



Estimating the risk of peripheral artery disease using different population strategies

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ABSTRACT

Objective. The objective of this study is to compare the clinical performance of different strategies, REASON, PREVALENT, Inter-Society Consensus (ISC), and the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines, in the selection of candidates for peripheral artery disease (PAD) screening using ankle-brachial index (ABI).

Method. Our work is a population-based cross-sectional study conducted in Extremadura (Spain) in 2007–2009. Participants were ≥ 50 years old and free of cardiovascular disease. ABI and cardiovascular risk factors were measured.

Result. In total, 1288 individuals (53% women), with a mean age of 63 years (standard deviation (SD) 9) were included. The prevalence of ABI < 0.9 was 4.9%. REASON risk score identified 53% of the sample to screen with sensitivity of 87.3%, quite similar to that identified in ISC and ACC/AHA strategies (both 90.5%), and specificity of 48.3%, higher than that of the ISC (30.9%) and ACC/AHA (31.1%) strategies. Although the Youden index was 0.4 for both REASON and PREVALENT risk scores, the latter's sensitivity was 60.3%, almost 30 points less than all other strategies.

Conclusion. REASON risk score was the strategy with the highest clinical performance and efficiency, with sensitivity of 87.3% and specificity higher than that of the ISC and ACC/AHA strategies. Although very specific, the PREVALENT strategy had low sensitivity making it difficult to be implemented as a screening tool.

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Introduction

The primary prevention of cardiovascular diseases (CVD), the main cause of death in the developed world (World Health Statistics, 2011), is a top priority in public health research. The common basis of these diseases is atherosclerosis, a chronic degenerative process mainly affecting the large and medium-sized arteries (Hansson, 2005). Lower extremity peripheral arterial disease (PAD) is relatively frequent in western countries, with 4.5% to 21.4% prevalence depending on PAD definition, sex, and age range (Alzamora et al., 2010; Brevetti et al., 2004; Félix-Redondo et al., 2012; Fowkes et al., 1991; Ramos et al., 2009; Stoffers et al., 1996).

Asymptomatic PAD, an early functional biomarker of atherosclerosis, prompts for intensive CVD risk factor treatment and control. Because most PAD cases are asymptomatic, reliable diagnosis depends upon systematic ankle-brachial index (ABI) screening (European Stroke Organisation, 2011; Norgren et al., 2007). A PAD diagnosis is defined as a resting ABI < 0.9 , caused by hemodynamically significant arterial stenosis (Norgren et al., 2007). Systemically, lower ABI is a potent predictor of future cardiovascular events (Aboyans and Criqui, 2006; Aboyans et al., 2012; Criqui et al., 1992; Heald et al., 2006). Particularly in individuals at intermediate risk, ABI more accurately predicts CVD risk than the Framingham score (Ankle Brachial Index Collaboration, 2008; Baena-Díez et al., 2011).

Several algorithms have been proposed at population scale to identify candidates for PAD screening using ABI (Bendermacher et al., 2007; Hirsch et al., 2006; Norgren et al., 2007; Ramos et al., 2011). Whether all strategies might similarly detect new PAD cases is unknown. Therefore, the clinical performance and efficiency of each algorithm should be assessed to select a preventive strategy for clinical practice.

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This study compared the clinical performance and efficiency of four population strategies: REGICOR and Arter Score for ABI screening (REASON) (Ramos et al., 2011), PREVALENT (Bendermacher et al., 2007), Inter-Society Consensus (ISC) for PAD management (Norgren et al., 2007), and American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the management of patients with PAD (Hirsch et al., 2006).

Methods

Population

The population-based cross-sectional HERMEX study in Badajoz, southwestern Spain, provided data and the methodology is described elsewhere (Félix-Redondo et al., 2011). Briefly, residents aged 25 to 79 years who held a healthcare identification card and signed their informed consent were included ($n = 2833$). Pregnant women, individuals with a disability or terminal disease, those living in long-term care institutions or at an address different than that registered in the census were excluded. The HERMEX study protocol was approved by the local ethics committee.

Due to the low prevalence of PAD in younger individuals (Alzamora et al., 2010; Brevetti et al., 2004; Fowkes et al., 1991; Ramos et al., 2009; Stoffers et al., 1996), we selected 1288 individuals aged 50 years and older with no history of CVD or revascularizations for analysis.

