to universal) screening may be appropriate. Taken together, the best available evidence on screening with ABI in primary care, the best prevalence estimates of abnormal ABI in general or primary care populations, and the known epidemiology of risk factors for PAD can inform which subgroups may benefit from ABI measurement, either to detect asymptomatic PAD or to predict risk for CAD or CVD events. We found that several key factors, including age, sex, smoking, and composite FRS, may inform targeted screening. Current guidelines by the ACCF/AHA recommend screening in persons age 50 years or older with a history of smoking or diabetes. The primary rationale for screening persons with diabetes has been the higher prevalence of PAD and more commonly asymptomatic disease in persons with diabetes. Our review purposely excluded the use of ABI in persons with known CVD and/or diabetes, however, as these persons should be receiving maximal CVD risk reduction interventions. Therefore, we do not address the value of ABI testing in these

populations.

First, evidence for screening ABI in our review is more consistent and robust for older adults age 65 years and older. The sole diagnostic accuracy study was conducted in adults age 70 years and older.[88] The results from the ARIC cohort study (ages 45 to 64 years) examining risk prediction (KQ 4) showed nonsignificant risk reclassification for future CVD events and no significant association with future cerebrovascular events.[91,98] Prevalence data from population-based studies support this finding, as the prevalence of low ABI is low in adults younger than age 60 years, as is test positivity or yield.[12]

Second, sex and different underlying cardiovascular risks may influence the relative magnitude of benefit. Included evidence suggests that persons at the thresholds of FRS risk categories have greater potential of being reclassified based on ABI results. The ABI Collaboration meta-analysis, with the most robust sex-specific analyses, suggests that women at low or intermediate FRS risk with a low ABI (≤0.9) have the greatest change (increase) in risk.[46] Because men have a higher FRS than women, the prevalence of low ABI is higher in low- to intermediate-risk women compared with men at low to intermediate risk (**Table 6a**), all other factors being equal. Targeting clinic populations with higher underlying prevalence of low ABI based on epidemiology may be reasonable. Based on multiple studies in general or primary care populations, current smoking is the strongest predictor for low ABI for both men and women, and across all ages.[19,26-30]

Finally, limited data from cohorts that include nonwhite populations suggest that this evidence should also apply to these populations. Available data, however, are most applicable to blacks and whites, as other races and ethnicities are grossly underrepresented. Contextual data show that while the FRS is well calibrated across a wide range of white and black populations, it may overestimate risk in other populations, such as patients of Asian, Native American, or Latino/Hispanic descent.[45]

Limitations

Our review has several important limitations. First, our review focuses on the use of ABI as a screening tool, rather than a diagnostic tool. As a result, we included studies that focused primarily on unselected or asymptomatic persons. The overwhelming majority of screening and treatment studies focused on selected populations (e.g., referred to a vascular laboratory or clinic) or persons with PAD symptoms. Few studies made a distinction between atypical symptoms and intermittent claudication. Our review explicitly excluded studies in which a large proportion of subjects had intermittent claudication. While we did allow for studies that included subjects with atypical symptoms, few studies described symptoms with such detail. In addition, our review excluded studies of populations with known existing CVD, diabetes, or severe chronic kidney disease. The current literature on screening or treating generally asymptomatic patients is very limited. Only one diagnostic study with a suitable reference standard has been conducted in an unselected population, and this population was small, older, and ethnically homogenous (conducted in Sweden). Experts have argued that diagnostic studies in symptomatic persons should be applicable to asymptomatic persons because 1) the resting ABI is done while

patients are asymptomatic (even if they experience intermittent claudication with activity), and 2) the reduced muscular metabolism (which causes symptoms) has no impact on arterial perfusion pressure. Empiric diagnostic accuracy studies have shown, however, that a distorted selection not also affects applicability but also the validity of these types of studies due to spectrum bias.[69-73] Spectrum bias refers to the phenomenon that the diagnostic test performance may change between clinical settings due to changes in patient case-mix. Therefore, this review focused on studies less prone to spectrum bias. For context in our discussion, we acknowledge other systematic reviews that have been conducted on the diagnostic accuracy of ABI in selected populations, as the existing evidence in asymptomatic persons is very limited.

Only two treatment trials focused on generally asymptomatic persons, and these trials were quite different from one another (aspirin and telephone counseling). Additionally, there is no evidence on other interventions to reduce CVD risk or on interventions that might delay the onset of lower-extremity symptoms in asymptomatic persons. Again, experts have argued that treatment in symptomatic persons should be applicable to asymptomatic persons because the rates of CVD events and mortality are similar in symptomatic versus asymptomatic persons with low ABI, as demonstrated in the getABI cohort. We acknowledge that interventions (i.e., antiplatelet therapy, statins, angiotensin-converting enzyme inhibitors) that are effective in CVD risk reduction in symptomatic persons with PAD may be applicable to persons without symptoms. Based on direct evidence in asymptomatic persons with low ABI, however, it is unlikely that low-dose aspirin benefits screen-detected persons with low ABI and no known CVD or diabetes.[100] Unfortunately, the effectiveness of treatments in persons with symptomatic PAD is not within the scope of this review. It is also important to acknowledge that many persons with symptomatic (or asymptomatic) PAD included in major CVD treatment trials (e.g., Heart Outcomes Prevention Evaluation trial, Heart Protection Study, Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events trial, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance trial) had comorbid CAD and/or diabetes.[121-126]

Our review focuses on the additional risk discrimination ABI adds to the FRS (as defined by ATP III). While ABI is the most commonly used risk prediction tool in the United States, it is not the only tool, and the current version is set to be updated with the release of ATP IV in early 2013.[92] It is likely that the new algorithm will focus on the risk for global CVD events, rather than CAD-specific risk. If the updated algorithm and recommendations change the definition of risk categories (e.g., intermediate risk) or shift the practice paradigm to lower thresholds of treatment (e.g., statins or lower LDL cholesterol goals for lower-risk individuals), however, the prognostic value of ABI will most certainly change and could possibly become less clinically important. There are also many other accepted risk tools, including the Framingham global CVD score,[51] QRISK,[52,53] and the Reynolds risk score,[54,55] that may perform better than the FRS to predict CVD events. None of the excluded studies, however, evaluated the ability of ABI to improve upon the risk prediction of these other risk tools. One included study (MESA; n=1,330) found no substantial reclassification for ABI in intermediate-risk persons when added to the Reynolds risk score to predict CAD (NRI, 0.002) or CVD (NRI, 0.008).[48] Another risk prediction study that was not included in our review evaluated reclassification of other risk markers in addition to the Coronary Risk in the Elderly (CORE) model.[127] This study demonstrated small (or negligible) NRIs for ABI alone in addition to the CORE model in the CHS and Rotterdam cohorts (0.033 [CHS] and 0.003 [Rotterdam] in men; 0.001[CHS] and 0.036

[Rotterdam] in women).[127] Although there are many population-based cohort studies examining the additional value of ABI in risk prediction, race/ethnic groups other than whites and blacks are not well represented.

It is also important to note that the NRI itself has important limitations. While the NRI's strength is the ability to interpret the "appropriateness" of risk reclassification, the measure itself is agnostic. In other words, movements across categories are weighed equally, so that persons move from low to high CAD or CVD risk in the same manner as persons move from high to intermediate risk. For clinical management, it is arguably more important if a person is reclassified from low to high risk, as this would change therapies and therapeutic goals, versus reclassification of someone from high to intermediate risk, as clinicians and patients may be less likely to change or withdraw therapies.[75] Therefore, the NRI should not be interpreted in isolation. As with any body of evidence, the results from well-conducted studies (i.e., in which ABI was measured under protocols) may be overly optimistic compared with results when ABI is used in clinical practice. ABI measurement techniques vary across studies and in clinical practice. Differences in techniques may affect its reproducibility and performance in detecting PAD, as well as predicting CAD and/or CVD events.

Emerging Issues and Future Research

The existing limitations in the current body of literature can help inform the areas of priority for future research.

First, researchers and clinicians in this field need clarity of language about describing PAD and should not automatically describe low ABI as equivalent to having PAD. It is clear from the risk prediction literature that having a low ABI is not equivalent to having a CAD risk equivalent or CVD.

Second, because risk prediction for CAD and CVD is an evolving science, with updates to ATP III expected in early 2013,[92] ongoing studies or re-analyses of existing population-based cohorts will be crucial to our understanding of the value of screening ABI to reclassify CAD and CVD risk beyond FRS and other risk prediction models.

Third, additional analyses for risk prediction will help us understand the relative value of ABI in important subgroups (e.g., those with higher prevalence of low ABI, those in whom traditional risk prediction does not perform well, or those near thresholds of risk categories), where ABI may help in the discrimination and calibration of existing models. This information will inform the utility or need for targeted screening. The ABI Collaboration represents the largest and most clinically important source of data with enough power to conduct these subgroup analyses. NRI for important subgroups (e.g., by age, sex, race/ethnicity) from the ABI Collaboration data would better clarify the clinical value of ABI in CVD risk prediction.

Fourth, more information about the value of high ABI (>1.30 or 1.40) in CVD risk prediction is needed to help us understand whether high values should be interpreted as predicting a normal risk, lower risk, increased risk, or differential risk depending on the patient's sex.

Fifth, more studies using valid reference standards are needed to describe the test performance characteristics of ABI for detecting PAD in unselected or asymptomatic individuals.

Sixth, more trials evaluating CVD risk factor modification (i.e., antiplatelet therapy, pharmacologic or nonpharmacologic therapies for lipid reduction, blood pressure control, smoking cessation, and weight management) are needed to determine whether treating asymptomatic or minimally symptomatic persons with low ABI reduces cardiovascular outcomes, prevents lower-extremity symptoms, or improves quality of life compared with treating persons with symptomatic PAD. Likewise, more trials are needed evaluating whether aggressive CVD risk factor modification in persons with low ABI detected by screening, without known CVD or diabetes, is beneficial compared with treatment based on known risk factors alone.

In our communication with Dr. Gerald Fowkes of the ABI Collaboration (October/November 2010), we understand that a re-analysis of the ABI Collaboration data is underway, which will address many of the limitations of the current meta-analysis, as outlined in the results of our report, including the calculation of the NRI. We believe that this re-analysis will provide crucial information in the understanding of the additional value of ABI to FRS in CVD risk prediction.

Our search of Clinicaltrials.gov identified five additional studies in progress that may address some of these outstanding issues (**Appendix C**). The most promising is a large population-based screening trial in Viborg, Denmark with planned enrollment of 40,000.[128] This study, the Viborg Vascular screening trial, is randomizing men (ages 65 to 74 years) to screening versus no screening for PAD and abdominal aortic aneurysm. Individuals with abnormal results will be treated for CVD risk factors. This study's outcomes will include CVD morbidity and mortality after 10 years. This trial started in September 2008 and is scheduled to have primary outcome data in late 2018.

Response to Public Comments

A draft version of this evidence report was posted for public comment on the USPSTF Web site from March 19 to April 15, 2013. We received comments from six unique individuals or organizations. All comments were reviewed and considered. There were no new substantive issues brought up during the public comment period that were not previously raised and adjudicated during the expert review phase. The major concern raised was our review's exclusions of studies conducted primarily in symptomatic individuals (i.e., persons with intermittent claudication). These studies are considered outside the USPSTF's scope and therefore no changes were incorporated into the final report. Please refer to the Limitations section for details.

