

Atherosclerotic Peripheral Vascular Disease Symposium II Screening for Atherosclerotic Vascular Diseases: Should Nationwide Programs Be Instituted?

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It has been proposed that vascular screening programs should be widely established to provide earlier detection of peripheral artery disease, carotid artery disease, renal artery disease, and abdominal aortic aneurysms (AAAs) to diminish the societal burden of these illnesses. Early detection of these conditions could lead to treatments that offer the potential to reduce the incidence of fatal and nonfatal myocardial infarction (MI) and stroke, death due to AAA rupture, and renal failure, as well as to improve quality of life. These goals engender considerable enthusiasm.

There are many reasons to propose a broad, population-based approach to establishment of vascular screening programs. Each arterial disorder is asymptomatic for a prolonged length of time, during which detection might be effective, defining a proposed "detection gap"¹; diagnostic tools are available that are accurate, safe, and relatively cost-effective; the database has improved overall such that these diagnostic methods could theoretically be applied selectively to targeted "at-risk" populations; and the publication of consensus-driven treatment guidelines now fosters use of effective treatments, while restraining the use of harmful or unproven treatments.² Thus, it might be feasible to detect preclinical atherosclerosis and stenotic or aneurysmal disease in screening programs applied to specific at-risk populations with achievable benefits and minimal harm.

Criteria for Screening Programs

The proposition of screening programs for at-risk populations must be considered in light of a yet incomplete scientific

database that would support the efficacy of this approach. What criteria should be applied if the public is to enjoy the putative benefits of vascular screening? These criteria include knowledge that the vascular disorder is an important public health problem; the vascular disorder should have an asymptomatic but detectable latent phase; treatment should be more effective at the latent stage than at a later stage (with improved efficacy, lower cost, or improved symptom-free survival); and the disease should have a high prevalence or be more prevalent in a high-risk population that can be defined for screening. In addition, the screening test must be safe, precise, feasible, and validated; be ethically acceptable and accepted by the target population; have defined cutoff levels validated by its test characteristics (sensitivity, specificity, and predictive value); and be cost-effective. Ideally, the proposed interventions should be effective, and vascular screening programs should be created in a national context that takes into account policy implications, including access and affordability, so as to not worsen health disparities. Finally, the screening process should be readily available to those targeted.

Each screening program ideally would be justified by convincing data from a randomized clinical trial; however, such data are limited, as well as expensive and time-consuming to obtain. At this time, it appears unlikely that such trial data will be forthcoming for the vast majority of putative screening modalities in the foreseeable future. Therefore, we must consider other forms of evaluation based on observational data that use detection and treatment efficacy modeling and cost-effectiveness analyses.

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Table 1. Methodology

	ABI	Carotid Artery Ultrasound	AAA Ultrasound	Renal Artery Ultrasound
Validated	+	+	+	+
Cutoff	<0.90	>0, 50%, 80%	>3 cm	>60%
Standardized technique	+/-	+	+	+
Safety	+	+	+	+
Cost	Low	Moderate	Moderate	Moderate
Ease of use	High	Moderate	Moderate	Low

The Subclinical Cardiovascular Disease Paradigm

Over the past several years, numerous measures of subclinical (used here as a synonym for asymptomatic) markers of cardiovascular disease have become available. Many of these measures have shown a predictive value for future incident cardiovascular disease events that persists after adjustment for known cardiovascular disease risk factors. Thus, such measures add independent and incremental information in assessing an individual's risk. Four measures of subclinical cardiovascular disease of potential value are reviewed here. These are the ankle-brachial index (ABI) to diagnose peripheral artery disease, ultrasound to diagnose carotid artery disease, ultrasound to diagnose AAAs, and ultrasound to diagnose renal artery disease. Table 1 summarizes selected methodological issues in the use of these 4 tests. These methodological issues are validation of the technique, usual cutoff values used, standardization of the technique, safety of the procedure, cost, and ease of use. Each of these techniques is addressed below.