The number of individuals with PAD in the sample ($n = 63$) enabled us to estimate 85% sensitivity with 95% confidence interval (CI) precision of $\pm 8.7\%$ units. Specificity can be estimated with 95% CI precision of $\pm 0.7\%$ units, given 47% population incidence (Ramos et al., 2011).

Measurements

Standard questionnaires were administered by trained nurses between November 2007 and December 2009. Height and weight, using a precision scale of easy calibration, were measured with participants in underwear. Body mass index (BMI) was calculated (kg/m^2). Blood pressure was measured with a periodically calibrated electronic sphygmomanometer (OMRON HEM 907), selecting an appropriate cuff size. Three measurements were taken in each arm after a 5-min rest, with a 2-min rest between measurements. The mean of the second and third measurements of the arm with the highest values was recorded.

Participants were classified as cigarette smokers (current or quit < 1 year), former smokers (quit ≥ 1 year), or never smokers. Previous diagnosis or treatment for hypertension, diabetes mellitus, and hypercholesterolemia and previous history of CVD (coronary artery disease (CAD) and stroke) were recorded. Intermittent claudication was assessed by using the Edinburgh questionnaire (Leng and Fowkes, 1992).

Blood was withdrawn after 8–10 h of fasting, in less than 60 s. The referral hospital laboratory performed tests using the Spanish Society of Clinical Chemistry quality standards. Esterase-oxidase-peroxidase was used to measure total cholesterol, glycerol-phosphate oxidase-peroxidase for triglycerides, selective accelerator detergent for high-density lipoprotein (HDL) cholesterol, homogeneous colorimetric tests for low-density lipoprotein (LDL) cholesterol, and glucose hexokinase for glycemia.

Population prevalence of hypertension was estimated from diagnoses or evidence of systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg. Similarly, diabetes prevalence was based on diagnoses or evidence of glucose ≥ 7 mmol/l. CAD risk was calculated by the REGICOR (Registre Gironí del Cor) adaptation of the original Framingham function, validated for the Spanish population aged 35 to 74 years (Marrugat et al., 2007).

Ankle-brachial index measurement

According to the current guidelines (Aboyans et al., 2012), after 5-min rest systolic blood pressure was measured in the brachial artery in the antecubital fossa in the right arm with a continuous Doppler device (HADECO® Minidop ES, 8 MHz probe), then in the distal calf, and the Doppler probe was used to determine systolic blood pressure in the supine position at the right and the left posterior and anterior tibial arteries. The right and the left ABI were calculated as the ratio of the higher of 2 systolic pressures in the lower limbs (posterior and anterior tibial arteries) to the right brachial systolic pressures. The lower of the values obtained was used for analysis. Individuals with ABI > 1.4 were

excluded because of the possible influence of arterial wall stiffness which made it impossible to discard arterial obstruction (Ankle Brachial Index Collaboration, 2008; Resnick et al., 2004).

Statistical analysis

Baseline characteristics were described for participants with ABI < 0.9 vs ≥ 0.9 , using percentages for categorical data, means (standard deviations) for normally distributed data, and median and interquartile range for non-normal distributions (e.g., glycemia and triglycerides). We tested for differences between groups using Student *t* test, U Mann–Whitney and χ^2 as appropriate.

Clinical performance and efficiency of screening strategies were tested on these two groups. The REASON score, validated for use in the Spanish population, was derived using data on sex, age, smoking status, pulse pressure, and diabetes. To identify candidates for PAD screening by using ABI, the authors applied a score $\geq 4.1\%$ because it yielded equal sensitivity to that obtained with the ISC algorithm (Ramos et al., 2011). The PREVALENT score uses data on age, smoking status, and prevalent and controlled hypertension. Individuals with a score ≥ 7 were considered for ABI measurement (Bendermacher et al., 2007). The ACC/AHA algorithm considered all individuals with symptoms suggesting intermittent claudication, all asymptomatic individuals older than 70 years, and those aged 50–69 years with diabetes or current smoking habit for PAD screening (Hirsch et al., 2006). The ISC algorithm considered all individuals meeting the same criteria as ACC/AHA and all asymptomatic individuals with a 10-year CAD risk of 10%–20% (Norgren et al., 2007) (Fig. 1).

