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## Brachial Flow-Mediated Dilation Predicts Incident Cardiovascular Events in Older Adults

### The Cardiovascular Health Study

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**Background**—The relationship between impaired brachial flow-mediated dilation (FMD) and subsequent clinical cardiovascular events is not well established, especially in older adults whose FMD is often diminished. We assessed the hypothesis that FMD predicts incident cardiovascular events in a population-based cohort of older adults.

**Methods and Results**—FMD was measured at the 1997 to 1998 Cardiovascular Health Study clinic visit in 2792 adults aged 72 to 98 years (82.7% white, 58.6% women) recruited at 4 clinic sites in the United States. Log-rank test and Cox proportional hazard models were used to examine the association between FMD and adjudicated cardiovascular events. A total of 674 subjects (24.1%) had an adjudicated event over the 5-year follow-up period. Event-free survival rates for cardiovascular events were significantly higher in subjects with FMD greater than the sex-specific medians than in subjects with FMD less than or equal to the sex-specific medians (78.3% versus 73.6%, log-rank  $P=0.006$ ). FMD remained a significant predictor of cardiovascular events after adjustment for age, gender, diabetes mellitus, cigarette smoking, systolic and diastolic blood pressure, baseline cardiovascular disease status, and total cholesterol (hazard ratio, 0.91 [95% CI, 0.83 to 0.99],  $P=0.02$  per unit SD of FMD) but added only  $\approx 1\%$  to the prognostic accuracy of the best Cox model. Brachial artery diameter was also predictive of CV events in the adjusted Cox proportional hazard model (hazard ratio, 1.12 [95% CI, 1.02 to 1.28],  $P=0.025$ ) and also added  $\approx 1\%$  to the accuracy of our best Cox model.

**Conclusions**—FMD is a predictor of future cardiovascular events but adds very little to the prognostic accuracy of traditional cardiovascular risk scores/factors in older adults. FMD and brachial artery diameter may have similar predictive values for cardiovascular events in older adults. (*Circulation*. 2007;115:2390-2397.)

**Key Words:** endothelium-derived factors ■ prognosis ■ cardiovascular diseases ■ aging ■ vasodilation

The vascular endothelium plays a central role in regulating vasomotor tone, thrombosis, and platelet adhesion.<sup>1</sup> Endothelial dysfunction, a state of impairment of these regulatory functions, is one of the initial pathological processes of atherosclerosis and has been associated with increased cardiovascular risk.<sup>2,3</sup> Brachial flow-mediated dilation (FMD) is a validated, noninvasive physiological measure<sup>3</sup> widely used as a research tool to quantify endothelial function.

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Although current theory supports the association of endothelial dysfunction and cardiovascular events,<sup>4</sup> the predictive value of brachial FMD for cardiovascular events is not well established. Brachial FMD has been shown to be an independent predictor of cardiovascular outcomes in some<sup>5-7</sup> but not all studies.<sup>8,9</sup> The discrepancy in the results of these studies is

likely due to a variety of factors, including the biological and measurement variability of brachial FMD, use of highly selected subgroups of subjects, and limited statistical power. In addition, much of the currently available data comes from relatively young adults. The relevance of brachial FMD in older adults remains unclear. To address these limitations in the currently available data, we examined the relationship between brachial FMD and adjudicated cardiovascular events over a 5-year period in a large number of older adults participating in the Cardiovascular Health Study (CHS).

#### Methods

##### Study Population

The CHS population has been described previously.<sup>10</sup> Briefly, CHS was a longitudinal multicenter study of 5888 adults aged  $\geq 65$  years designed to be representative of the US population. Recruitment of 5201 adults into the study began between May 1989 and May 1990

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at 4 clinic sites (University of California Davis, Sacramento County, California; The Johns Hopkins University, Baltimore, Md; Wake Forest University, Forsyth County, North Carolina; and University of Pittsburgh, Pittsburgh, Pa), with the coordinating center at the University of Washington (Seattle, Wash). Between 1992 and 1993, an additional 687 black participants were recruited from 3 of the 4 clinic sites (Sacramento County, Forsyth County, and Pittsburgh). All participants were either Medicare beneficiaries or eligible for Medicare during recruitment. The CHS was approved by the institutional review boards of each study site, and informed consent was obtained from all participants.

At the tenth annual examination (1997–1998), the 3032 participants who returned for their yearly visit were approached for participation in a brachial FMD ancillary study. Of the 3032 subjects, 130 were excluded (74 owing to a history of mastectomy, 20 because of a history of Raynaud's disease, and 36 for other miscellaneous reasons). Sixty-one participants refused the ultrasound examination, and an additional 49 discontinued the scan (19 because of discomfort during the examination, 9 because of equipment problems, and 21 for other reasons). In all, 2792 participants aged 72 to 98 years, 666 of whom had a prior history of cardiovascular disease, had brachial artery ultrasound measurements performed. This ancillary study was approved by the institutional review boards of each study site, and informed consent was again obtained from all participants.

