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Ankle–brachial index and cardiovascular risk prediction: An analysis of 11,594 individuals with 10-year follow-up

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ABSTRACT

Background: Low ankle–brachial index (ABI) is associated with increased risk of subsequent cardiovascular disease events, independent of Framingham risk factors, but its ability to improve risk prediction prospectively has not been examined.
Methods: We conducted post-hoc analysis of data from Atherosclerosis Risk in Communities Study (ARIC Study), a large prospective cohort study. 11,594 white and African American (24.2%) men and women, aged 45–64 years, with available Framingham Risk Score (FRS) variables and ABIs at baseline, and without known history of cardiovascular disease or diabetes mellitus or known peripheral arterial disease at baseline were assessed for hard cardiovascular events (hCVD; defined as heart attack, coronary death or stroke) over median follow-up of 10 years. Hazard ratios, C statistic, and net reclassification indexes were calculated to determine the independent predictive ability of ABI compared with FRS.
Results: 659 hCVD events occurred. Standardized ABI was significantly associated with hCVD events but with a relatively small effect on events (hazard ratios of 0.85 per standard deviation (95% CI 0.79–0.91) (p-value < 0.0001)). The C statistic of FRS modified with ABI was only modestly improved (0.756–0.758). Net reclassification improvement, an indicator of prospective prediction performance, using an ABI threshold of 0.9 was small and statistically insignificant (0.8%, $p = 0.50$).
Conclusions: Although the ABI adjusted for Framingham risk variables was independently associated with subsequent events in terms of hazard ratios, the independent effect of ABI when adjusted for FRS was small in magnitude, and the FRS performed similarly with or without integration or supplementation with ABI. These findings do not provide strong evidence to support FRS modification to include ABI.

1. Introduction

Current guidelines call for assessment of cardiovascular risk using accepted risk variables (age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, cigarette smoking, and family history of premature coronary heart disease) [1]. If two or more risk factors are present, an integrated risk prediction model, such as the Framingham Risk Score (FRS), is used to quantify short-term (10-year) risk [1]. Individuals with "high" risk (≥20% 10-year risk of "hard CHD" (heart attack or coronary-related death)) are considered "CHD equivalent" and are candidates for intensive medical risk reduction [1], and those at "intermediate" risk (≥10 < 20% 10-year risk) candidates for less intensive risk factor reduction. However the Framingham Risk Score does not fully explain cardiovascular risk [2] since 20% of MIs occur in those with no risk factors [3,4], and at least 60–80% of MIs in those without known CHD or CHD equivalent occur in those at low or intermediate risk of CHD using Framingham Risk Scores [5–7]. Methods to improve risk prediction, especially by means that are noninvasive and inexpensive, are of considerable interest [8,9] as they would allow more people at increased risk for cardiovascular events to receive intensive risk modification therapy and thereby reduce heart attacks, strokes, and related deaths.

The ankle–brachial index (ABI), which is the ratio of systolic pressure at the ankle to that in the arm, is inexpensive, widely available, and noninvasive. Recent data from National Health And

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Nutrition Examination Survey reveal that abnormal ABI is highly prevalent among individuals otherwise not considered at high risk of cardiovascular events [10]. Meta-analyses of many large observational studies with long-term follow-up have reported that ABI is associated with coronary heart events independent of traditional Framingham variables [11], and an abnormal ABI is accepted in current guidelines as a coronary-heart disease (CHD) equivalent [1]. Screening measurement of the ABI to supplement risk prediction has been recommended by American Heart Association and the American College of Cardiology [12], the Transatlantic Inter-Society Consensus Working Group [13], and the Fourth Joint European Task Force [14], among others [10,15]. Despite this, the usefulness of the ABI as a risk prediction variable when Framingham-based variables are known is complicated. Both the magnitude of ABIs independent relationship with subsequent cardiovascular disease events and how ABI is integrated into a risk prediction model have strong implications for its usefulness.

In this study, we critically examine claims that ABI can improve risk prediction for hard cardiovascular disease events (hCVD; defined as heart attack, coronary death, or stroke) by evaluating its performance using a modified risk-prediction model with traditional Framingham Risk Scores, and also by examining how abnormal ABI performs when used to establish CHD equivalence *per se*, as indicated in current guidelines [1].