We described the individuals identified with each strategy and estimated sensitivity, specificity, positive and negative predictive value, likelihood ratio of a positive and a negative test, percentage of population to screen, and the Youden index, a function of sensitivity and specificity commonly used to measure diagnostic effectiveness (Schisterman et al., 2005; Youden, 1950). Finally, for each strategy we estimated the percentage of individuals aged 50 to 74 years selected for PAD screening according to CAD risk categories: low ($< 5\%$), moderate (5–10%), and high ($\geq 10\%$).

Statistical analysis used R Statistical Package (R Foundation for Statistical Computing, Vienna, Austria; Version 2.14.1, R Development Core Team, 2011).

Results

Of the 1288 individuals (53% women, mean age 63 years [SD 9]) included in the analysis, 63 (4.9%, 95% confidence interval: 3.8%–6.2%) had ABI < 0.9 . These individuals were older, more frequently men, and had higher prevalence of symptomatic PAD, hypertension, diabetes, and 10-year CAD risk $> 10\%$. Individuals with abnormal ABI values had significantly higher systolic blood pressure, pulse pressure, glucose, triglycerides, and body mass index and lower HDL cholesterol levels (Table 1).

The ISC and ACC/AHA strategies identified the highest number of ABI candidates ($n = 903$, and $n = 901$, respectively), compared to the REASON ($n = 688$) and PREVALENT ($n = 336$) strategies (Fig. 1); Table 2 compares the distinctive characteristics of these patients. Candidates identified by the PREVALENT strategy were more frequently men, older, smokers, and had higher prevalence of hypertension, CAD risk $> 10\%$, and elevated systolic blood pressure and pulse pressure values. Candidates identified by REASON, ISC, and ACC/AHA algorithms had similar characteristics, except that REASON candidates had higher values for age, hypertension, and CAD risk $> 10\%$.

The most efficient strategy was a REASON probability of PAD $\geq 4.1\%$. Of the 688 screened individuals, 55 (8.0%) had positive ABI tests (87% sensitivity). This proportion was much lower for the ISC and ACC/AHA algorithms, which selected > 900 individuals to screen and obtained just 2 additional positive ABI tests. In contrast, PREVALENT selected just 366 individuals but detected only 38 (60%) of the 63 ABI < 0.9 cases (Fig. 1).

The percentage of screening candidates increased according to CAD risk category. The PREVALENT score ≥ 7 strategy selected only 25% of the individuals classified as moderate-risk, compared to 67% with REASON and 82% with ISC and ACC/AHA strategies (Fig. 2).

Clinical performance of each strategy is shown in Table 3. Using REASON, 53% of the sample would be screened. Although its sensitivity