Conclusions

One study showed that ABI in primary care has low sensitivity to detect PAD in older adults but adequate positive and negative predictive values. We found no evidence that suggested treatment

of low ABI detected by screening or treatment of generally asymptomatic PAD leads to fewer CVD outcomes. One trial showed that low-dose aspirin for persons with low ABI detected by screening does not prevent CVD outcomes. The potential utility of screening ABI in primary care is not only its ability to detect underlying PAD but its ability to aid in CVD risk prediction. Based on a large body of evidence (14 primary studies and one meta-analysis reflecting a total of 18 cohorts), ABI likely improves risk reclassification beyond FRS, but the magnitude of improvement is unclear and likely to be small. The net reclassification may be greatest for persons age 65 years and older and persons at the thresholds of FRS risk categories. There is limited evidence on how ABI might add to risk prediction tools other than the FRS, and it is unclear how the current evidence will apply to evolving recommendations. While there are unlikely to be important harms from screening ABI in primary care, there are issues with implementing ABI for routine screening due to the time needed to conduct the test, variation in ABI protocols, and equipment needed for reimbursement of testing in the current environment.

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Figure 1. Analytic Framework

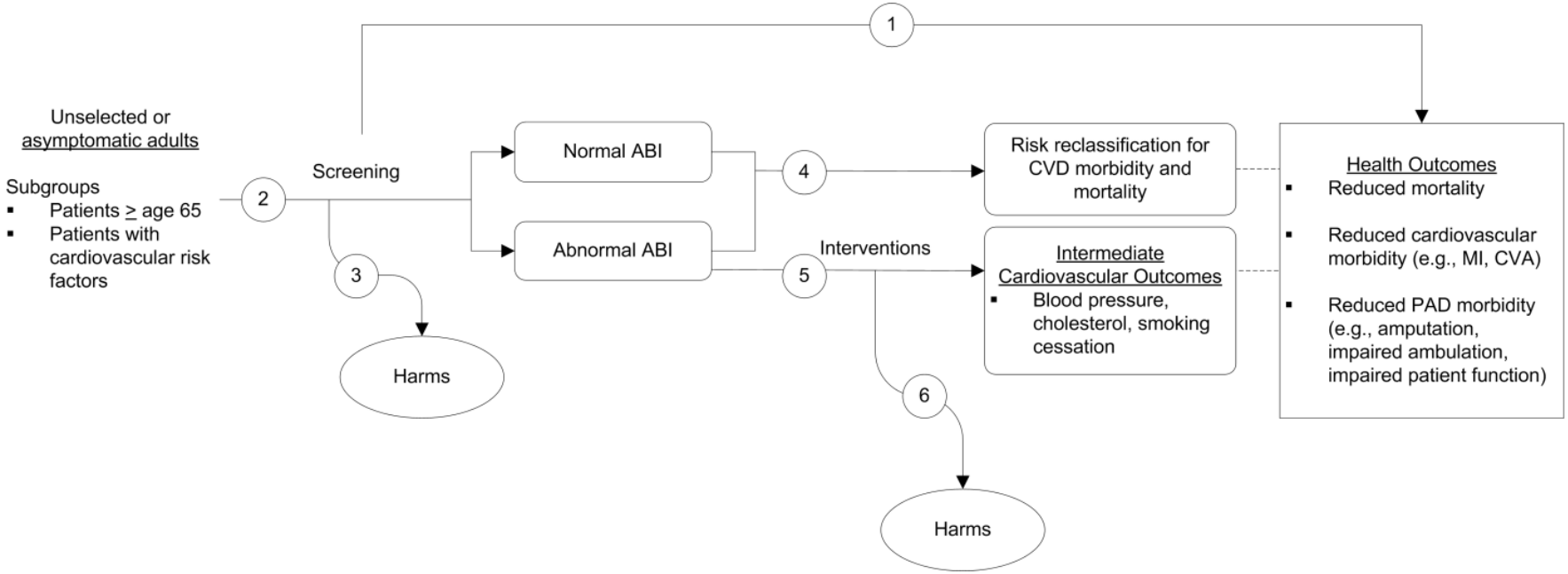

Table 1. Types of Outcome Measures for Comparing Prediction Models in This Report[74,75,78]

Purpose	Measures	Description
Risk association	Hazard ratio (HR) Risk ratio (RR) Odds ratio (OR)	Independent association of ABI and outcome of interest (CAD or CVD events), after adjusting for FRS
Discrimination	Change in area under the curve (AUC) or C-statistic (for binary outcomes)	The change in the probability that a model with FRS + ABI will assign a higher risk for a subject who will have an event than to a subject who will not have an event, compared with a model with FRS alone
Risk reclassification Useful only when there are accepted risk categories	Percent reclassified from a reclassification table	Table showing distribution of subjects classified using FRS model compared with classification based on a model with FRS + ABI **Does not account for correctness of reclassification
	Net reclassification index (NRI) or improvement	The sum of differences in proportions of individuals moving up minus those moving down with a CVD outcome, plus the proportion moving down minus those moving up without an outcome

Abbreviations: ABI = ankle-brachial index; CAD = coronary artery disease; CVD = cardiovascular disease.

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

Key Question	Study	USPSTF Reviews		
		1996[129]	2005[62]	Current
KQ 1 Morbidity	Fowler 2002[63]		X	
KQ 2 Test Performance	Wikstrom 2009[129]			X
	Wikstrom 2008[88]			X
	Vogt 1993[130]	X		
	Moneta 1987[131]	X		
	Strandness 1987[132]	X		
	Criqui 1985[133]	X		
	Barnes 1979[134]	X		
KQ 3 Harms	None			
KQ 4 Prediction	Hoorn 2012[97]			X
	Kavousi 2012[49]			X
	Murphy 2012[91]			X
	Yeboah 2012[48]			X
	Rodondi 2010[47]			X
	Fowkes 2008[46]			X
	Sutton-Tyrrell 2008[93]			X
	Price 2007[96]			X
	Weatherley 2007[94]			X
	O'Hare 2006[38]			X
	Lee 2004[50]			X
	Van der Meer 2004[135]			X
	Abbott 2001[99]			X
	Abbott 2000[95]			X
	Tsai 2001[98]			X
	Vogt 1993[131]	X		
KQ 5 Treatment	McDermott 2011[101]			X
	Fowkes 2010[100]			X
	McDermott 2003[65]		X	
	Tornwall 1997[64]		X	
KQ 6	Fowkes 2010[100]			X

Table 3. Study Characteristics and Results for KQ 2: In Generally Asymptomatic Adults, What Is the Diagnostic Accuracy of ABI as a Screening Test for PAD?

Cohort, Study, Year	Country, N Analyzed	ABI Cutoff	Mean Age	% Women	% White	% Risk Factor	% ABI <0.9	% Stenosis	% Sensitivity/Specificity (95% CI)	% PPV/NPV (95% CI)
PIVUS Wikstrom, 2008[88] Wikstrom, 2009[129]	Sweden 306	<0.9	70 years	47.4	100*	Current smoker: 7.8 Hx MI: 6.9 Hx CVA: 3.9 Hx DM: 10.6 HTN meds: 33	*Right leg* 12/268=4.5% *Left leg* 11/265=4.2%	≥50% stenosis *Right leg* 51/268=19.0% *Left leg* 61/265=23.0% 100% stenosis *Right leg* 34/268=12.7% *Left leg* 37/265=14.0%	*Right leg* Sensitivity: 20 (10 to 34) Specificity: 99 (96 to 100) *Left leg* Sensitivity: 15 (7 to 27) Specificity: 99 (96 to 100) *Right leg* Sensitivity: 24 (11 to 42) Specificity: 98 (95 to 99) *Left leg* Sensitivity: 16 (7 to 33) Specificity: 98 (95 to 99)	*Right leg* PPV: 83 (51 to 97) NPV: 84 (79 to 88) *Left leg* PPV: 82 (48 to 97) NPV: 80 (74 to 84) *Right leg* PPV: 67 (35 to 89) NPV: 90 (85 to 93) *Left leg* PPV: 55 (25 to 82) NPV: 88 (83 to 91)

* Assumed.

Abbreviations: ABI = ankle-brachial index; CI = confidence interval; CVA = cerebrovascular accident; DM = diabetes mellitus; HTN = antihypertension; Hx = history; MI = myocardial infarction; NPV = negative predictive value; PIVUS = Prospective Investigation of the Vasculature in Uppsala Seniors; PPV = positive predictive value.

Table 4. Study Characteristics for KQ 4: Does ABI in Generally Asymptomatic Adults Accurately Predict CVD Morbidity and Mortality Independent of FRS?

Cohort Study, Year Quality	Country N Analyzed	Reference Group	Followup, year*	Mean Age, year	% Women	% White	% Risk Factor	% ABI <0.9	MI (# events)	CVA (# events)	Death (# events)	Other outcomes (# events)
ABI Collaboration Fowkes 2008[46] Fair plus	Australia, Belgium, Italy, the Netherlands, Scotland, Sweden, US 48,294	ABI = 1.11–1.40	10	61.7	48.3	NR	*HTN:* NR *Tobacco use:* NR *DM*: NR	7.7	Composite (3884)	NR	*CVD (CAD or CVA):* alone (2718) and composite (3884) *All-cause:* alone (9924)	None
ARIC Tsai 2001[98] Good	US 14,306	ABI >1.20	7.2 (med)	NR range, 45–64	55.4	73.8	*HTN meds:* 24.4 *Tobacco use (current)*: 25.7 *DM*: 9.4	2.9	NR	Composite (206) Hemorrhagic CVA not included	*CVA:* composite (206)	None
ARIC Weatherley 2007[94] Good	US 13,588	ABI ≥0.90	13.1 (med)	54.0	56.8	73.8	*HTN: 33.2 Tobacco use (former)*: 31.5 *(current)*: 25.8 *DM*: 8.7	2.8	Composite (964)	NR	*CAD:* Composite (964)	None
ARIC Murphy 2012[91] Good	US 11,594	ABI = 1 SD	14 (med)	53.8	56.4	75.8	*HTN:* 33.4 *Tobacco use (current)*: 25.7 *DM*: excluded	2.3	Composite (659)	Composite (659)	*CVD (CAD or CVA):* composite (659) *All-cause:* alone (682)	None
CHS O'Hare 2006[38] Fair plus	US 5,748	ABI = 1.11–1.20	11.1	73	57	85	*HTN meds:* 47.1 *Tobacco use (current)*: 10.1 *DM*: 7.4	13.8	Composite (1491)	Composite (1491)	*CVD (CAD or CVA):* composite (953) *All-cause:* alone (2311)	*Angina, CABG, LE amputation or revascularization:* composite (1491)
Edinburgh Lee 2004[50] Fair plus	Scotland 1,507	ABI >0.9	12	64.7	47.7	NR	*SBP (mean):* 145 *Tobacco use (current)*: 25.7 *DM:* 9.4	16.3	Alone (fatal or nonfatal) (235)	Alone (fatal or nonfatal) (128)	*CAD:* alone (101) *CVA:* alone (49) *CVD (CAD or CVA):* composite (202) *All-cause:* alone (494)	None
Edinburgh Price 2007[96] Fair plus	Scotland 1,007	ABI >0.9	12	69.4	48.3	NR	*SBP (mean):* 146 *Tobacco use (pack-years):* 2.48 *DM:* 3.9	18.7	Composite (137)	Composite (137)	*CVD (CAD or CVA):* composite (137)	*Angina or IC* PPV/NPV only*
Health ABC Rodondi 2010[47] Good	US 2,191	ABI = 1.01–1.30	8.2 (med)	73.5	55.3	58.9	*HTN:* 46.1 *Tobacco use (former):* 43.6 *(current)*: 10.1 *DM:* 13.3	NR	Composite (hard event= 197) Composite (total event= 351)	NR	*CAD:* composite (hard event=197) *CAD:* composite (total event=351) *All-cause:* NR	*Angina hospitalization or revascularization:* composite (total event=351)

Table 4. Study Characteristics for KQ 4: Does ABI in Generally Asymptomatic Adults Accurately Predict CVD Morbidity and Mortality Independent of FRS?

