Derivation and validation of REASON: A risk score identifying candidates to screen for peripheral arterial disease using ankle brachial index

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Abstract

Background: The recommendation of screening with ankle brachial index (ABI) in asymptomatic individuals is controversial. The aims of the present study were to develop and validate a pre-screening test to select candidates for ABI measurement in the Spanish population 50–79 years old, and to compare its predictive capacity to current Inter-Society Consensus screening criteria.

Methods and results: Two population-based cross-sectional studies were used to develop (n = 4046) and validate (n = 3285) a regression model to predict ABI < 0.9. The validation dataset was also used to compare the model’s predictive capacity to that of ISC screening criteria.

The best model to predict ABI < 0.9 included age, sex, smoking, pulse pressure and diabetes. Assessment of discrimination and calibration in the validation dataset demonstrated a good fit (AUC: 0.76 [95% CI 0.73–0.79] and Hosmer–Lemeshow test: χ^2: 10.73 (df = 6), p-value = 0.097).

Predictions (probability cut-off value of 4.1) presented better specificity and positive likelihood ratio than the ABI screening criteria of the ISC guidelines, and similar sensitivity. This resulted in fewer patients screened per diagnosis of ABI < 0.9 (10.6 vs. 8.75) and a lower proportion of the population aged 50–79 than the ABI screening criteria of the ISC guidelines, and similar sensitivity. This resulted in fewer patients aged 50–79 years candidate to ABI screening (63.3% vs. 55.0%).

Conclusion: This model provides accurate ABI < 0.9 risk estimates for ages 50–79, with a better predictive capacity than that of ISC criteria. Its use could reduce possible harms and unnecessary work-ups of ABI screening as a risk stratification strategy in primary prevention of peripheral vascular disease.

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1. Introduction

A key strategy in primary prevention of cardiovascular diseases (CVD) is to use risk functions to identify high-risk individuals [1,2]. 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 [1,4–6].

Patients with ABI < 0.9, whether symptomatic or asymptomatic, have significantly higher risk of mortality and vascular events [7,8] and ABI provides independent risk information compared with the coronary risk functions [9,10]. Even though ABI is a simple, non-invasive and inexpensive technique [11], it requires access to a Doppler device and a well-trained professional who applies a standardized measurement of ABI [12]. The United States Preventive Services Task Force has stated that potential harms of routine ABI screening for PAD exceed benefits in asymptomatic adults [13,14]. This conclusion was controversial because it did not take into account the potential for preventing other CVD outcomes [15,16] through ABI screening.

Effectiveness of ABI screening is unknown, but the characteristics of the target population are probably a factor. Inter-Society Consensus (ISC) Practice Guidelines for the management of patients with PAD indicate that ABI should be performed in the high risk population [17]. The evidence level of these recommendations is limited and their accuracy in population detection of PAD has not been well studied. The aims of the present study were to develop and validate a pre-screening test to select the best candidates for ABI measurement in the Spanish population 50–79 years old and free of known CVD, and to compare its predictive capacity to identify PAD patients to that of the ISC screening criteria.

2. Methods

2.1. Patient data sources

2.1.1. Derivation data: the REGICOR-HERMES study

Derivation of the REGicor and Artpner Score for Ankle brachial index screening (REASON) was achieved using data from a population-based study conducted between 2005 and 2006 in Girona province (~600,000 inhabitants), northeastern Spain [18].

2.1.2. Validation data: the PERART study

Validation was carried out using data from a cross-sectional, multicenter study performed in 24 healthcare centers (~600,000 inhabitants) within the metropolitan area of Barcelona [18].

Personal history of CVD (myocardial infarction, angina, stroke and PAD) was recorded by questionnaire and verified using data from the electronic medical record. Intermittent claudication (IC) was assessed by the Edinburgh questionnaire [19]. Symptomatic PAD was defined when ABI < 0.9 and IC based on the Edinburgh questionnaire was present. From both original studies we selected participants free of previous history of CVD (angina, myocardial infarction stroke or symptomatic PAD) and, given the very low prevalence of ABI < 0.9 in the population younger than 50 years, limited the study to those aged 50–79 years.

