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Prevalence of Symptomatic and Asymptomatic Peripheral Arterial Disease and the Value of the Ankle-brachial Index to Stratify Cardiovascular Risk

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Abstract *Objectives:* To determine the prevalence of ankle-brachial index (ABI) < 0.9 and symptomatic peripheral arterial disease (PAD), association with cardiovascular risk factors (CVRF), and impact of adding ABI measurement to coronary heart disease (CHD) risk screening.
Design: Population-based cross-sectional survey of 6262 participants aged 35—79 in Girona, Spain.
Methods: Standardized measurements (CVRF, ABI, 10-year CHD risk) and history of intermittent claudication (IC), CHD, and stroke were recorded. ABI < 0.9 was considered equivalent to moderate-to-high CHD risk (≥10%).
Results: ABI < 0.9 prevalence was 4.5%. Only 0.62% presented low ABI and IC. Age, current smoker, cardiovascular disease, and uncontrolled hypertension independently associated with ABI < 0.9 in both sexes; IC was also associated in men and diabetes in women. Among participants 35—74 free

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of cardiovascular disease, 6.1% showed moderate-to-high 10-year CHD risk; adding ABI measurement yielded 8.7%. Conversely, the risk function identified 16.8% of these participants as having 10-year CHD risk $>$ 10%. In participants 75–79 free of cardiovascular disease, the prevalence of ABI $<$ 0.9 (i.e., CHD risk $\geq$ 10%) was 11.9%.

Conclusions: ABI $<$ 0.9 is relatively frequent in those 35–79, particularly over 74. However, IC and CHD risk $\geq$ 10% indicators are often missing. Adding ABI measurement to CHD-risk screening better identifies moderate-to-high cardiovascular risk patients.

Introduction

Primary prevention of cardiovascular diseases, a major public health challenge in developed and developing countries,[1] is guided by risk estimation using mathematical algorithms.[2] However, risk functions fail to identify many individuals who will develop a cardiovascular event within 10 years.[3] As a complement to risk estimation, some strategies, including diagnosing pre-symptomatic atherosclerosis, can improve detection of high-risk patients.[1]

The population prevalence of peripheral arterial disease (PAD), the atherosclerotic occlusive disease of arteries distal to the aortic bifurcation, ranges from 6.9% to 21.4% depending on PAD definition, sex, and age range in western countries.[4–8] PAD risk factors are common to other atherosclerotic diseases,[9] and PAD indicates high risk of coronary heart disease (CHD), stroke, and mortality irrespective of intermittent claudication (IC).[10–14] PAD is typically asymptomatic before progressing to clinical stages ranging from IC to critical limb ischemia.[10,11] Ankle-brachial index (ABI) is a simple, inexpensive, and non-invasive PAD measurement,[15] even at the pre-symptomatic phase when intervention can improve prognosis and prevent or delay severe complications.[16,17] Sensitivity and specificity of a 0.9 ABI cut-off value are ~95% for detecting angiographically positive PAD in symptomatic individuals.[16–19]

These characteristics imply the equivalent of high cardiovascular risk, suggesting that ABI can offer additional information about a patient's cardiovascular risk. Cardiovascular prevention programs could include ABI measurement for PAD screening.[5] The study aimed to determine the prevalence of ABI $<$ 0.9 and of symptomatic PAD, their association with cardiovascular risk factors, and the impact on identifying otherwise undetected moderate-to-high-risk individuals if ABI measurement were added to population screening for CHD risk.

Methods

Population

This population-based cross-sectional study was conducted between 2005 and 2006 in Girona province (~600,000 inhabitants), northeastern Spain.[20]

We selected a random population sample of participants aged 35–79 years from the city of Girona (~70,000 inhabitants) and two rural towns, stratified by age and sex. Although sample size was calculated for a cross-sectional risk factor prevalence study,[21] with a prevalence of low ABI of 5.2% and 3.9% for men and women, respectively, our comparisons in men and women were powered at 80% to detect as statistically significant (p-value $<$ 0.05) differences between low and normal ABI participants of at least 12% units in a categorical variable, with a point estimate of 50% (most conservative approach).

All participants were duly informed and signed their consent to participate in the study, approved by the local ethics committee.

Measurements

Examinations were performed by trained nurses and interviewers using standard questionnaires and measurement methods.[22]

Body mass index (BMI) was calculated as weight divided by squared height (kg/m^2).