### Clinical Evaluation and Biochemical Analysis

All participants provided a medical history and underwent clinical examination at baseline and then yearly thereafter. Standardized questionnaires were used to determine medical history, medication use, and cardiovascular risk assessment at baseline and then at yearly visits. Participants were contacted biannually for interim hospitalizations, diagnosis, or events. Health Care Financing Administration records were reviewed to supplement information provided by participants. Event ascertainment and adjudication of clinical events in the CHS was done by a formal adjudication committee as described previously.<sup>11–13</sup>

For the purpose of the present analysis, a cardiovascular event was defined as any of the following adjudicated events: cardiovascular disease (CVD) death, myocardial infarction, stroke, congestive heart failure, claudication, angioplasty, or cardiac bypass graft surgery. Incident events included all events (new-onset cardiovascular events for subjects without prevalent CVD and recurrent cardiovascular events for subjects with prevalent CVD) that occurred after the brachial artery examination.

Hypertension in CHS was defined as seated average systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg, history of hypertension, or antihypertensive medication usage. Diabetes mellitus was defined as fasting blood glucose  $\geq 126$  mg/dL, history of diabetes mellitus, or use of insulin/oral hypoglycemics. Race was defined by self-report with the following 5 choices: white, black, American Indian/Alaskan Native, Asian/Pacific Islanders, or other. For the sake of simplicity, race was recategorized into 3 categories: whites, blacks and others.

Blood for biochemical analysis was obtained from fasting venous samples, and total cholesterol was determined by standard enzymatic methods.<sup>14</sup> high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride levels were not obtained during the 1997 to 1998 CHS clinic visit. All the covariates used in the present analysis were collected at the tenth CHS clinic visit except data on body mass index, which were collected during the year 9 CHS clinic visit, and HDL cholesterol, which was measured during the year 5 CHS clinic visit.

### Flow-Mediated Brachial Artery Vasodilation

A detailed description of the scanning and reading protocol has been published previously.<sup>15</sup> Briefly, sonographers underwent centralized training in brachial FMD measurement at Wake Forest University School of Medicine and were certified after performing at least 20 acceptable scans on volunteers.

Participants were examined after 15 minutes' rest in the fasting state. With each participant supine, the left arm was used to monitor blood pressure (with an automated sphygmomanometer) and pulse at

5-minute intervals throughout the examination. A standard pediatric cuff was positioned around the right arm, 2 inches below the antecubital fossa. A 10-MHz Biosound Phase 2 ultrasound system (Biosound Esaote, Indianapolis, Ind) was used to acquire images of the right brachial artery. After baseline images of the right brachial artery were obtained for 2 minutes, the pediatric cuff was inflated to 50 mm Hg above the participant's systolic blood pressure to occlude the right brachial artery. The pediatric cuff was kept inflated for 4 minutes. Images of the right brachial artery were captured continuously for 2 minutes after cuff deflation. Images of the brachial artery diameters were captured in diastole (gated with ECG R wave). Videotapes of the acquired images of the brachial artery were analyzed at the Wake Forest University Cardiology Image Processing Laboratory with a previously validated semiautomated system. 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. %FMD was computed with the formula

$$(1) \quad \frac{\text{maximum diameter} - \text{baseline diameter}}{\text{baseline diameter}} \times 100\%$$

Correlations for repeated measures of baseline diameter, maximum diameter, and %FMD with 80 CHS participants scanned on 2 separate days more than 2 weeks apart were 0.94, 0.94, and 0.67, respectively.<sup>15</sup> The reproducibility of the method, including cuff placement below the antecubital fossa and the automated analysis, was tested with repeated examinations less than 1 week apart among 127 CHS participants. The mean  $\pm$  SD difference in percent change in diameter (brachial FMD) was  $0.02 \pm 1.54\%$ , and  $R^2$  was 0.7.<sup>16</sup>

### Statistical Analysis

Data are presented as mean  $\pm$  SD for continuous variables and the frequencies of subjects in each category for categorical variables. Life-table analysis and the log-rank test were used to compare the event-free survival rates for incident cardiovascular events among those above and below or equal to the median (sex-specific) %FMD. In a similar fashion, Cox proportional hazard models were used to evaluate the association between FMD treated as a continuous variable and event-free survival after adjustment for potential confounding covariates. The covariates were selected on the basis of prior evidence of an association with FMD or CVD events from previous studies and statistical evidence of an association with the primary outcome in the present study (inclusion a priori  $P \leq 0.20$  in the age- and gender-adjusted models). The covariates included age, gender, diabetes mellitus, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, smoking, HMG-CoA reductase inhibitor use, antihypertensive drug use, hormone therapy, and baseline CVD status. In the age- and gender-adjusted analysis, the %FMD did not vary by study site and was therefore not included in the final model. The extended Cox model, which used the time-dependent variable approach, was used to test for the proportionality assumption. The predictive value of FMD for the composite outcome (cardiovascular event) was tested in the entire cohort and in subgroups defined by the presence or absence of the CVD at the beginning of the FMD ancillary study, gender, and race/ethnicity.

