Microvascular Function Predicts Cardiovascular Events in Primary Prevention
Long-Term Results From the Firefighters and Their Endothelium (FATE) Study

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Background—Biomarkers of atherosclerosis may refine clinical decision making in individuals at risk of cardiovascular disease. The purpose of the study was to determine the prognostic significance of endothelial function and other vascular markers in apparently healthy men.

Methods and Results—The cohort consisted of 1574 men (age, 49.4 years) free of vascular disease. Measurements included flow-mediated dilation and its microvascular stimulus, hyperemic velocity, carotid intima-media thickness, and C-reactive protein. Cox proportional hazard models evaluated the relationship between vascular markers, Framingham risk score, and time to a first composite cardiovascular end point of vascular death, revascularization, myocardial infarction, angina, and stroke. Subjects had low median Framingham risk score (7.9%). Cardiovascular events occurred in 71 subjects (111 events) over a mean follow-up of 7.2±1.7 years. Flow-mediated dilation was not associated with subsequent cardiovascular events (hazard ratio, 0.92; P=0.54). Both hyperemic velocity (hazard ratio, 0.70; 95% confidence interval, 0.54 to 0.90; P=0.006) and carotid intima-media thickness (hazard ratio, 1.45; confidence interval, 1.15 to 1.83; P=0.002) but not C-reactive protein (P=0.35) were related to events in a multivariable analysis that included Framingham risk score (per unit SD). Furthermore, the addition of hyperemic velocity to Framingham risk score resulted in a net clinical reclassification improvement of 28.7% (P<0.001) after 5 years of follow-up in the intermediate-risk group. Overall net reclassification improvement for hyperemic velocity was 6.9% (P=0.24).

Conclusions—In men, hyperemic velocity, the stimulus for flow-mediated dilation, but not flow-mediated dilation itself was a significant risk marker for adverse cardiovascular outcomes. The prognostic value was additive to traditional risk factors and carotid intima-media thickness. Hyperemic velocity, a newly described marker of microvascular function, is a novel tool that may improve risk stratification of lower-risk healthy men. (Circulation. 2011;123:163-169.)

Key Words: atherosclerosis — endothelium — prevention

Measures of vascular function have emerged as potential surrogate markers of cardiovascular outcome. The endothelium plays a pivotal role in vascular homeostasis and if healthy abrogates atherosclerosis. Microvascular dysfunction contributes to adverse cardiovascular sequelae, but its ability to predict future events has not been well studied. A measure of conduit vessel function, brachial artery flow-mediated dilation (FMD) has been widely used as a research tool to evaluate endothelial function. Indeed, FMD is impaired early and has been shown to have predictive value in subjects with or at high risk of vascular disease. However, much less is known about the prognostic significance of FMD in apparently healthy subjects. In addition, the relationship between traditional cardiovascular risk factors and FMD is quite weak. Recent evidence suggests that the relationship with risk factors is much stronger for microvascular hyperemic velocity, the stimulus for FMD. This has prompted a reevaluation of the optimal vascular marker for risk prediction.

Clinical Perspective on p 169

The Firefighters and Their Endothelium (FATE) study was a longitudinal prospective cohort evaluation of the relationship between biomarkers of vascular health and incident cardiovascular events in a group of healthy men at low to intermediate Framingham risk. We report here the long-term follow-up of this cohort.

Received March 13, 2010; accepted October 25, 2010.
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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.110.953653
Methods

Patient Population
The study population consisted of 1574 male firefighters (mean age, 49.4±9.3 years) recruited from 4 research centers in Canada. Subjects were free of overt cardiovascular disease and had a low burden of cardiovascular risk factors. The study was approved by the ethics committee of each participating institution, and study participants provided written informed consent.