Blood pressure was measured with a calibrated oscillometric sphygmomanometer (OMRON 705 IT) using a cuff adapted to upper arm perimeter (young, adult, obese). After 5 min rest, two measurements were taken, at least 20 min apart, and the lower value recorded. Participants were considered hypertensive if previously diagnosed by a physician, under treatment, or presenting systolic blood pressure (SBP) $\geq$ 140 or diastolic blood pressure (DBP) $\geq$ 90 mmHg. Uncontrolled hypertension was defined as SBP $\geq$ 140 or DBP $\geq$ 90 mmHg (130/80 mmHg in participants with diabetes).

Blood was drawn after 10–14 h fasting, with >60 s of venostasis. Methods and quality control of determination of total cholesterol, HDL-c and triglyceride concentrations are detailed elsewhere.[21]

Diabetes was defined as history of diabetes, diabetes treatment or fasting glycemia $>$ 125 mg/dl.

CHD risk was calculated in all participants 35–74 years old and free of cardiovascular disease using the Framingham function adapted to Spain and validated in this population. In summary, this methodology maintains the original model structure (including variables) and the original β-coefficients but substitutes local incidence and risk factor prevalence for the Framingham coronary event incidence rate and risk factor prevalence. This function has been shown to accurately and reliably predict CHD risk for patients aged 35–74.[23,24]

A standardized smoking questionnaire was used to evaluate cigarette consumption.[22] Participants were classified as smokers (current or quit $<$ 1 year), former smokers (quit $\geq$ 1 year) or never smokers. In the multivariate analysis, former smokers and never smokers were considered non-current smokers in a dichotomized variable.

History of cardiovascular disease (myocardial infarction, angina, or stroke) was considered when diagnosed by a physician. Primary care and hospital clinical records of all participants were reviewed for history of arterial limb revascularization procedures.

ABI measurement

After a 5-min rest, systolic blood pressure was measured in the brachial artery in the antecubital fossa in both arms, with a continuous Doppler device (SONICAID 421, Oxford Instruments), 8 MHz probe. The cuff was then applied to the distal calf, and the Doppler probe was used to determine systolic blood pressure in supine position at the right and left posterior and anterior tibial arteries. Right and left ABI were calculated as the ratio of the highest of the two systolic pressures in lower limbs (posterior and anterior tibial arteries) to the average of the right and left brachial systolic pressures, unless there was a discrepancy $\geq$ 10 mmHg between the two arms (in which case the highest reading was used). The lower of the two ABI values obtained from the left and the right ankle was used for analysis. ABI $<$ 0.9 in either leg was considered moderate-to-high cardiovascular risk [5,10–15]; ABIs in the 0.9–1.39 range were considered normal; ABI $>$ 1.39 was excluded from evaluation since the possible influence of arterial wall stiffness made it impossible to discard arterial obstruction.[13,25] Operators were meticulously trained by a senior vascular surgeon. A protocol of independent measurements assessed operator performance and found low inter- and intra-operator variability, showing an intraclass correlation coefficient of 0.92 and 0.94, respectively.

Edinburgh questionnaire

Claudication was assessed using participants' answers (as noted) to the Edinburgh questionnaire[26]:

1. Do you get any pain or discomfort in your legs when you walk? (Yes)
2. Does this pain ever occur when you are standing still or sitting? (No)
3. Do you get this pain if you walk uphill or hurry? (Yes)
4. Do you get this pain if you walk at an ordinary pace on level ground? (No = mild, Yes = moderate/severe)
5. What happens to the pain if you stand still? (It goes away)
6. Does the pain disappear within 10 min or less when you stand still (Yes)
7. Where do you get the pain or discomfort? (leg diagram is presented to patient)

Based on the conditions fulfilled by the response, patients were classified as follows:

1) Definite claudication
   - All responses to questions 1–6 as noted above
   - Calf area marked on the diagram of the leg (question 7)
2) Atypical claudication
   - All responses to questions 1–6 as noted above
   - Thigh or buttock marked on the diagram of the leg, in the absence of calf pain (question 7)
3) No claudication. Any other combination of responses

PAD was considered asymptomatic when ABI $<$ 0.9 and the Edinburgh questionnaire showed no IC. Symptomatic PAD included patients with ABI $<$ 0.9 and definite or atypical IC based on the Edinburgh questionnaire.