Peripheral Artery Disease: The ABI

The ABI is the ratio of systolic blood pressure at the ankle to that in the arm. It is measured with the patient supine, usually with a sphygmomanometer and Doppler ultrasound probe. The precise technique and calculation of the ABI have not been standardized universally, but a common approach is to measure systolic pressure in both arms and at the posterior tibial and dorsalis pedis arteries in each ankle with the patient in a supine position. The ABI for each leg is then calculated as the higher pressure at the ankle divided by the higher of the left and right arm pressures.²

In theory, the ABI might be used for 2 linked but different screening purposes: (1) to detect asymptomatic arterial disease in the legs in order to prevent progression to claudication or critical limb ischemia and (2) to detect individuals at high risk of future cardiovascular events in order to initiate cardiovascular risk-reduction measures. More interest has been expressed in the latter approach, which will be discussed here. Only 20% of major cardiovascular events occur in subjects with a history of cardiovascular disease, and in those without such a history, risk factor scoring systems such as the Framingham Risk Score have limited accuracy. There is thus considerable interest in the potential of other markers to improve prediction of cardiovascular events.

An ABI <0.90 has been associated consistently with a 2- to 4-fold increased relative risk of cardiovascular events and death. For the evaluation of screening, however, measures of validity, such as sensitivity, specificity, and positive and negative predictive values, are more relevant. These test characteristics will be estimated in the ongoing ABI Collaboration of 16 studies worldwide,³ but meanwhile, a small systematic review found, without adjusting for risk factors, that an ABI cutpoint of 0.90 had a sensitivity of 41% and a specificity of 88% in detecting future cardiovascular deaths.⁴ Also, inclusion of the ABI has been shown to improve the accuracy of conventional risk factors in predicting cardiovascular events over a 5-year period.⁵ For example, in hypertensive smokers with normal cholesterol values, the positive predictive value of an event was 25%, but this rose to 44% if the subjects also had an ABI <0.90. In those with no risk factors, the positive predictive value was 9%, but this rose to 24% if an ABI <0.90 was found.

Several studies have investigated the variability in measuring the ABI, and overall, the 95% confidence interval (CI) of 1 measurement is $\approx 15\%$. Thus, for a single result of 1.0, the clinician can be 95% sure that the "true" result lies between 0.85 and 1.15.⁶ This variability is only slightly worse than for blood pressure but suggests that on occasion, a repeat measure at a different visit and taking the mean of the 2 results may be justified if the level will have an influence on clinical decisions. In assessing the value of the ABI for screening, the yield is also important, ie, the proportion of screenees who are identified to be at high risk. In the US National Health and Nutrition Examination Survey in 1999–2000, 4.3% of adults ≥ 40 years of age had an ABI <0.9 in either leg, but this rose dramatically with age so that among those ≥ 70 years of age, the prevalence was 14.5%.⁷ The overall prevalence was 3.3% among those with no history of cardiovascular disease and varied according to ethnic group. Thus, it could be that the yield from screening might only be worthwhile in certain subgroups, such as the elderly or those with multiple cardiovascular disease risk factors.⁸

The financial cost of an ABI test is relatively small. A handheld Doppler unit costs approximately \$500, with very few consumables required, so that the main cost is for staff time. An ABI examination takes ≈ 15 minutes, including a 5-minute pretest rest in the supine position. Nursing staff can be easily trained to perform the test. Although the ABI test is inexpensive, the relative cost-effectiveness of its use would need to be evaluated within the context of a cardiovascular screening program. From the patient's perspective, the test is eminently acceptable because it is noninvasive with minimal discomfort.

If an individual is found to have a low ABI and thus to be at risk, standard cardiovascular risk-reduction measures may be required, including exercise, smoking cessation, lipid lowering, antihypertensive drugs, treatment of diabetes mellitus, and antiplatelet therapy. Some decisions on risk reduction would not depend on an ABI result—for example, smoking cessation, glucose control, and exercise. On the other hand, the use of statins and antihypertensive medications might be determined by the level of cardiovascular risk

and thus might be affected by the ABI results, as would the use of antiplatelet agents.

No randomized trial data are available on the use of the ABI as a screening tool. Given its ease of measurement, low cost, and safety, a cost-effectiveness analysis would be timely and would likely support the use of the ABI in targeted higher-risk persons, as has been recommended by several groups.