Study Protocol
The study protocol has been described previously. Briefly, between March 1999 and October 2003, subjects underwent a baseline assessment of risk including fasting glucose, total cholesterol, triglycerides, and high-density lipoprotein cholesterol. Low-density lipoprotein was calculated from the Friedewald equation. A detailed interview and questionnaire documented demographics, traditional risk factors, exercise and dietary history, fire and smoke exposure, and family history. Physical examination characteristics included blood pressure, height, weight, waist, and hip circumference. C-reactive protein (CRP) was measured using a high-sensitivity assay with the Roche Diagnostics Tinaquant (latex) assay on a Hitachi 912 platform (Roche Diagnostics, Indianapolis, IN). Risk factors were defined according to current guidelines.

Risk Factor Definition
Current smoking was defined as daily cigarette smoking within the last year. Hypertension was deemed present if blood pressure was >140/90 mm Hg or the subject was on active antihypertensive therapy. Diabetes mellitus was defined as fasting glucose ≥7.0 mmol/L, self-report of diabetes, or the need for diabetes medications or insulin. A positive family history of premature coronary disease was defined as any first-degree relative with cardiovascular disease <60 years of age. The Framingham risk score (FRS) was based on the recently published risk engine that includes total cardiovascular risk.

Brachial Artery Assessment of FMD and Hyperemic Velocity
A standardized brachial artery ultrasound protocol was used in the 4 research sites as previously reported. Technical validation was done at each site by individuals from the core laboratory in Calgary. A blood pressure cuff was placed on the right upper arm above the antecubital fossa with a 5-minute occlusion time. On cuff release, hyperemic velocity was recorded for 30 seconds, and complete velocity envelope obtained after cuff release. Higher values represent better microvascular dilation. The intraobserver variability for repeated measurements of FMD using the above approach was 0.7%. In this study, the intraobserver variability for repeated measurements of FMD using the above approach was 0.7%. In this study, the intraobserver variability for repeated measurements of FMD using the above approach was 0.7%

Vascular Reproducibility Cohort
To evaluate repeatability of FMD and VTI, 51 subjects underwent endothelial function testing 16±4 months after the baseline study. The coefficient of variation for FMD was 14.3% and for hyperemic VTI was 14.0%.

Ultrasound Assessment of Carotid Intima-Media
B-mode images of the right common carotid extending over 1 cm were obtained just proximal to the flow divider. A circumferential scan was performed, aimed at identifying the thickest region of the common carotid artery segment. A minimum of 3 frames were measured offline by 2 sonographers who manually traced the lumen-to-intima and the media-to-adventitia interfaces with locally developed software at the core laboratory in Hamilton, ON, Canada. The primary measurement outcome was the mean intima-media thickness (IMT) of the frame with the largest measurement. Intra-class correlation coefficients within and between observers were 0.89 and 0.92.

Follow-Up and Cardiovascular End Points
Telephone follow-up was obtained for all subjects every 12 months. Documentation was obtained on events, verified by the local site investigator, and reviewed by the end-point committee. Of the 1574 participants, there were 18 subjects with non–end-point deaths and 15 subjects who were lost to follow-up or withdrew consent.

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The primary end point was a composite of cardiovascular death; resuscitated cardiac arrest; nonfatal myocardial infarction; revascularization in the coronary, carotid, or peripheral circulation; symptomatic vascular disease with a >50% stenosis documented by angiography; and documented stroke or transient ischemic attack. The outcome variable was time to first of the composite cardiovascular events. The coprimary vascular variables were FMD and hyperemic VTI.

Data Analysis and Statistics
Descriptive statistics are expressed as mean±SD or medians (25th to 75th percentile) for continuous variables and as percentages for categorical or binary variables. The data loss (not obtained) for the vascular end points and demographic data was 1% to 2%. Kaplan-Meier curves for the proportion who were free of the composite end point were estimated up to 9 years. Participants who died of unrelated causes or who were lost to follow-up before an event was observed were censored at the time of last observation, as were individuals who had <9 years of event-free follow-up.

