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Adding low ankle brachial index to classical risk factors improves the prediction of major cardiovascular events. The REGICOR study

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ABSTRACT

Objectives: Cardiovascular risk estimation is a key element of current primary prevention strategies, despite its limited accuracy. Several biomarkers are being tested to assess their capacity to improve coronary (CHD) and cardiovascular (CVD) prediction. One of these biomarkers is ankle brachial index (ABI). The aim of this study was to assess whether the inclusion of ABI improved the predictive capacity of the Framingham-REGICOR risk function in an area of low CVD incidence.

Methods: A total of 5248 individuals, aged 35–74 years, from a prospective population-based cohort study were followed up for a median 5.9 years. Baseline ABI was measured using a standardized method. All incident CHD (angina, myocardial infarction, coronary revascularization, CHD death) and CVD (also including fatal and non-fatal stroke) events were recorded. Improvements in discrimination (ΔC-statistics) and reclassification by net reclassification index (NRI) were assessed.

Results: During follow-up, 111 and 64 subjects presented with a coronary or cerebrovascular event. Pathological ABI (≤0.9) was associated with increased CHD and CVD risk (HR: 2.08 and HR: 2.24, respectively; p-value < 0.001). Including ABI in the Framingham-REGICOR function improved both its discrimination and its reclassification capacity for CVD events but not for CHD events; the ΔC-statistic for CVD events was 0.007 (95% Confidence Interval: 0.001; 0.017) and the NRI was 0.029 (95% CI: 0.014 –0.045; p-value < 0.001).

Conclusion: Inclusion of the ABI improves the predictive capacity of the Framingham-REGICOR risk function. The study results indicate the potential value of including this simple test in cardiovascular risk stratification and support current guidelines recommendations.

1. Introduction

Risk estimation is a key tool of current primary cardiovascular prevention strategies [1,2]. Most of the current risk functions are based on the individual's age, sex, and exposure to classical cardiovascular risk factors. These functions estimate an individual's absolute risk and provide useful information to determine the intensity of necessary preventive lifestyle interventions and treatments. Risk functions provide a valid estimation of cardiovascular risk at the population level; however, they have limited accuracy in identifying subjects who will develop a coronary (CHD) or cardiovascular (CVD) event in the future [3–5]. Therefore, several biomarkers and measures of subclinical atherosclerosis are being tested to assess their capacity to improve the capacity of risk functions to predict CHD/CVD events [6].

Ankle brachial index (ABI) is the ratio of ankle vs arm systolic blood pressure, which can be easily measured in the primary care setting, where cardiovascular primary prevention strategies are usually implemented. Initially proposed as a diagnostic tool for peripheral artery disease (cutoff value < 0.9), ABI is also an indicator of general atherosclerosis and has been independently associated

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[1] http://www.regicor.org/presentacio/en_index.html.

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with total mortality and cardiovascular and coronary heart disease events in prospective studies [7–16]. Therefore, ABI is a good candidate for testing in cardiovascular risk functions to improve their predictive capacity. Several studies have analyzed the added predictive value of ABI compared to classical risk factors alone in northern European and American populations [17–22].

The aim of this study was to assess whether the inclusion of ABI improves the predictive capacity of the adapted Framingham-REGICOR risk function for major CHD and CVD events in a Southern European Mediterranean population.

2. Methods

2.1. Study design and population

A prospective population-based cohort study was carried out in Girona province (~700,000 inhabitants), northeastern Spain. Individuals living in the city of Girona and three surrounding rural villages were randomly selected from the most recent census and invited to participate. At recruitment, participants were aged 35–79 years, had lived in the referral area for at least six months, were free of terminal disease, and were not institutionalized. Selected participants were contacted by a letter informing them of the aims of the study and the tests to be performed. Participants were asked to fast for at least 10 h before their appointment at the health examination site; a telephone number for inquiries was also supplied. Participants who provided a phone number were contacted 1 week before the examination to confirm attendance. A total of 6352 participants, aged 35–79 years, were recruited and examined from 2003 to 2006 [23] (participation rate 73.8%), with follow-up through December 2012. For the present study, we selected participants aged 35–74 years, with a valid ABI and without previous angina or myocardial infarction, or surgical or percutaneous coronary revascularization or stroke at baseline. These clinical diagnoses were self-reported and validated after reviewing medical records and physician notes. The study protocol was approved by the local ethics committee and all the participants signed an informed consent.

