Vascular and cardiac functional and structural screening to identify risk of future morbid events: preliminary observations

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Abstract

Risk factors have served to identify patients in need of antihypertensive and lipid-lowering therapy. Because of their limited sensitivity and specificity, we developed a screening program using noninvasive testing and a scoring system aimed at detecting functional and structural cardiovascular abnormalities in asymptomatic individuals. Ten cardiovascular tests were performed in 1 hour by a single technologist. Tests were scored as normal (0), borderline abnormal (1), or abnormal (2). Total disease score (DS) could range from 0 (all tests normal) to 20 (all tests abnormal). Scores of 0–2 were classified as normal, 3–5 as early disease, and 6+ as advanced disease. Morbid events during follow-up of 6 months to 8 years were determined from mailed questionnaires. Framingham risk scores (FRS) were calculated using published algorithms. Thirty-five morbid events (1 of 169 in the "normal" group, 8 of 214 in the "early disease" group, and 26 of 230 in the "advanced disease" group) occurred during the follow-up period among the 613 individuals who completed the questionnaire. Risk for morbid events was highly significantly different between the Kaplan-Meier curves based on disease detection (log rank 21.75, \(P \leq .0001\)). FRS were significantly different but less discriminating, with five morbid events in the 227 subjects with FRS <10, eight in 162 with FRS 10–13, and 22 of 227 with FRS >13 (log rank 9.80, \(P = .0074\)). The area under receiver operating characteristic curve for DS (0.74) surpassed that of FRS (0.66) and was not improved when both were included in the model. Neither blood pressure levels nor low-density lipoprotein cholesterol levels provided adequate discrimination. Identifying early disease in asymptomatic individuals provides a better guide to the need for preventive therapy than traditional risk factor assessment. J Am Soc Hypertens 2011;5(5):401–409. © 2011 American Society of Hypertension. All rights reserved.

Keywords: Atherosclerosis; early detection; blood pressure; cholesterol.

Introduction

Documentation in recent years of the effectiveness of preventive therapy in reducing cardiovascular morbidity

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and mortality in asymptomatic adults\textsuperscript{1–5} has heightened the need for strategies to identify individuals with a high enough risk to justify intervention.\textsuperscript{6,7} Risk factor assessment has served as the model for identifying the likelihood of individuals experiencing a future cardiovascular morbid event and for treatment aimed at reducing that risk. Scoring systems based on these risk factors\textsuperscript{8,9} have been used as the basis for lifestyle and pharmacologic intervention to reduce the risk of such events. The rationale for this approach is based on the epidemiologic evidence that each of the traditional risk factors included in the assessment—blood pressure, cholesterol, smoking, age—is significantly related to the risk of cardiovascular morbid events.\textsuperscript{10–14}

Most cardiovascular morbid events in developed countries are a consequence of target organ damage resulting
from hypertension and atherosclerosis, which is a progressive systemic disease that advances with age and involves the arteries, heart, kidney, and brain. Innovations in noninvasive methodology now make it possible to identify vascular and cardiac abnormalities long before they result in symptomatic cardiovascular disease (CVD). Although efforts have been made to demonstrate the predictive value of individual tests of vascular and cardiac health, the sensitivity and specificity of each individual test is limited. We therefore assessed the value of a scoring system based on a panel of 10 easily performed tests designed to assess disease in the arteries and heart in predicting future cardiovascular morbid events.

The screening program was initiated in 2000 at the University of Minnesota in the Rasmussen Center for Cardiovascular Disease Prevention. Ten tests of vascular and cardiac functional and structural health are performed in a single room by a single technologist in 1 hour. These screening tests are supplemented by blood testing for traditional risk factors and by a 1-hour session with a nurse practitioner who performs a cardiovascular examination, collects an extensive personal and family history, and provides appropriate dietary and lifestyle counseling. A comprehensive report of all findings and recommendations for therapy, overseen by a cardiologist reviewer, is provided to all patients and their health care providers.

The goal of this communication is to review the early experience with this screening program in predicting future morbid cardiovascular events in an asymptomatic presumably healthy population. The predictability of this early disease-based assessment compared with the traditional risk factor–based assessment is also examined.

Methods

Individuals are invited for screening at the Rasmussen Center through local lay and professional promotion and through letters directed to a selected target population of Twin Cities residents with higher income levels among adults aged 40–60 years. Individuals with prior known cardiovascular morbid events or symptoms of CVD are not invited for screening. The cost of screening is usually borne by the individual’s health insurance.

Individuals screened in the Center undergo the following tests that have been described in detail previously: Small artery elasticity and large artery elasticity (pulse contour methodology), blood pressure at sitting rest, blood pressure change during a 3-minute treadmill test at 5 metabolic equivalents (METS), fundoscopic digital photograph for vascular evaluation, carotid ultrasound for measurement of intima-media thickness (IMT) and detection of plaques (instituted in 2003 to replace ankle-brachial index), urine for microalbumin:creatinine ratio, ultrasound examination of the left ventricle for mass and volume, electrocardiogram, and a blood sample for B-type natriuretic peptide (BNP or NT-ProBNP). The result of each of the tests is analyzed based on a standardized range of normal (score 0), borderline abnormal (score 1), or abnormal (score 2). The range of scores for arterial elasticity and IMT scores are age-adjusted.15 A disease score (DS) is calculated as the sum of the 10 individual test scores for each patient; thus, scores can range from 0 to 20. Blood is also analyzed for total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, fasting glucose, and highsensitivity C-reactive protein. The Framingham Risk Score (FRS) is also calculated for each patient.

In 2008, questionnaires were sent to 1400 individuals screened more than 6 months before the date of the mailing. Follow-up was approved by the Institutional Review Board. The questionnaire inquired about a number of lifestyle and treatment issues but focused on any morbid events experienced after their screening visit. The events queried included myocardial infarction, angina, stroke, coronary artery bypass surgery, percutaneous coronary intervention, heart failure, and peripheral vascular disease. The approximate date of each event was also ascertained.