Statistical analysis

Prevalence is presented by sex and is standardized for age according to the age distribution of the standard world population.[27] Continuous variables are presented as mean and standard deviation or median and interquartile range when their distribution departs from normal (glycemia, triglycerides). Kruskall–Wallis or Student's t-test was used for differences in continuous variables and Chi square tests for categorical variables. Adjusted odds ratios (OR) of ABI $<$ 0.9 were estimated by a logistic model for demographic, comorbidity, clinical and severity variables that showed significant differences ($p < 0.05$) in the univariate analysis. Important variables based on clinical judgment, such as age, sex or diabetes, were also included as potential confounders.

Results

From a randomly selected population sample of 8485 eligible subjects aged 35–79 years, 6262 (73.8%) agreed to participate. The response rate did not vary substantially by age and sex groups. Therefore, it is reasonable to suppose that age and gender selection bias is minimized. Analysis included 2903 men and 3269 women ($n = 6172$); 78 participants with ABI $>$ 1.39, suggesting arterial wall stiffness, and 12 participants without ABI measurement were excluded.

Table 1 shows participant characteristics, comparing the presence of cardiovascular risk factors by sex in the total population sample aged 35–79. Table 2 shows prevalence of ABI $<$ 0.9 with symptomatic PAD by sex and age groups. ABI $<$ 0.9 was present in 277 participants (4.5%, 95%CI: 4.0–5.0%), 150 men (5.2%, 95%CI: 4.4–6.0%) and 127 women (3.9%, 95%CI: 3.2–4.6%). Only 0.62% (95%CI: 0.44–0.84%) with low ABI presented IC as assessed by the Edinburgh questionnaire (13.7% (95%CI: 9.9–18.3%) of all participants with ABI $<$ 0.9). Age-standardized prevalence of ABI $<$ 0.9 was 4.23 (95%CI: 3.57–4.89) in men and 3.75 (95%CI: 3.10–4.41) in women.

Prevalence of ABI $<$ 0.9 was highest in participants 75–79 years old (14.1%, 95%CI: 11.3–17.3%). Prevalence of ABI $<$ 0.9 in those individuals 75–79 years old free of known vascular disease was 11.9% (95%CI: 9.1–15.3%).

Low-ABI participants were older and more often diabetic, hypertensive, and, in men, current smokers. Myocardial infarction, angina, and stroke were significantly more prevalent in ABI $<$ 0.9 individuals, along with higher 10-year CHD risk in the 35–74 age group for whom this risk function is calibrated. Table 3 compares cardiovascular risk factors in individuals with and without ABI $<$ 0.9, by sex.

ABI $<$ 0.9 was independently and positively associated in the study population with age, current smoker, cardiovascular disease, and uncontrolled hypertension, and also with IC in men and diabetes in women (Table 4).

From the 6172 included individuals, CHD risk was calculated in all participants 35–74 years old and free of

Table 1 Comparison of presence of cardiovascular risk factors by sex in a population sample aged 35—79 years in Girona, Spain

	Men	Women	*p*-Value
N	2903	3269	
Age[a]	56.6 (12.3)	55.9 (12.3)	0.029
Hypertension	50.6%	41.1%	<0.001
Diabetes	18.6%	11.9%	<0.001
Smoking			
Current or former smoker ≤1 year	29.6%	15.9%	<0.001
Former smoker >1 year	41.2%	12.8%	<0.001
Never smoker (%)	29.1%	71.3%	<0.001
Systolic blood pressure[a]	131 (18)	125 (21)	<0.001
Diastolic blood pressure[a]	80 (10)	77 (10)	<0.001
Uncontrolled hypertension	36.4%	26.7%	<0.001
Total cholesterol[a]	209 (40)	213 (43)	<0.001
HDL cholesterol[a]	47 (12)	57 (14)	<0.001
LDL cholesterol[a]	136 (36)	135 (37)	0.103
Triglycerides[b]	104 (78—144)	86 (64—120)	<0.001
Body mass index[a]	27.8 (3.8)	27.0 (5.1)	<0.001
10-year CVD risk < 10%[c]	87.6%	98.4%	<0.001
History of arterial limb revascularization	0.34%	0.00%	0.001
Any cardiovascular disease	8.32%	4.02%	<0.001
ABI < 0.9	5.17%	3.88%	0.015
ABI < 0.9 and Edinburgh definite or atypical	1.17%	0.12%	<0.001
ABI < 0.9 and Edinburgh normal	3.92%	3.74%	0.712

