Predictive Value of Brachial Flow-Mediated Dilation for Incident Cardiovascular Events in a Population-Based Study
The Multi-Ethnic Study of Atherosclerosis

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Background—Although brachial artery flow-mediated dilation (FMD) predicts recurrent cardiovascular events, its predictive value for incident cardiovascular disease (CVD) events in adults free of CVD is not well established. We assessed the predictive value of FMD for incident CVD events in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods and Results—Brachial artery FMD was measured in a nested case-cohort sample of 3026 of 6814 subjects (mean ± SD age, 61.2 ± 9.9 years) in MESA, a population-based cohort study of adults free of clinical CVD at baseline recruited at 6 clinic sites in the United States. The sample included 50.2% female, 34.3% white, 19.7% Chinese, 20.8% black, and 25.1% Hispanic subjects. Probability-weighted Cox proportional hazards analysis was used to examine the association between FMD and 5 years of adjudicated incident CVD events, including incident myocardial infarction, definite angina, coronary revascularization (coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, or other revascularization), stroke, resuscitated cardiac arrest, and CVD death. Mean (SD) FMD of the cohort was 4.4% (2.8). In probability-weighted Cox models, FMD/unit SD was significantly associated with incident cardiovascular events in the univariate model (adjusted for age and sex) (hazard ratio, 0.79; 95% confidence interval, 0.65 to 0.97; P = 0.01), after adjustment for the Framingham Risk Score (FRS) (hazard ratio, 0.80; 95% confidence interval, 0.62 to 0.97; P = 0.025), and in the multivariable model (hazard ratio, 0.84; 95% confidence interval, 0.71 to 0.99; P = 0.04) after adjustment for age, sex, diabetes mellitus, cigarette smoking status, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, heart rate, statin use, and blood pressure medication use. The c statistic (area under the curve) values of FMD, FRS, and FRS + FMD were 0.65, 0.74, and 0.74, respectively. Compared with the FRS alone, the addition of FMD to the FRS net correctly reclassifies 52% of subjects with no incident CVD event but net incorrectly reclassifies 23% of subjects with an incident CVD event, an overall net correct reclassification of 29% (P < 0.001).

Conclusions—Brachial FMD is a predictor of incident cardiovascular events in population-based adults. Even though the addition of FMD to the FRS did not improve discrimination of subjects at risk of CVD events in receiver operating characteristic analysis, it improved the classification of subjects as low, intermediate, and high CVD risk compared with the FRS. (Circulation. 2009;120:502-509.)

Key Words: cardiovascular disease • endothelium-derived factors • population • prognosis • vasodilation

The vascular endothelium plays a major role in the control of vasomotor tone, platelet adhesion, and thrombosis. These functions of the vascular endothelium are in part due to the release of nitric oxide, prostaglandins, and other vasoactive compounds. Brachial flow-mediated dilation (FMD) is a measure of the release of nitric oxide by the endothelium due to a transient flow stimulus. Impaired brachial FMD is widely regarded as an early, and potentially reversible, manifestation of vascular disease and may represent an integrated measure of the impact of various insults to the endothelium.

Clinical Perspective on p 509
Despite the wealth of data linking impaired FMD to cardiovascular disease (CVD) risk factors and improvements in FMD to various therapies, the data linking impaired
FMD to subsequent clinical events are more limited and largely focused on studies in subjects with or at high risk for CVD events.9–14 Only 1 study by Shimbo et al15 has focused on subjects free of CVD. In this small study, there was an inverse association between impaired FMD and incident clinical CVD events; however, the association did not persist after adjustment for other risk factors. More data are needed to determine the extent to which FMD may be a useful predictor of CVD risk in subjects free of CVD and to determine whether it offers incremental predictive value over conventional risk factors.