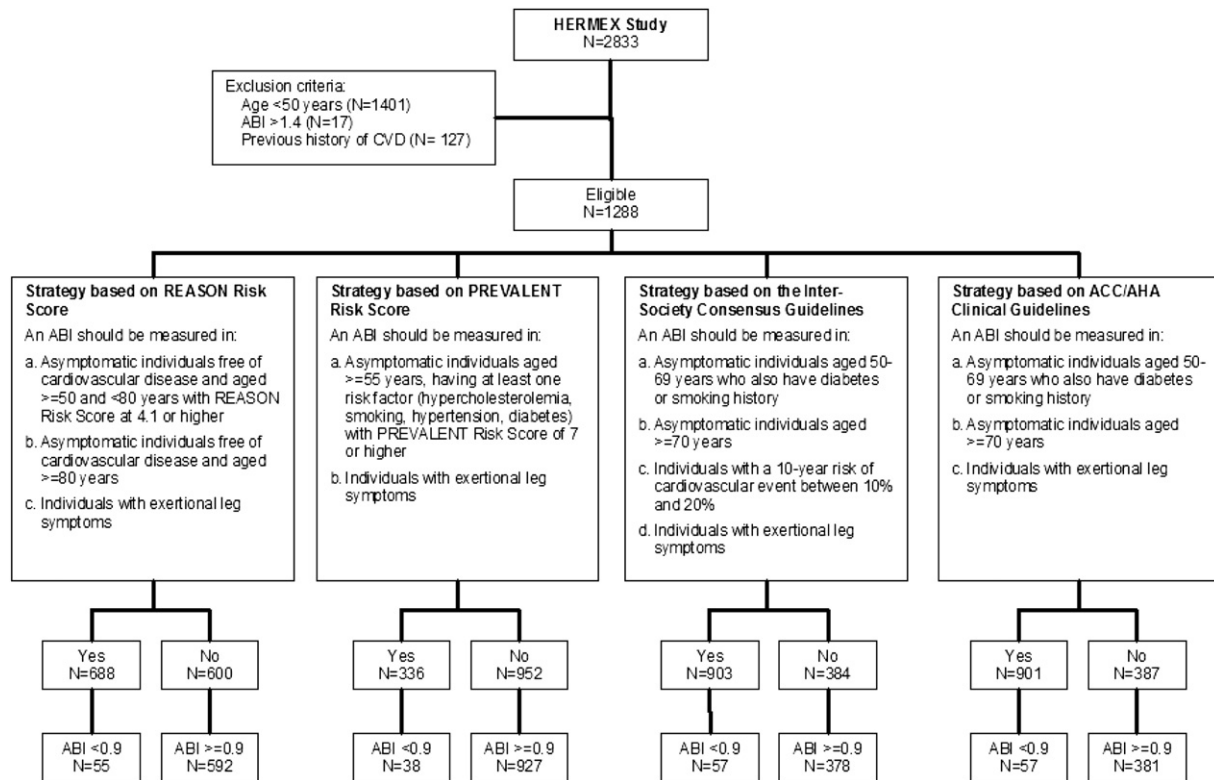


Fig. 1. Schematic diagram of population-based strategies to screen for peripheral artery disease. Adapted from REASON risk score (Ramos et al., 2011), PREVALENT risk score (Bendermacher et al., 2007), the ISC Guidelines for the management of peripheral artery disease (Norgren et al., 2007), and the ACC/AHA Guidelines (Hirsch et al., 2006). ABI, ankle-brachial index, CVD, cardiovascular disease.

Table 1

Baseline characteristics of HERMES participants using ankle-brachial index values of <0.9 and ≥0.9.

	ABI <0.9 n = 63	ABI ≥0.9 n = 1225	P value
Age; years; mean (SD)	71 (8)	63 (9)	<.001
Sex (women), n (%)	24 (38.1)	681 (55.6)	.010
Hypertension, n (%)	50 (79.4)	770 (62.9)	<.001
Diabetes, n (%)	25 (39.7)	267 (21.8)	.002
Hypercholesterolemia, n (%)	27 (42.9)	466 (38.0)	.526
Smoking status			.143
Never smokers, n (%)	28 (44.4)	699 (57.1)	
Former smokers, n (%)	19 (3.2)	288 (23.5)	
Smokers, n (%)	16 (25.4)	238 (19.4)	
Systolic blood pressure; mm Hg, mean (SD)	148 (22)	138 (21)	.001
Diastolic blood pressure; mm Hg, mean (SD)	78 (12)	79 (10)	.539
Pulse pressure, mm Hg, mean (SD)	70 (21)	59 (18)	<.001
Glucose; mmol/l; median (IQR)	6.05 (5.49–7.69)	5.72 (5.27–6.44)	.005
Total cholesterol; mmol/l, mean (SD)	5.50 (1.04)	5.58 (0.95)	.547
HDL-cholesterol; mmol/l, mean (SD)	1.38 (0.34)	1.49 (0.38)	.018
LDL-cholesterol; mmol/l, mean (SD)	3.22 (0.88)	3.26 (0.78)	.707
Triglycerides; mmol/l; median (IQR)	1.32 (0.99–1.64)	1.12 (0.82–1.55)	.004
Body mass index; kg/m ² , mean (SD)	31.7 (7.1)	29.9 (4.9)	.053
10-year coronary risk >10%, n (%)	11 (33.3)	101 (9.4)	<.001
Intermittent claudication identified by Edinburgh questionnaire, n (%)	8 (12.7)	19 (1.6)	<.001

Abbreviations: IQR, interquartile range; HDL, high density lipoprotein; LDL, low density lipoprotein; SD, standard deviation.