Cohort Study, Year Quality	Country N Analyzed	Reference Group	Followup, year*	Mean Age, year	% Women	% White	% Risk Factor	% ABI <0.9	MI (# events)	CVA (# events)	Death (# events)	Other outcomes (# events)
Health ABC Sutton-Tyrrell 2008[93] Good	US 2,886	ABI = 0.91–1.30	6.7	73.6	51.7	59.4	*HTN:* 49.9 *Tobacco use (former):* 45.3 *(current):* 10.1 *DM:* 14.6	13.3	Composite (487)	Composite (174)	*CAD:* composite (487) *CVA:* composite (174) *CVD (CAD or CVA):* alone (219) *All-cause:* alone (616)	*Angina hospitalization:* composite (487) *CHF hospitalization:* alone (296)
Honolulu Abbott 2000[95] Fair plus	US 2,863	ABI ≥1.0	NR range, 3–6	NR range, 71–93	0	0	*HTN:* NR *Tobacco use:* NR *DM:* NR	NR <0.8: 6.3	Composite (186)	NR	*CAD:* composite (186)	None
Honolulu Abbott 2001[96] Fair	US 2,767	ABI ≥0.9	NR range, 3–6	NR range, 71–93	0	0	*HTN:* 52.4 *Tobacco use (former):* 52.2 *(current):* 7.3 *DM:* 27.0	11.6	NR	Composite (91)	*CVA:* composite (91)	None
Hoorn Hanssen2012[97] Fair	The Netherlands 634	ABI ≥0.9	17.2† range, 0.5–19.2†	64.3† range, 50–75†	51.9†	NR	*HTN:* 39.1† *Tobacco use (ever):* 62.5† *DM:* 24.8†	10.4†	NR	NR	*CVD:* alone (85) *All-cause:* alone (289)	None
MESA Yeboah 2012[48] Fair	US 1,330	ABI = 1 SD	7.6 (med)	63.8	33.3	35.7	*HTN meds:* 38.2 *Tobacco use (current):* 16.5 *(former):* 37.1 *(never):* 46.3 *DM:* 0	NR 1.14, med	Composite (94)	Composite (123)	*CAD:* composite (94) *CVD:* composite (123)	None
Rotterdam van der Meer 2004[135] Fair plus	The Netherlands 6,389	ABI ≥1.21	9 (est)	69.3	61.9	NR	*HTN meds:* 29.4 *Tobacco use (current):* 21.5 *DM:* 10.1	NR <0.97: 25	Composite (258)	NR	*CAD:* composite (258)	None
Rotterdam Kavousi 2012[49] Good	The Netherlands 5,933	ABI= 0.91–1.40	6.8 (med)	69.1	59.4	NR	*HTN meds:* 23.5 *Tobacco use (current):* 17.5 *DM:* 12.9	≤0.9, 14	Composite (347)	NR	*CAD:* composite (347)	None

*Mean (years).
†For cohort including patients with diabetes; values for patients without diabetes not reported separately.

Abbreviations: ABC = Aging and Body Composition; ABI = ankle-brachial index; ARIC = Atherosclerosis Risk in Communities; CABG = coronary artery bypass graph; CAD = coronary artery disease; CHF = congestive heart failure; CHS = Cardiovascular Health Study; CVA = cerebrovascular accident; CVD = cardiovascular disease; DM = diabetes mellitus; est = estimated; HTN = hypertension; IC = intermittent claudication; LE = lower extremity; med = median; meds =medications; MESA = Multi-Ethnic Study of Atherosclerosis; MI = myocardial infarction; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; SBP = systolic blood pressure; SD = standard deviation.

Table 5. Comparison of 10-Year Risks for Hard CAD Events Versus Total CAD Events by FRS Category[42]

Risk category	Hard CAD events (CAD death or MI)	Total CAD events (CAD death, MI, or angina)
Low	<10%	<15%
Intermediate	10%–20%	15%–25%
High	>20%	>25%

Abbreviations: CAD = coronary artery disease; MI = myocardial infarction.

Table 6a. Risk Reclassification (by Sex) of ABI in Addition to FRS in the ABI Collaboration Cohorts[46]

Group	FRS Category	Total		ABI ≤ 0.90		ABI 0.91 to 1.10		ABI 1.11 to 1.40		ABI > 1.40	
		N (%)	Total CAD risk (%)	N (%)	Total CAD risk (%)	N (%)	Total CAD risk (%)	N (%)	Total CAD risk (%)	N (%)	Total CAD risk (%)
Men	Low (<10%)	5643 (26.3)	5	76 (0.4)	8	1076 (5.0)	5	4255 (19.9)	4	236 (1.1)	5
	Intermediate (10%-19%)	7392 (34.5)	13	245 (1.1)	16	2069 (9.7)	12	4815 (22.5)	12	263 (1.2)	8*
	High (≥ 20%)	8398 (39.2)	23	1149 (5.4)	40	3406 (15.9)	21	3668 (17.1)	18*	175 (0.8)	14*
Women	Low (<10%)	15505 (69.0)	11	1083 (4.8)	21*	6192 (27.5)	10*	7909 (35.2)	9	321 (1.4)	11*
	Intermediate (10%-19%)	5563 (24.7)	13	558 (2.5)	25*	2429 (10.8)	12	2433 (10.8)	11	143 (0.6)	13
	High (≥ 20%)	1418 (6.3)	27	200 (0.9)	44	598 (2.7)	21	577 (2.6)	22	43 (0.2)	34

Table 6b. Risk reclassification (by sex) of ABI in addition to Framingham Risk Score (FRS) when collapsing ABI scores 0.91 to 1.40

Group	FRS Category	Collapsing ABI scores: 0.91 to 1.40	
		N (%)	Total CAD risk (%)
Men	Low (<10%)	5331 (24.9)	4
	Intermediate (10%-19%)	6884 (32.1)	12
	High (≥ 20%)	7074 (33.0)*	19*
Women	Low (<10%)	14101 (62.7)	9
	Intermediate (10%-19%)	4862 (21.6)	11
	High (≥ 20%)	1175 (5.2)	21

*Risk category changed from that predicted by the FRS when ABI included

Table 7. Summary of NRI Results for KQ 4: Does ABI in Generally Asymptomatic Adults Accurately Predict CAD Morbidity and Mortality Independent of FRS?

Cohort Study, Year	N Followup (years)	Mean age, years % Women	% Risk factor	Intermediate risk definition	NRI (95% CI) or CAD outcomes	NRI (95% CI) for CVD outcomes
ARIC Murphy, 2012[91,136]	11,594 14.0	53.8 56.4	*HTN:* 33.4 *DM:* 0 *Tobacco use:* 25.7	10-y risk for CVD: 6%–19%	NR	Total events: NR Hard events All: 0.008 (p=0.50) Int: NR NRI-c‡ for hard CVD events, intermediate-risk subjects: -0.011
Health ABC* Rodondi, 2010[47]	2,191 8.2	73.5 55.3	*HTN:* 46.1 *DM:* 13.3 *Tobacco use:* 10.1	7.5-y risk for CAD: 7.5%–15%	Total events All: 0.033 (0.0004 to 0.065) Int: 0.07 (0.029 to 0.112) NRI-c‡ (95% CI) for total CAD events, intermediate-risk subjects: 0.038 (-0.029 to 0.105) Hard events All: 0.079 (NR) Int: 0.193 (NR)	NR
MESA*† Yeboah, 2012[48]	1,330 7.6	63.8 33.3	*HTN meds:* 38.2 *DM:* 0 *Tobacco use:* 16.5	7.5-y risk for CAD: 2.0%–15.4% 7.5-y risk for CVD: 3.4%–21.1%	Total events All: NR Int: 0.036 (NR) Hard events: NR	Total events All: NR Int: 0.068 (NR) Hard events: NR
Rotterdam Kavousi, 2012[49]	5,933 6.8	69.1 59.4	*HTN meds:* 23.5 *DM:* 12.9 *Tobacco use:* 17.5	10-y risk for CAD: 10%–20%	Total events: NR Hard events All: 0.006 (-0.018 to 0.029) Int: 0.073 (0.029 to 0.117)	NR

*Not included in the ABI Collaboration.
†MESA included only intermediate-risk individuals.
‡ NRI-c was calculated.

Abbreviations: ABC = Aging and Body Composition; ARIC = Atherosclerosis Risk in Communities; CAD = coronary artery disease; CVD = cardiovascular disease; DM = diabetes mellitus; HTN = hypertension; Int = intermediate; meds = medications; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not reported; NRI = net reclassification improvement; NRI-c = corrected NRI.

Table 8. Baseline Characteristics of ABI Collaboration Cohorts[46]

Cohort Study	Country	N	% Women	Mean Age, year	Group	FRS, % mean	ABI, mean
ARIC[98]	US	14,014	56.7	54	Men	12.8	1.17
					Women	7.3	1.12
Belgian Physical Fitness[103]	Belgium	2,068	0	47	Men	11.0	1.21
					Women	NA	NA
Cardiovascular Health Study[38]	US	4,625	60.1	73	Men	25.4	1.10
					Women	8.0	1.06
Edinburgh Artery Study[50]	Scotland	1,392	50.4	64	Men	26.2	1.07
					Women	11.5	1.01
Framingham Offspring[137]	US	3,126	54.5	58	Men	15.3	1.16
					Women	7.5	1.10
Health in Men[138]	Australia	2,771	0	72	Men	29.4	1.07
					Women	NA	NA
Honolulu Heart Program[95]	US	2,863	0	78	Men	31.6	1.05
					Women	NA	NA
Hoorn[139]	The Netherlands	554	51.3	63	Men	26.8	1.03
					Women	14.5	1.02
InCHIANTI[140]	Italy	1,050	54.2	67	Men	24.8	1.04
					Women	8.0	1.05
Limburg PAOD[107]	The Netherlands	2,351	56.1	57	Men	20.2	1.08
					Women	11.7	1.07
Men Born in 1914 Study[141]	Sweden	391	0	69	Men	31.5	1.02
					Women	NA	NA
Rotterdam[135]	The Netherlands	5,649	62.2	69	Men	29.6	1.10
					Women	10.2	1.05
San Diego Study[142]	US	558	56.3	66	Men	21.6	1.08
					Women	7.8	1.02
San Luis Valley Diabetes[143]	US	1,512	55.4	53	Men	15.6	1.16
					Women	9.1	1.10
Strong Heart Study[144]	US	4,326	60.6	56	Men	15.5	1.15
					Women	10.8	1.15
Women's Health and Aging[145]	US	689	100	78	Men	NA	NA
					Women	7.1	1.05

Abbreviations: ABI = ankle-brachial index; ARIC = Atherosclerosis Risk in Communities; FRS = Framingham risk score; InCHIANTI = Invecchiare in Chianti (Aging in the Chianti Area); NA = not applicable; PAOD = Peripheral Arterial Occlusive Disease.