To clarify the association between brachial FMD and incident cardiovascular events in subjects free of clinically evident CVD, we examined brachial FMD and incident cardiovascular events in a nested case-cohort subset of the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods

Study Population and Data Collection
The study design for MESA has been published elsewhere.16 In brief, MESA is a prospective cohort study that began in July 2000 to investigate the prevalence, correlates, and progression of subclinical CVD in individuals without known CVD at baseline. The cohort includes 6814 women and men aged 45 to 84 years recruited from 6 US communities (Baltimore, Md; Chicago, Ill; Forsyth County, NC; Los Angeles County, Calif; northern Manhattan, NY; and St Paul, Minn). MESA cohort participants were 38% white (n=2624), 28% black (n=1895), 22% Hispanic (n=1492), and 12% Chinese (n=803). Individuals with a history of physician-diagnosed myocardial infarction, angina, heart failure, stroke, or transient ischemic attack or who had undergone an invasive procedure for CVD (coronary artery bypass graft, angioplasty, valve replacement, pacemaker placement, or other vascular surgeries) were excluded from participation. This study was approved by the institutional review boards of each study site, and written informed consent was obtained from all participants.

Demographics, medical history, and anthropometric and laboratory data for the present study were taken from the first examination of the MESA cohort (July 2000 to August 2002). Current smoking was defined as having smoked a cigarette in the last 30 days. Diabetes mellitus was defined as fasting glucose ≥126 mg/dL or the use of hypoglycemic medications. Use of antihypertensive and other medications was based on review of prescribed medication containers. Resting blood pressure was measured 3 times in the seated position, and the average of the second and third readings was recorded. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of medication prescribed for hypertension. Body mass index was calculated as weight (kg)/height (m)². Total and high-density lipoprotein (HDL) cholesterol were measured from blood samples obtained after a 12-hour fast. Low-density lipoprotein (LDL) cholesterol was estimated by the Friedewald equation.17

Brachial FMD Measurement
Brachial FMD was documented with the use of ultrasound in the MESA cohort during the first examination. Participants were excluded from the FMD examination if they had uncontrolled hypertension (n=158), blood pressures in the left and right arms that differed by >15 mm Hg, a history of Raynaud phenomenon (n=55), a congenital abnormality of the arm or hand (n=12), or a radical mastectomy on either side (n=100), resulting in 6489 participants who underwent the brachial FMD examination. Participants were examined in the supine position after 15 minutes of rest and after at least a 6-hour fast. An automated sphygmomanometer (Dinamap device) was used to monitor blood pressure and pulse in the left arm at 5-minute intervals throughout the examination. A standard blood pressure cuff was positioned around the right arm, 2 inches below the antecubital fossa, and the artery was imaged 5 to 9 cm above the antecubital fossa. A linear-array multifrequency transducer operating at 9 MHz (GE Logiq 700 Device) was used to acquire images of the right brachial artery. After baseline images were obtained, the cuff was inflated to 50 mm Hg above the participant’s systolic blood pressure for 5 minutes. Digitized images of the right brachial artery were captured continuously for 30 seconds before cuff inflation and for 2 minutes beginning immediately before cuff deflation to document the vasodilator response. A detailed description of the scanning and reading protocol can be found at the MESA Web site (www.mesa-nhlbi.org).

Brachial ultrasound videotapes from the subset of the MESA participants included in the current nested case-cohort sample (see below) were analyzed at the Wake Forest University Cardiology Image Processing Laboratory with the use of a previously validated semiautomated system.18 The semiautomated readings (media-adventitial interfaces to media-adventitial interfaces) of these digitized images generated the baseline and maximum diameters of the brachial artery from which %FMD was computed, as follows: 

\[
\%\text{FMD} = \left(\frac{\text{maximum diameter} - \text{baseline diameter}}{\text{baseline diameter}}\right) \times 100\%
\]

Intrareader reproducibility for baseline diameter, maximum diameter, and %FMD was evaluated by comparing an original and a blinded quality control reread of ultrasounds from 40 MESA participants (32 male, 18 white, 2 Chinese, 10 black, and 10 Hispanic subjects). The intraclass correlation coefficients were 0.99, 0.99, and 0.93, respectively. Intrareader variability was evaluated by comparing results from repeated examinations of 19 subjects on 2 days a week apart. The intraclass correlation coefficients for baseline diameter, maximum diameter, and %FMD were 0.90, 0.90, and 0.54, respectively. Percent technical error of measurement was 1.39% for baseline diameter measurement, 1.47% for maximum diameter measurement, and 28.4% for %FMD measurement.