Proportional Hazards Models
Initially, an individual proportional hazards model was fitted for each of the potential predictor variables, including the vascular markers with censored observations as described above. Continuous variables were logarithm transformed if necessary and standardized. Proportional hazards assumptions were confirmed with Schoenfeld residuals.

Comparison of Proportional Hazards Models When the Vascular Markers Were Added to the FRS
We compared test characteristics of different prediction models in which the baseline model contained only the FRS and the subsequent extended models included the FRS and each of the vascular variables separately and together. All continuous variables were standardized to enable comparison of coefficients.

Hazard ratios (HRs) were estimated for each of the regression models. The incremental statistical significance of each of the vascular markers when added to the FRS was evaluated with the likelihood ratio test. Discrimination was assessed with the Harrell C index. The C index for each extended model was compared with the C index for the baseline model using bootstrap sampling. The models were also compared through the use of the Bayes information criteria and the Akaike information criteria. The goodness of fit for each model was compared by use of the Nagelkerke likelihood ratio-based R² measure. Calibration was assessed with the Gromesby and Borgan likelihood ratio test.
The net clinical improvement was calculated using only those individuals at intermediate risk.

Results

Baseline Patient Demographics

The overall study cohort (n=1574) consisted of mainly middle-aged men (mean age, 49.4 years) with low to medium Framingham risk (Table 1). There was a low prevalence of smoking and diabetes mellitus, and only 15% of subjects were taking cardiovascular medications at baseline. The majority of these were for hypertension (11%) or lipid lowering (8%).

Cardiovascular Events

There were 111 events in 71 subjects during a mean follow-up of 7.2±1.7 years; 95% of the participants were followed up for at least 5 years. Events included 21 nonfatal myocardial infarctions and 41 revascularizations (28 percutaneous and 13 coronary bypass surgeries). A minority of the events were cerebrovascular (n=12) or peripheral vascular (n=1) in nature. During the course of follow-up, 27% of subjects were on drug therapy for hypertension and 25% for lipid lowering, including those on therapy at baseline.

Predictors of Cardiovascular Events

The individual predictors of cardiovascular events are presented in Table 2. Neither baseline brachial diameter (P=0.16) nor FMD (P=0.54) was a significant predictor of cardiovascular events, but FMD corrected for shear stress was a significant predictor (HR, 1.18 per SD; 95% confidence interval [CI], 1.09 to 1.28; P=0.001). Nitroglycerin-mediated dilation was also a significant predictor (HR, 0.73 per SD; 95% CI, 0.57 to 0.95; P=0.018), as was hyperemic VTI (HR, 0.52 per SD; 95% CI, 0.41 to 0.66; P<0.001). Both (log) CIMT (HR, 1.86 per SD; 95% CI, 1.53 to 2.28; P<0.001) and (log) CRP (HR, 1.44 per SD; 95% CI, 1.17 to 1.78; P=0.001) were significant predictors of cardiovascular events.

Comparison of Proportional Hazards Models

The FRS was significantly related to cardiovascular events (HR, 2.28 per SD; 95% CI, 1.82 to 2.87; P<0.001). Of the vascular risk markers, hyperemic VTI was protective (HR,
0.70; per SD; 95% CI, 0.54 to 0.90; P=0.006; the Figure), and (log) carotid IMT (HR, 1.45 per SD; 95% CI, 1.15 to 1.82; P=0.002) and FMD corrected for shear stress (HR, 1.12 per SD; 95% CI, 1.02 to 1.24; P=0.016) increased risk when added to a model that included FRS. Neither FMD (P=0.69) nor (log) CRP (P=0.36) was related to outcomes when added to the FRS. Finally, in a model that included FRS and all 4 vascular markers together, both IMT (P=0.002) and hyperemic VTI (P=0.005) remained significant predictors of events in addition to the FRS. FMD corrected for shear stress was no longer significant after controlling for VTI and CIMT (P=0.17). CRP was not an independent predictor of outcome in any of the multivariable models examined.