The area under the curve (AUC) of a receiver operator curve reflects the sensitivity and specificity and hence the overall accuracy of a model.<sup>17</sup> To examine the accuracy of brachial FMD in predicting CVD events, we assessed whether the addition of brachial FMD to a logistic prediction model (best model) increased the AUC. A 2-tailed value of  $P < 0.05$  was considered significant. Statistical analysis was performed with SAS version 9.1 (SAS Institute, Cary, NC).

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.

## Results

### Subjects

In all, 2791 subjects aged  $78.6 \pm 4.4$  (mean  $\pm$  SD) years (58.6% women, 82.7% whites) had complete data and were

**TABLE 1. Characteristics of Subjects Above and Below or Equal to the Gender-Specific Median Brachial FMD at Baseline in the FMD Ancillary Study**

Variable	Gender-Specific %FMD >Median (n=1359)	Gender-Specific %FMD ≤Median (n=1432)	P
Age, y	78.4±4.3	78.8±4.6	0.06
Females, %	801 (59.0)	833 (58.2)	0.66
Race/ethnicity, n (%)			
White	1190 (87.6)	1117 (78.1)	<0.001
Black	161 (11.8)	306 (21.4)	...
Other	8 (0.6)	8 (0.5)	...
BMI, kg/m <sup>2</sup>	26.9±4.5	27.5±4.5	0.04
Cholesterol, mg/dL	202.4±39.4	204.0±39.1	0.75
HDL, mg/dL	53.8±14.2	53.4±13.9	0.46
Systolic BP, mm Hg	144.2±21.9	146.9±24.2	0.002
Diastolic BP, mm Hg	73.3±10.1	74.3±11.0	0.14
Heart rate, bpm	62.4±10.2	62.6±10.3	0.57
Cigarette smoking, n (%)			
Never	638 (46.9)	699 (48.8)	0.69
Former	623 (45.8)	639 (44.6)	...
Current	98 (7.3)	94 (6.6)	...
Diabetes mellitus, n (%)	174 (12.8)	222 (15.6)	0.12
Prior CVD, n (%)	286 (21.1)	380 (26.5)	0.001
Hormone therapy, n (%)	102 (10.2)	97 (8.9)	0.30
HMG-CoA inhibitors, n (%)	176 (13.0)	206 (14.4)	0.27
β-Blocker use, n (%)	222 (16.4)	242 (16.9)	0.70
ACE inhibitors, n (%)	197 (14.5)	258 (18.0)	0.01
Baseline brachial diameter, mm	4.33±0.8	4.67±0.9	<0.0001
Maximum brachial diameter, mm	4.52±0.8	4.75±0.9	<0.0001
Absolute change in diameter, mm	0.19±0.06	0.08±0.03	<0.0001
Brachial FMD, %	4.48±1.6	1.68±0.7	<0.0001

Values are mean±SD unless otherwise indicated. BMI indicates body mass index; HDL, high-density lipoprotein; BP, blood pressure; and ACE, angiotensin-converting enzyme.

\*Student *t* test for continuous variables and  $\chi^2$  test for categorical variables.

included in the present analysis. The median brachial FMD was 3.0% and 2.4% for women and men, respectively. As shown in Table 1, subjects with brachial FMD above the sex-specific median had a significantly lower body mass index, systolic blood pressure, baseline brachial diameter, and maximum brachial diameter than those below or equal to the gender-specific median. Fewer subjects in the group with brachial FMD above the median were blacks, had prior CVD at baseline, and were taking angiotensin-converting enzyme inhibitors.

Of the 2791 subjects with complete data, 674 (24.1%) had an adjudicated cardiovascular event within the 5-year follow-up period. One hundred forty-one of the events occurred in the subset of subjects with a history of CVD, and 533 events occurred in subjects free of CVD events at the beginning of the ancillary study.

As shown in Table 2, the significant age- and gender-adjusted predictors of incident cardiovascular events were

cigarette smoking, diabetes mellitus, systolic and diastolic blood pressure, HMG-CoA reductase inhibitor use, baseline CVD status, and brachial FMD (%). Race/ethnicity, total cholesterol, angiotensin-converting enzyme inhibitor use, hormone therapy, and HDL were not significantly associated with CVD events in the age- and gender-adjusted Cox proportional hazard analysis.