Ascertainment of Cardiovascular Events
At intervals of 9 to 12 months, an interviewer contacted each participant by telephone to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. To verify self-reported diagnoses, study personnel requested copies of all death certificates and medical records for all hospitalizations and outpatient cardiovascular diagnoses. Next-of-kin interviews were done for out-of-hospital cardiovascular deaths. Hospital records were obtained for an estimated 98% of hospitalized cardiovascular events, and some information was available for 95% of outpatient diagnostic encounters.

Hospital records that suggested possible cardiovascular events were abstracted by study personnel. The MESA coordinating center collated the abstracted or original end point records and sent them to 2 paired cardiologists, cardiovascular epidemiologists, or neurologists for independent end point classification and assignment of incidence dates. If, after review and adjudication, disagreements persisted, a full Mortality and Morbidity Review Committee made the final classification.

Reviewers assigned a diagnosis of myocardial infarction on the basis of combinations of symptoms, ECG findings, and cardiac biomarker levels. Death from coronary heart disease was classified as definite, probable, or absent on the basis of hospital records, death certificates, and conversations with families. Definite fatal coronary heart disease required a myocardial infarction within 28 days of death, chest pain within 72 hours before death, or history of coronary heart disease and the absence of a known nonatherosclerotic or noncardiac cause of death. If the definite fatal coronary heart disease criteria were not met, probable fatal coronary heart disease could be assigned with an underlying cause of death consistent with fatal coronary heart disease; this required the absence of a known nonatherosclerotic or noncardiac cause of death. Stroke required a focal deficit of >24 hours and was in most instances confirmed by neuroimaging. Stroke included subarachnoid hemorrhages, intraparenchymal hemorrhages, and brain infarctions. The definition of angina was adapted from the Women’s Health Initiative criteria and...
Definition of the Primary Outcome

For the purposes of this study, a CVD event was defined as an incident myocardial infarction, definite angina, coronary revascularization (coronary artery bypass grafting and percutaneous coronary intervention), resuscitated cardiac arrest, stroke, or CVD death as defined by the MESA protocol.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Nested Case-Cohort Sample and Statistical Analysis

Nested case-cohort study design has been shown to be very efficient and economical, and the findings have been shown to be representative of the whole cohort studies. Even though 6489 participants had FMD measured, for cost reasons only a subset (current cohort) had their tapes read and were included in the MESA FMD ancillary study.

was classified by reviewers as definite, probable, or absent. Definite or probable angina required clinical symptoms to be considered a MESA event, with definite angina requiring objective evidence of coronary atherosclerosis.

Table 1. Demographic Characteristics of the Subcohort (n=2843) and Incident Cases (n=182) in MESA