**Discrimination and Calibration**

The C index for FRS was 0.746. When tested alone, the C index for hyperemic VTI was 0.665, for carotid IMT was 0.672, and for CRP was 0.640. When the vascular parameters were added to the FRS, CRP did not change the C index (0.748). There was an increase in the C index with hyperemic VTI (0.761), carotid IMT (0.754), and their combination (0.768), but these increases did not achieve statistical significance. The effects of the vascular parameters on goodness of fit and calibration parameters are presented in Table 3. The largest decreases in Akaike and Bayes information criteria were observed when both carotid IMT and hyperemic VTI were added to the FRS.

**Reclassification Improvement**

The 5-year net reclassification improvement was 11.6% (P=0.044) for carotid IMT, 6.9% for hyperemic VTI (P=0.24), and −0.48% for CRP (P=0.93). The combination of hyperemic VTI, CRP, and IMT resulted in a net reclassification improvement of 14.8% (P=0.043). The 5-year net clinical reclassification improvement in intermediate-risk patients was 18.0% for IMT (P=0.034) and 28.7% for hyperemic VTI (P<0.001; Table 4). The combination of IMT and VTI created the highest net clinical reclassification improvement of 37.8% (P=0.002). The calculation of reclassification for the addition of VTI to FRS is illustrated in Table 5.

**Discussion**

We demonstrate for the first time an independent association with cardiovascular events and hyperemic brachial artery velocity, the microvascular stimulus for FMD, but not FMD itself in this primary prevention population. We also confirm carotid IMT and FRS as independent predictors of events. This study has important implications for the use of hyperemic velocity as a surrogate marker and ultimately for risk assessment.

The vascular endothelium is well situated both to be adversely affected by injurious stimuli and to serve as a barometer of vascular health. Through the release of factors such as nitric oxide, a healthy endothelium is antiatherogenic. It has been well documented that endothelial dysfunction is an early marker of atherosclerosis. The present study was the first to show a significant relationship between hyperemic velocity and cardiovascular outcomes in a primary prevention population. Hyperemic velocity is a measure of microvascular function that is only partly related to endothelium-dependent nitric oxide release. Additional determinants of hyperemia at the microvascular level include adenosine,

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**Table 3. Characteristics of Proportional Hazards Models**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>Wald P</th>
<th>LR $\chi^2$ (P)</th>
<th>C Index</th>
<th>AIC</th>
<th>BIC</th>
<th>G-B $\chi^2$ (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRS/unit SD</td>
<td>2.28</td>
<td>1.82–2.87</td>
<td>&lt;0.001</td>
<td>7.65 (0.006)</td>
<td>0.7465</td>
<td>912.23</td>
<td>917.55</td>
<td>7.78 (0.10)</td>
</tr>
<tr>
<td>FRS/unit SD</td>
<td>1.97</td>
<td>1.53–2.54</td>
<td>&lt;0.001</td>
<td>6.97 (0.009)</td>
<td>0.7606</td>
<td>906.06</td>
<td>916.70</td>
<td>2.79 (0.11)</td>
</tr>
<tr>
<td>VTI/unit SD</td>
<td>0.70</td>
<td>0.54–0.90</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRS/unit SD</td>
<td>1.97</td>
<td>1.53–2.54</td>
<td>&lt;0.001</td>
<td>9.57 (0.002)</td>
<td>0.7539</td>
<td>905.40</td>
<td>916.04</td>
<td>2.92 (0.57)</td>
</tr>
<tr>
<td>Log IMT/unit SD</td>
<td>1.45</td>
<td>1.15–1.82</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRS/unit SD</td>
<td>2.18</td>
<td>1.70–2.78</td>
<td>&lt;0.001</td>
<td>8.65 (0.355)</td>
<td>0.7479</td>
<td>913.52</td>
<td>924.17</td>
<td>2.48 (0.65)</td>
</tr>
<tr>
<td>Log CRP/unit SD</td>
<td>1.12</td>
<td>0.88–1.44</td>
<td>0.34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRS/unit SD</td>
<td>1.68</td>
<td>1.28–2.24</td>
<td>&lt;0.001</td>
<td>9.11 (0.001)</td>
<td>0.7684</td>
<td>899.06</td>
<td>915.02</td>
<td>1.35 (0.85)</td>
</tr>
<tr>
<td>VTI/unit SD</td>
<td>0.69</td>
<td>0.53–0.88</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Log IMT/unit SD</td>
<td>1.46</td>
<td>1.16–1.84</td>
<td>0.01</td>
<td></td>
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</table>