### Brachial FMD and Cardiovascular Events

As shown in Figure 1, event-free survival rates for cardiovascular events over the 5-year period were significantly higher in subjects with brachial FMD greater than the sex-specific medians compared with subjects with brachial FMD less than or equal to the sex-specific medians (78.3% versus 73.6%, log-rank *P*=0.006). In the multivariate Cox proportional hazard model, with brachial FMD treated as a continuous variable, FMD remained a significant predictor of

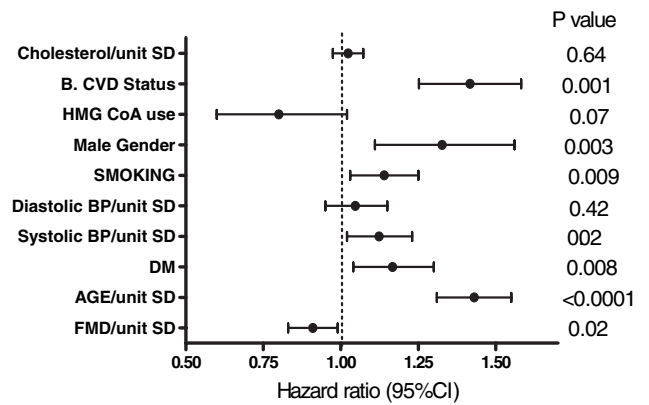
**TABLE 2. Predictors of Cardiovascular Event Using Age- and Gender-Adjusted Cox Proportional Hazard Analyses**

Covariates	Hazard Ratio (95% CI)	P
Age, y*	1.07 (1.06 to 1.09)	<0.0001
White	1.05 (0.89 to 1.25)	0.54
Male gender*	1.34 (1.15 to 1.56)	0.0001
BMI	1.00 (0.91 to 1.02)	0.84
Systolic BP/unit SD	1.17 (1.09 to 1.26)	<0.0001
Diastolic BP/unit SD	1.14 (1.05 to 1.23)	0.0009
Diabetes mellitus	1.15 (1.03 to 1.27)	0.01
Cigarette smoking	1.15 (1.05 to 1.26)	0.003
Cholesterol, mg/dL	1.04 (0.98 to 1.13)	0.20
HDL, mg/dL	0.99 (0.99 to 1.05)	0.74
HMG-CoA use	0.72 (0.56 to 0.93)	0.01
ACE inhibitor use	1.12 (0.92 to 1.37)	0.25
Hormone therapy	0.84 (0.61 to 1.15)	0.27
Baseline CVD status	1.38 (1.14 to 1.66)	0.001
FMD/unit SD	0.90 (0.83 to 0.98)	0.02

BMI indicates body mass index; HDL, high-density lipoprotein; BP, blood pressure; and ACE, angiotensin-converting enzyme.  
\*Single-variable analysis.

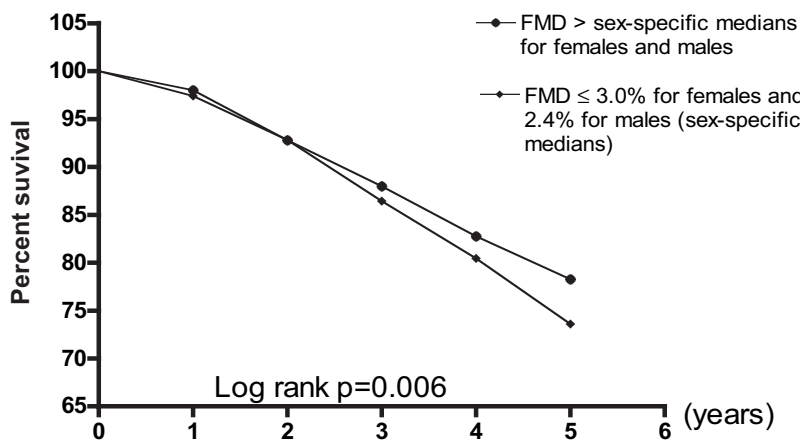
incident cardiovascular events after adjustment for age, gender, diabetes mellitus, systolic and diastolic blood pressure, cigarette smoking, total cholesterol, HMG-CoA reductase inhibitor use, and baseline CVD status (hazard ratio, 0.91 [95% CI, 0.83 to 0.99],  $P=0.02$  per unit SD of FMD; Figure 2). Brachial FMD was also a significant predictor of major adverse cardiovascular events, defined as nonfatal myocardial infarction, nonfatal stroke, or CVD death, in the present elderly cohort (hazard ratio, 0.91 [95% CI, 0.82 to 0.99],  $P=0.04$  per unit SD of FMD; Table 3).