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subcohort (n=2843)</th>
<th>Cases (n=182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.8±9.9</td>
<td>66.9±9.2</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>1451 (51.3)</td>
<td>68 (37.4)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>960 (33.8)</td>
<td>79 (43.4)</td>
</tr>
<tr>
<td>Chinese</td>
<td>579 (20.4)</td>
<td>18 (9.9)</td>
</tr>
<tr>
<td>Black</td>
<td>590 (20.7)</td>
<td>40 (22.0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>713 (25.1)</td>
<td>45 (24.7)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.8±5.3</td>
<td>28.8±5.3</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>124.1±19.6</td>
<td>135.9±21.2</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>71.8±10.1</td>
<td>75.0±10.2</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>194.4±34.9</td>
<td>197.0±40.9</td>
</tr>
<tr>
<td>HDL</td>
<td>50.7±14.5</td>
<td>48.1±14.2</td>
</tr>
<tr>
<td>LDL</td>
<td>117.1±30.2</td>
<td>119.5±35.6</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>133.9±96.4</td>
<td>147.3±81.9</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1528 (54.0)</td>
<td>71 (39.0)</td>
</tr>
<tr>
<td>Past</td>
<td>978 (34.6)</td>
<td>80 (44.0)</td>
</tr>
<tr>
<td>Current</td>
<td>323 (11.4)</td>
<td>31 (17.0)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>62.7±9.1</td>
<td>64.2±11.7</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>266 (9.4)</td>
<td>47 (25.8)</td>
</tr>
<tr>
<td>ACE inhibitor use, n (%)</td>
<td>277 (9.8)</td>
<td>41 (22.5)</td>
</tr>
<tr>
<td>HMG-CoA use, n (%)</td>
<td>381 (13.5)</td>
<td>48 (26.4)</td>
</tr>
<tr>
<td>Blood pressure medication</td>
<td>845 (29.7)</td>
<td>95 (52.2)</td>
</tr>
<tr>
<td>use, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial FMD, %</td>
<td>4.4±2.8</td>
<td>3.4±2.5</td>
</tr>
<tr>
<td>Brachial diameter, mm</td>
<td>4.3±0.8</td>
<td>4.7±0.8</td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%). ACE indicates angiotensin-converting enzyme; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

was classified by reviewers as definite, probable, or absent. Definite or probable angina required clinical symptoms to be considered a MESA event, with definite angina requiring objective evidence of coronary atherosclerosis.

A nested case-cohort of MESA participants involving a random sample of MESA participants (subcohort, n=2844) and all those who had an adjudicated cardiovascular event by October 10, 2005 (cases, n=182) were included in this analysis. A single subject with a sex-specific FMD >6 SDs above the mean was excluded. Descriptive data are presented as mean±SD for continuous variables or the frequencies of subjects for categorical variables. To account for the sampling probabilities for the case-cohort design, weighted survival curves (Cox model) and log-rank tests were used to compare the event-free survival rates for incident cardiovascular events among those above or below the sex-specific median %FMD. Similar analyses comparing event-free survival among those above and below the best threshold based on receiver operating characteristic analysis produced similar results (data not shown). Probability-weighted Cox proportional hazards models were also used to evaluate the association between FMD treated as a continuous variable and survival free of the primary and various secondary outcomes with and without adjustment for potential confounding variables. Potential confounders were selected on the basis of prior evidence of an association with FMD or CVD events from previous studies or statistical evidence of a univariate (age- and sex-adjusted) association with the primary outcome in the present study (a priori P≤0.20). A stepwise procedure was used to identify the subset of these covariates that remained significantly associated with the primary outcome in a multivariate probability-weighted Cox proportional hazards model (the full model). The covariates retained in the fully adjusted models included age, sex, diabetes mellitus, smoking status, systolic blood pressure, use of blood pressure medication, HDL cholesterol, LDL cholesterol, triglycerides, heart rate, and statin use. In a separate model, the Framingham Risk Score (FRS) was used as a single adjusting covariate.

We also examined the area under receiver operating curves (AUC) using probability-weighted Cox models to assess the individual and combined predictive accuracy of FMD and the FRS for incident CVD events and used probability-weighted Cox proportional hazards models to determine the potential for the addition of FMD to appropriately reclassify subjects into low-, intermediate-, and high-risk categories compared with the FRS. To compare the performance of the 2 different approaches (FRS versus FRS+FMD) using a common strategy for assignment to risk category, we first used a weighted logistic regression model of FRS alone to generate predicted probabilities for the primary outcome among those classified as low, intermediate, and high risk by FRS. The absolute event rate cut points for the primary outcome between the 3 FRS risk categories were as follows: low, <4.0%; intermediate, 4.0% to 7.5%; high, >7.5%. We then used a similar model to generate predicted probability for the primary outcome using FRS and FMD and assigned subjects to low, intermediate, or high risk using the same cut points obtained from the first model. This approach allowed us to
use comparable absolute event rates for the primary outcome during the period of observation rather than extrapolating beyond actual observations. All statistical analyses were performed with the use of SAS version 9.1 or JMP version 7.0 (SAS Institute, Cary, NC).