To convert glucose to mg/dl, multiply by 18.02. To convert total, HDL and LDL cholesterol to mg/dl, multiply by 38.61. To convert triglycerides to mg/dl, multiply by 88.50.

is similar to the ISC and ACC/AHA strategies, its specificity is > 17 points higher. The Youden index, a commonly used measure of diagnostic effectiveness, was similar for REASON ≥4.1 and PREVALENT ≥7. However, the latter's sensitivity was almost 30 points less than all other strategies. All strategies had similar clinical performance and efficiency in the sensitivity analyses, performed first with the 754 individuals not taking anti-hypertensives and then with 1261 having no signs of PAD (data not shown).

Discussion

At population scale, CVD primary prevention should be based on the best possible baseline risk characterization and efficiency. Identification of candidates for PAD screening by REASON ≥4.1% was the most efficient strategy and had good clinical performance. Compared to strategies proposed by the scientific societies, REASON identified a lower proportion of population for screening with similar sensitivity and much higher specificity. Since REASON estimations are based on routinely collected variables (age, sex, smoking status, pulse pressure, diabetes), this risk score is readily integrated into electronic medical records as a population strategy to identify candidates for PAD screening.

Ankle-brachial index and cardiovascular risk

Asymptomatic PAD places individuals at high risk for cardiovascular events (Aboyans and Criqui, 2006; Ankle Brachial Index Collaboration, 2008; Criqui et al., 1992; Heald et al., 2006). Due to the long asymptomatic induction period of atherosclerosis, subclinical measures of cardiovascular health such as ABI can provide early risk detection (Naghavi et al., 2006). Although a recent analysis indicated that including ABI in Framingham risk scores did not improve risk prediction (Murphy et al., 2012), ABI was particularly useful after initial CAD risk assessment to appropriately reclassify individuals from moderate to high risk

Table 2

Comparison of the characteristics of HERMEX study patients selected for peripheral artery disease screening using the four algorithms.

	REASON at 4.1 n = 688	PREVALENT at 7 n = 336	The ISC Guidelines n = 903	ACC and AHA Guidelines n = 901
Age; years; mean (SD)	68 (8)	69 (8)	65 (10)	65 (10)
Sex (women); n (%)	291 (42.3)	117 (34.8)	409 (45.3)	408 (45.3)
Hypertension; n (%)	539 (78.3)	274 (81.6)	619 (68.6)	617 (68.5)
Diabetes; n (%)	206 (29.9)	85 (25.3)	292 (32.3)	292 (32.4)
Hypercholesterolemia; n (%)	255 (37.1)	107 (31.9)	349 (38.7)	348 (38.6)
Smoking status				
Never smokers; n (%)	313 (45.5)	91 (27.1)	342 (37.9)	340 (37.7)
Former smokers; n (%)	203 (29.5)	92 (27.4)	307 (34.0)	307 (34.1)
Smokers; n (%)	172 (25.0)	153 (45.5)	254 (28.1)	254 (28.2)
Systolic blood pressure; mm Hg; mean (SD)	148 (20)	150 (22)	141 (22)	141 (22)
Diastolic blood pressure; mm Hg; mean (SD)	79 (11)	79 (11)	79 (11)	79 (11)
Pulse pressure; mean (SD)	69 (17)	71 (20)	62 (19)	62 (19)
Glucose; mmol/l; median (IQR)	5.94 (5.44–6.88)	5.83 (5.44–6.67)	5.94 (5.38–6.88)	5.94 (5.38–6.88)
Total cholesterol; mmol/l; mean (SD)	5.53 (0.95)	5.48 (0.97)	5.55 (0.97)	5.55 (0.98)
HDL-cholesterol; mmol/l; mean (SD)	1.46 (0.38)	1.48 (0.40)	1.44 (0.37)	1.45 (0.37)
LDL-cholesterol; mmol/l; mean (SD)	3.22 (0.80)	3.20 (0.79)	3.25 (0.80)	3.25 (0.80)
Triglycerides; mmol/l; median (IQR)	1.15 (0.88–1.62)	1.13 (.85–1.059)	1.16 (0.87–1.65)	1.16 (0.87–1.65)
Body mass index; kg/m ² ; mean (SD)	30.27 (4.85)	29.69 (4.92)	30.09 (5.04)	30.07 (5.02)
10-year coronary risk > 10%; n (%)	103 (2.3)	63 (31.2)	112 (15.5)	110 (15.3)
Intermittent claudication identified by Edinburgh questionnaire; n (%)	27 (3.9)	23 (6.9)	27 (3.0)	27 (3.0)

Abbreviations: ABI, ankle-brachial index; HDL, high density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein.