2.2. Ankle brachial index measurements

ABI was measured by nurses trained by a senior vascular surgeon using a standardized methodology [24]. After a 5-min rest, systolic blood pressure was measured in the brachial artery 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 measure 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 systolic pressure in each lower limb to the highest (right or left) brachial systolic pressure. The lower of the two ABI values obtained from left and right ankle was used in the analysis. PAD was defined by ABI $\leq$0.9. Subjects with an ABI >1.39 (typically corresponding to distal calcified arteries) in the right or left side and normal ABI in the other side, which precludes the diagnosis of PAD, were excluded from the study. Operator performance was assessed by inter- and intra-operator variability, which yielded an intraclass correlation coefficient of 0.92 and 0.94, respectively.

2.3. Coronary heart disease risk assessment

Examinations were performed by trained nurses and interviewers using standard questionnaires and measurement methods [25]. A standardized smoking questionnaire was used to evaluate cigarette consumption and 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. Body mass index (BMI) was calculated as weight divided by squared height (kg/m2). Patients were considered hypertensive if previously diagnosed by a physician, under treatment, or presenting systolic blood pressure (SBP) $\geq$140 mmHg or diastolic blood pressure (DBP) $\geq$90 mmHg. Fasting blood samples were taken and total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides concentrations were analyzed. Diabetes was defined as history of diabetes, diabetes treatment, or a single fasting glycemia determination >125 mg/dL.

CHD risk was calculated in all participants using the Framingham-REGICOR function, an adaptation of the Framingham risk function [26] that has been calibrated [27] and validated for the Spanish population [4], [28]. The function estimates the risk based on age, sex, smoking status, total cholesterol, high-density lipoprotein cholesterol, systolic and diastolic blood pressure, and diabetes.

2.4. Follow-up

Between 2009 and 2013, all participants in this cohort received a physical re-exam. All participants were also contacted by telephone every two years until the end of 2012 to ascertain, using a standardized questionnaire, whether they had experienced any CHD or cardiovascular event. In addition to this survey of non-fatal events during follow-up, researchers reviewed medical records, linked the data with a regional myocardial infarction population registry, and cross-checked all these data. Fatal events were identified from regional and national mortality registers (ICD9 codes: 410–414 for coronary events and 432–434, 436–438 for cerebrovascular events; ICD10 codes: I20–I22, I24, I25 for coronary events and I61–I67 for cerebrovascular events). After reviewing all medical records and physician notes, suspected CHD events were classified in committee according to standardized criteria: myocardial infarction was defined according to standardized criteria based on symptoms, electrocardiogram, and biomarkers of necrosis [29]; angina was defined according to the presence of symptoms and objective demonstration of ischemia on ECG or presence of coronary stenosis; coronary revascularization, including percutaneous invasive revascularization and surgery, was determined by review of medical records; and death due to CHD was determined by previous reported ICD codes. We also considered cardiovascular events (additionally including fatal and non-fatal stroke) as an outcome of interest and the TOAST criteria were used to define these events [30].

2.5. Statistical analysis

Standard parametric and non-parametric methods were used to compare the characteristics of different groups of individuals. The association between pathological ABI and CHD incidence was evaluated using Cox proportional survival models. Two different multivariate Cox models were considered, the first adjusted for CHD risk estimation as an offset (in which the regression coefficient associated to the REGICOR-Framingham estimated risk is fixed to be 1) and the second for individual cardiovascular risk factors. Three different statistics or metrics were used to assess the potential improvement in the predictive capacity of the model when including the ABI: i) goodness-of-fit of the models or calibration was evaluated using the Akaike Information Criterion (AIC); ii) the discrimination capacity of the models was assessed by the c-statistic using Somers D rank correlation test for a censored response variable [31]. A bootstrapping method was used to construct confidence intervals for the change in the c-statistics; iii) reclassification was evaluated using the net reclassification index (NRI) and