Table 9. Prevalence of Low ABI (≤0.9) by FRS Categories in the ABI Collaboration Cohorts[46]

FRS Category	Men	Women	Both Sexes
Low (<10%)	1.3%	7.0%	5.5%
Intermediate (10%–19%)	3.3%	10.0%	6.2%
High (≥20%)	13.7%	14.1%	13.7%

Abbreviation: FRS = Framingham risk score.

Table 10. CAD Outcomes for KQ 4: Does ABI in Generally Asymptomatic Adults Accurately Predict CAD Morbidity and Mortality Independent of FRS?

Cohort Study, Year	N	Years Followup	% ABI <0.9	Risk association HR or RR (95% CI) adjusted for FRS factors and other predictors*	Risk reclassification in addition to FRS factors
ABI Collaboration Fowkes 2008[46]	48,294	10	7.7 Men: 7.4 Women: 8.1	HR† (of major coronary events) for ABI 1.11–1.40: Men: 2.16 (1.76 to 2.66) Women: 2.49 (1.84 to 3.36) ABI ≤0.90: reference	Risk reclassification: For men: 19% would change risk category; greatest effect of ABI is among those at high risk by FRS; a normal ABI would reclassify them to intermediate risk. For women: 36% would change risk category; greatest effect of ABI is among those at low or intermediate risk by FRS; an abnormal ABI would reclassify them to high risk. 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 2007[94]	13,588	13.1 (median)	2.8	HR‡ of CAD event (definite CAD death, definite or probable hospitalized MI, or unrecognized MI) per 0.10 decrease in ABI: White men: 1.15 (1.08 to 1.24) White women: 1.11 (1.01 to 1.23) Black men: 1.25 (1.11 to 1.41) Black women: 1.20 (1.07 to 1.34)	NR
Edinburgh Artery Study Lee 2004[50]	1,507	12	16.3	RR§ of fatal and nonfatal MI for ABI ≤0.90: 1.10 (0.78 to 1.54) ABI >0.90: reference	AUC for fatal MI by predictors (p for significance of increase in predictive value): age + sex: 0.66 (p≤0.001) age + sex + DM + prevalent CVD: 0.74 (p≤0.001) age + sex + DM + prevalent CVD + FRS predictors: 0.77 (p≤0.001) age + sex + DM + prevalent CVD + FRS predictors + ABI: 0.78 (p≤0.01)
Health ABC Rodondi 2010[47]	2,191	8.2 (median)	NR	HR† (of total CAD events: nonfatal MI, coronary death, angina or revascularization): ABI ≤0.9: 1.57 (1.14 to 2.18) ABI 0.91–1.00: 1.05 (0.73 to 1.49) ABI 1.01–1.30: reference ABI 1.31–1.40: 1.29 (0.75 to 2.23) ABI >1.4: 2.89 (1.47 to 5.68)	NRI (95% CI) for total CAD events: all subjects: 0.033 (0.0004 to 0.065) intermediate-risk subjects: 0.07 (0.029 to 0.112) NRI-c‡‡ (95% CI) for total CAD events, intermediate-risk subjects: 0.038 (-0.029 to 0.105) NRI (95% CI) for hard CAD events: all subjects: 0.079 (NR) intermediate-risk subjects: 0.193 (NR) AUC for total CAD events by predictors: FRS+DM: 0.631 FRS+DM+ABI: 0.650

Table 10. CAD Outcomes for KQ 4: Does ABI in Generally Asymptomatic Adults Accurately Predict CAD Morbidity and Mortality Independent of FRS?

Cohort Study, Year	N	Years Followup	% ABI <0.9	Risk association HR or RR (95% CI) adjusted for FRS factors and other predictors*	Risk reclassification in addition to FRS factors
Health ABC Sutton-Tyrrell 2008[93]	2,886	6.7 (mean)	13.3	RR‖ (of total CAD events: coronary death, hospitalization for acute MI or angina): ABI ≤0.9: 1.41 (1.11 to 1.81) ABI 0.91–1.3: reference ABI ≥1.3: 1.50 (1.01 to 2.23) NC: 1.65 (1.02 to 2.68) RR‖ (CHF events): ABI ≤0.9: 1.51 (1.12 to 2.02) ABI 0.91–1.3: reference ABI ≥1.3: 1.03 (0.54 to 1.97) NC: 2.40 (1.40 to 4.10)	NR
Honolulu Heart Program Abbott 2000[95]	2,863	3–6	NR <0.8: 6.3	RR¶ (of nonfatal MI, death from CAD, or sudden death): ABI <0.8: 2.7 (1.6 to 4.5) ABI 0.8 to <1.0: 1.3 (0.9 to 1.9) ABI ≥1.0: reference	NA
MESA Yeboah 2012[48]	1,330	7.6 (median)	NR 1.14, median	HR# (95% CI) for CAD events (MI, CAD death, resuscitated cardiac arrest, angina with revascularization) with 1 SD change in ABI: ABI and other predictors: 0.79 (0.66 to 0.95); p=0.01	For incident CAD: NRI for FRS+ABI, intermediate-risk subjects: 0.036 AUC for FRS alone: 0.623 AUC for FRS+ABI: 0.650
Rotterdam Kavousi 2012[49]	5,933	6.8 (median)	NR	HR** (of nonfatal MI, fatal MI, or fatal CAD): ABI ≤0.9, overall: 1.3 (1.0 to 1.7) Men: 1.6 (1.1 to 2.2) Women: 1.1 (0.7 to 1.6) ABI 0.91–1.4: reference	NRI (95% CI) for all subjects: Overall: 0.006 (-0.018 to 0.029) Men: -0.016 (-0.065 to 0.033) Women: -0.009 (-0.027 to 0.010) NRI (95% CI) for intermediate-risk subjects: Overall: 0.073 (0.029 to 0.117) Men: 0.065 (-0.011 to 0.141) Women: -0.012 (-0.042 to 0.017) AUC (95% CI) for nonfatal MI, fatal MI, or fatal CAD with FRS predictors: 0.73 (0.71 to 0.75) Change in AUC (95% CI) adding PAD as a predictor: Overall: 0.00 (0.00 to 0.00) Men: 0.01 (0.00 to 0.01) Women: 0.00 (0.00 to 0.00)
Rotterdam van der Meer 2004[135]	6,389	9 (estimated)	NR	HR†† (of fatal or nonfatal incident MI): ABI <0.97: 1.59 (1.05 to 2.39) ABI 0.97–1.10: 1.55 (1.04 to 2.31) ABI 1.10–1.21: 1.12 (0.74 to 1.70) ABI >1.21: reference	NA

Table 10. CAD Outcomes for KQ 4: Does ABI in Generally Asymptomatic Adults Accurately Predict CAD Morbidity and Mortality Independent of FRS?

* HR or RR adjusted for age, sex, systolic blood pressure, total cholesterol level, high-density lipoprotein cholesterol level, and current smoking, at minimum.
† Also adjusted for diabetes.
‡ Also adjusted for center, low-density lipoprotein cholesterol, and diabetes.
§ Also adjusted for diabetes and prevalent CAD.
‖ Also adjusted for race, site, prevalent CVD, diabetes, body mass index, physical activity, and triglycerides.
¶ Also adjusted for diabetes, alcohol intake, fibrinogen, body mass index, distance walked per day, and past smoking.
# 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, use of aspirin, and antihypertension and cholesterol-lowering medications.
‡‡ NRI-c was calculated.

Abbreviations: ABI = ankle-brachial index; ARIC = Atherosclerosis Risk in Communities; AUC = area under the curve; CAD = coronary artery disease; CHF = congestive heart failure; CI = confidence interval; CVD = cardiovascular disease; DM = diabetes mellitus; FRS = Framingham risk score; HR = hazard ratio; MESA = Multi-Ethnic Study of Atherosclerosis; MI = myocardial infarction; NA = not applicable; NC = noncompressible arteries; NR = not reported; NRI = net reclassification improvement; NRI-c = corrected NRI; PAD = peripheral artery disease; RR = relative risk; SD = standard deviation.

Table 11. CVD Outcomes for KQ 4: Does ABI in Generally Asymptomatic Adults Accurately Predict CVD Morbidity and Mortality Independent of FRS?

Cohort Study, Year	N	Years Followup	% ABI <0.9	Risk association HR, RR, or OR (95% CI) adjusted for FRS factors and other predictors*	Risk Reclassification in addition to Framingham risk factors
ABI Collaboration Fowkes 2008[46]	48,294	10	7.7 Men: 7.4 Women: 8.1	HR† (of death due to CAD or CVA) for ABI 1.11–1.40: Among men: 2.92 (2.31 to 3.70) Among women: 2.97 (2.02 to 4.35) ABI ≤0.90: reference	
ARIC Murphy 2012[91]	11,594	14 (med) 16 (max) 10 (for analysis)	2.3	HR‡ (of hard CVD events: MI, cardiovascular death, or CVA) per standard deviation in ABI: 0.849 (0.79 to 0.91) ABI, 1 SD: reference	NRI for hard CVD events: All subjects: 0.008; p=0.50 Intermediate-risk subjects: 0.06; p=NR NRI-c†† for hard CVD events, intermediate-risk subjects: -0.011 AUC for hard CVD events: Model FRS: 0.756 (0.739 to 0.773) Model FRS + ABI: 0.758 (0.741 to 0.775) p=0.23
Cardiovascular Health Study O'Hare 2006[38]	5,748	9.6 (for CV events) 11.1 (for CVD mortality)	13.8	HR§ (of CV events: MI, CVA, angina, angioplasty, CABG, or lower-extremity amputation/revascularization): ABI ≤0.60: 1.60 (1.09 to 2.34) ABI 0.61–0.70: 1.57 (1.07 to 2.20) ABI 0.71–0.8: 1.63 (1.16 to 2.28) ABI 0.81–0.9: 1.72 (1.35 to 2.20) ABI 0.91–1.0: 1.37 (1.13 to 1.64) ABI 1.01–1.10: 1.08 (0.93 to 1.25) ABI 1.11–1.20: reference ABI 1.21–1.30: 0.90 (0.74 to 1.10) ABI 1.31–1.40: 0.97 (0.68 to 1.40) ABI >1.40: 1.00 (0.57 to 1.74) HR (of CVD mortality): ABI ≤0.60: 2.13 (1.49 to 3.05) ABI 0.61–0.70: 2.31 (1.56 to 3.42) ABI 0.71–0.8: 2.01 (1.43 to 2.81) ABI 0.81–0.9: 2.37 (1.77 to 3.16) ABI 0.91–1.0: 1.60 (1.25 to 2.05) ABI 1.01–1.10: 1.05 (0.85 to 1.30) ABI 1.11–1.20: reference ABI 1.21–1.30: 0.95 (0.71 to 1.26) ABI 1.31–1.40: 1.33 (0.83 to 2.13) ABI >1.40: 1.76 (0.97 to 3.18)	NR
Edinburgh Artery Study Lee 2004[50]	1,507	12	16.3	RR‖ (of nonfatal MI or CVA and CVD mortality): ABI ≤0.90: 1.06 (0.81 to 1.39) ABI >0.90: reference	

Table 11. CVD Outcomes for KQ 4: Does ABI in Generally Asymptomatic Adults Accurately Predict CVD Morbidity and Mortality Independent of FRS?

