Improved Prediction of Fatal Myocardial Infarction Using the Ankle Brachial Index in Addition to Conventional Risk Factors

The Edinburgh Artery Study

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Background—Prediction of major cardiovascular and cerebrovascular events using conventional risk factor models is limited. Noninvasive measures of subclinical atherosclerosis such as the ankle brachial index (ABI) could improve risk prediction and provide more focused primary prevention strategies. We wished to determine the added value of a low ABI in the prediction of long-term risk of cardiovascular and cerebrovascular events and death.

Methods and Results—In 1988, 1592 men and women 55 to 74 years of age were randomly selected from the age-sex registers of 11 general practices in Edinburgh, Scotland, and followed up over a period of 12 years for incident events. After adjustment for age and sex, an ABI ≤0.9 was predictive of an increased risk of fatal myocardial infarction (MI), cardiovascular death, all-cause death, combined fatal and nonfatal MI, and total cardiovascular events. After further adjustment for prevalent cardiovascular disease, diabetes, and conventional risk factors, a low ABI was independently predictive of the risk of fatal MI. Addition of the ABI significantly (P<0.01) increased the predictive value of the model for fatal MI compared with a model containing risk factors alone. Comparison of areas under receiver operator characteristic curves confirmed that a model including the ABI discriminated marginally better than one without.

Conclusions—Addition of the ABI significantly improved prediction of fatal MI over and above that of conventional risk factors. We recommend that the ABI be incorporated into routine cardiovascular screening and that the potential of its inclusion into cardiovascular scoring systems (with a view to improving their accuracy) now be examined. (Circulation. 2004;110:0000-0000.)

Key Words: atherosclerosis ■ cardiovascular diseases ■ risk factors ■ epidemiology

Cardiovascular disease (CVD) is the No. 1 cause of death in the United States. In 1999, of the 2 million deaths from all causes, CVD was listed as a primary or contributory cause in almost 70% of cases. Although numerous multifactorial primary prevention trials, based on the reduction of cardiovascular risk factors such as cigarette smoking, hypercholesterolemia, and hypertension, have been conducted in the general population, one review concluded that such strategies on the whole population were expensive and of limited value. In contrast, secondary prevention strategies, using antiplatelet therapy, for example, have proved effective in reducing the rate of further cardiovascular events in symptomatic subjects. However, the vast majority of cardiovascular and cerebrovascular events occur in the “healthy” population, with only 20% occurring in subjects with preexisting clinical disease. A major public health challenge is therefore to accurately identify, in an apparently healthy population, those who are at high risk and to target prevention at these individuals.

Although primary prevention measures, including aspirin, have been suggested for all individuals with an estimated intermediate to high cardiovascular risk of >2% per year, the best method of identifying such individuals has not been established. In addition, models based on conventional risk factors have been shown to have limited predictability and several restrictions. They were not designed for people with preexisting CVD, and when risk factors are at extreme levels, the equations may underestimate or overestimate risk. In this regard, interest is increasing in the use of noninvasive markers that allow the identification of subclinical atherosclerosis, including the ankle brachial index (ABI, ratio of ankle to arm systolic blood pressure). Although quick and easy to perform with a high patient acceptability, the ABI was originally used to identify lower-limb atherosclerosis. How-
ever, it has subsequently been shown to be an accurate and reliable marker of generalized atherosclerosis. Cohort studies with between 5 and 10 years of follow-up have shown that people with a low ABI have an increased risk of both cardiovascular morbidity and mortality. We have previously reported that the 5-year incidence of total cardiovascular events in subjects with an ABI ≤0.9 was almost twice that in subjects with an ABI >0.9. Furthermore, examination of positive predictive values showed that a low ABI was better at predicting risk of future cardiovascular and cerebrovascular events than conventional risk factors alone.

The present analysis used data collected over 12 years of follow-up from the Edinburgh Artery Study, and our aims were 2-fold. First, we wished to determine whether, in the general population, a low ABI was predictive of the long-term risk of cardiovascular and cerebrovascular events and death. Second, we wished to improve the precision of estimated increases in cardiovascular risk associated with a low ABI after adjustment for conventional risk factors.