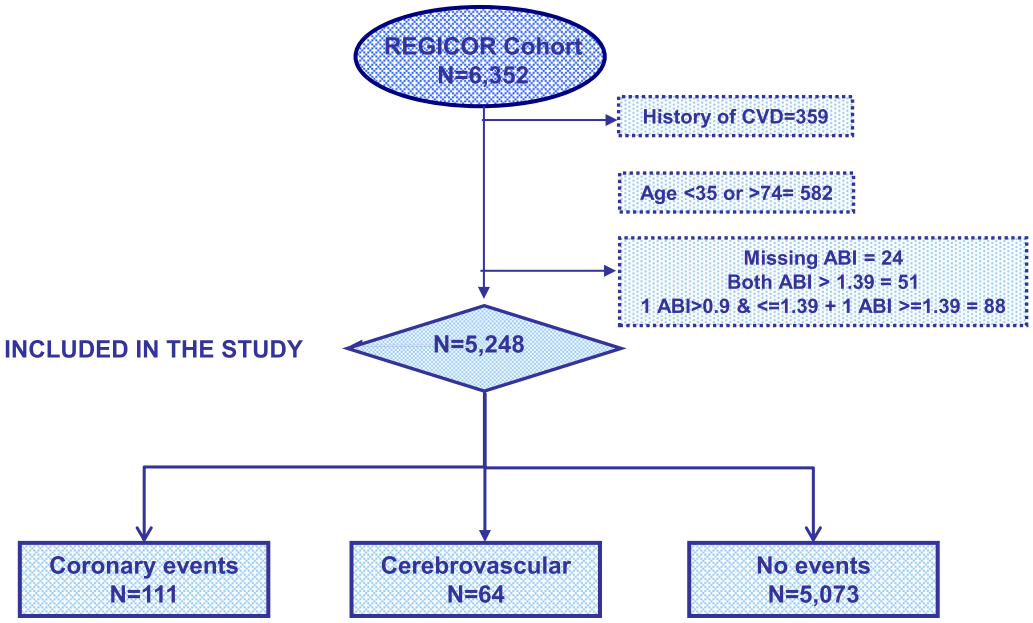

Fig. 1. Flow chart of participant selection and categories of cardiovascular events.

integrated discrimination improvement (IDI) [32]. Three risk categories were defined (low, intermediate, and high risk groups) with cut-off points according to local guidelines (0–5%, 5–10%, and ≥10%, respectively). We calculated the expected number of events at 10-years in each risk category and in each cohort using Kaplan–Meier estimates [33]. A bootstrapping method was used to construct confidence intervals for IDI and NRI in order to account for uncertainty in the Kaplan–Meier estimates, as suggested by Steyerberg et al. [33].

All analyses were performed using the R statistical package (version 3.1.0) [34].

3. Results

From a randomly selected population sample of 6352 eligible subjects, 5248 were included in the study. The flow chart defining the exclusion criteria is shown in Fig. 1. The characteristics of all participants, stratified by ABI, are shown in Table 1. Those with a pathological ABI (n = 168) were older, with increased prevalence of hypertension and diabetes, and higher coronary risk and CHD incidence. No significant association was observed in the whole cohort between pathological ABI and active smoking, lipid profile, or stroke incidence (Table 1). However, smoking was associated with a higher prevalence of pathological ABI in men but not in women (data not shown).

Median follow-up was 5.9 years. During the follow-up, 111 subjects had a CHD event and 175 had a cardiovascular event (Fig. 1). Participant characteristics, stratified by incidence of a CHD event, are shown in Table 2. Those with a CHD event were older and had lower HDL cholesterol and higher total cholesterol, LDL cholesterol, triglycerides, body mass index, systolic and diastolic blood pressure, and coronary risk, with a higher

Table 1
Baseline characteristics of the study population, overall and by ankle-to-brachial index (ABI). REGICOR study, Girona (Catalonia-Spain), 2005.