Ultrasound for Carotid Artery Disease

A screening program that uses carotid duplex ultrasound (B-mode and Doppler) aims to detect individuals with asymptomatic carotid artery stenosis for several purposes: (1) to identify individuals at risk of having a cardiovascular event, particularly in the cerebrovascular and coronary circulations, (2) to select individuals who need significant risk factor modification, and (3) to potentially intervene with carotid endarterectomy or carotid stenting to prevent a stroke. Screening studies using carotid duplex ultrasound have shown that 4% to 8% of individuals >50 years of age will have an asymptomatic carotid stenosis that is $\geq 50\%$.^{9,10} Between 1% and 3% of these individuals will have a stroke in the carotid territory each year. Furthermore, carotid lesions are responsible for 20% to 30% of all strokes, either by leading to carotid occlusion or as a source of artery-to-artery emboli.⁹ Therefore, the detection of carotid stenosis is an important step in stroke prevention.

Numerous past studies have shown that carotid ultrasound is a safe, accurate, noninvasive, and relatively inexpensive method for the detection of carotid stenosis. The wide availability of carotid ultrasound and its ease of performance also make it a useful screening technique.¹¹ According to large meta-analyses,^{12,13} its overall accuracy (sensitivity and specificity) is in the range of 85% to 90%. Some centers and operators may achieve higher or lower levels of accuracy because there is still significant variability caused in part by operator training and skills, techniques, and technical factors.¹⁴

A potential limitation is that in some screening programs, carotid ultrasound may image only a few centimeters of the carotid arteries in the neck, with a focus on detecting lesions in or near the cervical carotid bifurcation. However, accredited diagnostic ultrasound laboratories should be able to image the extracranial carotid arteries both proximal and distal to the bifurcation. Other techniques, such as contrast-enhanced magnetic resonance angiography or computed tomographic angiography, can also be used to image the extracranial and intracranial vasculature, although they have not been studied as part of a screening paradigm.

Prior screening programs using carotid ultrasound have produced results that depict some of the practical and public health issues with this approach to stroke prevention. A study of 2559 seniors found that 7.5% had carotid stenoses of $>50\%$, of which two thirds (5%) were confirmed by further ultrasound study.¹⁵ It is likely that no more than half of these patients had a stenosis $\geq 80\%$, a level that many clinicians now use as a criterion for intervention (endarterectomy or stenting) in asymptomatic patients. Of these patients, even if two thirds agreed to surgery, only 1.7% of the total screened

cohort would undergo surgery. No data on outcomes were provided in this study, but overall, it appears that the yield in terms of identifying patients who might benefit from an intervention is low. Another community-based screening program studied 610 individuals using duplex ultrasound and found that 11% had carotid stenosis $\geq 50\%$.¹⁶ If we assume that the accuracy rate is two thirds, that yields 8% with 50% stenosis. If we further assume that one fourth to one half of these patients have $\geq 80\%$ stenosis, the yield would be 2% to 4%. If half elect to undergo surgery, then the overall yield would be 1% to 2%.

Several studies have examined clinical factors that may predict the presence of significant carotid stenosis in an attempt to identify a target population that would improve the yield and efficiency of screening programs. A number of clinical factors emerged as predictive of carotid stenosis, including advanced age, hypertension, heart disease, smoking, hyperlipidemia, peripheral artery disease, and AAA.^{10,17} Many of these risk factors would also predict the presence of atherosclerotic disease in other vascular beds. Patients who have been treated with neck irradiation appear to have a particularly high rate of developing carotid stenosis, perhaps up to $\geq 40\%$ in some series.¹⁸ Such patients may warrant carotid screening with serial ultrasounds.

Carotid screening programs have potential limitations, including low rates of progression, low yields for predicting future strokes, and concerns about screening protocols and patient follow-up. Many prior screening programs had relatively brief follow-ups, typically only 2 to 4 years. Many did not routinely use contemporary intensive medical therapy, such as high-dose statin drugs, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers; antiplatelet agents; strict glycemic control in persons with diabetes; and aggressive smoking cessation programs. The impact of such measures on progression or regression of disease and clinical outcomes is unknown. Critics of existing screening programs have raised important issues. The training and expertise of the ultrasound operators may not be standardized in all cases.¹⁴ The screening protocol is often not standardized among different vendors. Defining a 50% stenosis as "significant" may be true in the hemodynamic sense but not necessarily as a clinical criterion for endovascular or surgical intervention. Providing the patient with an isolated ultrasound result without any medical context can be confusing or upsetting. Many screened persons do not have a primary care physician, so potential follow-up is problematic.¹⁹ In some studies, the stroke end points used to assess the benefit of a carotid screening program are lumped together, with little attention given to the vascular territory of the stroke and the stroke mechanism.