2.2. Measurements

Examinations were performed by trained nurses and interviewers using standard questionnaires and measurement methods. Both studies followed the same methods in the data collection [10,18].

Personal history of hypercholesterolemia, diabetes mellitus, arterial hypertension and smoking were recorded. All diagnoses were verified using data from the electronic medical record. Body mass index (BMI) was calculated as weight divided by squared height (kg/m²).

Blood pressure was measured with a calibrated oscillometric sphygmomanometer (OMRON 705 IT). Pulse pressure was calculated as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Blood was drawn after 10–14 h fasting. Methods and quality control for the determination of glycaemia, total cholesterol, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c) and triglyceride concentrations are detailed elsewhere [10,18].

Coronary heart disease (CHD) risk was calculated in all participants 50–74 years old and free of CVD using the Framingham function adapted to Spain and validated in this population [20].

A standardized smoking questionnaire was used to evaluate cigarette consumption [10]. Participants were classified as smokers (current or quit <1 year), former smokers (quit ≥1 year) or never smokers.

2.3. ABI measurement

A continuous Doppler device was used in both studies to measure systolic pressure of the posterior tibial and dorsalis pedis arteries of each leg. Right and left ABI were calculated as the ratio of the highest systolic pressure in each lower limb to the highest (right or left) brachial systolic pressure. The lowest resulting ABI value was used for analysis.

Participants with ABI >1.39 were excluded from evaluation because the possible influence of arterial wall stiffness made it impossible to discard arterial obstruction.

2.4. Statistical analysis

2.4.1. Statistical power

Our sample size in the derivation cohort (235 cases with ABI < 0.9 and 3811 participants with ABI ≥ 0.9) allowed us to estimate a sensitivity of 85% with a precision of ±4.5 percent units, and of ±1.5 percent units for a specificity of 50%, which yields the largest standard deviation and in consequence requires the highest sample size.

The sample size in the derivation dataset, also provided a statistical power of 80% to detect as statistically significant (p-value <0.05) an odds ratio of 1.5 for a factor that is present in 40% of normal ABI participants, assuming that low ABI prevalence is approximately 6% [10].

The sample size in the validation dataset gave our tests 80% power to detect as statistically significant (p-value <0.05) a difference of 8 percent units between expected and observed low ABI in the most adverse situation, i.e., 30% observed low ABI. These estimations yielded a minimum sample size of approximately 400 individuals per risk-stratified validation group, which allows 8 groups for the Hosmer–Lemeshow tests of goodness of fit.

2.4.2. Model derivation and development procedure

Univariate analysis: Pearson’s chi-squared test was used for categorical variables and unpaired Student’s t-test for continuous variables if a normal distribution for that variable could be shown. Non-parametric continuous variables were analyzed using the Mann–Whitney U-test. Logistic regression was then used to derive a model to predict ABI <0.9. The regression coefficients were estimated for variables that showed significant differences (p <0.05) in univariate analysis. Important clinical variables, such as age, sex or diabetes, were also included as potential confounders.
2.4.3. Validation of REASON

Accuracy and reliability of the classification provided by the model was assessed as follows:

1. Coefficients estimated by the regression model that best fitted the validation data (best regression model) were compared with those of the original derived function by a z score test.
2. A calibration test assessed the accuracy of the REASON function by comparing the estimated risk with the observed event rate in the 8 risk groups. The Hosmer–Lemeshow goodness-of-fit test was used to calculate a $\chi^2$ value; $\chi^2$ values $<12.59$ were considered to indicate a substantial fit for the 8 groups (corresponding to a $p$-value $>0.05$).
3. The discrimination capacity of the new function was analyzed by comparing the area under the curve obtained by the REASON receiver operator characteristics (ROC) and that obtained by the regression model of ABI $< 0.9$ event best fitted to the study data.