Six hundred and thirteen questionnaires were returned from screened patients. Morbid events reported by these individuals were verified by further inquiry and hospital records when necessary. At the time of screening, 111 (18.1%) were taking lipid-lowering therapy, and 59 (9.6%) were taking an antihypertensive drug.

DS in these 613 individuals are displayed in Figure 1. The distribution of scores in this subgroup of questionnaire responders, compared with the distribution in the entire population to whom the questionnaire was mailed, suggests that individuals with higher disease scores were somewhat more likely to return the questionnaire. Based on the distribution of scores, three groups of scores (0–2, 3–5, 6+)...
Table 1

<table>
<thead>
<tr>
<th>Morbid events in 35 patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>18</td>
</tr>
<tr>
<td>Angina (documented)</td>
<td>2</td>
</tr>
<tr>
<td>Stroke</td>
<td>6</td>
</tr>
<tr>
<td>Heart failure</td>
<td>5</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>3</td>
</tr>
</tbody>
</table>

divided the population into nearly equal tertiles. Furthermore, it had been our prestudy hypothesis that scores of 0, 1, or 2 should be indicative of no disease, scores of 3–5 as evidence for early disease and scores of 6 or above as evidence of advancing disease.

Using the traditional FRS system, few of our screened population fell into the high 10-year coronary risk group of 20%. To allow comparable analysis, therefore, the Framingham risk was also analyzed in tertiles, which resulted in FRS categories of <10, 10–13, and >13.

Kaplan-Meier (KM) methods were used to estimate the cumulative rate of CVD events subsequent to time of initial screening. Subjects with no reported events were censored at the time of the questionnaire return. Log-rank tests were used to compare the cumulative CVD rates among DS and FRS strata. T-tests and chi-square were used to compare risk factors at baseline between subjects having CVD events with those not reporting events. Components of the DS were also compared between groups to assess which components were the major contributors to increased risk found for the DS. Cox regression was used to assess whether the DS was significantly related to CVD risk independent of the FRS by: 1) including both DS and FRS variables in the same model and 2) running separate regressions with DS for those with a FRS <10 and those with a FRS >10. Spearman correlations were computed between each component score and the total score to determine which components were associated most strongly with the total FRS.

Receiver operating characteristic (ROC) curves were also calculated for DS, FRS, and a model containing both scores.

Results

Thirty-five individuals reported and were confirmed to experience a morbid event between the time of their screening visit and submission of the questionnaire. A summary of these events is provided in Table 1. Twenty-six of these events occurred in the DS “advanced disease” group, 8 in the “early disease” group, and 1 in the “no disease” group. No morbid events were reported by 578 patients. The baseline demographic and traditional risk factor data in the 35 patients with an event compared with those without an event are summarized in Table 2. As might be expected, the age was older and there were fewer women in the “event” group. Very few patients were smokers. The average DS was significantly higher in the “event” versus “non-event” group (7.3 versus 4.6, respectively, \(P < .001\)). The FRS was also significantly higher in the CVD group (\(P = .003\)).

The mean measurements of components of the DS in the “event” and “non-event” groups are displayed in Table 3. All components of the DS were more “abnormal” in the CVD group and most components were significantly different between CVD and non-CVD groups. Small artery elasticity was lower, resting blood pressure higher, the left ventricular mass greater, the BNP higher, microalbumin more likely present in the “event” group, and the retinal vasculature and carotid artery more likely abnormal (\(P = .05\) or less).

Risk factors in the three DS subgroups are shown in Table 4. Except for age, traditional risk factors were weakly or not associated with the DS.

To examine the contribution of each of the 10 measurements to the DS, Spearman correlation coefficients were calculated between each test and the DS (Table 5). All tests

Table 2

<table>
<thead>
<tr>
<th>Risk factors for cardiovascular disease</th>
<th>Events n = 35</th>
<th>No Events n = 578</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>61.6 ± 8.1</td>
<td>53.7 ± 10.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>%women</td>
<td>25.7 ± 44.3</td>
<td>45.9 ± 49.9</td>
<td>.020</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.8 ± 3.5</td>
<td>27.2 ± 5.2</td>
<td>.191</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>194.7 ± 38.6</td>
<td>204.0 ± 40.7</td>
<td>.584</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (mg/dL)</td>
<td>123.8 ± 32.0</td>
<td>127.3 ± 37.0</td>
<td>.184</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mg/dL)</td>
<td>47.6 ± 13.2</td>
<td>51.3 ± 16.2</td>
<td>.227</td>
</tr>
<tr>
<td>Log triglycerides</td>
<td>4.6 ± 0.5</td>
<td>4.7 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>97.9 ± 13.9</td>
<td>93.8 ± 16.2</td>
<td>.149</td>
</tr>
<tr>
<td>C-reactive protective (mg/dL)</td>
<td>0.4 ± 0.6</td>
<td>0.3 ± 0.7</td>
<td>.595</td>
</tr>
<tr>
<td>Framingham Risk Score</td>
<td>12.7 ± 2.6</td>
<td>10.3 ± 4.7</td>
<td>.003</td>
</tr>
<tr>
<td>Rasmussen Score</td>
<td>7.3 ± 2.8</td>
<td>4.6 ± 3.2</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Table 3
Assessment of early cardiovascular disease