CVD: cardiovascular disease. HDL: high density lipoproteins. LDL: low density lipoproteins. Edinburgh: Edinburgh intermittent claudication questionnaire.
[a] Mean (Standard deviation).
[b] Median (1st quartile—3rd quartile).
[c] Calculated for CVD-free participants aged 35—74 years free of cardiovascular disease.

cardiovascular disease (necessary use conditions of Framingham CHD-risk functions), for a total of 5228 participants who fulfilled this condition. Mean 10-year CHD risk in the subgroup of 161 patients with ABI < 0.9 was 9.2% in men and 3.0% in women. Only 1.9% (95%CI: 0.4—5.3%) of participants with ABI < 0.9 presented CHD risk ≥ 20%; in 16.8% (95%CI: 11.4—23.5%) it was ≥10% (Fig. 1). Although ABI and 10-year CHD risk were significantly and inversely correlated in participants aged 35—74 and free of cardiovascular disease, the Spearman correlation was modest: −0.15 ($p < 0.001$) in men and −0.11 ($p < 0.001$) in women. Among participants with ABI < 0.9, this coefficient increased to −0.37.

Combining CHD-risk estimation with ABI measurement changed the proportion of participants aged 35—74 years with moderate-to-high (≥10%) CHD risk from 6.1% (95%CI: 5.5—6.8%) to 8.7% (95%CI: 7.9—9.5%), a change of 11.4 to 13.5% in men, and 1.6 to 4.6% in women.

Table 2 Prevalence of ankle-brachial index less than 0.9 by sex and age groups in a population sample aged 35—79 years in Girona, Spain

	Men			Women		
	d/n	ABI < 0.9	95% CI	*d/n*	ABI < 0.9	95% CI
Ages groups						
35—44 years	7/607	1.2%	(0.5%; 2.4%)	25/730	3.4%	(2.2%; 5.0%)
45—54 years	8/709	1.1%	(0.5%; 2.2%)	18/841	2.1%	(1.3%; 3.4%)
55—64 years	27/719	3.8%	(2.5%; 5.4%)	24/768	3.1%	(2.0%; 4.6%)
65—74 years	60/599	10.0%	(7.7%; 12.7%)	30/646	4.6%	(3.2%; 6.6%)
75—79 years	48/269	17.8%	(13.5%; 23.0%)	30/284	10.6%	(7.2%; 14.7%)
All	150/2903	5.2%	(4.4%; 6.0%)	127/3269	3.9%	(3.2%; 4.6%)
All age standardized by world population	150/2903	4.2%	(3.6%; 4.9%)	127/3269	3.8%	(3.1%; 4.4%)
ABI < 0.9 and Edinburgh definite or atypical	34/2903	1.2%	(0.8%; 1.6%)	4/3269	0.1%	(0.0%; 0.3%)
ABI < 0.9 and Edinburgh normal	116/2903	4.0%	(3.3%; 4.8%)	123/3269	3.8%	(3.1%; 4.5%)

d: Diagnosed ABI < 0.9; n: number of participants; ABI: ankle-brachial index; CI: Confidence interval.

Table 3 Comparison of presence of cardiovascular risk factors between individuals with and without ankle-brachial index < 0.9 in men and women aged 35–79 years