	Population n = 5248	ABI > 0.9 n = 5080	ABI ≤ 0.9 n = 168	p-value
Age, years[a]	53.7 (10.9)	53.5 (10.8)	58.8 (12.0)	<0.001
Sex: male, n (%)	2388 (45.5%)	2311 (45.5%)	77 (45.8%)	0.993
Smoking, n (%)				0.157
Never smoker	2681 (51.6%)	2606 (51.8%)	75 (44.6%)	
Ex-smoker	1262 (24.3%)	1218 (24.2%)	44 (26.2%)	
Current smoker	1254 (24.1%)	1205 (24.0%)	49 (29.2%)	
Body mass index, Kg/m^2[a]	27.2 (4.64)	27.2 (4.64)	26.8 (4.56)	0.276
Diabetes, n (%)	661 (12.6%)	629 (12.4%)	32 (19.0%)	0.015
Hypertension, n (%)	2153 (41.8%)	2062 (41.3%)	91 (54.2%)	0.001
SBP, mmHg[a]	126 (18.8)	125 (18.6)	134 (22.9)	<0.001
DBP, mmHg[a]	78.7 (10.2)	78.7 (10.2)	79.5 (11.0)	0.375
Total cholesterol, mg/dL[a]	212 (41.7)	212 (41.5)	213 (45.0)	0.609
LDL cholesterol, mg/dL[a]	137 (36.8)	137 (36.8)	134 (35.6)	0.338
HDL cholesterol, mg/dL[a]	52.6 (13.9)	52.6 (13.9)	52.1 (14.9)	0.662
Triglycerides, mg/dL[a]	112 (74.1)	112 (73.6)	115 (87.6)	0.602
CHD incidence (/100,000 y^{-1})	374 (153)	346 (0.00)	1215 (0.00)	<0.001
Stroke incidence (/100,000 y^{-1})	180 (11.6)	177 (0.00)	243 (0.00)	0.660
CVD incidence (/100,000 y^{-1})	590 (287)	537 (0.00)	2167 (0.00)	<0.001
REGICOR 10-year risk (%)[a]	3.83 (3.67)	3.77 (3.60)	5.73 (4.94)	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: Low density lipoprotein; HDL: High density lipoprotein; CHD: coronary heart disease; CVD: cardiovascular disease.

[a] Mean (standard deviation).

Table 2
Characteristics of the study population, stratified by incident coronary event, and hazard ratio corresponding to univariate associations and risk of developing a coronary event during follow-up.

	Incident coronary event		
	No n = 5137	Yes n = 111	Hazard ratio (95% confidence interval)
Sex			
Female, n (%)	2826 (55.0%)	34 (30.6%)	0.34 (0.23:0.51)
Age, years[a]	53.5 (10.8)	60.9 (9.0)	1.07 (1.05:1.09)
Body mass index, Kg/m^2[a]	27.1 (4.6)	28.3 (4.5)	1.04 (1.01:1.08)
Smoking, n (%)			
Never or ex-smoker	3874 (76.2%)	69 (62.7%)	Ref.
Current smoker	1213 (23.8%)	41 (37.3%)	1.99 (1.35:2.93)
Hypertension, n (%)	2075 (41.1%)	78 (70.3%)	3.23 (2.15:4.85)
SBP, mmHg[a]	125 (19)	137 (19)	1.03 (1.02:1.04)
DBP, mmHg[a]	79 (10)	82 (11)	1.03 (1.01:1.05)
Diabetes, n (%)	626 (12.2%)	35 (31.5%)	3.28 (2.20:4.89)
Total cholesterol, mg/dL[a]	211 (42)	228 (43)	1.01 (1.00:1.01)
LDL cholesterol, mg/dL[a]	136 (37)	149 (38)	1.01 (1.00:1.01)
HDL cholesterol, mg/dL[a]	53 (14)	47 (15)	0.96 (0.95:0.98)
Triglycerides, mg/dL[a]	111 (72)	167 (138)	1.00 (1.00:1.01)
REGICOR 10-year risk (%)[a]	3.75 (3.58)	7.67 (5.35)	1.16 (1.13:1.19)
ABI $\leq$ 0.9, n (%)	158 (3.08%)	10 (9.01%)	3.55 (1.85:6.80)

SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: Low density lipoprotein; HDL: High density lipoprotein; ABI: ankle brachial index.
[a] Mean (standard deviation).

proportion of males, smoking, hypertension and diabetes. The prevalence of pathological ABI was also higher among those with a CHD event (9.0% vs 3.1%). Similar results were observed when the data were stratified by total CVD events, with a prevalence of pathological ABI higher among those with CVD events (10.3% vs 3.0%) (Table 3).