<table>
<thead>
<tr>
<th>Measure</th>
<th>Events n = 35</th>
<th>No Events n = 578</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables contributing to score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large artery elasticity (mL/mm Hg × 10)</td>
<td>16.2 ± 6.5</td>
<td>16.7 ± 5.7</td>
<td>.581</td>
</tr>
<tr>
<td>Small artery elasticity (mL/mm Hg × 100)</td>
<td>5.0 ± 2.7</td>
<td>6.2 ± 3.1</td>
<td>.024</td>
</tr>
<tr>
<td>Resting systolic blood pressure (mm Hg)</td>
<td>132.2 ± 16.6</td>
<td>126.6 ± 16.6</td>
<td>.053</td>
</tr>
<tr>
<td>Resting diastolic blood pressure (mm Hg)</td>
<td>79.9 ± 10.9</td>
<td>79.0 ± 9.9</td>
<td>.617</td>
</tr>
<tr>
<td>Change in systolic blood pressure (mm Hg)</td>
<td>25.2 ± 19.3</td>
<td>23.6 ± 15.6</td>
<td>.559</td>
</tr>
<tr>
<td>Change in diastolic blood pressure (mm Hg)</td>
<td>−8.9 ± 9.9</td>
<td>−10.1 ± 8.8</td>
<td>.430</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>87.1 ± 24.7</td>
<td>73.7 ± 18.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Microalbuminuria (mg/mmol)</td>
<td>2.3 ± 8.2</td>
<td>0.9 ± 2.2</td>
<td>.007</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/dL)</td>
<td>99.4 ± 133.3</td>
<td>59.5 ± 73.4</td>
<td>.003</td>
</tr>
<tr>
<td>Retinal score</td>
<td>1.1 ± 0.9</td>
<td>0.6 ± 0.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Carotid ultrasound score</td>
<td>0.9 ± 0.9</td>
<td>0.5 ± 0.8</td>
<td>.014</td>
</tr>
<tr>
<td>Electrocardiogram score</td>
<td>0.9 ± 1.0</td>
<td>0.2 ± 0.6</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

were positively associated with the DS (correlations 0.25–0.57), with resting blood pressure and small artery elasticity the most powerful contributors.

The time course of morbid events during 6 years of follow-up in these three groups is shown in Figure 2. No events were observed in the 169 patients in the “no disease” group (0–2 score). In the 214 “early disease” group (scores 3–5), events were rare until year 4, when the incidence began to rise briskly. In the 230 patients in the “advanced disease” group (DS 6 or higher), events began occurring soon after screening and reached approximately 13% by 6 years. Two cerebrovascular events occurred after 72 months, one at 78 months in the “early disease” group and one at 84 months in the “no disease” group. Based on the log-rank test, differences among DS strata were highly significant (P < .0001).

Events based on the traditional groupings of FRS are shown in Table 6. More than 10% of the events occurred in the low-risk group that would not have been candidates for preventive therapy. Because so few individuals exhibited risk factors in the high-risk category, it is clear that traditional FRS classification is not an adequate discriminator in this population.

Analysis of events based on observed tertiles of the FRS is displayed in Figure 3. Event rates between strata were significantly different (P < .01). Event rates in the three groups were similar for the first year and then separated. By 6 years, all three groups had experienced some events, but the cumulative incidence was directly related to FRS. Log-rank value was less for the FRS than the DS (9.80 versus 21.75).

Because age is a major contributor to FRS but is not an independent component in the DS, a separate analysis was performed to determine the effect of age on event rates (Figure 4). As expected, age itself is a powerful predictor of events over a 6-year period with a higher log rank (15.2) than FRS. During the first 2 years, however, age does not serve as an adequate discriminator.

Univariate and multivariate analysis of DS and FRS was carried out (Table 7). The standardized hazard ratio (HR) for DS was greater than that for FRS and, on multivariate analysis the HR for DS remained independently significant.

Table 4
Risk factors in three disease score groups

<table>
<thead>
<tr>
<th>Disease Scores</th>
<th>0–2</th>
<th>3–5</th>
<th>6+</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.6 ± 10.2</td>
<td>53.3 ± 9.5</td>
<td>59.0 ± 9.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>%women</td>
<td>42.3 ± 49.5</td>
<td>41.6 ± 49.4</td>
<td>49.6 ± 50.1</td>
<td>.180</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.5 ± 4.4</td>
<td>27.4 ± 5.4</td>
<td>27.6 ± 5.3</td>
<td>.078</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>199.3 ± 36.1</td>
<td>201.3 ± 39.2</td>
<td>208.6 ± 44.6</td>
<td>.049</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (mg/dL)</td>
<td>123.8 ± 32.0</td>
<td>126.8 ± 37.4</td>
<td>129.8 ± 39.2</td>
<td>.281</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mg/dL)</td>
<td>50.3 ± 15.1</td>
<td>50.4 ± 16.0</td>
<td>52.3 ± 16.9</td>
<td>.342</td>
</tr>
<tr>
<td>Log triglycerides</td>
<td>4.7 ± 0.5</td>
<td>4.7 ± 0.5</td>
<td>4.8 ± 0.6</td>
<td>.349</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>92.7 ± 14.6</td>
<td>93.4 ± 19.3</td>
<td>95.6 ± 13.7</td>
<td>.176</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>0.3 ± 0.6</td>
<td>0.3 ± 0.7</td>
<td>0.4 ± 0.6</td>
<td>.387</td>
</tr>
</tbody>
</table>
Table 5

Correlation coefficients for individual test contribution to disease score

<table>
<thead>
<tr>
<th>Test</th>
<th>Correlation Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting blood pressure</td>
<td>0.570</td>
</tr>
<tr>
<td>Small artery elasticity</td>
<td>0.561</td>
</tr>
<tr>
<td>Exercise rise in blood pressure</td>
<td>0.487</td>
</tr>
<tr>
<td>Retinal vasculature</td>
<td>0.461</td>
</tr>
<tr>
<td>Left ventricular ultrasound</td>
<td>0.459</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>0.438</td>
</tr>
<tr>
<td>Large artery elasticity</td>
<td>0.403</td>
</tr>
<tr>
<td>Carotid ultrasound</td>
<td>0.363</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>0.350</td>
</tr>
<tr>
<td>B-type natriuretic peptide</td>
<td>0.252</td>
</tr>
</tbody>
</table>

(1.752, P < .001), whereas the FRS did not (P = .26). DS remained significantly discriminating in strata of FRS above and below 10%.

ROC curves depicting sensitivity and specificity are displayed in Figure 5. The area under the curve for DS (0.74) is significantly greater than for FRS (0.66) and is not improved by the model including both scores.

Because physicians are urged to focus on blood pressure and cholesterol as targets for therapy we also examined the level of these risk factors as predictors of future morbid events. As shown in Table 8, neither blood pressure levels nor low-density lipoprotein cholesterol levels served as adequate discriminators.