$LR$ indicates likelihood ratio, $\chi^2$; C index, Harrell C index; AIC, Akaike information criteria; BIC, Bayes information criteria; and GB, Gronnesby and Borgan likelihood ratio and $\chi^2$. The initial model includes only FRS (standardized). Each subsequent model includes FRS (standardized) plus the variables indicated in column 1.
Table 4. Net Reclassification Improvement

<table>
<thead>
<tr>
<th>Reclassification Improvement</th>
<th>Clinical Reclassification Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>% I1</td>
<td>% I2</td>
</tr>
<tr>
<td>VTI/unit SD</td>
<td>0</td>
</tr>
<tr>
<td>Log IMT/unit SD</td>
<td>8.00</td>
</tr>
<tr>
<td>Log CRP/unit SD</td>
<td>-2.04</td>
</tr>
<tr>
<td>VTI/unit SD</td>
<td>6.12</td>
</tr>
<tr>
<td>Log IMT/unit SD</td>
<td></td>
</tr>
</tbody>
</table>

NRI indicates net reclassification improvement; NCRI, net clinical reclassification improvement. I1 (relative improvement for controls) equals percent moving up minus percent moving down. I2 (relative improvement for cases) equals percent moving down minus percent moving up.

Addition, in previous studies from this cohort, we demonstrated minimal relationship between FMD and traditional cardiovascular risk factors, CRP, or carotid IMT. The data from other earlier studies were mixed, but these studies tended to be smaller, retrospective, and from subjects with established disease or at high risk. More recently, Shimbo et al. demonstrated no relationship between FMD and cardiovascular outcomes in a primary prevention population. However, both the Cardiovascular Health Study (CHS) and the Multi-Ethnic Study of Atherosclerosis (MESA) have shown a significant relationship between FMD and cardiovascular outcomes in large cohorts. However, the magnitude of effect was small when added to traditional risk factors and only modestly altered reclassification indices. The FATE cohort was distinctly different from the CHS and MESA cohorts in that the population studied was both younger and at lower cardiovascular risk. In addition, we used an upper arm cuff position for FMD determination. This has been suggested to reflect a less purely endothelium-dependent stimulus. It is also possible that microvascular dysfunction and not FMD was predictive because it is an earlier marker in this healthy younger cohort.

The present study also confirmed the relationship between carotid IMT and adverse events. This had been shown in a number of populations, but the present study was one of very few that evaluated both endothelial function and carotid IMT simultaneously. Both IMT and hyperemic VTI added complementary and incremental information to the FRS for the prediction models and reclassification. The present data thus suggest that a marker of both vascular function and structure will provide added prognostic information. This would be intuitive because they measure different aspects of the biology of atherosclerosis and are not well correlated. Chan et al. were among the first to demonstrate added benefit of carotid IMT and FMD in a small study of subjects with CAD.

Finally, CRP was a univariate predictor of events in this cohort, but this was not sustained after the addition of FRS, unlike previous reports. Some recent studies have not demonstrated robust reclassification indices for CRP.