It is now well established that carotid disease and coronary disease often coexist. Several studies of patients with ischemic stroke have shown that 20% to 30% of such patients will have evidence of significant coronary artery disease. If patients with carotid artery atherosclerosis are studied specifically, the prevalence of significant or severe coronary artery disease increases to 40% or more in some series.²⁰ Likewise, significant carotid artery stenosis is seen in 8% to 18% of patients who undergo coronary artery bypass surgery or other

cardiac surgeries.^{16,21,22} Therefore, the finding of carotid stenosis might prompt further evaluations for clinically silent coronary artery disease in some cases.

Epidemiological studies have shown that in the absence of detectable carotid stenosis, differences in the thickness of the intimal–medial layer in the common or internal carotid artery have independent prognostic significance for future cardiovascular events.²³ Nevertheless, the predictive value is relatively small compared with a finding of stenosis, and the technique requires careful training and standardization.

In summary, carotid artery ultrasound identifies with reasonable accuracy individuals who are at increased risk of cardiovascular events, including myocardial infarction and stroke. These include elderly persons, patients with risk factors for atherosclerosis, and particularly patients with known atherosclerosis (eg, coronary artery disease, peripheral artery disease) and persons who have had neck irradiation. No randomized clinical trials are available to support routine screening, even in “at-risk” patients, but such studies along with cost-effectiveness analyses would be helpful. Measurement of carotid wall thickness appears to allow discrimination of risk even in young adults, but methods are technically challenging and need further evaluation and refinement before being considered for population-based screening programs.

Ultrasound for AAA

AAAs account for \approx 15 000 deaths and 53 000 hospital discharges annually in the United States. AAAs contribute to at least two thirds of annual aneurysm-related deaths.^{24,25} The prevalence of AAA is approximately 4% to 5% among men >50 years of age, and AAA is 5 to 6 times more common among men than women. The major risk factors associated with aneurysm development include age >65 years, male sex, smoking, and a history of AAA disease among first-degree relatives. Aneurysm-related death equates with rupture, the risk for which varies directly with aneurysm size. Additional factors associated with rupture include smoking and female sex. Women experience rupture more frequently and at smaller aortic diameters than men.

Case-fatality rates for AAA rupture approximate 75%, and hence, referral for elective repair, which is associated with a perioperative death rate of 2% to 6%, is indicated once certain size and/or clinical criteria are met. Current recommendations for surgical repair derive from the US and UK small (4.0- to 5.5-cm) aneurysm trials and include maximal diameter >5.5 cm, an increase in aneurysm size >1.0 cm per year, or symptoms referable to the aneurysm.^{26,27}

Although a variety of imaging modalities are available for visualization of the abdominal aorta, ultrasonography is the noninvasive procedure of choice for screening because of its widespread availability, reasonable accuracy, relatively low cost, and excellent safety. The sensitivity and specificity of ultrasound for the detection of AAA disease are 95% and 100%, respectively.²⁸ Computed tomography or magnetic resonance imaging can be used for selected patients whose body size or habitus precludes accurate ultrasound interrogation. These imaging modalities are not appropriate, however, for widespread population-based screening programs.

Randomized clinical trial data are available to help guide decision making for AAA disease detection. The Multicenter Aneurysm Screening Study (MASS) enrolled 67 800 men 65 to 74 years of age to study the effect of ultrasound scanning and surveillance on AAA-related death rate.²⁹ Secondary end points included all-cause death, the frequency of AAA rupture, and the effect of screening on the quality of life. Over a mean follow-up of 4.1 years, there were 65 AAA-related deaths in the invited group (absolute risk 0.19%) and 113 in the control group (absolute risk 0.33%, hazard ratio 0.58, 95% CI 0.42 to 0.78, $P=0.0002$). The incidence of nonfatal AAA rupture was also lower in the invited group (17 versus 27 events). The all-cause death rate was not different between groups (hazard ratio 0.97, 95% CI 0.93 to 1.02, P =not significant). AAA-related deaths accounted for only 2% of all deaths in the invited group and 3% in the control group. There were fewer deaths due to ischemic heart disease in the invited group (26% versus 28%, $P=0.03$). The study findings did not indicate an adverse effect of screening on the emotional states of men in whom an aneurysm was detected. The authors estimated that among men invited to screening, the risk of AAA-related death over 4.1 years was reduced from 3.3 per 1000 to 1.9 per 1000 and that 710 men would need to be screened to prevent 1 AAA-related death over this time interval.