(Ankle Brachial index Collaboration, 2008; Baena-Díez et al., 2011; Korhonen et al., 2009).

Detection of asymptomatic PAD should motivate patients to accept recommendations on exercise, diet and smoking cessation (Hirsch et al., 2006). However, the control of cardiovascular risk factors in these patients is supported only by low-grade scientific evidence (Hirsch et al., 2006; Norgren et al., 2007). In cost-effectiveness analysis, treatment (particularly angiotensin-converting enzyme inhibitor) to prevent cardiovascular events was cost-effective in asymptomatic PAD patients (Sigvant et al., 2011). Further clinical trials are required to establish whether patient outcomes benefit from these therapies.

The efficiency of ABI to screen individuals with advanced diabetes is under discussion. Use of the toe-brachial index has been proposed because the medial arterial calcification in the lower extremities, which could falsely elevate the index value, is less frequent in the toe than in the ankle (Aboyans et al. Circulation., 2012; Aso et al., 2004; Fukui et al., 2012; Potier et al., 2011). However, comparing ABI and toe-brachial index measures showed that the latter was advantageous

only in individuals with diabetes and overt medial arterial calcification (i.e. ABI > 1.3) (Brooks et al., 2001).

Clinical performance of the population strategies

The ABI meets the requirements of a good screening test: ability to detect subclinical disease when early treatment is known to improve outcomes, simple to administer, inexpensive, and associated with minimal patient discomfort and morbidity (Greenland and Lloyd-Jones, 2008). However, considering resource limitations, candidate selection priorities must be established to achieve effective, feasible population strategies. Algorithms that identify PAD screening candidates are only useful when they have acceptable accuracy and reliability to characterize individual risk.

Previous studies have modeled the population impact of different screening strategies for identifying high risk of cardiovascular events (Chamnan et al., 2010; Marshall and Rouse, 2002). These studies concluded that, compared to universal screening, preselecting individuals

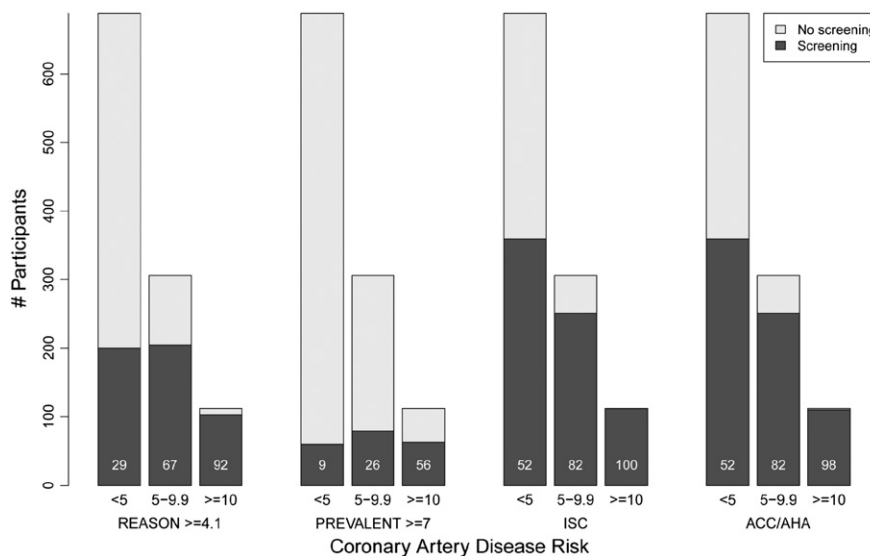


Fig. 2. Total number of individuals by coronary artery disease risk categories with the 4 screening strategies. Numbers are the percentage to be screened in each risk category.