Results

The demographic characteristics of the study sample are as shown in Table 1. Half (50.2%) of the cohort was female. There were 34.3% white, 19.7% Chinese, 20.8% black, and 25.1% Hispanic subjects. A total of 182 subjects (6.0%) had an adjudicated CVD event over a maximum of 5 years of follow-up (log-rank P=0.0001; Figure 1). In univariate probability-weighted Cox proportional hazards analysis, FMD/unit SD was a significant predictor of CVD events (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.0001). In similar analyses, FMD remained significantly associated with incident CVD events after adjustment for (1) age (hazard ratio, 0.70; 95% CI, 0.60 to 0.85; P=0.001); (2) age and sex (hazard ratio, 0.79; 95% CI, 0.65 to 0.97; P=0.010); (3) age, sex, diabetes mellitus, smoking status, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, use of hypertension medications, resting heart rate, and statin use (the full model); and (4) the FRS (hazard ratio, 0.80; 95% CI, 0.63 to 0.97; P=0.025) (Figure 2).

Table 2 shows the hazard ratios of variables in the univariate (adjusted for age and sex) probability-weighted Cox model, the variables that made it into the multivariable model based on the a priori P<0.20, and the hazard ratios of the variables in the multivariable probability-weighted Cox model.

In stratified analyses, the inverse association between FMD and CVD events was similar across sex, smoking, hypertension, and diabetes mellitus strata, and there were no significant interactions between any of these predictors of CVD events and FMD in determining prognosis (data not shown). In a similar fashion, FMD was similarly associated with CVD events in all 4 ethnic groups; however, the confidence limits all included unity in fully adjusted models (Figure 3).

Significant associations were also observed between FMD/unit SD and the major elements of the primary outcome in univariate probability-weighted Cox proportional hazards analysis.
analyses; despite reduced sample size, FMD remained significantly associated with both myocardial infarction and CVD death in fully adjusted models (Table 3).

In receiver operating characteristic analyses, the c statistic (AUC) for a univariate model of FMD was 0.65, whereas the c statistic for a model containing the FRS was 0.74. Addition of FMD to the FRS or to our full model did not increase the c statistic to 0.74 (Figure 4). Examination of the reclassification properties of FMD indicates that a risk model that adds FMD to the FRS net correctly reclassifies 52% of subjects with no incident CVD event but net incorrectly reclassifies 23% of subjects with an incident CVD event. The overall net correct reclassification was 29% (P<0.001; Table 4). In the FRS intermediate-risk subgroup, the net correct reclassification was similar (28%; P<0.001).

Brachial artery diameter (height adjusted) was a significant predictor of CVD event in the univariate probability-weighted Cox analysis (hazard ratio, 1.52; 95% CI, 1.34 to 1.72; P<0.0001) after adjustment for FRS (hazard ratio, 1.307; 95% CI, 1.14 to 1.50; P=0.029) but was not an independent predictor of events in our final model (hazard ratio, 1.13; 95% CI, 0.75 to 1.63; P=0.59) (Figure 5). The c statistic of brachial artery diameter was 0.64, and addition of brachial artery diameter also failed to increase the c statistic of the FRS (c statistic=0.74).

Discussion

The goal of this nested case-cohort study was to assess the predictive value of brachial FMD for incident cardiovascular events in population-based adults free of CVD at baseline. Our study, which is the largest thus far that has attempted to address this important topic, found that brachial FMD was significantly and inversely associated with incident cardiovascular events independent of other major cardiovascular risk factors. Brachial FMD was not better than, nor did it provide incremental discrimination to, the FRS alone as a predictor of CVD events on the basis of receiver operating characteristic analysis. However, it provided a net improvement in the classification of subjects into low-, intermediate-, or high-risk categories compared with the FRS alone. These data provide additional evidence supporting the potential role of endothelial dysfunction in the pathogenesis of CVD. However, until the findings of the present study are replicated in other cohorts and the variability of FMD is improved or eliminated, the authors of this article will not recommend FMD as a clinical risk stratification tool.