Discussion

Cardiovascular morbid events occur as a complication of functional or structural changes in the large conduit arteries, the small nourishing arteries, or the left ventricle. Abnormalities in these target organs should be present long before symptoms develop. Advances in methodology have made it possible to efficiently evaluate these target organs to detect the early stages of disease in asymptomatic patients.

DS has been developed as a comprehensive assessment of abnormalities in the large arteries (large artery elasticity, rest and exercise blood pressure, carotid IMT), small arteries (small artery elasticity, rest and exercise blood pressure, retinal vasculature, microalbuminuria), and left ventricle (electrocardiogram, left ventricular ultrasound, BNP or NT-ProBNP). A score summing these abnormalities, therefore, should provide a quantitative guide to the severity of CVD likely to contribute to future morbidity and mortality.

Follow-up after screening revealed that the DS calculated from the cardiovascular screening provided a better predictive value for morbid events than did the Framingham Risk Scores (FRS). The 28% of the screened population with DS of 0, 1, or 2 sustained no cardiovascular morbid events during 6 years of follow-up, and the one morbid event identified at 8 years occurred in an individual in whom rescreening at that time revealed a score that had increased to 7.

Scores of 3–5, in which at least three of the tests were borderline or abnormal, were observed in 35% of the population. This group was more likely to experience a morbid event in 6 years. The risk, however, was only about 5% and most events occurred more than 4 years after the screening visit. In contrast, individuals with scores of 6 or above (37% of the population) exhibited a high likelihood for early morbid events that were experienced by nearly 15% of the group by 6 years.

This apparent discrimination in risk based on early disease detection has allowed us to provide more

![Figure 2](image-url)  

**Figure 2.** Kaplan-Meier curves of time to morbid events during 6 years of follow-up in the three Rasmussen Disease Score (DS) Groups. The difference among the curves (P = .0000) is highly significant. Two events after 72 months are not depicted.
individualized and targeted therapy. Individuals with scores of 0–2 are encouraged to follow public health guidelines for a healthy lifestyle and return for follow-up in 5–10 years. Individuals with scores of 3–5, implying early disease, are instructed regarding more vigorous and individualized lifestyle changes if there are no guideline indications for pharmacotherapy, and they are advised to return for follow-up screening in 3 years. Individuals with scores of 6 or higher are usually treated with drugs, regardless of the level of their risk factors, and asked to return in 1 year. This therapy, usually including at least a statin drug and an inhibitor of the renin-angiotensin system, is instituted not to necessarily control abnormal risk factors but to prevent further vascular and cardiac damage.

The traditional approach advocated for primary prevention has been to measure blood pressure and cholesterol levels and base therapy on thresholds of these variables. Calculation of a FRS using these measurements in addition to age, family history, and other risk factors in established algorithms is encouraged. The FRS can be simply calculated online and is widely advocated. The FRS generally recommended and used in our analysis is a Framingham calculation based on hard coronary disease end points and using age, gender, smoking history, blood pressure, and total and high-density lipoprotein cholesterol levels. The Framingham group more recently published a revised algorithm based on hard and soft vascular end points, including all the events noted in our patient population. The same risk markers were used in this analysis with the addition of diabetes. This revised FRS provided differences between our event and non-event groups that were similar to the traditional FRS. The DS still demonstrated a statistically significantly hazard ratio than the FRS when both were included in the model.

Data from our population thus raise concerns about the sensitivity and specificity of the risk-factor approach. Cholesterol levels did not discriminate between the patients with and without subsequent morbid events and did not differ between groups based on DS. Although blood pressure was higher in those who sustained an event and bore a direct relationship with DS, few patients exhibited pressures above any treatment threshold guideline. Furthermore, the FRS did not effectively discriminate early risk, whereas long-term risk predicted from the FRS could be attributable predominately to age, which is not a factor in the DS.

Therefore, the early disease assessment performed in the Rasmussen Center appears to be more discriminating than traditional risk factors for identifying individuals likely and not likely to sustain morbid events. Because the testing is performed in 1 hour at a moderate cost it represents a potentially practical strategy for wider application. Although it is intuitively attractive to use this early disease evidence to steer

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**Table 6**

<table>
<thead>
<tr>
<th>Framingham Score</th>
<th>No Events</th>
<th>Events</th>
<th>% Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>209</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>10–19</td>
<td>356</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>20+</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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**Figure 3.** Event rates based on Framingham Risk Scores (FRS) divided into tertiles. The curves are significantly different ($P = .0074$) but less discriminating than Rasmussen Disease Score (DS) (log-rank 9.80 versus 21.75).
pharmacopreventive therapy, clinical trials to assess outcomes and calculate cost-effectiveness are necessary.

Another potential benefit of early disease assessment is the possibility of monitoring progression of disease. Such progression cannot be assessed from risk factors but could be identified by worsening of vascular and cardiac function or structure. A favorable effect on DS of an intervention could then serve as a guide to efficacy. A recent trial with an angiotensin receptor blocker in patients with DS of 6 or above has documented the drug's effectiveness in reducing an elevated DS score.25 Documentation that a change in DS tracks with improved outcomes needs verification in a large-scale study.

Weaknesses of this analysis can hopefully be addressed in the future. Follow-up in this study was dependent on a questionnaire mailed to our screened patients. The return rate was less than 50%, so our analysis was limited to those who responded. Although event rates may vary between the responders and nonresponders, there is no reason to suspect that the predictive value of the DS would be influenced by missing data. Of the 35 morbid events, 18 were coronary revascularization procedures. Although such events may be in part dependent on arbitrary decision-making, the fact that they were performed in previously healthy subjects with new symptoms and that they had no temporal relationship to the screening examination reassures us that they represented disease progression. The influence of therapy on event rates was not assessed in this analysis. Detailed recommendations for treatment were provided to all patients with high DS. Whether they or their health care providers followed the recommendations and whether treatment altered their risk will be a subject of future study. Our patient population is expanding continuously and will be augmented by data from other centers that are now utilizing our program. This should allow for a far more robust future analysis. Furthermore, we are currently evaluating the utility of a simple prescreen assessment using measurement of blood pressure, arterial elasticity, and exercise blood pressure response to identify individuals in need of a more comprehensive screening. Such prescreening could

![Figure 4](image)

**Figure 4.** Event rates based on age divided into tertiles. Not surprisingly, age is a significant predictor of events ($P = .0005$).