Methods

The Edinburgh Artery Study began in 1988 as a cross-sectional survey of 1592 men and women 55 to 74 years of age. The population was selected at random, in 5-year age bands, from 11 general practices serving a range of socioeconomic and geographic areas throughout the city. The follow-up of a sample of nonresponders showed no substantial bias in distribution of age, sex, or social class. Details of the study recruitment have been described previously. Subjects completed a detailed questionnaire and underwent a comprehensive clinical examination at baseline, 5 and 12 years after commencement of the study. The study was approved by a Lothian Health Board Ethics subcommittee, and informed consent was obtained from each participant.

Baseline Examination

Subjects attended a university clinic and completed a questionnaire including validated questions on smoking, history of diabetes, and angina using the World Health Organization (WHO) questionnaire. A comprehensive clinical examination included recording systolic and diastolic (phase V) blood pressures in the right arm after 10 minutes of rest, using a random-zero sphygmomanometer. Ankle systolic pressures were measured in the posterior tibial artery of the right then the left leg using a Doppler ultrasound probe (Sonicaid, Chichester, UK) and a random-zero sphygmomanometer with the cuff positioned just proximal to the malleoli. The pulse was located using the Doppler probe. The cuff was then inflated until the pulse was obliterated; the cuff was then deflated and the pulse recorded at the point when the pulse reappeared. A 12-lead ECG was also performed and coded independently by two observers using the Minnesota code.

A sample of fasting blood was taken after 5 minutes of rest in the supine position for estimation of serum lipids, including total cholesterol, on a Cobas Bio analyser (Roche Products Ltd), using standard kits. Laboratory standardization was carried out by using commercially available standards (Wellcome scheme), and quality was assessed by examining systematic and random error against two control materials (Precipath UBS [universal bovine serum], Boehhinger Mannheim) and pooled donated sera. The laboratory was standardized against the WHO Regional Lipid Reference Laboratory, Prague, Czech Republic. A sample was also taken for fasting blood glucose and then each subject consumed 75 g of glucose in the form of 335 mL Solripe Gluctoza Health Drink (Strathmore Mineral Water Company). A second blood glucose specimen was taken 2 hours after the oral glucose load.

Identification of Cardiovascular Events

To obtain details on nonfatal cardiovascular or cerebrovascular events, information was sought from the following: general practitioners, the Information and Statistics Division of the Scottish Office Home and Health Department, and the participants themselves (by annual questionnaire). To identify deaths, each participant’s record was flagged at the United Kingdom National Health Service Central Registry. All possible cardiovascular and cerebrovascular events were further investigated by using hospital or general practitioner records to ensure that the protocol criteria were fulfilled. Criteria to define fatal or nonfatal myocardial infarction (MI) and stroke were adapted from those proposed by the American Heart Association and have previously been described in full.

Statistical Methods

Information on the questionnaire and recording forms was checked by the clinic staff, coded, and entered onto a DBASE IV database. Error rates were determined by dual entry of all data, and any discrepancies were checked by reference to the original records.

The ABI for each leg was calculated by dividing the ankle systolic pressure by the brachial pressure. The lower of the indexes obtained for the two legs was used as the measure of disease severity in all subsequent analysis. Three subjects with an ABI >1.5 were excluded from the present analysis because this ratio is associated with arterial calcification and increases in wall stiffening. In addition, a further 72 subjects with WHO evidence of intermittent claudication at baseline were excluded to avoid contamination of the analysis with clinical peripheral vascular disease. Multiple events of the same type occurring in the same subject, such as two MIs, were counted only once.

The χ² test for trend was used to examine the association between event and baseline ABI group. To gain some insight as to the usefulness of a “low” ABI in practice, positive predictive values were calculated. A cutoff point of 0.9 was used to define a low ABI because this has been shown to be a highly sensitive and specific measure of peripheral vascular disease in a clinical setting. For comparative purposes, positive predictive values were also calculated for a range of conventional risk factors. Using recent Scottish Intercollegiate Guidelines Network (SIGN) guidelines, hypertensives were defined as having systolic blood pressure >140 and/or diastolic blood pressure >90 mm Hg. For total cholesterol, a cutpoint of >5 mmol/L was used to denote high versus normal levels. This figure is based on SIGN’s treatment target for primary prevention in patients receiving drug therapy. Because there is no universally recognized cutpoint for a low HDL cholesterol, its positive predictive values were not included here, although HDL cholesterol was included as a continuous factor in the multivariate analyses. Prevalent CVD at baseline was defined as stroke (recall of a doctor’s diagnosis), angina (WHO questionnaire evidence and either ECG ischemia or doctor recall) or MI (two out of three of doctor recall, WHO questionnaire, and ECG evidence). Diabetes at baseline was defined by the glucose tolerance test and doctor recall. Smoking status was coded into a binary variable that compared current smokers and ex-smokers who had given up less than 5 years ago with the combined group of never-smokers and ex-smokers who gave up more than 5 years ago.