The results of the multivariate adjusted Cox models are shown in Table 4. When adjusted for CHD risk estimation based on the Framingham-REGICOR function, abnormal ABI was significantly associated with CHD and CVD events (HR = 2.72; 95% CI = 1.42–5.22; HR = 3.03; 95% CI = 1.86; 4.95, respectively). In the second model, adjusted for the characteristics included in the Framingham-REGICOR risk function, the magnitude of the associations decreased slightly but remained significant (HR = 2.08; 95% CI = 1.08–4.03 for CHD events; HR = 2.24; 95% CI = 1.36; 3.69 for CVD events).

The improvement in the Framingham-REGICOR risk function's predictive capacity with the inclusion of pathological ABI was assessed with different criteria (Table 5) and yielded the following results:

a) Calibration – the model including classical CV risk factors plus ABI showed a lower AIC than the model without ABI, which indicates a better calibration capacity of the risk function, both for CHD and CVD events.
b) Discrimination – the c-statistic did not change for CHD events but increased 0.008 (95%CI = 0.001; 0.017; p-value = 0.049) for CVD events when ABI was included in the risk function, showing a better discrimination capacity for CVD events.
c) Reclassification – the inclusion of ABI in the Framingham-REGICOR function yielded an appropriate and significant improvement in IDI for CHD events and in both IDI and NRI for CVD events, indicating a correct reclassification of participants. The reclassification among the participants included in the intermediate risk group was also significant for CVD events. The reclassification of individuals based on the 10-year predicted

Table 3
Characteristics of the study population, stratified by incident cardiovascular event and hazard ratio corresponding to univariate associations and the risk of developing a cardiovascular event during follow-up.

	Incident cardiovascular event		
	No n = 5073	Yes n = 175	Hazard ratio (95% confidence interval)
Sex			
Female, n (%)	2802 (55.2%)	58 (33.1%)	0.39 (0.28:0.53)
Age, years[a]	53.4 (10.8)	62.3 (9.06)	1.08 (1.07:1.10)
Body mass index, Kg/m^2[a]	27.1 (4.6)	28.3 (4.6)	1.04 (1.01:1.07)
Smoking, n (%)			
Never or ex-smoker	3823 (76.1%)	120 (69.4%)	Ref.
Current smoker	1201 (23.9%)	53 (30.6%)	1.50 (1.08:2.07)
Hypertension, n (%)	2032 (40.8%)	121 (69.5%)	3.05 (2.21:4.22)
SBP, mmHg[a]	125 (19)	138 (19)	1.03 (1.02:1.03)
DBP, mmHg[a]	79 (10)	82 (11)	1.03 (1.02:1.04)
Diabetes, n (%)	605 (11.9%)	56 (32.0%)	3.31 (2.41:4.55)
Total cholesterol, mg/dL[a]	211 (42)	221 (43)	1.01 (1.00:1.01)
LDL cholesterol, mg/dL[a]	136 (37)	144 (37)	1.01 (1.00:1.01)
HDL cholesterol, mg/dL[a]	53 (14)	48 (14)	0.97 (0.96:0.98)
Triglycerides, mg/dL[a]	110 (72)	153 (122)	1.00 (1.00:1.00)
REGICOR 10-year risk[a]	3.71 (3.53)	7.55 (5.18)	1.16 (1.14–1.19)
ABI $\leq$ 0.9, n (%)	150 (3.0%)	18 (10.3%)	4.09 (2.51:6.66)

SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: Low density lipoprotein; HDL: High density lipoprotein; ABI: ankle brachial index.
[a] Mean (standard deviation).

Table 4
Multivariate adjusted association between the presence of a pathological ankle brachial index (ABI ≤ 0.9) and the incidence of coronary and cardiovascular events. Model 1: adjusted for coronary risk obtained with the Framingham-REGICOR function; Model 2: adjusted for individual variables included in the Framingham risk function.