The US Preventive Services Task Force (USPTSF) incorporated the results of the MASS Trial with those from 3 additional but less robust screening studies in a meta-analysis of the utility of screening to prevent AAA-related death.²⁵ On the basis of this meta-analysis, the USPTSF in 2005 recommended 1-time ultrasonography screening for AAA in men 65 to 75 years of age who have ever smoked (total cigarettes consumed in a lifetime \geq 100; grade B recommendation). The USPTSF did not make a recommendation for men 65 to 75 years old who have never smoked (grade C recommendation) and recommended against routine screening for AAA in women (grade D recommendation). These recommendations differ from those previously provided by a consensus panel of experts representing the Society of Vascular Surgery and the Society for Vascular Medicine and Biology.³⁰ This consensus group advocated for screening in all men 60 to 85 years of age, in women 60 to 85 years of age who had cardiovascular risk factors, and in men and women \geq 50 years of age with a family history of AAA. The American College of Cardiology/American Heart Association guidelines on peripheral artery disease gave a Class I recommendation for screening for men \geq 60 years of age who are the offspring or siblings of patients with AAAs (Level of Evidence B) and a Class IIa recommendation for men 65 to 75 years of age who ever smoked (Level of Evidence B).² Since 2007, free screening is available to new Medicare enrollees considered at high risk for the development of AAA disease.

Estimates of the cost-effectiveness of screening programs vary. The 2005 USPSTF findings were heavily influenced by the cost-effectiveness analysis provided by the MASS investigators in 2002.^{31,32} Compared with no screening, the cost-effectiveness of population-based screening of asymptomatic persons for AAA to reduce AAA-related mortality and morbidity ranged from \$14 000 to \$72 000 per quality-

Table 2. Cautions

Will diagnostic "labeling" adversely affect patients? Could health insurance be jeopardized?
Will screening be linked to education and treatment in a multidisciplinary care setting?
Will technology advances make screening easier, cheaper, or more accurate, leading to changes in the cost-effectiveness considerations?

adjusted life-year in 2003 US dollars. These estimates implied that screening, and particularly targeted screening, was reasonably cost-effective compared with other population-based interventions. At the 7-year follow-up, cost-effectiveness had improved to \$19 500 (CI \$12 400 to \$39 800) per life-year gained on the basis of AAA-related death rate and \$7600 (CI \$3300 to ∞) per life-year gained on the basis of all-cause death rate.³³ Recommendations have also varied about the frequency with which surveillance imaging is indicated for persons found to have an AAA on index ultrasound screening. The UK Small Aneurysm investigators have shown that intervals of 36, 24, 12, and 3 months for aneurysms of 35, 40, 45, and 50 mm, respectively, would restrict the probability of an aneurysm enlarging beyond 55 mm at the time of next screening to <1%.³⁴ A single negative screening study at ≥ 65 years of age obviates the need for any follow-up studies, because the risk of the development of important aneurysm disease thereafter is negligible.²⁵

In summary, ultrasound imaging can identify asymptomatic individuals at risk for AAA-related death effectively and at reasonable cost. Referral of appropriate patients for elective intervention on the basis of AAA size, change in size, or symptoms can reduce AAA-related death rate. The evidence base is strongest for men 65 to 75 years of age, but relative indications for screening can be justified in other patients.

Ultrasound for Renal Artery Disease

Screening for renal artery disease is predicated on the assumption that detection of renal artery stenosis would lead to a treatment (medical or endovascular) that would improve either clinically relevant cardiovascular (heart attack, stroke, or death) or renal outcomes. Renal artery stenosis occurred in $\approx 7\%$ of an elderly population in the Cardiovascular Health Study.³⁵ Renal artery stenosis occurs in $\approx 40\%$ of patients with AAA or peripheral artery disease³⁶ and is common in patients with coronary artery disease. In patients undergoing