The predictive value of brachial FMD for incident cardiovascular events in either high-risk subjects or subjects with recurrent cardiovascular events has been well explored, and

Table 3. Hazard Ratio (95% CI) of FMD/Unit SD for the Primary Outcome (CVD Events) and its Major Constituents* in Probability-Weighted Univariate (Adjusted for Age and Sex) and Multivariable Models†

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Events</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>P</th>
<th>Multivariable Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>182</td>
<td>0.79 (0.65–0.97)</td>
<td>0.01</td>
<td>0.84 (0.71–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hard CHD</td>
<td>75</td>
<td>0.65 (0.44–0.96)</td>
<td>0.01</td>
<td>0.74 (0.56–0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>64</td>
<td>0.72 (0.41–0.97)</td>
<td>0.04</td>
<td>0.74 (0.55–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>103</td>
<td>0.81 (0.52–0.94)</td>
<td>0.03</td>
<td>0.85 (0.63–1.06)</td>
<td>0.15</td>
</tr>
<tr>
<td>Definite angina</td>
<td>67</td>
<td>0.84 (0.61–1.05)</td>
<td>0.15</td>
<td>1.09 (0.84–1.43)</td>
<td>0.56</td>
</tr>
<tr>
<td>Stroke</td>
<td>36</td>
<td>0.81 (0.42–1.23)</td>
<td>0.23</td>
<td>0.87 (0.56–1.42)</td>
<td>0.58</td>
</tr>
<tr>
<td>CVD death</td>
<td>20</td>
<td>0.42 (0.18–0.95)</td>
<td>0.04</td>
<td>0.51 (0.22–0.98)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Hard CHD indicates myocardial infarction, resuscitated cardiac arrest, or coronary heart disease (CHD) death.

*Resuscitated cardiac arrest not included (n=5).

†Adjusted for age, sex, diabetes mellitus, smoking status, systolic blood pressure, use of blood pressure medication, HDL cholesterol, LDL cholesterol, triglycerides, heart rate, and statin use.
findings are mixed. Some studies have shown an independent inverse association between brachial FMD and CVD events, but others have not. A recent large meta-analysis suggested that the association between FMD and the estimated 10-year risk of coronary heart disease, assessed by the FRS, was strongest in the low-risk populations compared with medium- or high-risk populations. There is, however, a paucity of data on the predictive value of brachial FMD for incident cardiovascular events in low-risk populations or subjects free of CVD at baseline. The study by Shimbo et al attempted to address this question, but their findings were inconclusive because of small sample size and a less ethnically diverse cohort compared with the US population. In contrast, in the present study, an inverse association between FMD and clinical CVD events remained significant after adjustment for multiple CVD risk factors or for the FRS.

The consistency of the inverse association across risk factor and ethnicity strata (univariate) and across the various elements of the composite outcome provides additional reassurance of the internal validity of the observed association. However, the provocative observation of a nominal $P$ value of 0.05 for both myocardial infarction and CVD death should be interpreted with caution given the small numbers of events and the post hoc nature of these additional analyses.

The predictive accuracy of the FRS for incident cardiovascular events in the present study was good (AUC $= 0.74$), whereas the predictive accuracy of brachial FMD alone for incident cardiovascular event in the present study was fair at best (AUC $= 0.65$). Furthermore, the addition of brachial FMD to the FRS model did not increase the model discrimination (AUC $= 0.74$) for incident cardiovascular events. However, despite that lack of discrimination value when considered across the full range of FMD values, when used to produce a categorical assignment to low, intermediate, or high risk, FRS+FMD offered an improvement over FRS alone, principally by identifying intermediate-risk subjects who are less likely to have an incident CVD event in the subsequent 5 years of follow-up. On the basis of these data, it is tempting to conclude that FMD could therefore be used to screen intermediate-risk subjects to clarify whether or not to initiate more aggressive preventive interventions. However, before such a clinical strategy could be generally recommended, several other things are required, including (1) confirmation that modifying clinical decisions on the basis of FMD indeed results in a more favorable outcome than treatment decisions based solely on the FRS alone, (2) assessment of the cost of the additional FMD testing required to produce the potential net improvement in outcomes, and (3) a determination of the feasibility of implementing FMD on a wide scale in clinical practice. Given the technical nature