Cohort Study, Year	N	Years Followup	% ABI <0.9	Risk association HR, RR, or OR (95% CI) adjusted for FRS factors and other predictors*	Risk Reclassification in addition to Framingham risk factors
Edinburgh Artery Study Price 2007[96]	1,007	12	18.7	OR† (of MI or CVA): ABI ≤0.9: 1.70 (1.07 to 2.70) ABI >0.9: reference	AUC (95% CI) for MI or CVA by predictors: FRS + DM: 0.61 (0.56 to 0.67) FRS + DM + ABI: 0.64 (0.59 to 0.69) (p for difference= 0.02)
Health ABC Sutton-Tyrrell 2008[93]	2,886	6.7 (mean)	13.3	RR¶ (of cardiovascular mortality: death due to atherosclerotic CVD or CVA): ABI ≤0.9: 2.18 (1.57 to 3.02) ABI 0.91–1.3: reference ABI ≥1.3: 1.32 (0.66 to 2.63) NC: 2.62 (1.39 to 0.92)	
Hoorn Hanssen 2012[97]	624 (469 without DM)	17.2	10.4	RR# (95% CI) of CVD mortality (in persons without DM): ABI <0.9: 1.95 (0.88 to 4.33)	
MESA Yeboah 2012[48]	1,330	7.6 (med)	NR 1.14 (med)	HR** (95% CI) of CVD events (CAD death, MI resuscitated cardiac arrest, angina with revascularization, CVA, or CVD death) with 1 SD change in ABI: ABI and other predictors: 0.81 (0.68 to 0.95) p=0.012	For incident CVD: NRI for FRS + ABI: 0.068 AUC for FRS alone: 0.623 (95% CI, NR) AUC for FRS + ABI: 0.650 (95% CI, NR)

* HR, RR, or OR adjusted for age, sex, systolic blood pressure, total cholesterol level, high-density lipoprotein cholesterol level, and current smoking, at minimum.
† Also adjusted for diabetes.
‡ Also adjusted for race and low-density lipoprotein cholesterol.
§ Also adjusted for race, diabetes, prevalent CVD (CAD, CVA, CHF), low-density lipoprotein, triglycerides, diastolic blood pressure, antihypertension medications, creatinine, body mass index, and C-reactive protein.
‖ Also adjusted for diabetes and prevalent CAD.
¶ Also adjusted for race, site, prevalent CVD, diabetes, body mass index, physical activity, and triglycerides.
# Also adjusted for triglycerides, 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.
†† NRI and corrected NRI for intermediate-risk group were calculated.

Abbreviations: ABC = Aging and Body Composition; ABI = ankle-brachial index; ARIC = Atherosclerosis Risk in Communities; AUC = area under the curve; CABG = coronary artery bypass graft; CAD = coronary heart disease; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; CVA = cerebrovascular accident; CVD = cardiovascular disease; DM = diabetes mellitus; FRS = Framingham risk score; HR = hazard ratio; max = maximum; med = median; MESA = Multi-Ethnic Study of Atherosclerosis; MI = myocardial infarction; NC = noncompressible arteries; NR = not reported; NRI = net reclassification improvement; NRI-c = corrected NRI; OR = odds ratio; PAD = peripheral artery disease; RR = relative risk; SD = standard deviation.

Table 12. CVA (Alone) Outcomes for KQ 4: Does ABI in Generally Asymptomatic Adults Accurately Predict CVA Independent of FRS?

Cohort Study, Year	N	Years Followup	% ABI <0.9	Risk association HR or RR (95% CI) adjusted for FRS factors and other predictors*	Risk reclassification in addition to FRS factors
ARIC Tsai 2001[98]	14,306	7.2 (median)	2.9	HR† (of nonhemorrhagic CVA): ABI ≤0.80: 1.93 (0.78 to 4.78) ABI 0.81–0.90: 1.45 (0.56 to 3.76) ABI 0.91–1.00: 1.23 (0.67 to 2.26) ABI 1.01–1.10: 1.46 (0.94 to 2.25) ABI 1.11–1.20: 1.18 (0.77 to 1.79) ABI ≥1.20: reference	NR
Edinburgh Artery Study Lee 2004[50]	1,507	12	16.3	RR‡ (of nonfatal CVA): ABI ≤0.90: 1.29 (0.77 to 2.19) ABI >0.90: reference RR‡ (of fatal and nonfatal CVA): ABI ≤0.90: 1.05 (0.67 to 1.65) ABI >0.90: reference	NR
Health ABC Sutton-Tyrrell 2008[93]	2,886	6.7	13.3	RR§ (of all CVA): ABI ≤0.9: 1.67 (1.13 to 2.45) ABI 0.91–1.3: reference ABI ≥1.3: 0.78 (0.31 to 1.93) NC: 2.09 (1.00 to 4.37)	NR
Honolulu Heart Program Abbott 2001[99]	2,767	3 to 6	11.6	HR‖ (of all CVA): ABI <0.9: 2.0 (1.1 to 3.5) ABI ≥0.9: reference HR‖ (of thromboembolic CVA): ABI <0.9: 1.9 (1.0 to 3.7) ABI ≥0.9: reference HR‖ (hemorrhagic CVA): ABI <0.9: 3.3 (1.2 to 9.4) ABI ≥0.9: reference	NR

* HR or RR adjusted for age, sex, systolic blood pressure, total cholesterol level, high-density lipoprotein cholesterol level, and current smoking, at minimum.
† Also adjusted for diabetes, prevalent CAD, low-density lipoprotein cholesterol, antihypertension medication, and pack-years smoking.
‡ Also adjusted for diabetes and prevalent CAD.
§ Also adjusted for race, site, diabetes, prevalent CVD, body mass index, physical activity, and triglycerides.
‖ Also adjusted for diabetes, fibrinogen, distance walked per day, and atrial fibrillation.

Abbreviations: ABC = Aging and Body Composition; ABI = ankle-brachial index; ARIC = Atherosclerosis Risk in Communities Study; CAD = coronary artery disease; CI = confidence interval; CVA = cerebrovascular accident; FRS = Framingham risk score; HR = hazard ratio; NC = noncompressible arteries; NR = not reported; RR = relative risk.

Table 13. Study Characteristics for KQs 5 and 6: What Are the Benefits and Harms of Treatment of Generally Asymptomatic Adults With PAD?

Study, Year	USPSTF Quality	N	Mean Age, years	% Female	Mean ABI	Mean SBP, mm Hg	Mean total cholesterol, mg/dL	% Current smokers	Description of Intervention
Fowkes 2010[100]	Good	3,350	62.0	71.5	0.86	147.5	238.5	32.5	IG: Enteric-coated aspirin 100 mg daily CG: Placebo daily
McDermott 2011[101]	Fair	335	70.5	40.6	0.68	NR	183.5	25.4	IG1: 8 phone calls (25 minutes each) for 6 weeks focused on behavioral counseling to improve lipid control CG1: Attention control (education only) CG2: Usual care (no phone calls)

Abbreviations: ABI = ankle-brachial index; CG = control group; IG = intervention group; SBP = systolic blood pressure; USPSTF = U.S. Preventive Services Task Force.

Table 14. Study Outcomes for KQs 5 and 6: What Are the Benefits and Harms of Treatment of Generally Asymptomatic Adults With PAD?

Study, Year	Primary outcome	IG	CG	IG vs. CG	Secondary outcome	IG	CG	IG vs. CG	Harms	IG	CG	IG vs. CG
Fowkes 2010[100]	Initial MI, CVA or revascularization	Events/ 1000 py (95% CI): 13.7 (11.8 to 15.9)	Events/ 1000 py (95% CI): 13.3 (11.4 to 15.4)	HR (95% CI): 1.03 (0.84 to 1.27)	All initial vascular events	Events/ 1000 py (95% CI): 22.8 (20.2 to 25.6)	Events/ 1000 py (95% CI): 22.9 (20.3 to 25.7)	HR (95% CI): 1.00 (0.85 to 1.17)	Major bleeding requiring hospital admission	Events/ 1000 py (95% CI): 2.5 (1.7 to 3.5)	Events/ 1000 py (95% CI): 1.5 (0.9 to 2.3)	HR (95% CI): 1.71 (0.99 to 2.97)
McDermott 2011[101]	12-month change in LDL, adjusted for baseline LDL	mg/dL (95% CI): -18.4 (-24.8 to -12.1)	mg/dL (95% CI): CG1: -6.8 (-13.0 to -0.5) CG2: -11.1 (-17.0 to -5.1)	3-way ANOVA: p=0.035 IG vs. CG1: p=0.010 IG vs. CG2: p=0.208	12 month proportion of participants with LDL <100 mg/dL	% (95% CI): 21.6 (11.5 to 31.8)	% (95% CI): CG1: 9.0 (-3.2 to 21.2) CG2: 9.1 (-2.7 to 20.2)	3-way ANOVA: p=0.009 IG vs. CG1: p=0.003 IG vs. CG2: p=0.018	NR	N/A	N/A	N/A

Abbreviations: ANOVA = analysis of variance; CG = control group; CI = confidence interval; CVA = cerebrovascular accident; HR = hazard ratio; IG = intervention group; LDL = low-density lipoprotein; MI = myocardial infarction; N/A = not applicable; NR, not reported.

Table 15. Overall Summary of Evidence

KQ	# and design of studies	Quality	Applicability	Consistency	Diagnostic accuracy or magnitude of association or effect (including precision)
KQ 1	None	N/A	N/A	N/A	N/A
KQ 2	1 (n=306) Dx accuracy	Fair	Fair: asymptomatic, age ≥70 years, Sweden, ABI cutoff of <0.9	N/A Only one study	Sensitivity: 15%–20%, wide confidence intervals Specificity: 99% Positive predictive value: 82% to 83% Negative predictive value: 80% to 84%
KQ 3	1 (n=306) Dx accuracy	Fair	Fair: asymptomatic, age ≥70 years, Sweden, did not directly address harms	N/A Only one study	No potential harms. Diagnostic accuracy study (KQ 2) reported one person had a vasovagal episode prior to receiving contrast for the MRA.
KQ 4	14 primary studies, 1 meta-analysis (n=52,510) 18 population-based cohorts	Fair to good	Good: broad range of cohorts with good age, sex, country (Australia, European countries, United States) representation	Inconsistencies in magnitude of risk reclassification and which subgroups will benefit most may be due to study heterogeneity in 1) populations, 2) definitions of composite outcomes, 3) definitions of FRS categories, and 4) choice of risk reclassification measure	Low ABI (≤0.9) can predict future CAD and CVD events after adjusting for FRS factors. Clinical implications of the incremental prognostic value of ABI to FRS is unclear due to limitations in the existing research and evolving practices in CVD risk assessment. The magnitude for appropriate CAD or CVD risk reclassification for ABI across all risk categories is likely small (at best). However, the total appropriate CAD risk reclassification for ABI may be greater in older persons. Because changes in the absolute magnitude in 10-year risk are likely small, ABI may be most useful for patients who are near the thresholds for different risk categories. The changes in absolute magnitude of 10-year risk may be greater in women. The value of ABI for CVD risk reclassification may be less or nonexistent for adults younger than age 65 years.
KQ 5	2 (n=3,705) RCT	Fair to good	Good for aspirin: screen-detected persons, ages 50 to 75 years, Scotland Fair for lipid lowering therapy: very intensive counseling intervention	Inconsistent, different populations and interventions	No benefit for aspirin 100 mg (vs. placebo) in persons with ABI of ≤0.90 to prevent CVD outcomes (8.2 years followup); HR, 1.02 (95% CI, 0.80 to 1.29) Some benefit for intensive telephone counseling intervention (vs. attention control) in persons with PAD; proportion with LDL <100 mg/dL at 12 months, 21.6% vs. 9.0% (p=0.003)
KQ 6	1 (n=3,350) RCT	Good	Good: screen-detected persons, ages 50 to 75 years, Scotland	N/A Only one study	Nonstatistically significant trend in major bleeding for aspirin 100 mg (vs. placebo) in persons with low ABI; HR, 1.71 (95% CI, 0.99 to 2.97)

Abbreviations: ABI = ankle-brachial index; CAD = coronary artery disease; CVA = cerebrovascular accident; CVD = cardiovascular disease; Dx = diagnostic; HR = hazard ratio; KQ = key question; LDL = low-density lipoprotein; N/A = not applicable; RCT = randomized, controlled trial.

