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# UNIVERSITÀ DEGLI STUDI DI TORINO

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## **Implications of routinely measuring Ankle-Brachial Index (ABI) among patients attending at a Lipid Clinic**

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### **Abstract**

#### **Background**

Low ( $\leq 0.90$ ) Ankle Brachial Index (ABI) values identify patients at high risk for cardiovascular (CV) disease and mortality. Implications for CV risk classification from routinely measuring ABI in the context of a Lipid Clinic have not been fully investigated. We aimed to evaluate whether and to what extent routine ABI determination on top of conventional risk prediction models may modify CV risk classification.

#### **Methods**

Consecutive asymptomatic non-diabetic individuals free from previous CV events attending for a first visit at a Lipid Clinic underwent routine ABI determination and conventional CV risk classification according either to national CUORE model (including age, gender, smoking, total and high density lipoprotein cholesterol, systolic blood pressure and current use of blood pressure lowering drugs) and SCORE model for low risk countries.

#### **Results**

In the overall sample (320 subjects, mean age 64.8 years) 77 subjects (24.1%) were found to have low ABI value. Forty-two of 250 subjects (16.8%) and 47 of 215 individuals (21.3%) at low or moderate risk according to the CUORE and SCORE models, respectively, were found to have low ABI values, and should be reclassified at high risk.

#### **Conclusion**

In a series of consecutive asymptomatic individuals in a Lipid Clinic, we observed a high prevalence of low ABI values among subjects deemed at low or moderate risk on conventional prediction models, leading to CV high-risk reclassification of roughly one fifth of patients. These findings reinforce recommendations for routine determination of ABI at least within referral primary prevention settings.

### **1. Introduction**

In the last decades, several models have been developed and validated for cardiovascular (CV) risk prediction and have been incorporated in national guidelines in several primary prevention settings [1]. Despite modest differences among these models, most of them include major CV risk factors such as age, male gender, blood pressure values, cigarette smoking, presence of diabetes and lipid values (usually total or low-density lipoprotein cholesterol, occasionally high-density lipoprotein cholesterol). These models have proved to be reliable in identifying those high risk subjects who will experience the greatest incidence of fatal and non-fatal coronary heart disease (CHD). However, most of the CHD events yet occur in those

subjects deemed to be at low or moderate CV risk and who represent by far the vast majority of the western population [2] and [3]. Therefore, efforts have been devoted in recent years to improve risk stratification in the primary prevention setting [4]. Unfortunately, inclusion of multiple biomarkers did not add to conventional risk prediction models [5]. It has been demonstrated that ultrasonography measurement of carotid intima-media thickness (IMT) and CT evaluation of coronary artery calcification might improve conventional CV risk prediction, but these procedures are costly, time-expensive and not yet widely available for routine clinical practice in the primary prevention setting [6], [7] and [8].

Peripheral Arterial Disease (PAD) is a serious CV disorder affecting more than 25 million individuals in Europe and USA [9] and [10]. In addition to clinical symptoms and functional impairment, individuals with PAD are at markedly increased risk of CV events, even in the asymptomatic stage of the disease. Patients with Ankle-Brachial Index (ABI)  $\leq 0.90$  have a 2- to 3-fold increased risk of death from any cause and a 3- to 6-fold increased risk of CV mortality [10]. Moreover, a 50% 10-year mortality risk in these patients, mainly for CV fatal events, has been reported in several studies [11] and [12]. Therefore, recent CV prevention guidelines have included PAD as a CHD risk equivalent and suggest measurement of ABI as a simple way to identify high-risk subjects, irrespective of conventional risk prediction models, for whom aggressive medical treatment is strongly recommended [13], [14] and [15]. However, ABI measurement is not routinely performed in most primary prevention setting, and there remains a widespread lack of awareness of these recommendations among healthcare professionals [16] and [17], even in selected primary prevention settings caring for moderate to high risk patients (such as Lipid, Hypertension or Diabetes Clinics) wherein ABI determination, accordingly with some clinical recommendations [18], is mostly performed as a second-line test in patients at intermediate risk.

To our knowledge, the prevalence of patients with low ABI values among those classified not at high-risk with conventional models has not been fully investigated, and the clinical implications for CV risk stratification of routinely measuring ABI in a primary prevention setting have not been elucidated. Therefore, in the present study we aimed to evaluate whether and to what extent routine ABI determination on top of conventional risk prediction models may lead to CV risk reclassification among consecutive non-diabetic individuals free from previous CV events attending at a Lipid Clinic.

## **2. Methods**

The study protocol was in accordance with the recommendations of the World Medical Association for biomedical research involving human subjects, and it was approved by the local ethics committee.