	Men			Women		
	ABI < 0.9	ABI ≥ 0.9	*p*	ABI < 0.9	ABI ≥ 0.9	*p*
N	150	2753		127	3142	
Age[a]	68.2 (10.0)	56.0 (12.1)	<0.001	61.0 (14.0)	55.7 (12.2)	<0.001
Hypertension	72.0%	49.5%	<0.001	58.3%	40.4%	<0.001
Diabetes	28.7%	18.0%	0.001	22.8%	11.5%	<0.001
Smoking						
Current or former smoker ≤1 year	31.3%	29.5%	<0.001	16.0%	15.9%	0.154
Former smoker >1 year	57.3%	40.4%	<0.001	7.20%	13.0%	0.154
Never smoker	11.3%	30.1%	<0.001	76.8%	71.1%	0.154
Systolic blood pressure[a]	139 (19)	130 (18)	<0.001	137 (27)	124 (20)	<0.001
Diastolic blood pressure[a]	78 (11)	81 (10)	0.009	79 (11)	77 (10)	0.057
Uncontrolled hypertension	58.0%	35.2%	<0.001	45.7%	25.9%	<0.001
Total cholesterol[a]	202 (43.5)	209(39.8)	0.035	216 (49)	213 (43)	0.423
HDL cholesterol[a]	47 (14)	47 (12)	0.679	57 (17)	57 (14)	0.782
LDL cholesterol[a]	128 (37)	137 (36)	0.003	132 (37)	135 (37)	0.442
Triglycerides[b]	107 (80–142)	103 (78–144)	0.520	91 (71–123)	86 (64–120)	0.194
Body mass index[a]	27.7 (3.8)	27.8 (3.8)	0.962	26.5 (5.0)	27.0 (5.1)	0.293
10-year CVD risk < 10%[c]	65.3%	88.3%	<0.001	96.5%	98.4%	0.163
Cardiovascular disease	26.8%	7.32%	<0.001	16.5%	3.51%	<0.001
Edinburgh definite or atypical	22.7%	3.49%	<0.001	3.15%	3.34%	1.000

ABI: ankle-brachial index. CVD: cardiovascular disease. HDL: high density lipoproteins. LDL: low density lipoproteins. Edinburgh: Edinburgh intermittent claudication questionnaire.
[a] Mean (Standard deviation).
[b] Median (1st quartile–3rd quartile).
[c] Calculated for CVD-free participants aged 35–74 years.

Discussion

Although most classical CHD-risk factors were associated to PAD, less than 20% of those 35–74 years old and free of CHD with ABI < 0.9 were at ≥10% 10-year CHD risk. Including ABI < 0.9 in the screening process results in a considerable increase in the proportion of moderate-to-high-risk population when combined with 10-year CHD risk ≥ 10% by risk functions. Many participants aged 75–79, not amenable to CHD-risk function calculations, presented ABI < 0.9 (i.e., symptomatic or asymptomatic PAD) and could be considered at high risk.[5,10–15] Furthermore, the Edinburgh questionnaire revealed IC symptoms in only a modest portion of participants with ABI < 0.9. Therefore, our results support the idea that cardiovascular risk screening strategies could be improved by adding ABI measurement, particularly for those beyond age 74. These findings concur with recently published data[13] of countries with high incidence of CHD. Our study confirms this data in a Mediterranean population with a known low risk of CHD.

Table 4 Adjusted odds ratios and 95% confidence interval for factors independently related to ankle brachial index < 0.9 in participants aged 35–79 years

Variable	Odds ratio	95%	CI
Men			
Age (1 year)	1.09	1.07	1.11
Current smoker	2.14	1.43	3.21
Cardiovascular disease	2.13	1.38	3.28
Edinburgh definite or atypical	5.22	3.25	8.38
Uncontrolled hypertension	1.52	1.06	2.19
Women			
Age (1 year)	1.02	1.01	1.04
Current smoker	1.89	1.10	3.24
Cardiovascular disease	3.26	1.88	5.68
Diabetes	1.59	1.00	2.51
Uncontrolled hypertension	1.74	1.16	2.61

CI: confidence interval. Edinburgh: Edinburgh intermittent claudication questionnaire.

Age, smoking, hypertension and diabetes mellitus are the cardiovascular risk factors most often associated with PAD.[4,9,16] In our study, although diabetes was more prevalent in the PAD group in both sexes, it independently associated with PAD only in women. This finding is consistent with the more deleterious effect of diabetes on CHD development observed in women.[28] Uncontrolled hypertension was independently associated with low ABI in both sexes, displacing hypertension in the multivariate model.