Limitations
Several important limitations must be acknowledged. The determination of brachial vascular function was performed with the occluding cuff on the upper arm. Although there is no clear consensus, a majority of studies performed now use a forearm cuff position, and the results may have been...
different with this position. The determination of carotid IMT used a single-site measurement of the far wall of the right common carotid. It is acknowledged that there are several alternative approaches using more detailed carotid IMT assessment that may have yielded potentially stronger associations to risk.\textsuperscript{31} Despite this, a strong and independent relationship was demonstrated in the present study.

An important limitation concerns the numbers used for the reclassification analysis presented in Tables 4 and 5. This analysis cannot include any censored observation. We chose the 5-year time point for this analysis because the data are quite complete at 5 years (<5% of the observations are censored) but become heavily censored after 5 years, and the large number of observations censored each year (eg, 317 observations were censored between 5 and 6 years) outweighs the small number of events that occurred (eg, 6 events occurred between 5 and 6 years). Thus, in the interpretation of the results of this reclassification analysis, it must be remembered that the statistics represent the reclassification rate after 5 years of follow-up.

Implications

The present study provided novel information on the prognostic value of a relatively simple measure of microvascular function, hyperemic VTI, in risk stratification. First, these results add to the literature demonstrating that measures of vascular function are surrogate markers of atherosclerosis. This finding has implications for studies of atherosclerosis that use vascular end points as surrogates of risk. In addition, because VTI is more reliably measured than FMD and is less dependent on operator expertise, this measure has the potential to be translated into clinical practice. Individuals with abnormal IMT and VTI even when at low risk by FRS are at substantially higher risk for future cardiovascular events; combined, these relatively simple surrogate measures of vascular structure and function can identify individuals at increased risk for events. These observations will certainly need to be studied in other cohorts to determine the clinical utility of these measurements. Whether such measures can identify individuals more likely to benefit from pharmacological risk reduction requires formal evaluation.\textsuperscript{32,33} There are many surrogate markers of atherosclerosis risk that have not been well integrated into clinical practice.

Conclusions

In healthy men, hyperemic velocity, the stimulus for FMD, was associated with adverse cardiovascular outcomes. The strength of the association was additive to FRS and measures of structural atherosclerosis and resulted in significant reclassification of risk. This measurement may aid in risk stratification of low- to intermediate-risk subjects.

Acknowledgment

We are deeply indebted to the research staff and study participants at the 4 coordination centers for their dedication and diligence to this project.

Sources of Funding

Funding was provided by Pfizer Canada, the Canadian Institutes of Health Research, and the Heart and Stroke Foundation of Alberta.

Disclosures

None.

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**CLINICAL PERSPECTIVE**

The endothelium plays a prominent role in vascular homeostasis and in health inhibits atherosclerosis formation and its complications. Conduit vessel function can be readily measured noninvasively by assessing flow-mediated dilation after a hyperemic stimulus. Blood flow at the tissue level determines organ viability and is controlled mainly at the microvascular level. Thus, there has been recent interest in measures of microvascular function and its clinical relevance. In the present study, we demonstrated in a large, long-term, prospective cohort of healthy men a number of important and novel findings. First, unlike some previous studies, flow-mediated dilation was not associated with vascular events. However, the hyperemic stimulus was an independent risk marker after Framingham risk score was considered. Second, carotid intima-media thickness was also associated with events, and this association remained after correction for Framingham risk and the hyperemic stimulus. This suggests that measures of both structure and microvascular function are risk predictors for adverse outcomes and provide synergistic information. The present study adds further evidence to the literature that these end points are surrogate measures of atherosclerosis outcomes and can be used in clinical research. Finally, because hyperemic velocity is a readily measured outcome variable, it has the potential to be incorporated into clinical care if further studies support our reported association. This would be most applicable to intermediate-risk individuals in whom additional testing has been advocated for clinical decision making.
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Circulation. published online January 3, 2011;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
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:
http://circ.ahajournals.org/content/early/2011/01/03/CIRCULATIONAHA.110.953653

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