This cross-sectional single-centre study was conducted at the Lipid Clinic of a University-teaching hospital in Turin, northern Italy, in the period between April and December, 2006. Subjects usually attending at the Lipid Clinic include mainly patients with dyslipidemia (regardless of its nature and severity) with multiple risk factors and/or with history of previous cardiovascular events, mostly referred to the centre by their general practitioners [19].

Aims and methods of the study were described to all patients who were invited to consent to study participation. Consecutive apparently healthy asymptomatic subjects aged 18 or older, without history of previous CV disease (primary prevention setting) – including stable angina, acute coronary syndromes, stroke and transient ischemic attacks, symptomatic peripheral arterial disease or prior surgical or percutaneous revascularization procedures on coronary or peripheral arterial districts –, admitted for a first visit, were eligible to the study. The only reasons for exclusion from the study were presence of diabetes, evidence of familial dyslipidemia or current/previous treatment with lipid-lowering drugs and estrogen replacement therapy. Consecutive subjects admitted for the first visit in the period April–December 2006 and fulfilling the inclusion criteria were invited to participate, after a careful description of the design of the study. All participants provided informed consent to participate in the study.

### **2.1. Anthropometric measurements**

In each patient the following measures were obtained: weight (kilograms), height (meters), Body Mass Index [BMI, calculated according to the formula weight (kg)/height (m<sup>2</sup>)], waist and hip circumferences (centimeters), measured according to current guidelines [20], systolic and diastolic blood pressure, SBP and DBP, (mean value of 3 measures obtained with a an appropriately sized cuff and standard mercury sphygmomanometer at both upper arms after a 5-minute rest in the supine position). Patients were considered diabetic if they were receiving glucose-lowering therapy or if fasting blood glucose levels exceeded 126 mg/dl.

### **2.2. Biochemical analysis**

For patients free from previous CV events (primary prevention setting) attending for a first visit at our Lipid Clinic, a careful and thorough evaluation of conventional and minor risk factors is usually performed. Blood samples were collected from an antecubital vein into vacutainer tubes containing EDTA after a 12-hour overnight fast for the measurement of baseline routine measurements (complete blood cell count, glucose, creatinine, liver enzymes, total bilirubin, total protein, albumin, immunoglobulin, thyroid stimulating hormone, creatine-kinase, uric acid), plasma lipid and lipoprotein levels, inflammatory markers (fibrinogen and hs-CRP), insulin and homocysteine, according to standardized procedures which have been described elsewhere [19] and [21].

### **2.3. Assessment of cardiovascular risk**

Calculation of 10-year cardiovascular risk was performed according to current national recommendations (Istituto Superiore Sanità, ISS), using the web-site CUORE algorithm ([www.cuore.iss.it](http://www.cuore.iss.it)), which includes the following variables: age (years), gender, current smoking habits (yes/not), SBP value (mm Hg), total and high-density lipoprotein cholesterol values (mg/dl), current use of blood-pressure lowering treatment (yes/not). According to the score obtained, patients were defined at 10-year CV low risk ( $\leq 10\%$ ), moderate risk (11–19%) and high risk ( $\geq 20\%$ ). The 10-year risk of fatal events was also evaluated according to the SCORE model for low-risk southern Europe countries [13]. According to the score obtained patients were defined at 10-year CV low risk ( $\leq 1\%$ ), moderate risk (2–4%) and high risk ( $\geq 5\%$ ).

### **2.4. Ankle-brachial index**

In each patient the Ankle-Brachial Index (ABI) was evaluated by a senior physician according to current recommendations and carefully standardized procedures were followed in the non-invasive vascular diagnostic lab of the Lipid Clinic [10] and [22]. Briefly, with the patient in supine position, BP cuffs were applied to both upper and lower limbs and the systolic BP was measured using an 8-Mhz Doppler probe and an ultrasonic Doppler flow detector. BP in the lower limbs was measured both in the anterior and posterior tibial arteries; the higher value was defined as the ankle pressure. To calculate the ABI, the higher systolic BP in each ankle was divided by the higher systolic BP in the upper limbs. To better estimate the atherosclerotic burden of lower limbs, the lower of the two ABI measures (right and left) calculated at study entry was considered for analysis [10].

## 2.5. Statistical analysis

Data were analyzed using SPSS/PC+. Frequencies, mean and standard deviations were calculated, and kurtosis and skewness were evaluated. Not normally distributed variables were described using median and interquartile range. The concordance between risk models was evaluated through the Kendall's W coefficient of concordance.