### Table 4. Reclassification of Subjects Based on FRS+FMD vs FRS Alone

<table>
<thead>
<tr>
<th>FRS+FMD Risk Category</th>
<th>Reclassified to Higher Risk</th>
<th>Reclassified to Lower Risk</th>
<th>Net Correct Reclassification, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong></td>
<td>567</td>
<td>24</td>
<td>161</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>1210</td>
<td>351</td>
<td>1644</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>175</td>
<td>259</td>
<td>110</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1952</td>
<td>634</td>
<td>247</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FRS risk category</th>
<th>Reclassified to Higher Risk</th>
<th>Reclassified to Lower Risk</th>
<th>Net reclassification improvement, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>16</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Intermediate</td>
<td>44</td>
<td>32</td>
<td>26</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>64</td>
<td>55</td>
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<th>Net reclassification improvement (intermediate risk only), %</th>
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<td>29 &lt;0.001</td>
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The predictive accuracy of the FRS for incident cardiovascular events in the present study was good (AUC=0.74), whereas the predictive accuracy of brachial FMD alone for incident cardiovascular event in the present study was fair at best (AUC=0.65). Furthermore, the addition of brachial FMD to the FRS model did not increase the model discrimination (AUC=0.74) for incident cardiovascular events. However, despite that lack of discrimination value when considered across the full range of FMD values, when used to produce a categorical assignment to low, intermediate, or high risk, FRS+FMD offered an improvement over FRS alone, principally by identifying intermediate-risk subjects who are less likely to have an incident CVD event in the subsequent 5 years of follow-up. On the basis of these data, it is tempting to conclude that FMD could therefore be used to screen intermediate-risk subjects to clarify whether or not to initiate more aggressive preventive interventions. However, before such a clinical strategy could be generally recommended, several other things are required, including (1) confirmation that modifying clinical decisions on the basis of FMD indeed results in a more favorable outcome than treatment decisions based solely on the FRS alone, (2) assessment of the cost of the additional FMD testing required to produce the potential net improvement in outcomes, and (3) a determination of the feasibility of implementing FMD on a wide scale in clinical practice. Given the technical nature

### Figure 5. Hazard ratio (95% CI) for cardiovascular event for brachial diameter (BD)/unit SD (height adjusted) in univariate and 4 multivariable models. *FRS indicates Framingham Risk Score. **Full model was adjusted for age, sex, diabetes mellitus, cigarette smoking, systolic blood pressure, blood pressure medication use, HDL cholesterol, LDL cholesterol, triglycerides, heart rate, and statin use.

#### Full model
- $P$ value: 0.59

#### BD+FRS
- $P$ value: 0.029

#### BD+ Age, gender
- $P$ value: 0.04

#### BD + Age
- $P$ value: <0.0001

#### Brachial Diameter (BD)
- $P$ value: <0.0001

### Yeboah et al. Brachial FMD Predicts Incident CVD Events

507

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of the current FMD image acquisition and analysis techniques, it seems implausible that it could be successfully deployed on a wide scale and in a cost-effective fashion. However, these data provide additional incentives to search for other simple, reproducible, and inexpensive strategies to evaluate endothelial function or other biomarkers that could be considered an adjunct to conventional CVD screening. Recently, similar improvements in risk classification have been observed with the use of C-reactive protein and parental history of heart disease.25,26

We showed in the Cardiovascular Health Study12 that brachial artery diameter (height adjusted) was similar in predictive value and accuracy to brachial FMD for cardiovascular events in older adults. We hypothesized that brachial artery diameter may also be a measure of endothelial function and questioned the utility of whole brachial FMD measurement if brachial artery diameter (which is less variable and easy to measure) provides information comparable to brachial FMD. In the present study, brachial artery diameter (height adjusted) also showed a similar but inverse association with incident cardiovascular events in the univariate model but failed to achieve statistical significance in the multivariable model, unlike FMD. The exact nature of the relationship between brachial artery diameter and cardiovascular risk warrants further investigation.