Brachial FMD was a significant predictor of cardiovascular events in the subset of subjects free of CVD at the beginning of the FMD ancillary study (hazard ratio, 0.86 [95% CI, 0.78 to 0.95],  $P=0.001$  per unit SD), and FMD showed a trend



**Figure 2.** Multivariable predictors of cardiovascular events (n=2791) using Cox proportional hazard model with an inclusion a priori  $P\leq 0.2$ . B CVD status indicates baseline CVD status; HMG-CoA use, HMG-CoA reductase inhibitor use; Cholesterol/unit SD, total cholesterol per unit SD; systolic BP/unit SD, systolic blood pressure per unit SD; diastolic BP/unit SD, diastolic blood pressure per unit SD; DM, diabetes mellitus; FMD/unit SD, percent brachial FMD per unit SD.

toward significance (hazard ratio, 0.85 [95% CI, 0.72 to 1.02],  $P=0.08$  per unit SD) in the subset of subjects with a prior CVD event at the beginning of the FMD ancillary study in a single-variable Cox proportional hazard analysis (data not shown). In the subsequent multivariable Cox proportional hazard model, FMD showed a trend toward significance as a predictor of the cardiovascular event in both groups (hazard ratio, 0.92 [95% CI, 0.84 to 1.01],  $P=0.08$  per unit SD of FMD for the subset free of CVD and hazard ratio, 0.84 [95% CI, 0.69 to 1.02],  $P=0.08$  per unit SD of FMD for the subset with a history of CVD, respectively; Figure 3). Stratified multivariable Cox proportional hazard analyses also showed FMD per unit SD as a predictor of the incident CVD event in women (hazard ratio, 0.89 [95% CI, 0.80 to 0.99],  $P=0.04$ ) but not in men (hazard ratio, 0.93 [95% CI, 0.82 to 1.07],  $P=0.32$ ) and in whites (hazard ratio, 0.91 [95% CI, 0.83 to 0.99],  $P=0.04$ ) but not in blacks (hazard ratio, 0.82 [95% CI, 0.62 to 1.07],  $P=0.14$ ; Figure 3). Other race/ethnicity was



**Figure 1.** Life-table analysis of event-free survival for cardiovascular events of subjects above, below, or equal to sex-specific medians of FMD (%). \*Indicates number at risk.

> Median*	1359	1332	1259	1194	1123
≤ Median*	1432	1394	1328	1237	1151

**TABLE 3. Single-Variable and Multivariable Cox Proportional Hazard Regression Analysis With FMD/Unit SD as a Continuous Variable\***

Outcome	No. of Events	Single Variable		Multivariable	
		Hazard Ratio (95% CI)	<i>P</i>	Hazard Ratio (95% CI)	<i>P</i>
CVD event	674	0.86 (0.79 to 0.94)	0.0006	0.91 (0.84 to 0.99)	0.02
MACE	533	0.84 (0.77 to 0.93)	0.0003	0.90 (0.82 to 0.99)	0.04
CVD death	341	0.83 (0.74 to 0.93)	0.002	0.89 (0.79 to 1.01)	0.06
MI	154	0.89 (0.76 to 1.06)	0.19	0.97 (0.82 to 1.16)	0.74
CHF	244	0.83 (0.74 to 0.97)	0.01	0.92 (0.80 to 1.06)	0.25
Stroke	142	0.85 (0.71 to 1.01)	0.07	0.85 (0.70 to 1.02)	0.08
Claudication	19	0.62 (0.36 to 1.10)	0.10	0.63 (0.35 to 1.13)	0.12
Angioplasty	56	1.04 (0.81 to 1.34)	0.76	1.12 (0.86 to 1.47)	0.40
CABG	71	1.01 (0.81 to 1.27)	0.91	1.13 (0.90 to 1.10)	0.31

MACE indicates major adverse cardiovascular events (defined as nonfatal myocardial infarction, nonfatal stroke, or CVD death); CHD, coronary heart disease; MI, myocardial infarction; CHF, congestive heart failure; and CABG, coronary artery bypass graft surgery.

\*Multivariable Cox model included age, gender, diabetes mellitus, systolic blood pressure, diastolic blood pressure, total cholesterol, cigarette smoking, HMG-CoA reductase inhibitor use, and baseline CVD status.

omitted from this analysis because of the very small sample size ( $n=12$ ). However, a formal test for interaction in the adjusted Cox proportional hazard model showed no significant interaction between brachial FMD and either age, gender, race/ethnicity, or baseline CVD status (data not shown). This suggests that the differences in hazard ratios and 95% CIs seen in the stratified analyses were likely due to a loss of power.

Brachial FMD was not a significant predictor of any of the components of the cardiovascular events (Table 3). However, the point estimates of the hazard ratios for FMD per unit SD were less than unity for all outcomes except coronary artery bypass graft surgery and angioplasty.