## 3. Results

Three hundred and twenty subjects (mean age 64.8 years, 35.8% men) were enrolled. The characteristics of the population investigated are presented in Table 1: 130 subjects (40.6%) had hypertension and 100 (31.3%) were current smokers. Median total and low density lipoprotein (LDL) cholesterol values were 281 and 178 mg/dl, respectively. In the overall sample, an  $ABI \leq 0.90$  was found in 77 subjects (24.1%): 17.2% of these patients complained of leg discomfort without typical claudication. The calculated median 10-year CV risk was 10 and 3, according to CUORE and SCORE models, respectively.

Table 1.  
Baseline characteristics of the sample investigated (320 subjects).

Men <sup>a</sup>	114 (35.8%)
Hypertension <sup>a</sup>	130 (40.6%)
Cigarette smoking <sup>a</sup>	100 (31.3%)
Age (years) <sup>b</sup>	63 (60–67.5)
BMI (kg/m <sup>2</sup> ) <sup>b</sup>	25.6 (23.0–28.0)
SBP (mm Hg) <sup>b</sup>	140 (120–150)
DBP (mm Hg) <sup>b</sup>	80 (80–90)
ABI <sup>b</sup>	1.0 (1.0–1.1)
Total cholesterol (mg/dl) <sup>b</sup>	281 (247–312)
HDL cholesterol (mg/dl) <sup>b</sup>	60 (52–71)
LDL cholesterol (mg/dl) <sup>b</sup>	178 (151.5–217.5)
Triglycerides (mg/dl) <sup>b</sup>	140.5 (103.5–184.0)
Apo A (mg/dl) <sup>b</sup>	165 (140–192)
Apo B (mg/dl) <sup>b</sup>	131.5 (114.0–157.5)
Glucose (mg/dl) <sup>b</sup>	86 (78–93)
Creatinine (mg/dl) <sup>b</sup>	0.82 (0.70–0.92)
Hs-CRP <sup>b</sup> (mg/l)	1.97 (1.04–3.40)
10-year CV risk (CUORE) <sup>b</sup>	10 (6–18)
10-year CV risk (SCORE) <sup>b</sup>	3 (2–5)

*Abbreviations:* BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABI, ankle-brachial index; HDL, high density lipoprotein; LDL, low density lipoprotein; Hs-CRP, high sensitivity C-reactive protein; CV, cardiovascular.

a

Dichotomous variables: number (%).

b

Continuous variables: median (interquartile range).

According to the CUORE risk model, 70 subjects were deemed to be at high risk, whereas 106 and 144 individuals were classified at moderate and low risk, respectively. According to the SCORE model, 105 patients were found to be at high risk, whereas 154 and 61 individuals were classified at moderate and low risk, respectively (Table 2). A very poor concordance has been observed between these two prediction models (Kendall's W coefficient: 0.18).

Table 2.

Cross-match between risk classification models (CUORE and SCORE).

CUORE	SCORE			
	≤ 1% (low)	2%–4% (moderate)	≥ 5% (high)	
≤ 10% (low)	<b>47</b>	75	22	144
11%–19% (moderate)	6	<b>50</b>	50	106
≥ 20% (high)	8	29	<b>33</b>	70
	61	154	105	TOT: 320

Kendall's coefficient of concordance: 0.18. Bold characters identify subjects whose CV risk class allocation is similar with the two risk models used (CUORE and SCORE).

Table 3 reports the prevalence of patients with low ABI ( $\leq 0.90$ ) within each risk class according to both CV risk prediction models. Overall, 42 of the 250 subjects (16.8%) classified not at high-risk according to the CUORE model had low ABI, which was detected in 12.5% of the low-risk subjects and 22.6% of the moderate risk individuals. Very similar figures were observed when the SCORE risk estimation model was used: 47 of the 215 subjects (21.3%) not classified at high-risk were found to have low ABI values, which

Table 3.

Prevalence of patients with low ABI ( $\leq 0.90$ ) according to CV risk categories (CUORE and SCORE).

	Low	Moderate	High
CUORE	18/144 (12.5%)	24/106 (22.6%)	35/70 (50%)
SCORE	11/61 (18.0%)	36/154 (23.4%)	30/105 (28.6%)

#### 4. Discussion

Results of the present study demonstrate that, among asymptomatic non-diabetic subjects attending at a Lipid Clinic, there is a high prevalence of mostly asymptomatic PAD, affecting roughly one fourth of these patients. Low ABI values were observed in a remarkable proportion of individuals deemed at low or moderate risk according to conventional CV risk prediction models: more than one fifth of individuals classified at low or moderate risk according to the SCORE model, and roughly one sixth of those who received the same classification according to the CUORE model, should be reclassified as CHD risk equivalent. These findings demonstrate that routine ABI determination may significantly modify CV risk classification in this primary prevention setting. A recent meta-analysis has demonstrated that low ABI was

associated with approximately twice the 10-year total and cardiovascular mortality compared with the overall rate in each Framingham risk score category [23]. In this context our findings reinforce the evidence for routine ABI measurement at least in selected primary prevention settings.