The present study has the following limitations. Endothelial-independent vasodilation after nitroglycerin administration was not examined because of the risk-benefit considerations of nitroglycerin administration in a population-based cohort study. Thus, we cannot determine whether impaired flow-mediated responses were the result of abnormal endothelial production, release and delivery of nitric oxide to the vascular smooth muscle, or impaired ability of the vascular smooth muscle to respond to nitric oxide (a non-endothelial-dependent effect). However, other studies have consistently documented the specificity of FMD to the endothelium,27 and, regardless, the associations with CVD events and the effect on reclassification remain valid. The present study consists of population-based adults free of clinical cardiovascular events at baseline. The findings of the present study should not be extrapolated to other dissimilar samples. Finally, even though sonographers were centrally trained and standardized FMD measuring protocols were employed at all study sites, the retest and reread performance measures indicate considerable within-subject variability. In addition, FMD was also measured once in this population-based study, even though multiple measurements have been shown to improve its variability. This variability limits the resolution possible for estimating effect sizes and likely obscures other important relationships between FMD, conventional CVD risk factors, and cardiovascular risk.

Conclusion

Brachial FMD is a predictor of incident cardiovascular events in population-based adults free of clinical CVD at baseline. FMD in isolation or in addition to FRS did not improve overall discrimination of subjects at risk for future events on the basis of receiver operating characteristic analysis. However, FMD provided significant improvement in classification of subjects as low, intermediate, or high risk compared with FRS alone. These data provide justification for additional research on the utility of FMD and other measures to enhance the management of subjects at risk for CVD.

Sources of Funding

This research was supported by contracts N01-HC-95159 through N01-HC-95166 and N01-HC-95169 and grants NHLBI T32 HL076132, all from the National Heart, Lung, and Blood Institute, Bethesda, Md.

Disclosures

None.

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**CLINICAL PERSPECTIVE**

Since Celermajer et al introduced brachial flow-mediated dilation (FMD) testing as a measure of endothelial function, numerous studies have associated FMD with cardiovascular risk factors. Some authors have even hypothesized that FMD is a “barometer” of cumulative cardiovascular insult to the vascular endothelium, implying that accurate measurement of FMD will in fact be an important way of assessing global cardiovascular risk. Current methods of FMD measurement coupled with unknown biological factors that influence the acquisition have contributed to the variability of FMD. Despite this variability, FMD has been shown to be predictive of cardiovascular events in elderly and high-risk cohorts. Data on the predictive value of FMD in subjects free of cardiovascular events and cohorts with low cardiovascular risk are limited. The present study uses the largest cohort thus far studied and showed that FMD predicts incident cardiovascular events in population-based adults free of clinical cardiovascular disease. Like other new biomarkers, the addition of FMD to the Framingham Risk Score (FRS) did not improve the discriminative ability of the FRS for cardiovascular events in this population in receiver operating characteristic analysis. However, reclassification analysis showed that the addition of FMD to FRS net reclassified 29% of subjects in this cohort correctly as low, intermediate, and high risk compared with FRS alone. The addition of FMD to FRS mainly improved the net reclassification of the intermediate-risk group (28%), a group that the FRS has been less accurate in classifying. Standardization and studies addressing the variability of FMD are needed.

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_Circulation_. 2009;120:502-509; originally published online July 27, 2009;
doi: 10.1161/CIRCULATIONAHA.109.864801

_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

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