2. Methods

For this analysis we used data collected in the Atherosclerosis Risk in Communities (ARIC) Study [16], a prospective cohort study of middle-aged individuals with long-term follow-up. Our objective is to determine if ankle–brachial index provides information on risk of subsequent hCVD events independent of a standard risk factors' model based on the Framingham Risk Score variables [1], by: (1) determining the incremental value of ABI when added in a standard FRS variables model; and (2) performing a sensitivity and specificity analyses of abnormal ABI compared with a model that readjusts the FRS threshold of "high" risk so that comparable numbers of individuals are categorized as "high" risk under each model. The study was approved by the institutional review board at Rhode Island Hospital (Providence, Rhode Island).

2.1. Population

The Atherosclerosis Risk in Communities Study is a longitudinal cohort study of 15,792 White and African American men and women between the ages of 45 and 64 at baseline who were recruited in 1987–89 from 4 US communities [16]; minority oversampling was done in the city of Jackson, Mississippi. The study population includes follow-up through 2002, with a median of 14 years and maximum of 16 years. The ARIC Study is the largest modern study of a broad spectrum of middle-aged Americans, a population age for which Framingham risk prediction is optimized [1], that includes all necessary variables needed for Framingham risk calculation, as well as ankle–brachial index, with sufficient follow-up to reliably assess risk prediction.

Of the 15,732 participants at the baseline examination, 1852 were excluded from analysis due to prevalent CHD, stroke, transient ischemic attack, or known peripheral arterial disease and further 1621 due to diabetes (diabetes mellitus is considered a CHD-equivalent and excluding these individuals is consistent with ATP III recommendations for risk scoring procedures [1]). Of the remaining 12,259 individuals, 265 had missing cardiovascular disease risk factors and further 400 had missing ABI and all of these were excluded from the analysis. After all exclusions 11,594 (6540 women, 2802 African American) participants without known CHD or CHD-equivalent conditions remained eligible for the analysis. Population baseline characteristics are presented in Table 1.

2.2. Baseline measurements

Baseline measurements in the ARIC Study have been described previously [16]. Variables that were obtained include medical histories, body habitus, and fasting blood samples including measurement of total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL). Presence of symptomatic peripheral arterial disease was assessed using the Rose questionnaire [17]. Physical examination data include, among others, blood pressure and ankle–brachial index. Coronary heart disease at baseline was determined to be present if there was (1) electrocardiographic evidence of a prior myocardial infarction, (2) prior coronary artery bypass surgery or angioplasty, or (3) a self-reported history of a physician-diagnosed heart attack [16].

Qualified sonographers measured ankle and brachial systolic blood pressures using a Dinamap^{TM} 1846 SX automated oscillometric device (Critikon, Inc., Tampa, Florida) [16]. In order to obtain ABI they examined the posterior tibial artery at one randomly selected ankle. Sonographers took two ankle pressure measurements 5–8 min apart while the participant was in the prone position. They subsequently took measurements of the brachial blood pressures, usually in the right brachial, 5 min apart while the participant was in the supine position undergoing carotid artery ultrasound scan. The ABI was calculated as the average of the two ankle systolic measurements divided by the average of the first two brachial readings [16].

2.3. Follow-up methods

ARIC outcomes were obtained during annual phone interviews, 3-yearly follow-up examinations, community hospital surveillance, and death records. All events and potential events were reviewed and adjudicated by the ARIC Morbidity and Mortality Classification Committee [16]. Hospitalized myocardial infarction was classified as definite or probable based on chest pain symptoms, cardiac enzyme levels, and electrocardiographic findings [16]. CHD death was classified "definite" based on chest pain symptoms, hospital records, and medical history. A stroke event was classified as definite or probable based on 1) sudden onset neurological symptoms {one major (*e.g.*, aphasia or hemiparesis) or two minor (*e.g.*, diplopia or dysarthria)} that lasted >24 h or caused death within 24 h (2) with no evidence of any other pathology that might have mimicked stroke [16].

2.4. Statistical methods

The primary outcome examined was incident hard cardiovascular disease (hCVD, defined as MI, stroke or cardiovascular death). Hard coronary heart disease ("hCHD", defined as MI or coronary-related death) and all-cause mortality were analyzed as secondary outcomes. Stroke was included in the definition of primary outcome which is often done in the contemporary practice of epidemiological studies and clinical trials [18–20]. Follow-up time was the number of years from the baseline visit to either the hard CVD first event, death from other causes, lost to follow-up, or 10-years, whichever occurred first.

The "Framingham" Risk Score was calculated based on a model comprised of "Framingham" risk factors [1] applied to the ARIC cohort during a course of 10-year follow-up. The FRS is a continuous variable, however, in practice the FRS is used to identify individuals categorically as "low" (<6% 10-year risk), "intermediate" (≥6 < 20% risk), or "high" risk (≥20% risk). For clinical purposes,