<table>
<thead>
<tr>
<th>Table 7</th>
<th>Univariate and multivariate analysis of risk score and disease score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standardized Variable</td>
<td>Beta</td>
</tr>
<tr>
<td>Risk score alone</td>
<td>0.620</td>
</tr>
<tr>
<td>Disease score alone</td>
<td>0.655</td>
</tr>
<tr>
<td>Multivariate risk score</td>
<td>0.252</td>
</tr>
<tr>
<td>Multivariate disease score</td>
<td>0.561</td>
</tr>
<tr>
<td>Disease score (risk score &lt; 10)</td>
<td>1.164</td>
</tr>
<tr>
<td>Disease score (risk score &gt; 10)</td>
<td>0.465</td>
</tr>
</tbody>
</table>
drastically reduce the number of individuals referred for the full testing battery.

In summary, a practical and efficient noninvasive screening program to assess vascular and cardiac health has provided remarkable discrimination of apparently healthy individuals into those with no risk, delayed risk, and high risk. This screening surpassed the discriminatory ability of more traditional risk factor assessment. This screening approach needs further assessment as a potentially attractive strategy to reduce the cost of health care by more effectively targeting therapy to those at risk.

Table 8
Blood pressure and low-density lipoprotein cholesterol levels and subsequent morbid events

<table>
<thead>
<tr>
<th>Blood Pressure (mm Hg)</th>
<th>No Cardiovascular Events</th>
<th>Cardiovascular Events</th>
<th>% Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120/&lt;80</td>
<td>451</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>120–129/&lt;80–84</td>
<td>66</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>&gt;129/&lt;84</td>
<td>54</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Low-density lipoprotein cholesterol (mg/dL)

| <100                   | 135                      | 9                     | 7       |
| 100–129                | 161                      | 13                    | 8       |
| >129                   | 254                      | 13                    | 5       |

References


Original Contribution

Structural and Functional Vascular Alterations and Incident Hypertension in Normotensive Adults

The Multi-Ethnic Study of Atherosclerosis

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Vascular abnormalities may exist before clinical hypertension. Using Poisson regression, the authors studied the association of coronary artery calcium (CAC), common carotid intima-media thickness (CIMT), aortic distensibility, and large and small arterial elasticity with incident hypertension among 2,512 normotensive US adults free of cardiovascular disease. Incidence rate ratios for incident hypertension (blood pressure ≥140/90 mm Hg or new antihypertensive medication) were calculated. Increased CAC was associated with incident hypertension in demographics-adjusted models (incidence rate ratio (IRR) = 1.35, 95% confidence interval (CI): 1.04, 1.75; IRR = 1.35, 95% CI: 1.02, 1.78; and IRR = 1.59, 95% CI: 1.12, 2.25 for CAC scores of 30–99, 100–399, and ≥400, respectively) but was attenuated after further adjustment. Increased common CIMT was associated with incident hypertension (IRR = 1.77, 95% CI: 1.28, 2.46 for quintile 4; IRR = 1.80, 95% CI: 1.28, 2.53 for quintile 5). Participants with the lowest, compared with the highest, aortic distensibility had an increased risk of hypertension (IRR = 1.75, 95% CI: 1.10, 2.79), as did those with the lowest large arterial elasticity (IRR = 1.49, 95% CI: 1.11, 1.99). Lower small arterial elasticity was incrementally associated with incident hypertension starting at quintile 2 (IRR = 2.01, 95% CI: 1.39, 2.91; IRR = 2.47, 95% CI: 1.71, 3.57; IRR = 2.73, 95% CI: 1.88, 3.95; and IRR = 2.85, 95% CI: 1.95, 4.16). Structural and functional vascular abnormalities are independent predictors of incident hypertension. These findings are important for understanding the pathogenesis of hypertension.

arteries; elasticity; hypertension

Abbreviations: MESA, Multi-Ethnic Study of Atherosclerosis; MRI, magnetic resonance imaging.

Hypertension affects almost 30% of the US population and is associated with increased risk of stroke, cardiovascular disease, and mortality (1, 2). Despite this high prevalence and serious health consequences, the pathogenesis of essential hypertension remains largely unknown. One possible mechanism to explain the initiation of hypertension may be vascular abnormalities that develop before the systolic or diastolic pressures become persistently elevated.

Hypertension is characterized by increased arterial stiffness and endothelial dysfunction, which themselves are associated with increased cardiovascular risk (3, 4). Studies suggest that structural and functional blood vessel abnormalities predate the development of clinical hypertension in prehypertensive patients (5, 6). Most recently, large-vessel stiffness (measured by pulse wave velocity) has been associated with rising systolic blood pressure levels among hypertensives and may also predict incident hypertension longitudinally (7). The relation of structural and/or functional vascular abnormalities to incident clinical hypertension is not well understood.

We designed these analyses to study the association between comprehensive subclinical measurements of blood vessel structure and function and the development of incident hypertension in a large, community-based, multiethnic
Figure 1. Case ascertainment for each examination of participants in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, United States, 2000–2007. Cohort definition: baseline blood pressure—<130 systolic blood pressure and <80 diastolic blood pressure.

MATERIALS AND METHODS

Subjects

The Multi-Ethnic Study of Atherosclerosis (MESA), a large study sponsored by the National Heart, Lung, and Blood Institute, aimed to understand subclinical cardiovascular disease and its progression in a multiethnic cohort. Details on study recruitment and design have been previously published (8). Briefly, MESA recruited 6,814 men and women who were aged 45–84 years, who were free of cardiovascular disease, and who self-identified as white, African American, Hispanic, or Chinese American. Subjects were recruited from Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan and the Bronx, New York; and St. Paul, Minnesota, between July 2000 and August 2002. Individuals were excluded from this study if they had physician-diagnosed heart attack, angina, heart failure, stroke, or transient ischemic attack; had atrial fibrillation or had undergone coronary artery bypass grafting, angioplasty, or valve replacement; had a pacemaker; or weighed more than 300 pounds (136 kg). The institutional review boards at all participating centers approved the study, and all participants gave informed consent.