Relative risks were estimated by using logistic regression (PROC GENMOD of SAS). Age and sex-adjusted and then multiajusted relative risks of fatal and nonfatal events were calculated for subjects with an ABI ≤0.9 at baseline by comparing incidence rates with those subjects with an ABI >0.9. Finally, a logistic regression score was established for any disease end point with which ABI showed an independent association. Four consecutive models were performed containing (1) age and sex, (2) prevalent CVD and diabetes added, (3) total and HDL cholesterol, systolic blood pressure, and smoking status added, and (4) ABI added. To assess the impact on the predictive value of the model of adding in risk factors, the change in −2 log likelihood was calculated for each consecutive model and compared with a χ² distribution, with the degrees of freedom reflecting the parameters in each model. In addition, receiver operating characteristic (ROC) curves were constructed, and the
Results

During more than 12 years of follow-up of the Edinburgh Artery Study cohort, 259 subjects (16.3%) had an MI, of which 42.9% (111) were fatal. A stroke occurred in 143 (9%) subjects, and 37.1% (53) were fatal. There were a total of 559 deaths (35.1%), of which 40.3% (225) were due to cardiovascular or cerebrovascular causes. One thousand five hundred and three (35.1%) had an ABI \( \geq 1.68 \) in predicting total cardiovascular events after more than 12 years of follow-up. The positive predictive value for a future total cardiovascular event was 35.5% (95% CI, 29.5 to 41) for subjects with an ABI \( \leq 0.9 \), compared with 22.7% (95% CI, 20.4 to 25) for those with an ABI \( > 0.9 \) (Figure 1). Positive predictive values for total cardiovascular event were also higher for current/recent ex-smokers compared with never/long-term ex-smokers, for hypertensives compared with those with normal blood pressure, and for diabetics compared with nondiabetics. Positive predictive values were

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**TABLE 1. Twelve-Year Incidence of Nonfatal Cardiovascular Events and Mortality According to Baseline ABI**

| No. (%) of Events According to Baseline ABI* |  
|-------------------------------------------|---|
| \( >1.1 \) (n=524)                        |  
| \( 1.1–1.01 \) (n=470)                    |  
| \( 1.0–0.91 \) (n=268)                    |  
| \( 0.9–0.71 \) (n=182)                    |  
| \( \leq 0.7 \) (n=63)                     |  

| No. (%) |  
|---------|---|
| Deaths  |  
| Myocardial infarction | 25 (4.8) 23 (4.9) 19 (7.1) 23 (12.6) 11 (17.5) \( P \leq0.001 \) |
| Stroke  | 12 (2.3) 15 (3.2) 12 (4.5) 4 (2.2) 6 (9.5) \( P =0.041 \) |
| All cardiovascular causes† | 51 (9.7) 48 (10.2) 44 (16.4) 36 (19.8) 23 (36.5) \( P \leq0.001 \) |
| Noncardiovascular causes | 93 (17.7) 92 (19.6) 47 (17.5) 43 (23.6) 17 (27.0) \( P =0.060 \) |
| All causes | 144 (27.5) 140 (29.8) 91 (34.0) 79 (43.4) 40 (63.5) \( P \leq0.001 \) |

| Combined fatal and nonfatal events |  
|-----------------------------------|---|
| Myocardial infarction | 69 (13.2) 68 (14.5) 44 (16.4) 35 (19.2) 19 (30.2) \( P \leq0.001 \) |
| Stroke | 33 (6.3) 36 (7.7) 28 (10.4) 19 (10.4) 12 (19.0) \( P \leq0.001 \) |

†Death from all cardiovascular causes, including aneurysm, thromboembolism, stroke, and myocardial infarction.
especially high for those with prevalent CVD at baseline compared with those without. However, positive predictive values were lower for those with high (\(>5.0\) mmol/L) total cholesterol levels compared with those with "normal" (\(<5.0\) mmol/L) levels.