aortography to evaluate the renal arteries at the time of cardiac catheterization, the prevalence of renal artery stenosis >50% is 15% to 19%.^{37,38} In one study, severe renal artery stenosis (>75%) was present in 4.8% of subjects, and bilateral stenosis of >75% was present in only 0.8% of subjects.³⁹ The 4-year survival rate is 89% in patients with <75% stenosis, compared with 57% in patients with >75% stenosis,³⁹ but whether renal artery stenosis adds incremental risk beyond known atherosclerosis risk factors is unknown. Renal artery disease may progress, but renal artery occlusion occurs in only $\approx 10\%$ of patients with >60% stenosis detected by duplex ultrasonography, and even fewer progress to end-stage renal disease.^{40–42} Finally, few, if any, patients will develop severe renal artery stenosis without clinical clues to suggest its presence.⁴³

Renal artery stenosis may be discovered in 4 ways: (1) Clinical clues that suggest the presence of renal artery disease may lead the clinician to order a test to search for renal artery stenosis. Theoretically, the patient would then undergo treatment if significant stenosis were discovered. (2) An imaging test is performed for some other reason, and renal artery stenosis is discovered incidentally. (3) A screening program is initiated with duplex ultrasound to search for renal artery stenosis. This is the least likely scenario, because there are few centers capable of performing high-quality duplex ultrasound of the renal arteries, and there is no reimbursement for such screening. (4) Abdominal aortography or renal angiography is performed at the time of cardiac catheterization to screen for renal artery disease.

Of all the potential subclinical vascular disease screening programs described in this section, renal artery disease has the weakest evidence base to support the deployment of routine screening. No evidence indicates that screening provides any benefit to the patient. Although duplex ultrasound can diagnose renal artery disease with a high degree of accuracy (in excess of 95%),⁴⁴ the noninvasive screening technique utilizing duplex ultrasound is not as readily available in most vascular laboratories as duplex ultrasound for carotid artery disease or AAA. Far fewer laboratories are capable of performing high-quality renal artery duplex ultrasound than ultrasound in other vascular territories. Screening with computed tomographic angiography or magnetic resonance angiography would not be cost-effective.

In summary, evidence is insufficient to support screening for the presence of renal artery stenosis in patients without acceptable clinical clues. Results of the Cardiovascular Out-

Table 3. Recommendations: Should We Screen in Selected Groups?

ABI	Carotid Artery Ultrasound	AAA Ultrasound	Renal Artery Ultrasound
Probably:	Possibly:	Yes:	No:
Low cost	Higher cost	Good randomized, controlled trial evidence	Much work to be done before considering as a screening test
High yield	Needs cost-effectiveness evaluation		
Strong predictor	Randomized, controlled trial would be ideal		
Needs cost-effective evaluation			
Randomized, controlled trial would be ideal			

comes for Renal Atherosclerotic Lesions (CORAL) trial may provide evidence that stenting of the renal arteries improves cardiovascular and renal outcomes.⁴⁵ If so, this position may need to be modified.

Cautions

Several issues require discussion in the context of screening. These are listed in Table 2. Will positive findings “label” patients, and could medical coverage be jeopardized? Will screening be linked to education and treatment in a multidisciplinary care setting? Will technology advances make screening easier, cheaper, or more accurate, leading to changes in efficacy and cost-effectiveness considerations? Each of these questions involves moving targets that will need to be monitored continuously as screening tests are evaluated.

Recommendations

Recommendations about the appropriateness of use of each of these 4 tests are summarized in Table 3. These recommendations refer to the use of the 4 tests discussed above for screening in appropriately targeted populations. The low cost, high yield, and strong prognostic significance of the ABI suggest it would be appropriate as a screening tool. No randomized trial data for this exist, nor is such an evaluation planned. A careful cost-effectiveness analysis is a high priority. Carotid duplex ultrasound is more expensive and more technically challenging than the ABI; however, positive findings carry significant import. Randomized screening trial data for carotid duplex ultrasound are unavailable, and no trials of this technology are currently planned. A cost-effectiveness analysis would be useful. Ultrasound for AAA detection has strong clinical trial support in the appropriate populations, and its use is likely to become more widespread. Finally, ultrasound for renal artery disease has the least data among the screening tests discussed herein and thus is the most problematic for use in screening; however, an ongoing therapeutic (not screening) trial should provide additional insight.

Disclosures

Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary, which is available online at <http://circ.ahajournals.org/cgi/reprint/118/25/2811>.

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