For these analyses, we included those participants who had their blood pressure measured at baseline and were not hypertensive at the baseline visit—defined as having a systolic blood pressure of <130 mm Hg and a diastolic blood pressure of <80 mm Hg—were not using any antihypertensive medication, and reported no history of hypertension. We chose the cutpoint 130/80 mm Hg to increase the likelihood that participants were free of the outcome at the beginning of the study. We excluded participants who had no follow-up data for all subsequent MESA examinations, for a total 2,512 participants available for these analyses (Figure 1).

Primary outcome ascertainment: incident hypertension

Blood pressure and medication use were assessed during the second, third, and fourth follow-up MESA examinations. During each examination, 3 blood pressure measurements
were obtained 5 minutes apart in the seated position by using an automated oscillometric sphygmomanometer (Dinamap; Critikon, General Electric, Madison, Wisconsin). The mean of the second 2 measurements was used for analysis. Participants were asked to bring all medications to each examination, and medication use was assessed by medication inventory. Incident hypertension was defined as a systolic blood pressure of $\geq 140$ mm Hg, a diastolic blood pressure of $\geq 90$ mm Hg, or the use of medication for hypertension during the second, third, or fourth follow-up examinations. Because angiotensin-converting enzyme inhibitors and angiotensin II antagonists may be prescribed to diabetics who do not have hypertension, sensitivity analyses were conducted to explore whether study findings were similar after excluding participants who had diabetes at baseline. A flowchart of case ascertainment for each examination is presented in Figure 1.

**Primary predictors**

**Subclinical measures of structural vascular changes.** We defined structural measures as those that assess the anatomy of the vessel, including calcification and intima size. Coronary artery calcification was measured by using computed tomography of the chest. Three field centers used an electrocardiogram-triggered electron-beam scanner (Imatron C-150; Imatron, San Francisco, California), and the others used prospectively electrocardiogram-triggered scan acquisition at 50% of the R-R interval with a multidetector computed tomography system (Lightspeed; General Electric Medical Systems, Waukesha, Wisconsin, or Volume Zoom; Siemens, Erlanger, Germany). All participants are scanned over phantoms of known physical calcium concentration. Scans were read centrally at the Harbor-UCLA Research and Education Institute in Torrance, California, to identify and quantify coronary calcification, calibrated according to the readings of the calcium phantom. Details on measurement of coronary artery calcification in MESA have been previously published (8, 9).

The intima-media thickness of the common and internal carotid arteries was measured on the right and left sides of the neck by using high-resolution B-mode ultrasound (Logiq 700 ultrasound machine; General Electric Medical Systems). This procedure has previously been described in detail (8, 9). In brief, 4 longitudinal images were obtained on each side of the neck: 1 of the common carotid artery and 3 of the internal carotid artery centered on the carotid bulb. All scans were read in a central location, using a standard protocol at the Tufts Medical Center, Boston, Massachusetts.

**Subclinical measures of functional vascular changes.** We defined measures of functional vascular changes as those that assess the ability of vessels to adapt to distending pressures throughout the cardiac cycle. For the large and small artery elasticity index, MESA investigators used the HDI PulseWave CR-2000 Research CardioVascular Profiling Instrument (Hypertension Diagnostics, Inc., Eagen, Minnesota) to acquire and analyze pulse waveforms from the radial artery. Using the pulse contour analysis technique, this method enables both large and small arterial characteristics to be studied. By incorporating pressure fluctuations, it provides a way to study changes in large and small arteries by measuring their response to distending pressures throughout the cardiac cycle. This process is accomplished by analyzing the diastolic pulse contour and calculating each parameter by using a third-order, 4-element Windkessel modified model. Briefly, this model divides total systemic arterial compliance into contributions from the pool of large arteries (capacitive) and from the pool of small arteries (oscillatory). The elasticity indices are then estimated by multiplying these parameters by systemic vascular resistance, which is estimated by dividing the mean arterial pressure by cardiac output (in liters/minutes). Cardiac output was calculated after directly measuring ejection time (in milliseconds) from the pulse waveform and including heart rate, height, age, and body surface area (in square millimeters). These estimates have been shown to be comparable to corresponding findings using direct invasive techniques (10), with high degrees of correlation and high reproducibility in repeated measures (11, 12).

Because the estimates of large arterial elasticity and small arterial elasticity were calculated based on measures including mean arterial blood pressure, heart rate, age, weight, and height, easily obtained physical measures that may be associated with hypertension, we performed 2 sensitivity analyses in an attempt to isolate the information given by the pulse waveform only. Because these values estimate large arterial elasticity and small arterial elasticity only by estimating systemic vascular resistance, in our first sensitivity analysis, we multiplied large arterial elasticity and small arterial elasticity by systemic vascular resistance to isolate the information from the pulse waveform only. In our second sensitivity analysis, we constructed a model adjusting for age, gender, race/ethnicity, income, education, diabetes, height, weight, heart rate, pulse pressure, C-reactive protein, urine albumin/creatinine ratio, and cystatin C. This procedure was performed to adjust for variables included in the formula to estimate elasticity.

The magnetic resonance imaging (MRI) aortic distensibility index was calculated by assessing the diameter of the aorta at end systole and end diastole using MRI (1.5 T whole-body MRI systems, Signa CV/i or Signa LX; General Electric Healthcare, Chalfont St. Giles, United Kingdom) of the ascending aorta. Aortic wall measurements were performed by using FLOW software (Medis, Leiden, the Netherlands). A detailed description of the protocol has been previously published (13, 14). Briefly, these measures were incorporated into the following equation to estimate aortic distensibility throughout the cardiac cycle: aortic distensibility = [(maximum aortic cross-sectional area − minimum aortic cross-sectional area)/minimum area]/pulse pressure. Pulse pressure used was the average pulse pressure of measures immediately before and after the MRI examination in the supine position.