Table 2 shows that the ABI was predictive of subsequent fatal and nonfatal events. Independent of age and sex, a baseline ABI \(<0.9\) was predictive of an increased risk of fatal MI, cardiovascular death, all-cause death (all \(P<0.001\)), combined fatal and nonfatal MI, and total cardiovascular events (both \(P<0.01\)). After adjustment for baseline prevalent CVD and diabetes, a low ABI was independently predictive of fatal MI (\(P<0.01\)), all cardiovascular deaths, and all-cause death (both \(P<0.05\)). However, additional adjustment for total and HDL cholesterol, smoking, and systolic blood pressure further reduced the magnitude of the relative risks, resulting in a low ABI having an independent association with fatal MI only (\(P<0.05\)).

With fatal MI as the end point, four consecutive logistic models of increasing saturation were performed. For each model, likelihood statistics were examined, an ROC curve constructed, and the AUC calculated. The first model incorporating age and sex had an AUC of 0.66, a change in \(-2\) log likelihood was 31.533 with 4 \(df\), and AUC was 0.77. The final model was supplemented by the ABI and led to another significant increase (\(P<0.01\)) in its predictive value (\(-2\) log likelihood 7.027 on 1 \(df\)). Figure 2 shows the ROC curve for this final model and its associated AUC of 0.78.

### Discussion

Interest in the use of formulas and tables to predict an individual’s risk of a subsequent cardiovascular event is...
increasing. To date, these have been based on conventional risk factors, such as cigarette smoking, hypertension, and hypercholesterolemia, and have used data from large observational studies, including the Framingham study.22 Such predictions are increasingly being used in clinical practice to determine whether the benefits of preventive treatment (for example, aspirin administration) outweigh the potential side effects of such interventions. The results of the present analyses suggest that the ABI may add to the sensitivity, specificity, and predictive values of cardiovascular risk tables. After multiple adjustment, the risk of a future fatal MI was significantly higher in subjects with an ABI ≤0.9 compared with those with an ABI >0.9 (P≤0.05). In addition, the predictive value of a logistic regression model incorporating the ABI was significantly better than a model containing the conventional risk factors and prevalent CVD alone (P≤0.01).

More than 18% of all 1592 subjects 55 to 74 years of age had an ABI ≤0.9 at baseline examination of the Edinburgh Artery Study. If this cutpoint were to be used to screen a population of this age for early atherosclerosis, almost 1 in 5 subjects would be identified as “at risk.” Similarly, the Rotterdam study of 7715 subjects ≥55 years of age reported a prevalence of 19.1% for an ABI ≤0.9,23 whereas in the Cardiovascular Health Study, only 12.5% of subjects ≥65 years of age had an ABI <0.9.24 In southern Scotland, as part of the AspIn for Asymptomatic Atherosclerosis (AAA) trial, 4725 (16.2%) volunteers >50 years of age from the general population, without preexisting clinical cardiovascular disease, were found to have an ABI ≤0.95 (F.G.R.F., unpublished data, 2003). Such differences in the prevalence of a low ABI may be attributed to its unstandardized measurement and to variation in both the risk factor structure of the study populations and in the predominance of concomitant atherosclerotic disease.

It is now well established that subjects with a low ABI are at an increased risk of both cardiovascular morbidity11 and mortality.11–13,25 An ABI ≤0.9 has been consistently associated with a 2- to 5-fold increase in all-cause death and a 3- to 8-fold increase in cardiovascular death when compared with an ABI >0.9.11–13,26 However, there are still some issues to be addressed about the use of the ABI as a diagnostic tool. First, there is limited research on how the risk of vascular events varies across the whole range of ABI in the general population. In keeping with results from the Atherosclerosis Risk in Communities Study27 and the Honolulu Heart Program study,28 we have shown significant linear trends in the incidence of cardiovascular and noncardiovascular deaths across ABI categories. Second, there is no ABI cutpoint that is universally accepted as being the best predictor of cardiovascular events, although for screening purposes, it may be hypothesized that an ABI ≤0.9 is likely to be more sensitive in identifying asymptomatic atherosclerosis than a lower cutpoint. Finally, although change in ABI has been related to worsening peripheral arterial disease7 or outcome after vascular operation,4 its predictive value for subsequent vascular events has not been investigated in any detail.