Appendix A. Literature Search Strategies

SER Search

Cochrane Database of Systematic Reviews

(peripheral):ti,ab,kw and (arterial or artery or vascular):ti,ab,kw and (disease*):ti,ab,kw, from 2006 to 2011

DARE

(peripheral):TI AND ((artery):TI OR (arterial):TI OR (vascular):TI OR (angiopathy):TI OR (angiopathies):TI) IN DARE FROM 2006 TO 2011

PubMed search strategy

1) "Peripheral Vascular Diseases"[Mesh]
2) #1 AND systematic[sb] Limits: English, Publication Date from 2006 to 2011
3) peripheral[Title/Abstract] AND (vascular[Title/Abstract] OR artery[Title/Abstract] OR arterial[Title/Abstract]) AND (disease[Title/Abstract] OR diseases[Title/Abstract])
4) peripheral[Title/Abstract] AND (angiopathy[Title/Abstract] OR angiopathies[Title/Abstract])
5) #3 OR #4
6) #5 AND systematic[sb]
7) #6 AND (in process[sb] OR publisher[sb] OR pubmednotmedline[sb]) Limits: English, Publication Date from 2006 to 2011
8) #2 OR #7

Key Question Search

Databases searched

- MEDLINE
- Cochrane Central Register of Controlled Trials
- PubMed (publisher subset only)

Key:
/ = MeSH subject heading
ti = word in title
ab = word in abstract
$ = truncation
adj# = adjacent within x number of words
pt = publication type
fs = MeSH subheading
next = words next to each other
* = truncation
kw = keyword
sb = subset of articles in PubMed

Ovid MEDLINE(R) 1946 to December Week 4 2011, Ovid MEDLINE(R) Daily Update January 10, 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 10, 2012

All key questions except KQ4

#	Searches	Results
1	Peripheral Arterial Disease/	581
2	peripheral arter$ disease$.ti,ab.	5699
3	peripheral arter$ occlusive disease$.ti,ab.	1572
4	Arterial Occlusive Diseases/	23526

5	Peripheral Vascular Diseases/	10268
6	1 or 2 or 3 or 4 or 5	36089
7	Ankle Brachial Index/	598
8	(brachial adj1 ankle adj4 (ratio$ or index$ or indices or gradient$ or pressure)).ti,ab.	2985
9	(arm adj1 ankle adj4 (ratio$ or index$ or indices or gradient$ or pressure)).ti,ab.	492
10	ankle index$.ti,ab.	29
11	Ankle/bs [Blood Supply]	1049
12	Brachial Artery/ph, pp, us [Physiology, Physiopathology, Ultrasonography]	3972
13	7 or 8 or 9 or 10 or 11 or 12	7560
14	6 and 13	2284
15	Mass Screening/	72046
16	screen$.ti,ab.	376815
17	15 or 16	399357
18	14 and 17	232
19	"Sensitivity and Specificity"/	239856
20	"Predictive Value of Tests"/	114990
21	False Negative Reactions/	14837
22	False Positive Reactions/	22287
23	Diagnostic Errors/	27861
24	"Reproducibility of Results"/	221956
25	ROC Curve/	20968
26	Reference Values/	134590
27	Reference Standards/	29007
28	Observer Variation/	26726
29	specificit$.ti,ab.	293693
30	sensitivit$.ti,ab.	456717
31	predictive value.ti,ab.	46653
32	accuracy.ti,ab.	180121
33	false positive$.ti,ab.	36725
34	false negative$.ti,ab.	21640
35	miss rate$.ti,ab.	171
36	error rate$.ti,ab.	6743
37	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	1322092
38	13 and 37	1539
39	"tobacco use cessation"/ or smoking cessation/	16838
40	smoking cessation.ti,ab.	12552
41	Hypercholesterolemia/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]	9813
42	Hyperlipidemias/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]	8442
43	Anticholesteremic Agents/	11981
44	(lower$ adj3 cholesterol).ti,ab.	12415
45	(reduc$ adj3 cholesterol).ti,ab.	9864

46	Diabetes Mellitus/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]	25997
47	Diabetes Mellitus, Type 2/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]	25341
48	Hypoglycemic Agents/	34196
49	Hemoglobin A, Glycosylated/	18177
50	Blood Glucose/an, me [Analysis, Metabolism]	96225
51	Glycemic Index/	1411
52	glycemic control$.ti,ab.	10136
53	glycaemic control$.ti,ab.	4338
54	glucose control$.ti,ab.	4877
55	body weight changes/ or weight loss/	19206
56	weight loss.ti,ab.	44006
57	Hypertension/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]	68525
58	Antihypertensive Agents/	46382
59	blood pressure control$.ti,ab.	6379
60	(hypertension adj2 control$).ti,ab.	5028
61	Platelet Aggregation Inhibitors/	22492
62	Blood Platelets/de [Drug Effects]	15910
63	((anti platelet or antiplatelet) adj2 (therapy or treatment$)).ti,ab.	4949
64	39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63	393959
65	6 and 64	1920
66	limit 65 to yr="1990 -Current"	1730
67	(clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.	612912
68	clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/	234057
69	Meta-Analysis as Topic/	11683
70	random$.ti,ab.	573069
71	clinical trial$.ti,ab.	170249
72	controlled trial$.ti,ab.	86330
73	67 or 68 or 69 or 70 or 71 or 72	1130823
74	66 and 73	537
75	Safety/	30253
76	safety.ti,ab.	216625
77	adverse event*.ti,ab.	56621
78	adverse effects.fs.	1199031
79	adverse effect*.ti,ab.	82091
80	side effect*.ti,ab.	152404
81	product surveillance, postmarketing/	4891
82	Adverse reaction*.ti,ab.	19973
83	Adverse drug reaction*.ti,ab.	6919
84	drug toxicity/	4685

85	drug toxicity.ti,ab.	3106
86	Harm*.ti,ab.	78767
87	75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86	1578372
88	66 and 87	428
89	18 or 38 or 74 or 88	2440
90	limit 89 to english language	2251
91	remove duplicates from 90	2244

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to January Week 3 2012**, Ovid MEDLINE(R) Daily Update** January 26, 2012**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations** January 26, 2012

Key question 4 only (Does ABI predict cardiovascular morbidity?)

#	Searches	Results
1	Ankle Brachial Index/	602
2	(brachial adj1 ankle adj4 (ratio$ or index$ or indices or gradient$ or pressure)).ti,ab.	2609
3	(arm adj1 ankle adj4 (ratio$ or index$ or indices or gradient$ or pressure)).ti,ab.	242
4	ankle index$.ti,ab.	6
5	Ankle/bs [Blood Supply]	725
6	Brachial Artery/ph, pp, us [Physiology, Physiopathology, Ultrasonography]	3525
7	1 or 2 or 3 or 4 or 5 or 6	6261
8	exp Cardiovascular Diseases/	791061
9	cardiovascular.ti,ab.	166393
10	heart.ti,ab.	294993
11	cardiac.ti,ab.	220598
12	Myocardial.ti,ab.	124490
13	Coronary.ti,ab.	161894
14	Stroke.ti,ab.	87660
15	cerebral.ti,ab.	127147
16	Cerebrovascular.ti,ab.	19654
17	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	1177740
18	7 and 17	5107
19	meta analysis.pt.	28737
20	Meta-Analysis as Topic/	9737
21	cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/	808203
22	cohort$.ti,ab.	174319
23	followup stud$.ti,ab.	354
24	follow up stud$.ti,ab.	18510
25	19 or 20 or 21 or 22 or 23 or 24	915791
26	18 and 25	1623
27	limit 26 to english language	1528
28	limit 27 to yr="2007 -Current"	791
29	remove duplicates from 28	791

Appendix A. Literature Search Strategies

Cochrane Central Register of Controlled Trials (Central)
Issue 4 of 4, Oct 2011

#1 (peripheral next arter* next disease*):ti,ab,kw, from 1990 to 2012 = 449
#2 ankle:ti,ab,kw AND (brachial OR arm):ti,ab,kw AND (index* OR indices OR ratio* OR gradient* OR pressure):ti,ab,kw = 494
#3 (ankle next index*):ti,ab,kw = 2
#4 (#1 OR #2 OR #3) = 843

PubMed (publisher subset only)
1/11/2012

All key questions except KQ4

#1 (peripheral artery disease OR peripheral arterial disease) AND screening AND publisher[sb] = 33
#2 (peripheral artery disease OR peripheral arterial disease) AND (cholesterol OR smoking OR glycemic OR glycaemic OR glucose OR weight loss OR blood pressure OR hypertension OR anti platelet OR antiplatelet) AND (random* OR trial OR trials OR systematic OR meta analysis OR metaanalysis) AND publisher[sb] = 26
#3 ankle AND (brachial OR arm) AND (index* OR indices OR ratio* OR gradient* OR pressure) AND publisher[sb] = 98
#4 ankle index AND publisher[sb] = 127
#5 #1 OR #2 OR #3 OR #4 = 190
#6 #1 OR #2 OR #3 OR #4 Limits: English = 183

PubMed (publisher subset only)
1/26/2012

Key question 4 only (Does ABI predict cardiovascular morbidity?)

#1 ankle AND (brachial OR arm) AND (index* OR indices OR ratio* OR gradient* OR pressure) = 4487
#2 ankle index = 5413
#3 (#1 OR #2) AND publisher[sb] = 147
#4 (cardiovascular[tiab] OR heart[tiab] OR cardiac[tiab] OR myocardial[tiab] OR coronary[tiab] OR cerebral[tiab] OR stroke[tiab] OR cerebrovascular[tiab]) AND publisher[sb] = 20913
#5 #3 AND #4 = 18
#6 cohort*[tiab] OR "follow up study"[tiab] OR "follow up studies"[tiab] OR "followup study"[tiab] OR "followup studies"[tiab] = 232247
#7 #5 AND #6 Limits: English, Publication Date from 2007 to 3000 = 7

Appendix B. Systematic Reviews Used for Reference

1. Aboyans V, Lacroix P. Regarding: "A modified calculation of ankle-brachial pressure index is far more sensitive in the detection of peripheral arterial disease". Journal of Vascular Surgery 2007;46(3):617-8. PMID: 17826263.
2. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008 Jul 9;300(2):197-208. PMID: 18612117.
3. Aung PP, Maxwell HG, Jepson RG, et al. Lipid-lowering for peripheral arterial disease of the lower limb. [Update of Cochrane Database Syst Rev. 2000;(2):CD000123; PMID: 10796489]. Cochrane Database of Systematic Reviews 2007(4):CD000123. PMID: 17943736.
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Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006 Mar 21;113(11):e463-e654. PMID: 16549646.
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Appendix C. Ongoing Studies and Trials Pending Assessment