**Covariates**

Age, gender, race/ethnicity, socioeconomic status (i.e., income, education, occupation), past or present smoking, and diagnosed diabetes were ascertained by questionnaire at the baseline visit. Height and weight were measured with participants wearing light clothing and no shoes. Body
mass index was calculated as weight in kilograms divided by height in meters squared. Fasting blood was collected and stored at -70°F (-56.7°C) until needed for the appropriate assays, including high density lipoprotein cholesterol, triglycerides, glucose, and C-reactive protein. Low density lipoprotein cholesterol was calculated by using the Friedewald equation. Serum creatinine was measured by rate reflectance spectrophotometry using thin film adaptation of the creatinine amidinohydrolase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, New York) at the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center (Minneapolis, Minnesota). Cystatin C was measured by using a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring Inc., Deerfield, Illinois). Estimated glomerular filtration rate was calculated by using the Modification of Diet in Renal Disease equation (15) for creatinine and the equation 76.7 × cystatin C⁻¹.¹⁹ for cystatin C (16). Urine albumin and creatinine were measured by nephelometry and the rate Jaffe reaction, respectively. A urine albumin to creatinine ratio was calculated, and a ratio of ≥30 mg/g was defined as albuminuria.

Statistical analysis

First, we evaluated sociodemographic and clinical characteristics of the study cohort. We then used Poisson (log-link) regression models to study the association of subclinical vascular changes and incident hypertension. We modeled the incidence rate ratio of hypertension as a function of each subclinical measure of vascular dysfunction with robust variance estimation and an offset for the log of follow-up time. Risk time was calculated as elapsed time from baseline to the fourth MESA examination, unless a participant either developed hypertension or was lost to follow-up at the time of the second or third MESA examination, in which case risk time was calculated as elapsed time from baseline to the second or third examination. We calculated unadjusted hypertension rates as the number of events divided by the person-years at risk and then examined their association with each of the vascular measures.

The primary predictors were examined as continuous variables (per standard deviation or per doubling for coronary artery calcification) and were also categorized into quintiles based on prior literature (9, 17–20). We used nested models, with the first model adjusted for sociodemographic variables: age, gender, and self-reported race/ethnicity. The second model adjusted for age, gender, race/ethnicity, income, education, diabetes, body mass index, C-reactive protein, urine albumin:creatinine ratio, cystatin C, and baseline systolic blood pressure. These variables were chosen a priori based on available literature on risk factors for hypertension (21).

RESULTS

Study cohort

Among the 2,512 MESA participants in these analyses, the mean age of our cohort was 58 years (standard deviation, 10), 19% had an income of less than $20,000 per year, and 58% had less than a college education. Approximately 48% (n = 1,215) were either past or current smokers, 143 (6%) had diabetes, and 123 (5%) had chronic kidney disease, which was defined as estimated glomerular filtration rate <60 mL/minute per 1.73 m² per the Modification of Diet in Renal Disease. Characteristics of study participants are detailed in Table 1.

We compared baseline participant characteristics with those of the 131 participants who did not return for any follow-up visits. Age, gender, baseline blood pressure, diabetes, body mass index, and cystatin C levels were similar. Those lost to follow-up were more likely to be of Hispanic origin.

Incident hypertension

Overall, 545 cases of incident hypertension were identified among the 2,512 participants, corresponding to 22% of the cohort. Forty percent (n = 218) were identified by high blood pressure alone, and 55% (n = 302) were identified by the use of a new antihypertensive medication alone. Mean follow-up time was 4.3 years (standard deviation, 1.1).

Structural vascular measures and incident hypertension

Increased coronary artery calcification was associated with incident hypertension in models adjusted for age, gender, and race/ethnicity, starting at a coronary artery calcification score of >30 (Table 2). However, this association was attenuated after further adjustment.

Increased maximum common carotid intima-media thickness was significantly and incrementally associated with incident hypertension starting at the third quintile after adjustment for age, gender, and race/ethnicity. This association was significant after full adjustment starting at the fourth quintile. Those in the fifth quintile of common carotid intima-media thickness were at an almost 2-fold risk of incident hypertension (Table 3).

Functional vascular measures and incident hypertension

Decreased aortic distensibility and decreased large and small arterial elasticity were significantly associated with increased risk of incident hypertension. The magnitude of these associations varied by vessel caliber.

Lower aortic distensibility was also associated with increased risk of hypertension. In analyses adjusted for age, gender, and race/ethnicity, risk of incident hypertension increased with lower distensibility. In the fully adjusted model, a graded association persisted, but only those with the lowest aortic distensibility (i.e., the highest aortic stiffness) were at higher risk of developing hypertension (Table 4).

Lower large arterial elasticity was also associated with incident hypertension, but this association was significant only for those in the fifth quintile (lowest elasticity) compared with those with the highest large arterial弹性.
Table 1. Characteristics of 2,512 MESA Study Cohort Participants Without Prevalent Hypertension at Baseline, United States, 2000–2007

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>%</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>561</td>
<td>54</td>
<td>6.2 (1.9)</td>
</tr>
<tr>
<td>Female</td>
<td>1,368</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1,114</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Chinese American</td>
<td>347</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>467</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>584</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Income group, $</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20,000</td>
<td>458</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>20,000–34,999</td>
<td>465</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>35,000–49,999</td>
<td>373</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>50,000–99,999</td>
<td>734</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>≥100,000</td>
<td>434</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Education ≤college</td>
<td>1,460</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>No health insurance</td>
<td>272</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>376</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Current alcohol consumption</td>
<td>1,531</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>145</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>234</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
<td>27.0 (5.1)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>110</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>67</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>119</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>52</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>122</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>1.5</td>
<td>0.7, 3.6</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.93</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Cystatin C, mg/L</td>
<td>0.84</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>MDRD eGFR, mL/minute per 1.73 m²</td>
<td>81.4</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td>Cystatin C eGFR, mL/minute</td>
<td>98.6</td>
<td>20.4</td>
<td></td>
</tr>
<tr>
<td>Urine albumin/creatinine ratio, mg/g</td>
<td>4.1</td>
<td>2.9, 6.6</td>
<td></td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen (among females)</td>
<td>362</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>NSAIDs and/or COX₂ inhibitors</td>
<td>110</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Thyroid agents</td>
<td>151</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: COX₂, cyclooxygenase-2; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; MDRD, Modification of Diet in Renal Disease; MESA, Multi-Ethnic Study of Atherosclerosis; NSAIDs, nonsteroidal antiinflammatory drugs; SD, standard deviation.