No study has previously specifically investigated the impact on CV risk classification of routinely measuring ABI in the primary prevention setting of a Lipid Clinic. Our findings show that 16.8% and 21.3% of individuals deemed at low or moderate risk according to the CUORE and SCORE models, respectively, should be reclassified at high risk on the basis of a low ABI value. Not few cases of low ABI value were detected even among those subjects classified at low risk with both models (12.5% and 18%, respectively). Relevance of these findings is further increased by the concomitant observation of an unexpected poor concordance between the prediction models used in the present study. Although these prediction models stratify patients according to different hard clinical end-points (events in the CUORE model and mortality in the SCORE model), they are assumed to be largely concordant and are both currently recommended for CV risk stratification by national [24] and [25] and European [13] guidelines. Therefore, given persistent uncertainties on reliability of risk classification based on conventional risk factors alone [2] and [3], routine ABI measurement appears to be an easy and reliable tool for identification of high risk subjects irrespective of conventional risk models.

The place of subclinical atherosclerosis testing in the context of models for CHD prediction is still debated. The crucial question of whether and to what extent abnormal findings from subclinical atherosclerosis investigation should allow risk reclassification is unclear. Moreover, different types of subclinical atherosclerosis tests (ABI, carotid intima-media thickness, coronary artery calcification) have different prognostic significance [18]. Compared with other subclinical atherosclerosis tests, measurement of ABI is simple, inexpensive and non-invasive. Low ABI values were originally used to identify PAD; however they have subsequently been shown to be an accurate and reliable marker of generalized atherosclerosis and increased risk of CV morbidity and mortality [10], [11] and [12]. Moreover, it has been shown that a low ABI is better at predicting risk of future cardiovascular and cerebrovascular events than conventional risk factors alone [26], and that addition of the ABI significantly improves prediction of CHD mortality over and above conventional risk factors [15]. Although there is yet no evidence that better risk prediction through ABI measurement may translate into reduced incidence of CV events or longer survival, it is reasonable to infer that aggressive treatment for higher risk patients identified by low ABI values irrespective of conventional risk prediction might provide additional benefit in primary prevention of CV events. Therefore, evaluation of subclinical atherosclerosis through ABI determination should have its place in the context of risk classification among asymptomatic subjects. Currently, most international guidelines recommend to consider PAD (diagnosed on the basis of low ABI) as a CHD risk equivalent, for which aggressive medical therapies are strongly recommended [10], [13], [14] and [27]. Despite this bulk of evidence, there remains a lack of awareness of this item among healthcare professionals, and ABI determination is largely underused for CV risk stratification [16] and [17].

Some limitations of the present study should be addressed. The selected sample investigated does not allow generalization of our findings to other primary care settings. However, the place of subclinical atherosclerosis testing on population basis is not defined. Although some have recently proposed to screen non invasively in a systematic way men aged 45–75 and women aged 55–75 for subclinical atherosclerosis [28], screening of subclinical atherosclerosis on a population-wide basis should be discouraged [18]. As expected, prevalence of PAD in this selected sample of asymptomatic subjects referred to a Lipid Clinic for



CV risk stratification is slightly higher than that reported in population-based surveys [15], [29] and [30], but in keeping with that reported in individuals with diabetes within population-based studies [31]. Although the sample investigated was derived from a single Lipid Clinic in northern Italy, use of the SCORE model should allow an easy comparison with other primary prevention settings of care within and outside our country.

We conclude that, in the primary prevention setting, routine ABI measurement in individuals attending for a first visit at a Lipid Clinic may modify risk classification in a substantial number of patients: roughly one fifth of subjects deemed not at high risk by conventional prediction models should be reclassified at high risk on the basis of low ABI. Because ABI is a reliable, non-invasive, simple and inexpensive test, present findings reinforce evidence for routinely ABI measurement at least in all Lipid Clinics and other referral primary prevention settings.

## 5. Learning points

Routine determination of ABI in primary prevention settings, such as a Lipid Clinic, should be considered as a reliable, non-invasive, simple and inexpensive test. It could lead to a reclassification of cardiovascular risk score of asymptomatic subjects considered at low cardiovascular risk.

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