Model 1	Hazard ratio	95% confidence interval	p-value
A) Coronary events			
ABI ≤ 0.9[a]	2.72	1.42:5.22	0.003
REGICOR 10-year risk	1.16	1.13:1.19	<0.001
B) Cardiovascular events			
ABI ≤ 0.9[a]	3.03	1.86:4.95	<0.001
REGICOR 10-year risk	1.16	1.13:1.18	<0.001

Model 2	Regression coefficient	Hazard ratio (95% confidence interval)	p-value	Standardized regression coefficient
A) Coronary events				
ABI ≤ 0.9[a] (yes = 1; no = 0)	0.733	2.08 (1.08:4.03)	0.030	0.733
Age (1 year)	0.064	1.07 (1.04:1.09)	<0.001	0.690
Sex (female = 1; male = 0)	−0.691	0.50 (0.32:0.79)	0.003	−0.691
Smoker (yes = 1; no = 0)	0.770	2.16 (1.42:3.29)	<0.001	0.770
Diabetes (yes = 1; no = 0)	0.581	1.79 (1.18:2.71)	0.006	0.581
Total cholesterol (1 mg/dL)	0.009	1.01 (1.01:1.01)	<0.001	0.363
HDL cholesterol[a] (1 mg/dL)	−0.028	0.97 (0.96:0.99)	<0.001	−0.396
SBP[a] (1 mmHg)	0.010	1.01 (1.00:1.02)	0.057	0.188
B) Cardiovascular events				
ABI ≤ 0.9[a] (yes = 1; no = 0)	0.807	2.24 (1.36:3.69)	0.001	0.807
Age (1 year)	0.076	1.08 (1.06:1.10)	<0.001	0.822
Sex (female = 1; male = 0)	−0.610	0.54 (0.38:0.77)	<0.001	−0.610
Smoker (yes = 1; no = 0)	0.581	1.79 (1.26:2.54)	0.001	0.581
Diabetes (yes = 1; no = 0)	0.556	1.74 (1.26:2.42)	<0.001	0.556
Total cholesterol (1 mg/dL)	0.007	1.01 (1.00:1.01)	<0.001	0.288
HDL cholesterol[a] (1 mg/dL)	−0.026	0.98 (0.96:0.99)	<0.001	−0.356
SBP[a] (1 mmHg)	0.010	1.01 (1.00:1.02)	0.021	0.180

[a] ABI: ankle brachial index; HDL: High density lipoprotein; SBP: systolic blood pressure.

Framingham-REGICOR risk with and without the ABI according to the presence of CHD or CVD events is shown in Supplementary Table 1.

4. Discussion

In this study, we showed that the inclusion of pathological ABI in the Framingham-REGICOR risk function improves the predictive capacity of cardiovascular events in a southern European population. This improvement is reflected in better calibration, discrimination, and reclassification, compared to the risk function based only on classical risk factors.

In 2009, the American Heart Association (AHA) proposed five essential steps for assessing the potential value of novel biomarkers in risk estimation [6]: (i) an initial proof of concept demonstrating the association between the proposed biomarker and event risk, (ii) prospective validation of this association in cohort studies, (iii) assessment of the improvement of the predictive capacity related to the addition of the biomarker compared with the classical risk

Table 5
Improved predictive capacity of the Framingham-REGICOR risk function for coronary and cardiovascular events in a Southern European Mediterranean population with pathological ankle-brachial index (ABI) included in the calculation.

	Framingham-REGICOR risk function	Framingham-REGICOR risk function + ABI ≤ 0.9	P-value
A) Coronary events			
Calibration: AIC	1653.0	1650.2	
Discrimination: C-statistics	0.795	0.797	–
Δ C-statistics (95% CI)	Ref	0.002 (−0.001:0.007)	0.529
Reclassification			
IDI, (95% CI)	Ref	0.63 (0.32:0.95)	<0.001
NRI- all, (95% CI)	Ref	0.001 (−0.060:0.058)	0.983
NRI-cases		−0.010 (−0.070:0.045)	0.698
NRI-non cases		0.011 (0.007:0.017)	<0.001
NRI in the intermediate risk group	Ref	0.059 (−0.080:0.191)	0.411
NRI-cases		0.013 (−0.110:0.136)	0.858
NRI-non cases		0.046 (0.023:0.070)	<0.001
B) Cardiovascular events			
Calibration: AIC	2571.0	2562.2	
Discrimination: C-statistics	0.787	0.795	–
Δ C-statistics (95% CI)	Ref	0.008 (0.001:0.017)	0.049
Reclassification			
IDI, (95% CI)	Ref	1.11 (0.67:1.55)	<0.001
NRI- all, (95% CI)	Ref	0.029 (0.014:0.045)	<0.001
NRI-cases		0.006 (−0.007:0.022)	0.358
NRI-non cases		0.023 (0.017:0.029)	<0.001
NRI in the intermediate risk group	Ref	0.051 (0.015:0.106)	0.025
NRI-cases		0.026 (0:0.072)	0.183
NRI-non cases		0.025 (0.005:0.044)	0.010

AIC, Akaike information criterion; IDI, integrated discrimination improvement; NRI, net reclassification index; 95% CI, 95% confidence interval.

function, (iv) assessment of effects of this new approach on patient management and outcomes, and (v) cost-effectiveness analysis. In this study, we assessed the first three steps suggested by the AHA.