2.4.4. Comparison of the REASON predictive capacity of ABI $< 0.9$ to that of current ISC guidelines

ISC guidelines for the management of PAD [17] recommend ABI screening in all asymptomatic subjects aged 50–69 years who also have diabetes or smoking history, all patients over the age of 70 years, and subjects with a 10-year risk of a cardiovascular event between 10% and 20% in whom further risk stratification is warranted.

A classification matrix with the ISC guidelines screening criteria was calculated on the validation cohort. We looked then for a cut-off value in the REASON score that yielded equal sensitivity to that obtained with the ISC guidelines and compared the rest of test characteristics: specificity, predictive values, likelihood ratios, number of individuals screened to diagnose one participant (NSD), and proportion of participants to screen.

Statistical analysis was done with R Statistical Package (R Foundation for Statistical Computing, Vienna, Austria; Version 2.0).

3. Results

Baseline participant characteristics and frequency of cardiovascular risk factors are summarized in Table 1. The ABI $< 0.9$ rate was higher in the validation dataset (7.0%; 230 participants, 149 men and 84 women), $p$ = 0.037.

3.1. Predictors of ABI $< 0.9$ in the derivation study

Results of univariate analysis for all potential predictors are shown in Table 2. Low-ABI participants were older, more often men, diabetic and hypertensive, and more frequently smokers than participants with ABI $\geq 0.9$. The multivariate model is shown in Table 3. The best logistic regression model to predict ABI $< 0.9$ included age, sex (female), smoking, pulse pressure and diabetes. The corresponding beta values for each factor are described in Table 3.

3.2. Model validation

Participants of the validation dataset were divided in 8 equal groups attending to the distribution of REASON probability values (i.e.: $\leq$1.7; 1.7–2.5; 2.6–3.3; 3.4–4.5; 4.6–6.2; 6.3–8.4; 8.5–12.5; $>12.5$). Overall, the proportion of observed ABI $< 0.9$ did not differ from that predicted by REASON in the 8 groups of predicted risk in the validation dataset (Supplementary Figure 1).

We fitted a regression model with the validation study data to estimate the coefficients for each risk factor. None of these coefficients significantly differed from those of REASON (Table 4). The
Table 4
Estimates of the coefficients for each variable included in the REASON pre-screening test and in the best regression model of the validation dataset.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>ED</th>
<th>p-Value</th>
<th>Coefficient</th>
<th>ED</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>−9.493</td>
<td>0.676</td>
<td></td>
<td>−9.601</td>
<td>0.762</td>
<td>0.916</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.134</td>
<td>0.189</td>
<td></td>
<td>0.107</td>
<td>0.202</td>
<td>0.384</td>
</tr>
<tr>
<td>Age</td>
<td>0.075</td>
<td>0.010</td>
<td></td>
<td>0.074</td>
<td>0.011</td>
<td>0.918</td>
</tr>
<tr>
<td>Never smoker (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smoker &gt;1 year</td>
<td>0.814</td>
<td>0.203</td>
<td></td>
<td>0.750</td>
<td>0.224</td>
<td>0.833</td>
</tr>
<tr>
<td>Current or former smoker ≤1 year</td>
<td>1.264</td>
<td>0.226</td>
<td></td>
<td>1.388</td>
<td>0.231</td>
<td>0.699</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.020</td>
<td>0.004</td>
<td></td>
<td>0.025</td>
<td>0.005</td>
<td>0.443</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.193</td>
<td>0.157</td>
<td></td>
<td>0.526</td>
<td>0.151</td>
<td>0.125</td>
</tr>
</tbody>
</table>

ED: Standard deviation of the coefficient.

area under the ROC curve obtained with the best-fitting regression model in the validation dataset (AUC: 0.76; 95% CI: 0.72–0.79) was similar to that of REASON (AUC: 0.76; 95% CI: 0.73–0.79) in the validation dataset (Supplementary Figure 2).

3.3. Prediction capacity of REASON to detect individuals with ABI < 0.9, compared to that of current guidelines or consensus criteria

Fig. 1 shows the sensitivity, specificity and proportion of candidates for ABI screening in the population according to REASON probability cut-off values.