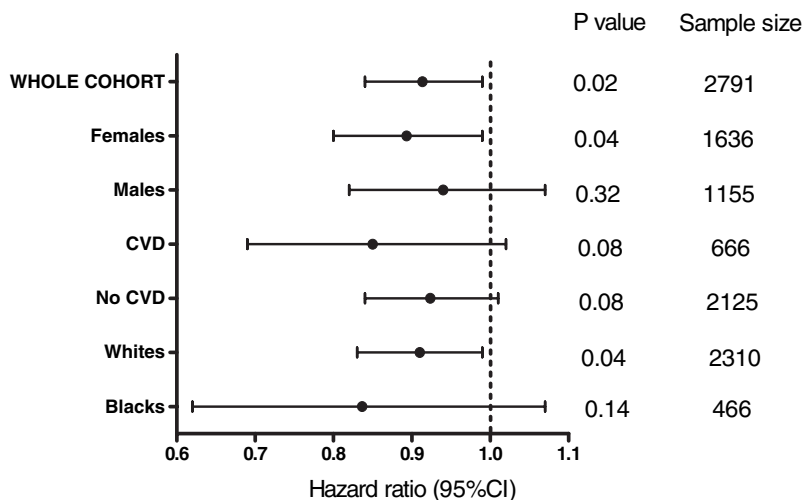
### Risk Prediction of the Best Cox Model With or Without %FMD

Figure 4 shows the receiver operator curves of the best Cox model with or without brachial FMD. The Akaike information criterion (AIC) of the best Cox model was 2810.7

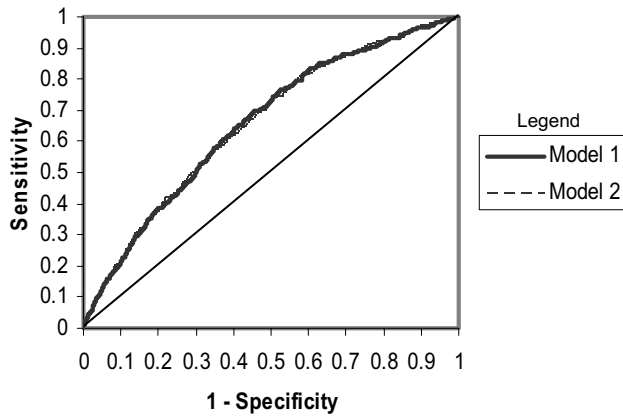
compared with an AIC of 2823.4 when %FMD was omitted from the model. The C statistic (AUC) for the best Cox model was 0.66, with a slightly higher C statistic in women (0.67) than in men (0.62). The C statistic (AUC) of the best Cox model without %FMD was 0.65 ( $P=NS$  for difference in AUC).

### Baseline Brachial Artery Diameter and Cardiovascular Events

The median baseline brachial artery diameter for men was 5.11 mm and that for women was 4.06 mm. As shown in Figure 5, the event-free survival rate for cardiovascular events over the 5-year period for subjects with brachial artery diameter below or equal to the sex-specific median was higher than for those with brachial diameter above the sex-specific median (78.2% versus 73.6%, log-rank  $P=0.004$ ). Baseline brachial artery diameter was a significant predictor of cardiovascular events in the age- and gender-adjusted Cox proportional hazard analysis (hazard ratio, 1.15 [95% CI, 1.03



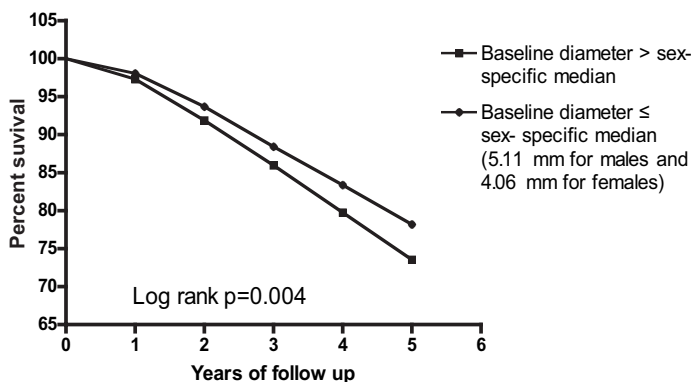
**Figure 3.** Predictive value of FMD per unit SD for cardiovascular events (stratified analysis) using Cox proportional hazard models adjusted for age, gender, diabetes mellitus, systolic and diastolic blood pressure, total cholesterol, smoking, HMG-CoA reductase inhibitor use, and baseline CVD status. CVD indicates cardiovascular event at baseline; No CVD, no cardiovascular event at baseline; and Whole Cohort, total sample ( $n=2791$ ).