We found a strong association between pathological ABI and CHD and CVD events incidence (HR = 2.46 and 2.64, respectively), similar to that reported in the ABI Collaboration Meta-analysis (HR = 2.97 in men and 3.05 in women, for major coronary events) [16], which included 16 population cohort studies and more than 48,000 individuals. This association also has been reported in Mediterranean populations [15,35], with a magnitude of association similar to that observed in our study.

Moreover, we report an improved predictive capacity of classical risk functions when ABI-related information was incorporated. This improvement has been analyzed in previous studies [17–21], with discordant results. Our study showed a slight increase in the c-statistic for CVD events. A similar increase in the discrimination capacity for CVD events was also observed in two of the published studies, the MESA study [18] and in women in the ABI Collaboration [21]. In these two studies an improvement in the discrimination capacity for CHD events was also reported [18,21].

We also found an improvement in the reclassification for CVD events when ABI was added to the risk function (NRI = 0.029). This improvement was also observed in the MESA study (NRI = 0.068) [18] and in the ABI collaboration (NRI = 0.057 in men and 0.016 in women) [21], but not in ARIC (NRI = 0.008) [20]. Several studies also report a significant NRI ranging from 0.033 to 0.096 for CHD events [17–19,21]. When we analyzed the reclassification for CHD events we only found a significant improvement in the IDI but not in the NRI.

Some studies have analyzed the reclassification capacity considering only the intermediate risk group. The selection of this group is based on three main clinical arguments: first, there is agreement that an intensive preventive approach should be implemented in individuals with high cardiovascular risk [1,2]; second, a high proportion of CHD events occur originate in this intermediate group and new biomarkers could help to identify and reclassify individuals to high risk in order to implement an intensive preventive approach; and third, although ABI measurement is easy and cheap, a population-based screening approach could have limited feasibility in daily clinical practice. This type of screening could be more feasible in a selected subgroup of the population as a second step in the screening approach [36]. Some authors have reported a better reclassification in the intermediate-risk population subgroup both for CHD [19,21] and CVD events [21]; we also observed a higher NRI in the intermediate-risk group than in the whole population for CVD events (NRI = 0.051). We also observed a NRI with a similar magnitude for CHD events (NRI = 0.059), although it was not statistically significant. The lack of statistical significance for reclassification of CHD events in the intermediate risk group observed in our study could be related to a low statistical power. However, the approach of calculating the NRI in population subgroups has been criticized by some authors, as the estimation obtained tends to be overly optimistic [37] and the results should be interpreted with caution.

All these results support current recommendations to include ABI as a screening tool in an effort to improve cardiovascular risk prediction, especially in the intermediate-risk population [1,2,38–40].

4.1. Strengths and limitations

Previous studies analyzing the value of ABI in cardiovascular prediction have been undertaken in populations with higher CHD incidence [17–21]. A contribution of the present research, a prospective follow-up of a population-based cohort from an area with low CHD incidence, is that the results obtained reinforce the value of ABI and expand its usefulness as a predictive tool. The ABI measurements were done with standardized methods, operators were meticulously trained by a senior vascular surgeon, and very low intra- and inter-observer variability was observed. A study limitation was that we did not assess the value of an ABI >1.39, an exclusion criterion that is considered indicative of distal calcified artery. Moreover, only data from one cohort were included in this study.

5. Conclusion

Our study confirmed that an ABI ≤0.9 is strongly associated with coronary and cardiovascular events. Moreover, an ABI ≤0.9 improves the predictive ability of the Framingham-REGICOR function for major cardiovascular events. These results indicate the potential value of the inclusion of this simple test in cardiovascular risk stratification. However, formal decision analytic modeling or cost-effectiveness evaluations are warranted.

Conflict of interest

The authors have no potential conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2015.05.017.

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