A REASON value of 4.1 or over, presented the same sensitivity and better specificity and positive likelihood ratio than the ISC guidelines. This resulted in fewer patients screened per positive diagnosis of ABI < 0.9 and a lower proportion of the population considered candidates for ABI measurement (Table 5).

Using ISC criteria to determine candidates for ABI measurement, 10.6 individuals (95% CI: 9.3–12.1) were screened to obtain one positive diagnosis of ABI < 0.9, while using REASON with a 4.1 cut-off value required only 9.0 individuals (CI 95%: 7.9–10.3). Therefore, the candidate population for ABI screening decreases from 63.3% (CI 95%: 61.3–64.6) with ISC criteria to 55.0% (CI 95%: 53.3–56.7) with REASON criteria.

4. Discussion

This study provides the first population-derived and validated model to predict risk of ABI < 0.9 in people 50–79 years old who are initially free of CVD. The estimates are based on routine measurements of known CVD risk factors. REASON has proven to reliably provide accurate ABI < 0.9 risk estimates for those aged 50–79 years in Spain. This predictive capacity better determines good candidates for ABI measurement, with equal sensitivity and better specificity, than that of the ISC screening criteria. This improvement in the predictive capacity results in a considerable reduction of the NSD and of the candidate population for ABI screening. Therefore, by reducing the number of false positives at similar sensitivity, the use of REASON should limit the potential harms including needless
work-ups, and possible adverse events associated with diagnostic procedures and medical treatments [13–15].

Furthermore, the predictive capacity of REASON can be modulated by changing the risk cut-off value (Fig. 1). This feature may be helpful in adapting the screening criteria to the resources that can be allocated for cardiovascular prevention in each world region. REASON is especially better at predicting low ABI in men. This finding must be highlighted because men are typically more likely to progress to symptomatic and critical phases of PAD and other CVD [17].

Previous pre-screening systems have been designed for patients with symptoms of claudication [21] and for older individuals [22], but only one system has been developed for asymptomatic individuals [23]. The PREVALENT clinical prediction model included an asymptomatic population older than 54 with at least one risk factor (smoking, hypertension, diabetes, or hypercholesterolemia), but it has not been validated and its predictive capacity has not yet been evaluated [23].

REASON used clinical data routinely collected in general practice for cardiovascular risk estimation. This improves the feasibility of applying REASON in initial cardiovascular risk screening, using classical risk factors in computerized clinical calculators. A strategy that combines classical risk functions and the probability of ABI < 0.9 with REASON would allow us to detect individuals with low or moderate cardiovascular risk who require ABI measurement. It is plausible that ABI information could help to reclassify patients into a more accurate CVD risk estimation [9,15,24,25], which in turn should result in higher motivation for patients to accept recommendations on smoking cessation, exercise and diet. The preventive effect of anti-platelet, anti-hypertensive and statin treatment has been established in patients with symptomatic PAD [26]. It is likely that these interventions may also benefit individuals with asymptomatic PAD, although this likelihood will need to be confirmed in future clinical trials [25].

### 4.1. Study characteristics

The population with known CVD was excluded from the data used to derive REASON because strict control of CVD risk factors is already necessary in those patients. The validity of the REASON approach has been proven: β-coefficient comparison, the calibration test and analysis of discrimination capacity all indicated that REASON accurately predicts the probability of ABI < 0.9. The area under the ROC curve obtained with the model when applied to the validation data indicates good discrimination capacity.

The REASON model may require further validation in other populations and in prospective studies.

In conclusion, REASON provides accurate ABI < 0.9 risk estimates for ages 50–79, especially in men, with a better predictive capacity than that of current screening criteria, reducing NSD and the candidate population for ABI screening by 15%, compared to ISC criteria. Its use could reduce possible harms and unnecessary work-ups of ABI screening as a risk stratification strategy in primary prevention of cardiovascular diseases.

### Conflicts of interest

The authors have no potential conflicts of interest to report for any of the funding listed at the first page of the article.

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### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2010.11.015.

### References