Presence of IC was significantly related to ABI < 0.9 in men. Male sex increased the risk of a symptomatic obstruction; asymptomatic PAD prevalence was similar in both sexes (Table 2). This suggests that atherosclerotic obstruction progresses faster in men who present a worse

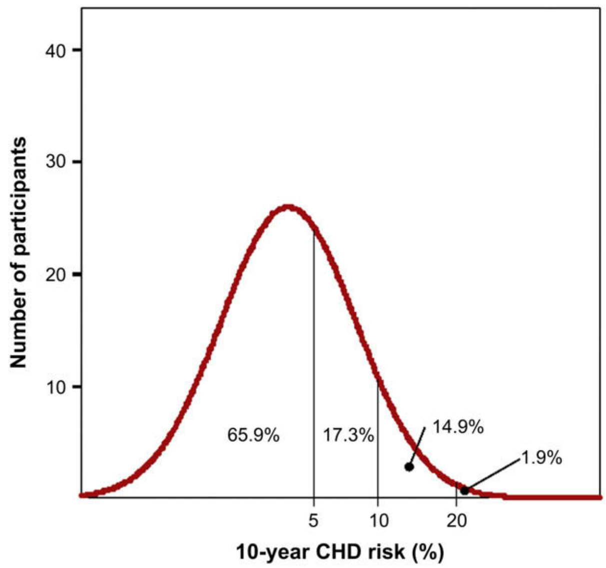

Figure 1 Distribution of 10-year coronary heart disease risk estimation in participants aged 35—74 years free of cardiovascular disease with ankle-brachial index < 0.9.

cardiovascular risk profile, particularly smoking, which is consistent with the higher arterial limb revascularization rate observed in men. The low prevalence of individuals with ABI < 0.9 and IC indicates that PAD can only be comprehensively diagnosed by systematic screening that includes ABI measurement.

The prevalence of ABI < 0.9 in our study was similar to that described elsewhere,[12,29,30] slightly lower than in northern Europe.[4,6] The large variability in reported PAD prevalence is probably due to differing definitions of PAD and participant inclusion criteria, particularly age ranges.[4–8]

Indeed, age is of particular interest in our study. Our findings show that the prevalence of PAD, as defined by ABI < 0.9, is relatively high in the 35 to 79-year-old population in Spain; almost 14.1% of the population aged 75—79 presented some stage of this disease. The crude prevalence of ABI < 0.9 was higher in men than in women, with the highest PAD prevalence in men observed in subjects older than 65 years. Age-standardized prevalence canceled the sex-based difference.

Implications of the study results

Systematic CHD-risk screening that combines ABI measurement — a quick, easy, and low-cost technique to diagnose inferior limb arterial obstruction with high sensitivity and specificity[16,18,19] — with 10-year CHD-risk functions is supported by the considerable prevalence of ABI < 0.9 in the 35—79 age group. In addition, diagnosing asymptomatic PAD identifies individuals at increased risk of suffering cardiovascular events[10–16] despite an apparently low 10-year CHD risk by risk functions. Information provided by ABI measurement could be combined with 10-year CHD-risk estimation by CHD-risk functions, or incorporated in future cardiovascular prediction functions. The preventive effect of interventions in individuals with symptomatic PAD is well known,[31–34] and it is likely that these interventions have beneficial effects of early risk factor modification and medication (e.g., anti-platelet drugs and statins) in subjects with subclinical disease. However, this likelihood remains to be ascertained in future clinical trials. Cost-effectiveness of ABI screening is unknown. Our data show that some 48 (100/2.1) men have to be screened with ABI to detect 1 more subject with an elevated risk of CHD, and some 33 (100/3) women. Current knowledge supports the international consensus criteria for PAD screening,[15,16] but more studies are needed to determine whether adding the ABI measurement in a screening strategy would be cost-effective and feasible in the general population.

Study characteristics

The sample size and high participation rate (~74%) yield adequate statistical power and guarantee external validity and representativeness of the studied population. However, the cross-sectional nature of the study and the age range (35—79 years) may be considered potential limitations to the observed associations and to the generalizability of our findings. We chose to extend the screening age range down to 35 years to test the magnitude of prevention achievable with early primary prevention in younger subjects, which was unknown in Spain.

In conclusion, we found ABI < 0.9 to be associated with most classical CHD-risk factors, as expected, but also relatively frequent in the population aged 35—79 (and particularly those aged 74—79) with no claudication symptoms and an apparent 10-year coronary risk < 10%, based on CHD-risk functions. Incorporating systematic ABI measurement into screening for CHD risk may improve cardiovascular risk stratification and increase early identification of patients with moderate-to-high cardiovascular risk, particularly in those beyond the age range for which risk functions were established.

Conflict of Interest

We have no potential conflicts of interest to report for any of the funding sources listed in acknowledgements.

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