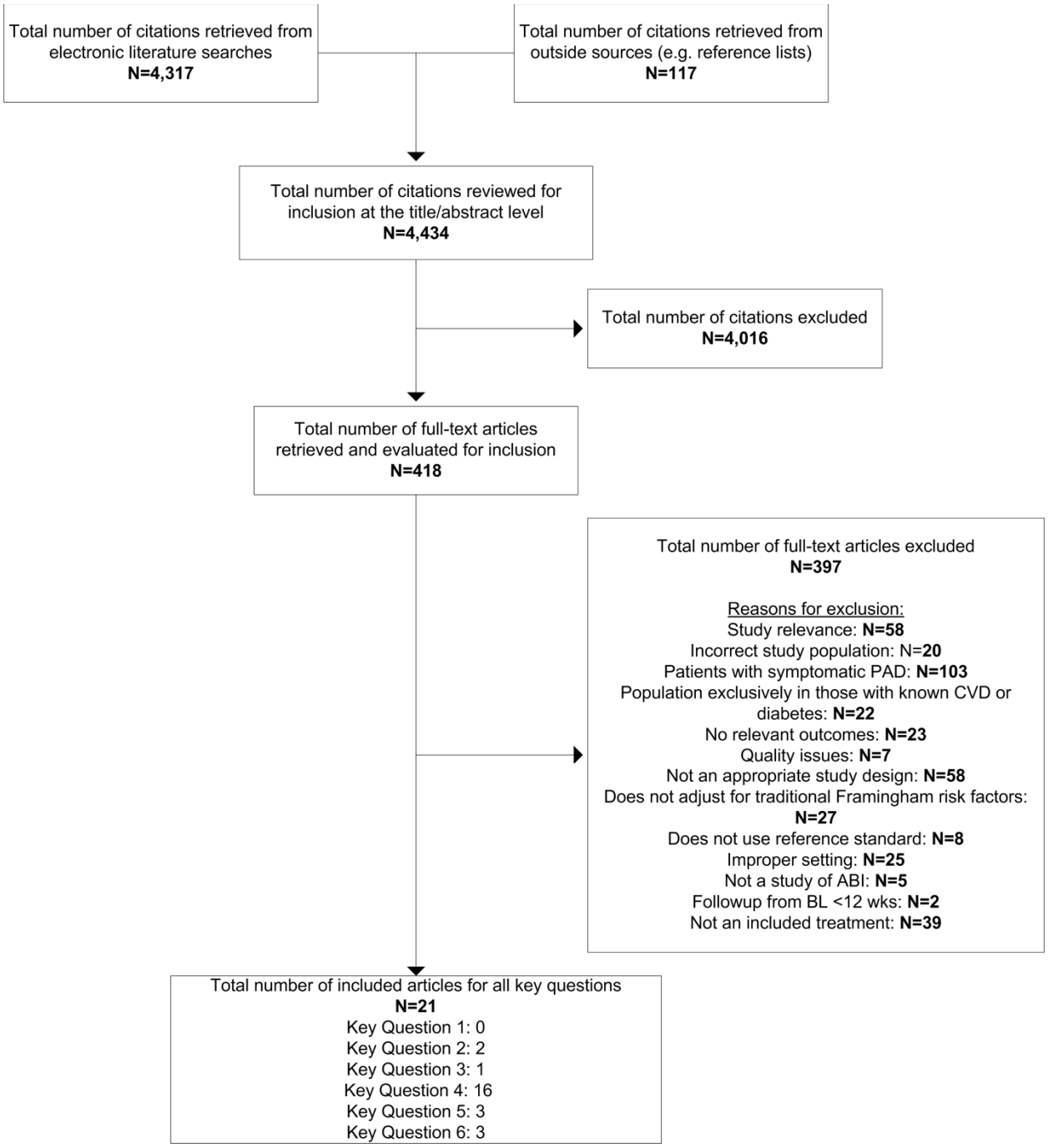
Study reference	Study name NCT #	Relevant KQ Study design	Aim	Location	# of participants Inclusion criteria	Intervention description	Relevant outcomes	2012 Status
Grøndal N et al. The Viborg Vascular (VIVA) screening trial of 65–74 year old men in the central region of Denmark: study protocol. *Trials*. 2010;11:67. PMID: 20507582	Viborg Vascular Screening Trial (VIVA) 00662480	KQ 1 RCT	To establish the effectiveness of a joint circulation screening program (AAA, ABI, hypertension)	Denmark	40,000 Men ages 65 to 74 years	IG: Invitation to screening ultrasound of the aorta and ABI; interventions (risk factor reduction or AAA surgery) for those who screen positive CG: No invitation to screening; usual care	All-cause mortality, cardiovascular and AAA-related mortality; cardiovascular events at 3, 5, and 10 years	Currently recruiting participants Estimated primary completion date: September 2018
Marti R et al. Improving intermediate risk management. MARK study. *BMC Cardiovasc Disord*. 2011;11:6. PMID: 21992621	Improving Intermediate Risk Management (MARK) 01428934	KQ 4 Cohort	To analyze if ABI and other cardiovascular biomarkers are independently associated with incidence of vascular events and if they improve the prediction of current risk equations in the intermediate-risk population	Spain	2,688 Men and women ages 35 to 74 years with intermediate cardiovascular risk by FRS or SCORE	ABI along with other cardiovascular biomarkers and CVD screening tests	Vascular events (fatal or nonfatal): MI, angina, stroke, or PAD at 18 months and 10 years	Currently recruiting participants Estimated primary completion date: January 2013
Muntendam P et al. The Bioimage Study: novel approaches to risk assessment in the primary prevention of atherosclerotic cardiovascular disease—study design and objectives. *Am Heart J*. 2010;160(1):49-57. PMID: 20598972	BioImage 00738725	KQ 4 Cohort	To identify imaging and serum biomarkers that predict athero-thrombotic events after 3 years, with incremental improvement over the FRS	Chicago, IL; Louisville, KY; and Ft. Lauderdale, FL	7,687 Men age >55 years and women age >60 years who are members of the Humana Health Plan	IG: CAC score; cIMT, carotid atherosclerotic Plaques, and AAA by ultrasound; ABI; and serum biomarkers; those with abnormal results are offered MRA, CTA, or PET/CT CG1: Survey only CG2: FRS only	MI (fatal and nonfatal), coronary death, unstable angina, ischemic stroke (fatal and nonfatal), and arterial revascularization at 3 years or when 600 major atherothrombotic events have occurred	Ongoing but not recruiting participants Estimated study completion date: July 2012

Appendix C. Ongoing Studies and Trials Pending Assessment

Study reference	Study name NCT #	Relevant KQ Study design	Aim	Location	# of participants Inclusion criteria	Intervention description	Relevant outcomes	2012 Status
Evaluation of Non-invasive Measurements of Atherosclerosis in Cardiovascular Risk Stratification (NIMA)	NIMA Substudy of Nijmegen Biomedical Study 01555294	KQ 4 Cohort	To evaluate whether noninvasive measurements of atherosclerosis are independent predictors of cardiovascular disease	The Netherlands	1,960 Men and women ages 50 to 70 years without recent CVD	Noninvasive measurements of atherosclerosis (including ABI)	Cardiovascular events (fatal and nonfatal)	Completed May 2011 No study results posted on ClinicalTrials.gov or retrieved through PubMed
Casasnovas JA et al. Aragon workers' health study: design and cohort description. *BMC Cardiovasc Disord*. 2012;12:45. PMID: 22712826	Aragon Workers' Health Study (NR)	KQ 4 Cohort	To characterize the factors associated with metabolic abnormalities and subclinical atherosclerosis in a middle-aged population in Spain free of clinical cardiovascular disease	Aragon, Spain	5,400 Male and female workers of a large car assembly plant without clinically overt CVD or a condition limiting survival to <3 years	Subclinical atherosclerosis imaging (including ABI; CAC; and ultrasound of the carotid, aortic, femoral and iliac arteries); biobanking	Clinical events and hospitalizations	Recruitment and baseline examinations 2009–2010; planned 10 years' followup Estimated study completion date: 2020
Early detection of atherosclerosis: a randomized trial in the Primary Prevention of Cardiovascular Diseases. (PRIMARIA) http://www.udetma.com/documents/productes/pdf/38_1.pdf	PRIMARIA 00734123	KQ 5 RCT	To quantify the burden of subclinical atherosclerosis using noninvasive techniques and to study the impact of this assessment and consequent treatment in the progression of atherosclerosis and in the incidence of cardiovascular diseases	Vilanova, Spain	2,948 Men and women ages 40 to 74 years without history of cardiovascular events but with 1 major or 2 minor risk factors for CAD	All participants have cIMT (or CAC score, if problems measuring cIMT) and ABI. Those with abnormal results are randomized: IG: Intensive treatment CG: Usual care	cIMT/CAC score at 2 years Incidence of CVD at 5 years Secondary analysis will examine ABI at 2 years as outcome	Currently recruiting participants

Abbreviations: AAA = abdominal aortic aneurysm; ABI = ankle-brachial index; CAC = coronary artery calcium; CAD = coronary artery disease; CG = control group; cIMT = carotid intima media thickness; CTA = computed tomography angiography; CVD = cardiovascular disease; FRS = Framingham risk score; IG = intervention group; KQ = key question; MI = myocardial infarction; MRA = magnetic resonance angiography; PAD = peripheral artery disease; PET = positron emission tomography; RCT = randomized, controlled trial.

Appendix D. Search Results



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

Appendix E. Inclusion/Exclusion Criteria

	Inclusion	Exclusion
Population	**Screening (KQs 1–4):** Community-dwelling, generally asymptomatic adults (may include populations with atypical symptoms or minor symptom not recognized as PAD); unselected, primary care–relevant populations or primary care–relevant populations selected based on Framingham or other traditional CVD risk factors (e.g, age, smoking history, hypertension, hyperlipidemia) **Treatment (KQs 5–6):** Asymptomatic or minimally symptomatic (mild claudication or Fontaine Stage I or IIa)	Symptomatic adults, populations exclusively of persons with known CVD, diabetes, or severe chronic kidney disease (stage 4–5)
Setting	**KQs 1–4:** Primary care, outpatient settings (ambulatory care) **KQs 5–6:** Outpatient settings	Hospital/inpatient settings, long-term care facilities, vascular clinics
Disease/Condition	Lower-extremity PAD secondary to atherosclerosis	
Screening (KQs 1–4)	Resting ABI	History taking, questionnaires, digital subtraction arteriography, duplex ultrasound, magnetic resonance angiography, CT angiography, toe pressure measurement, treadmill testing (exercise ABI), pulse oximetry, near-infrared spectroscopy, and all invasive diagnostic testing
Treatment or management interventions (KQs 5–6)	Pharmacologic or lifestyle interventions primarily aimed at CVD reduction: interventions for smoking cessation, cholesterol lowering, weight loss, blood pressure control, antiplatelet therapy	Vitamins or nutritional or herbal supplement Interventions aimed only at symptomatic persons or persons with critical limb ischemia: pharmacologic symptom management (pentoxyfylline, cilostazol, prostaglandins); nonpharmacologic symptom management (lower-extremity rehabilitation, supervised exercise training and physical therapy*); revascularization (angioplasty, thrombolytics, stenting, bypass) * Exercise interventions whose primary aim is to reduce CVD risk or treat CVD risk factors are included
Comparisons	**KQ 1:** No screening **KQ 2:** Reference standard **KQ 4:** Framingham CVD risk factors (age, sex, blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking) **KQ 5:** True control group (receiving placebo, no intervention, or usual care), intervention/treatment at later or symptomatic stage of disease (vs. treatment at earlier or asymptomatic stage)	
Outcomes	**KQ 1:** Cardiovascular morbidity (MI, CVA), PAD morbidity (ambulation, patient function, amputation), or mortality (all-cause, PAD-related, or CVD-related) **KQ 2:** Sensitivity, specificity, PPV, NPV for PAD, incidence or prevalence **KQ 4:** Risk of cardiovascular morbidity or mortality, reclassification of risk of morbidity/mortality **KQ 5:** Intermediate cardiovascular outcomes (blood pressure, cholesterol, smoking cessation), cardiovascular or lower extremity–related health outcomes (listed	Surrogate markers for atherosclerosis including imaging (e.g., carotid intima-media thickness) or biochemical markers (e.g., C-reactive protein) Patient satisfaction Cost-related outcomes (for screening and treatment)