As expected, hypertensive subjects and current/recent ex-smokers had significantly higher positive predictive values for a subsequent cardiovascular event than normotensives and nonsmokers, respectively. Higher predictive values for diabetics compared with nondiabetics and significant differences between those with and without CVD at baseline were also noted. In contrast, there was no significant difference in the predictive value of an event comparing subjects who had high versus “normal” total cholesterol values. In fact, those with high cholesterol values had lower predictive values than those with “normal” cholesterol values. Potential explanations of this apparent anomaly include the extremely high prevalence (94%) of total cholesterol levels ≥5 mmol/L in this population, the high incidence of cardiovascular events in the “normal” cholesterol group, and the impact of cholesterol-lowering medication prescribed during follow-up. Compared with conventional risk factors, a low ABI was associated with higher positive predictive values for subsequent total cardiovascular and cerebrovascular events. However, as Figure 1 shows, the confidence interval of the positive predictive value for low ABI overlapped with those of all other risk factors with the exception of high total cholesterol. Because the ABI is a marker of generalized atherosclerosis, this may be a reflection of the cumulative combined exposure of many risk factors over a person’s lifetime.

We have previously reported the relation of ABI with the 5-year incidence of cardiovascular events in the Edinburgh Artery Study.10 However, it should be noted that this earlier report did not exclude baseline claudicants or those with an ABI >1.5. Similar to some other studies, it did not assess the impact of adjusting the relative risks for the full range of conventional risk factors. Instead, it presented a more simplistic view of the influence of a low ABI on the positive predictive values of total cardiovascular events for different combinations of the conventional risk factors and was restricted by the relatively low number of cardiovascular events. We have now shown that the positive predictive value of an ABI ≤0.9 for subsequent total cardiovascular events increased significantly with the longer duration of follow-up (from the previously reported 17.6%; 95% CI, 13.1 to 22.1 to the current 35.5%; 95% CI, 29.5 to 41.5). Similarly, the positive predictive value of an ABI >0.9 increased proportionally (from 9.6%; 95% CI, 8.0 to 11.2 up to 22.7%; 95% CI, 20.4 to 25.0). The longer follow-up obviously increased the number of first events that, in turn, enabled us to use a more robust multivariate logistic regression approach and to calculate ROC curves. We found that a low ABI remained an independent predictor of fatal MI after multiple adjustment for conventional risk factors and prevalent CVD. Furthermore, addition of the ABI into a model containing conventional risk factors and baseline CVD resulted in a significant improvement in its predictive value compared with the model without the ABI. The magnitude of change in the AUCs of the consecutive ROC curves was generally small. For example, there was an increase of only 0.03 when the 4 conventional risk factors were added to a model already containing age, sex, diabetes, and prevalent CVD. Similarly, although the absolute change in AUC after inclusion of the ABI to this previous model was only 0.01, it was comparable to the average change for any one of the 4 conventional risk factors. When the ROC analysis was repeated after exclusion of...
diabetics and those with prevalent CVD, the AUCs were marginally decreased and the impact of adding in the ABI reduced (data not shown).

Measurement of ABI is simple, inexpensive, and noninvasive, and the results from this general population cohort study of middle-aged subjects suggest that incorporation of the ABI into screening programs for cardiovascular disease may be useful. Although it is difficult to identify the exact risk factor profile of subjects in which the ABI will contribute the most in terms of prediction of events, it is logical to hypothesize that subjects with a low ABI and few or no other risk factors may benefit the most by being placed into a higher risk category for intervention with aspirin or other secondary prevention measures. The results of ongoing, unpublished, randomized controlled trials examining the influence of aspirin on individuals identified as at risk on the basis of a low ABI will affect any recommendations about treatment. Such trials include the AAA trial on 3350 healthy subjects >50 years of age and the Prevention Of Progression of Asymptomatic Diabetic Arterial Disease (POPADAD) trial among diabetics. In addition, we can theorize that inclusion of the ABI may improve the prognostic utility of cardiovascular risk scoring systems. This should be examined by using multiple logistic modeling and ROC analysis on data from other established cohort populations. Furthermore, it is recommended that future studies measure the ABI as well as conventional risk factors to enable further stratification of cardiovascular risk among apparently intermediate- and low-risk subjects.

**Acknowledgments**

Financial support for the Edinburgh Artery Study was provided by the British Heart Foundation. We thank the 11 general practices for their contribution to this study.

**References**

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Circulation. published online October 11, 2004;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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