Table 3
Comparison of clinical performance of the four strategies for identifying individuals to screen with ankle-brachial index.

	REASON at 4.1		PREVALENT at 7		The ISC Practice Guidelines		The ACC/AHA Practice Guidelines	
	Estimation	95% confidence interval	Estimation	95% confidence interval	Estimation	95% confidence interval	Estimation	95% confidence interval
Sensitivity, %	87.3	76.5–94.4	60.3	47.2–72.4	90.5	80.4–96.4	90.5	80.4–96.4
Specificity, %	48.3	45.5–51.2	75.7	73.2–78.1	30.9	28.3–33.6	31.1	28.5–33.8
Positive predictive value, %	8.0	6.1–10.3	11.3	8.1–15.2	6.3	4.8–8.1	6.3	4.8–8.1
Negative predictive value, %	98.7	97.4–99.4	97.4	96.1–98.3	98.4	96.6–99.4	98.4	96.7–99.4
Likelihood ratio of a positive test	1.7	1.5–1.9	2.5	2.0–3.1	1.3	1.2–1.4	1.3	1.2–1.4
Likelihood ratio of a negative test	0.3	0.1–0.5	0.5	0.4–0.7	0.3	0.1–0.7	0.3	0.1–0.7
Percentage to screen	53.4	50.6–56.2	26.1	23.7–28.6	70.2	67.6–72.7	70.0	67.4–72.4
Youden index	0.4	0.2–0.5	0.4	0.2–0.5	0.2	0.1–0.3	0.2	0.1–0.3

for risk assessment may reduce staff time and prevent more new cases within available resources. Our analysis, which focused on PAD prevention, found similar efficiency. For instance, both the ISC and ACC/AHA strategies achieved good clinical performance. However, to achieve sensitivity >90%, both recommended screening 70% of the population, 40% of them at low CAD risk. The REASON probability $\geq 4.1\%$ identified almost the same number of true positive cases after screening 53% of the population, a third of them at low CAD risk and another third at moderate CAD risk, the group that has traditionally shown the highest proportion of coronary events (Marrugat et al., 2011). The Youden index is much lower for ISC and ACC/AHA strategies than for the REASON strategy. This efficiency indicator points to the strategies with greater clinical benefit but its results require cautious interpretation.

Thus, REASON probability of PAD $\geq 4.1\%$ and a PREVALENT score ≥ 7 needed to screen 12 and 9 individuals, respectively, to find 1 individual with an ABI <0.9. PREVALENT only selected 26% of the sample for screening, or half the percentage selected by the REASON strategy. However, PREVALENT's clinical performance was less than that desired, particularly compared to the other strategies. Our results concurred with a previous comparison between a REASON cut-off point of 4.1 and the ISC algorithm (Ramos et al., 2011) that used REASON derivation and validation datasets.

Public health implications

Although our population-based study assessed 4 published screening strategies, only REASON had been validated (Ramos et al., 2011). This strategy had good clinical performance in populations with higher prevalence of cardiovascular risk factors (Grau et al., 2011). Its complex mathematical operations require computer software in a clinical setting, although this should not be a major inconvenience because electronic medical records could automatically compute this useful risk score (REASON calculator, 2012).

The choice of the best strategy to identify candidates to screen for PAD should be evidence-based. Our results clearly identified the strategy with the highest clinical performance and efficiency, conditions that are highly recommended for effective screening. As a result, individuals with an atypical expression of the disease are less likely to be selected for ABI screening. Thus, population strategies are not valid tools for estimating the population prevalence of a particular disease.

Due to the cross-sectional study design, we lacked information on the incidence of intermittent claudication and other cardiovascular events. The next step should be for further studies to determine the utility and cost-effectiveness of using REASON as a strategy to prevent intermittent claudication and other cardiovascular events.

Conclusion

A REASON-derived probability of PAD $\geq 4.1\%$ provided the highest clinical performance and efficiency. Sensitivity exceeded 87.3% and specificity surpassed that of the ISC and ACC/AHA algorithms. Although

the PREVALENT strategy was very specific, its low sensitivity argues against its implementation as a screening tool.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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