Appendix E. Inclusion/Exclusion Criteria

	Inclusion	Exclusion
	above for KQ 1)	
Harms	**KQ 3:** Adverse outcomes related to ABI test itself (diagnostic inaccuracy) or harms of subsequent testing **KQ 6:** Serious adverse events (e.g., death, serious adverse drug reactions), unexpected medical attention (e.g., emergency department visits, hospitalizations)	Patient satisfaction
Study Designs	**KQs 1, 5:** Good-quality systematic reviews, randomized or clinically controlled trials **KQ 2:** Good-quality systematic reviews, diagnostic accuracy studies **KQ 4:** Good-quality systematic reviews, cohort risk prediction studies **KQs 3, 6:** Good-quality systematic reviews, trials (randomized or clinically controlled), cohort or case-control studies	Poor-quality studies based on established design-specific quality criteria **KQs 2, 4:** Case-control studies of diagnostic accuracy or risk prediction **KQ 5:** Less than 3 months followup
Language	English only	Non-English languages

Appendix F. Excluded Studies

Exclusion Codes:
E1: Study relevance
E2: Population
  E2a: Patients with symptomatic PAD
  E2b: Exclusively persons with known CVD, diabetes
E3: No relevant outcomes
E4. Quality
  E4a. High or differential attrition
  E4b. Poor study quality: other quality issue
  E4c. Poor study quality: does not use reference standard
E5: Setting: hospital, inpatient, LTC, vascular clinics
E6. Not an included study design
  E6a. Study design: case control (applies to KQ2 only)
  E6b. Not an RCT, CCT, or SER
  E6c. Study design: CER
  E6d. Study design: followup from BL <3 months/12 weeks
  E6e. Does not adjust for traditional Framingham risk factors
E7a. Not a study of ABI
E7b. Not an included treatment

1. Randomized placebo-controlled, double-blind trial of ketanserin in claudicants. Changes in claudication distance and ankle systolic pressure. PACK Claudication Substudy. Circulation 1989;80:1544-8. PMID: 2688971. **KQ5E2a.**
2. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002 Jul 6;360(9326):7-22. PMID: 12114036. **KQ5E2a.**
3. Aboyans V, Lacroix P, Postil A, et al. Subclinical peripheral arterial disease and incompressible ankle arteries are both long-term prognostic factors in patients undergoing coronary artery bypass grafting. J Am Coll Cardiol 2005 Sep 6;46(5):815-20. PMID: 16139130. **KQ4E2b.**
4. Aboyans V, Lacroix P. Regarding: "A modified calculation of ankle-brachial pressure index is far more sensitive in the detection of peripheral arterial disease". Journal of Vascular Surgery 2007;46(3):617-8. PMID: 17826263. **KQ2E6.**
5. AbuRahma AF, Diethrich EB. Doppler ultrasound in evaluating the localization and severity of peripheral vascular occlusive disease. Southern Medical Journal 1979 Nov;72(11):1425-8. PMID: 505077. **KQ2E2a.**
6. Ahimastos AA, Lawler A, Reid CM, et al. Brief communication: ramipril markedly improves walking ability in patients with peripheral arterial disease: a randomized trial. Annals of Internal Medicine 2006;144:660-4. PMID: 16670135. **KQ5E2a.**
7. Ahimastos AA, Dart AM, Lawler A, et al. Reduced arterial stiffness may contribute to angiotensin-converting enzyme inhibitor induced improvements in walking time in peripheral arterial disease patients. Journal of Hypertension 2008;26:1037-42. PMID: 18398348. **KQ5E2a.**
8. Ahimastos AA, Pappas EP, Buttner PG, et al. A meta-analysis of the outcome of endovascular and noninvasive therapies in the treatment of intermittent claudication. Journal of Vascular Surgery 2011 Nov;54(5):1511-21. PMID: 21958561. **KQ5E2a.**
9. Allen J, Murray A. Comparison of three arterial pulse waveform classification techniques. Journal of Medical Engineering & Technology 1996 May;20(3):109-14. PMID: 8877751. **KQ2E1.**

10. Allison MA, Ho E, Denenberg JO, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. Am J Prev Med 2007 Apr;32(4):328-33. PMID: 17383564. **KQ4E3.**
11. Allison MA, Aboyans V, Granston T, et al. The relevance of different methods of calculating the ankle-brachial index: the multi-ethnic study of atherosclerosis. Am J Epidemiol 2010 Feb 1;171(3):368-76. PMID: 20042436. **KQ4E3.**
12. Alnaeb ME, Boutin A, Crabtree VP, et al. Assessment of lower extremity peripheral arterial disease using a novel automated optical device. Vascular & Endovascular Surgery 2007 Dec 20;41(6):522-7. PMID: 18166634. **KQ2E2.**
13. Alonso-Coello P, Bellmunt S, McGorrian C, et al. Antithrombotic therapy in peripheral artery disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012 Feb;141(2:Suppl):Suppl-90S. PMID: 22315275. **KQ5E6.**
14. Alzamora MT, Baena-Diez JM, Sorribes M, et al. Peripheral Arterial Disease study (PERART): prevalence and predictive values of asymptomatic peripheral arterial occlusive disease related to cardiovascular morbidity and mortality. BMC Public Health 2007;7:348. PMID: 18070367. **KQ4E3.**
15. Alzamora MT, Fores R, Baena-Diez JM, et al. The peripheral arterial disease study (PERART/ARTPER): prevalence and risk factors in the general population. BMC Public Health 2010;10:38. PMID: 20529387. **KQ4E6.**
16. Angeli F, Reboldi G, Verdecchia P. Lowering blood pressure with beta-blockers in peripheral artery disease: the importance of comorbidity. Journal of Hypertension 2011 Jul;29(7):1298-302. PMID: 21659823. **KQ1E4, KQ2E4, KQ3E4, KQ4E4, KQ5E4, KQ6E4.**
17. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008 Jul 9;300(2):197-208. PMID: 18612117. **KQ4E2.**
18. Antithrombotic TC. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. [Erratum appears in BMJ 2002 Jan 19;324(7330):141]. BMJ 2002 Jan 12;324(7329):71-86. PMID: 11786451. **KQ5E2a.**
19. Aquarius AE, Smolderen KG, Hamming JF, et al. Type D personality and mortality in peripheral arterial disease: a pilot study. Archives of Surgery 2009 Aug;144(8):728-33. PMID: 19687376. **KQ4E1.**
20. Arain FA, Khaleghi M, Bailey KR, et al. White blood cell count predicts all-cause mortality in patients with suspected peripheral arterial disease. American Journal of Medicine 2009 Sep;122(9):874-7. PMID: 19699384. **KQ4E1.**
21. Arain FA, Ye Z, Bailey KR, et al. Survival in patients with poorly compressible leg arteries. J Am Coll Cardiol 2012 Jan 24;59(4):400-7. PMID: 22261162. **KQ4E5.**
22. Aronow WS, Ahmed MI, Ekundayo OJ, et al. A propensity-matched study of the association of peripheral arterial disease with cardiovascular outcomes in community-dwelling older adults. American Journal of Cardiology 2009 Jan 1;103(1):130-5. PMID: 19101243. **KQ4E6e.**
23. Aung PP, Maxwell HG, Jepson RG, et al. Lipid-lowering for peripheral arterial disease of the lower limb. [Update of Cochrane Database Syst Rev. 2000;(2):CD000123; PMID: 10796489]. Cochrane Database of Systematic Reviews 2007(4):CD000123. PMID: 17943736. **KQ5E6.**
24. Auteri A, Angaroni A, Borgatti E, et al. Triflusal in the treatment of patients with chronic peripheral arteriopathy: multicentre double-blind clinical study vs placebo. International Journal of Clinical

Pharmacology Research 1995;15(2):57-63. PMID: 8593974. **KQ5E7.**

25. Baena-Diez JM, Alzamora MT, Fores R, et al. Ankle-brachial index improves the classification of cardiovascular risk: PERART/ARTPER Study. Revista Espanola de Cardiologia 2011 Mar;64(3):186-92. PMID: 21330032. **KQ4E6.**
26. Bagi P, Sillesen H, Bitsch K, et al. Doppler waveform analysis in evaluation of occlusive arterial disease in the lower limb: comparison with distal blood pressure measurement and arteriography. European Journal of Vascular Surgery 1990 Jun;4(3):305-11. PMID: 2191879. **KQ2E2a.**
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30. Bampi AB, Rochitte CE, Favarato D, et al. Comparison of non-invasive methods for the detection of coronary atherosclerosis. Clinics (Sao Paulo, Brazil) 2009;64(7):675-82. PMID: 19606245. **KQ4E2.**
31. Bavry AA, Anderson RD, Gong Y, et al. Outcomes Among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the INternational VErapamil-SR/Trandolapril STudy. Hypertension 2010 Jan;55(1):48-53. PMID: 19996066. **KQ4E1, KQ5E6.**
32. Baxter GM, Polak JF. Lower limb colour flow imaging: a comparison with ankle: brachial measurements and angiography. Clinical Radiology 1993 Feb;47(2):91-5. PMID: 8435971. **KQ2E2a.**
33. Beckman JA, Preis O, Ridker PM, et al. Comparison of usefulness of inflammatory markers in patients with versus without peripheral arterial disease in predicting adverse cardiovascular outcomes (myocardial infarction, stroke, and death). American Journal of Cardiology 2005 Nov 15;96(10):1374-8. PMID: 16275181. **KQ4E5.**
34. Benchimol D, Pillois X, Benchimol A, et al. Accuracy of ankle-brachial index using an automatic blood pressure device to detect peripheral artery disease in preventive medicine. Archives of Cardiovascular Diseases 2009 Jun;102(6-7):519-24. PMID: 19664571. **KQ2E4c, KQ3E4c.**
35. Bennett CL, Weinberg PD, Rozenberg-Ben-Dror K, et al. Thrombotic thrombocytopenic purpura associated with ticlopidine. A review of 60 cases. Ann Intern Med 1998 Apr 1;128(7):541-4. PMID: 9518398. **KQ6E2.**
36. Bennett CL, Connors JM, Carwile JM, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel 1. N Engl J Med 2000 Jun 15;342(24):1773-7. PMID: 10852999. **KQ6E2.**
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secondary prevention and high-risk primary prevention: rationale and design of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. Am Heart J 2004 Aug;148(2):263-8. PMID: 15308995. **KQ5E6c.**

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46. Bounameaux H, Holditch T, Hellemans H, et al. Placebo-controlled, double-blind, two-centre trial of ketanserin in intermittent claudication. Lancet 1985;2:1268-71. PMID: 2866336. **KQ5E2a.**
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62. Catalano M, Tomasini M, Scandale G, et al. Isradipine in the treatment of peripheral occlusive vascular disease of the lower limbs: a pilot study. The Journal of International Medical Research 1992;20:323-30. PMID: 1387369. **KQ5E4b.**
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