**Figure 4.** Receiver operating characteristic curves for 5-year cardiovascular event prediction models. Model 1 included age, gender, total cholesterol, systolic and diastolic blood pressure, diabetes mellitus, cigarette smoking, baseline CVD status, and brachial FMD. Model 2 is model 1 minus brachial FMD.

to 1.29],  $P=0.01$  per 1-mm increase in brachial artery diameter). In the multivariable Cox proportional hazard analysis, baseline brachial artery diameter was also a significant independent predictor of CVD events after adjustment for age, gender, diabetes mellitus, systolic and diastolic blood pressure, cigarette smoking, total cholesterol, HMG-CoA reductase inhibitor use, and baseline CVD status (hazard ratio, 1.12 [95% CI, 1.02 to 1.28],  $P=0.025$  per 1-mm increase in diameter). Baseline brachial artery diameter remained a significant predictor of CVD events after body mass index or height (found to be associated with vessel diameter in other studies) was forced into the multivariable Cox proportional model (hazard ratio, 1.13 [95% CI, 1.00 to 1.27],  $P<0.05$ ).

The AIC of the best Cox model that included baseline brachial diameter (%FMD substituted with brachial diameter) was 2811.0 compared with the AIC of the best Cox model without baseline brachial diameter (2823.4). The C statistic (AUC) of the full model (best Cox model that included brachial diameter) was 0.658, and the C statistic (AUC) of the Cox model without brachial diameter was 0.650 ( $P=NS$  for the difference in AUC; not shown).



**Figure 5.** Life-table analysis of event-free survival for cardiovascular events of subjects above, below, or equal to sex-specific median baseline brachial artery diameter (in millimeters). \*Indicates subjects at risk.

>median*	1389	1362	1301	1228	1158
≤median*	1402	1364	1288	1205	1118

### Discussion

In this population-based cohort study of 2791 older adults, impaired brachial FMD was a significant predictor of incident cardiovascular events. However, brachial FMD added very little to the prognostic accuracy of current traditional cardiovascular risk factors in this cohort of older adults. The present data also showed that baseline brachial artery diameter had similar predictive value as brachial FMD for cardiovascular events and added a percentage similar to that added by brachial FMD to the prognostic accuracy of our best Cox model in the present elderly cohort. The present study adds substantial data to current literature on the predictive value of brachial FMD for cardiovascular events in population-based cohorts.

Previously published data on the association of brachial FMD and cardiovascular events are incomplete and show mixed results. The majority of earlier studies on the association between brachial FMD and incident CVD events were conducted in relatively young subjects with established cardiovascular disease. Some of these studies showed an association between brachial FMD and incident CVD events,<sup>5,7,8,18-21</sup> but other studies did not show an association.<sup>8,9</sup> Shimbo et al<sup>22</sup> studied the association between brachial FMD and incident CVD events in an asymptomatic population-based cohort of a relatively small sample size ( $n=842$ ). Although Shimbo et al<sup>22</sup> found an association between brachial FMD and incident CVD events, the predictive value of FMD was not independent of traditional cardiovascular risk factors. The results of the study by Shimbo et al<sup>22</sup> are consistent with the results obtained in the present subset free of prior CVD at the beginning of the brachial FMD ancillary study, with the difference in significance level probably being due to differences in statistical power between the present study's subgroup and their study. The present study, which consisted of population-based older adults with or without prior CVD, is the largest sample studied thus far and suggests that brachial FMD predicts CVD events and may provide additional prognostic information beyond traditional cardiovascular risk factors.

Age is an independent CVD risk factor and is associated with diminished brachial FMD<sup>23</sup> and an increase in atherosclerotic burden. Because endothelial dysfunction is an early

process in the pathogenesis of atherosclerosis, its measurement might be less informative in older adults, whose brachial FMD is greatly diminished and who are likely to have advanced atherosclerosis. Despite this and the previously mentioned issues with the variability, the present study was able to show that FMD is predictive of incident cardiovascular events.

The vascular endothelium may serve as a "barometer" for the cumulative insults on the cardiovascular system.<sup>24</sup> Nitric oxide bioavailability, which is assayed by brachial FMD, has been shown to be associated with cardiovascular health.<sup>25</sup> Current evidence suggests that the differences in nitric oxide bioavailability may distinguish subjects with good vascular health who are less likely to have a cardiovascular event from subjects with poor vascular health who are more likely to have a cardiovascular event. Studies have therefore tried to measure nitric oxide bioavailability using brachial FMD and have used this measure to predict cardiovascular events. However, brachial FMD is variable owing to physiological factors and technical problems encountered during measurement, and adherence to current guidelines for measuring brachial artery reactivity<sup>26</sup> minimizes but does not eliminate the variability of brachial FMD. The relatively small sample sizes of prior studies and the biological and measurement variability of brachial FMD may have accounted for the mixed findings in the literature. More research addressing the variability of brachial FMD is needed to further standardize this unique measure of vascular health.<sup>27</sup>

Although brachial FMD predicted CVD events independent of traditional cardiovascular risk factors in the present study, it only added  $\approx 1\%$  to the accuracy of the best Cox model. Our best Cox model consisted of almost all the constituents of the Framingham risk score except HDL cholesterol, as well as other factors noted to be associated with CVD events, such as HMG-CoA reductase inhibitor use. The present study underscores the importance of distinguishing between new risk predictors and their utility in the presence of already established risk factors/scores in clinical practice. Thus, similar to other new CVD risk markers, the clinical utility of brachial FMD is very limited in older adults. More studies are needed to evaluate how much brachial FMD adds to CVD risk prediction in younger populations.

The present study not only found brachial artery diameter to be predictive of cardiovascular events in this elderly cohort but also found that its predictive value was similar to that of brachial FMD. Brachial artery diameter also added to the prognostic accuracy of our best Cox model in a similar fashion to brachial FMD. Brachial artery diameter measurement, however, is more reproducible and less variable, and its acquisition is easier for both investigators and participants than brachial FMD, which is derived. If brachial artery diameter provides the same information as brachial FMD in older adults, then one could question the necessity of the entire ritual and techniques that investigators go through to obtain brachial FMD and the discomfort and possible pain that participants are subjected to during brachial FMD measurements. More studies validating this finding are needed in older adults and in other age groups.

The CHS brachial FMD ancillary study has the following limitations. The analyses do not take into account lifestyle changes or changes in comorbidities and medications subsequent to the FMD measurement. However, it is unlikely that such changes would have occurred differentially by FMD status, because the meaning of the FMD measurement was not known by participants or their physicians. On the other hand, such changes in behavior could have introduced noise that would tend to weaken any real association.

The present multivariable Cox proportional hazard model included major independent cardiovascular risk factors according to current American Heart Association/American College of Cardiology guidelines. New risk markers such as C-reactive protein, interleukin-6, and abdominal adiposity were not measured during the tenth CHS clinic visit and were therefore not included in the multivariable models. The HDL levels used in the present analysis were obtained on an earlier clinic visit, and forcing them into the Cox model did not change the hazard ratio (95% CI) of %FMD. It is uncertain whether inclusion of a more recent HDL level or these new risk markers in the multivariable Cox model would affect the predictive value of FMD for incident cardiovascular events.

Endothelium-independent vasodilation with nitroglycerin was not examined in the present study participants owing to their age (72 to 98 years) and the risk-benefit considerations of nitroglycerin administration in a population-based cohort study. Thus, although brachial FMD was predictive of incident cardiovascular events in the present study, we cannot be certain that the relationship between FMD and prognosis in the present study was entirely due to endothelium-dependent vasodilation.

Finally, the present study was conducted in older adults, and therefore, the conclusions of the study may not apply to other age groups. However, other studies have shown similar trends and have drawn similar conclusions in relatively younger populations, except that the amount of prognostic accuracy added to current risk scores/factors has not been well evaluated.

In summary, brachial FMD is a predictor of future clinical cardiovascular events in older adults, even after adjustment for other conventional CVD risk factors; however, brachial FMD added very little to the prognostic accuracy of current traditional cardiovascular risk scores/factors in the present study. This is probably because the brachial FMD of the present cohort was greatly diminished. Brachial FMD and brachial artery diameter may have similar predictive values in older adults. More research is warranted to determine the utility and prognostic accuracy that brachial FMD may add to traditional risk scores/factors in younger populations.

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## Disclosures

None.

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## CLINICAL PERSPECTIVE

Brachial flow-mediated dilation (FMD) is a validated physiological measure of endothelial dysfunction. %FMD has been associated with traditional cardiovascular risk factors and has been shown to predict cardiovascular events in some but not all studies. We assessed the predictive value of %FMD for future cardiovascular events in a population-based cohort of older adults with and without prior cardiovascular events. Our cohort had a mean age of 78 years, and the majority of study participants were white and were women. %FMD was predictive of future cardiovascular events, defined as myocardial infarction, stroke, congestive heart failure, cardiovascular disease death, angioplasty, or coronary artery bypass graft surgery, after adjustment for traditional cardiovascular risk factors such as age, sex, diabetes mellitus, systolic and diastolic blood pressure, total cholesterol, cigarette smoking, statin use, and prior cardiovascular disease status. %FMD, however, added only  $\approx 1\%$  to the prognostic accuracy of our best Cox model, which contained almost all the constituents of the Framingham risk score and statin use. Brachial artery diameter showed similar associations with cardiovascular events as %FMD and added to our best Cox model in a similar fashion as %FMD. We conclude the following: (1) %FMD is predictive of cardiovascular events in older adults; (2) %FMD adds very little to the prognostic accuracy of current traditional cardiovascular risk factors/scores in older adults; and (3) in older adults, brachial artery diameter may be as informative as %FMD in cardiovascular event prediction.