In unadjusted and adjusted analyses, lower small arterial elasticity was significantly and incrementally associated with incident hypertension even at the second quintile. Those in the fifth quintile (lowest elasticity) had an almost 3-fold risk of developing hypertension compared with those with the highest elasticity levels (Table 4). When we modeled our predictor as small arterial elasticity × systemic vascular resistance, the findings were not materially different.

Sensitivity analyses

To avoid case misclassification by including participants who may have begun using an antihypertensive drug for an indication other than hypertension, we performed a sensitivity analysis as follows: we reassigned to “noncase” status those who were identified as having hypertension because they used an antihypertensive medication alone (angiotensin-converting enzyme/angiotensin receptor blockers) AND either had 1) diabetes at baseline or follow-up prior to hypertension diagnosis and chronic kidney disease (estimated glomerular filtration rate <60 mL/minute per 1.73 m²) at baseline or 2) an adverse cardiovascular event during the follow-up period and prior to their hypertension diagnosis (n = 82). The findings were not significantly different.

Another sensitivity analysis of the whole cohort was performed for the elasticity measures by constructing a model adjusting for age, gender, race/ethnicity, income, education, diabetes, height, weight, heart rate, pulse pressure, C-reactive protein, urine albumin/creatinine ratio, and cystatin C. The results were not materially different.

DISCUSSION

Hypertension is a costly public health problem with a large burden of disease complications, including cardiovascular disease, chronic kidney disease, and increased mortality (22). However, the pathogenesis of essential hypertension is not known. In these analyses, we found that structural measures (higher common carotid intima-media thickness by ultrasound) and functional measures, lower aortic distensibility by MRI, and lower large and small arterial elasticity by pulse contour analysis are independent predictors of incident hypertension. Most importantly, we found that the strength of these associations varied significantly by vessel caliber, with the strongest associations observed for the index relating to the pool of small arteries. These findings suggest that subclinical vascular abnormalities present before the onset of hypertension may be important in the pathway of development of hypertension.

Our findings confirm prior findings that subclinical measures of central stiffness predict incident hypertension (7, 23, 24). Increased pulse wave velocity (a measure of central stiffness) predicted hypertension among only those participants followed up for more than 4 years in the Baltimore Longitudinal Study of Aging. Dernellis and Panaretou (23) found that aortic stiffness, measured by echocardiography, was associated with incident hypertension in a Greek cohort. Moreover, Liao et al. (24) found that arterial stiffness...
### Table 2. Association of Coronary Artery Calcification With Incident Hypertension Among MESA Participants, United States, 2000–2007

<table>
<thead>
<tr>
<th>Baseline Group of Coronary Artery Calcification, Agatston units</th>
<th>No.</th>
<th>No. of Cases</th>
<th>Incidence Rate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model 1&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IRR</td>
<td>IRR</td>
</tr>
<tr>
<td>0</td>
<td>1,593</td>
<td>284</td>
<td>4.0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1–29</td>
<td>354</td>
<td>90</td>
<td>6.1</td>
<td>1.26 0.99, 1.59</td>
<td>1.17 0.92, 1.47</td>
</tr>
<tr>
<td>30–99</td>
<td>216</td>
<td>63</td>
<td>7.0</td>
<td>1.35 1.04, 1.75</td>
<td>1.20 0.92, 1.56</td>
</tr>
<tr>
<td>100–399</td>
<td>238</td>
<td>67</td>
<td>7.0</td>
<td>1.35 1.02, 1.77</td>
<td>1.05 0.76, 1.40</td>
</tr>
<tr>
<td>≥400</td>
<td>111</td>
<td>41</td>
<td>9.7</td>
<td>1.59 1.12, 2.25</td>
<td>1.26 0.90, 1.77</td>
</tr>
<tr>
<td>Per doubling&lt;sup&gt;d&lt;/sup&gt;</td>
<td>919</td>
<td>251</td>
<td>6.9</td>
<td>1.04 0.99, 1.09</td>
<td>1.01 0.96, 1.06</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; MESA, Multi-Ethnic Study of Atherosclerosis.

<sup>a</sup> Per 100 person-years.

<sup>b</sup> Adjusted for age, gender, and race/ethnicity.

<sup>c</sup> Adjusted for age, race/ethnicity, gender, income, education, diabetes, body mass index, ln(C-reactive protein), ln(albumin/creatinine ratio), cystatin C, and baseline systolic blood pressure.

<sup>d</sup> Includes those with a baseline coronary artery calcification score of >0.

measured by ultrasound of the left common carotid artery was associated with hypertension defined as ≥160/95 mm Hg, which already represents stage II hypertension (22), or the use of an antihypertensive medication. Our study extends these findings to both structural and functional measures of subclinical vascular disease in a large multiethnic cohort.

It is noteworthy that, in our study, the strength of the associations varied by vessel caliber. Even small changes in small arterial elasticity (the second quintile) were independently associated with hypertension, whereas only the highest quintiles of large arterial elasticity and aortic distensibility had independent associations. It is possible that the small arteries, which represent the oscillatory compliance of the vascular tree, are uniquely important in the development and initiation of hypertension, relative to the vascular stiffness and atherosclerotic plaque deposition of the larger vessels.

The fact that increased coronary artery calcification was not associated with incident hypertension after adjustment for comorbidities and inflammation suggests that deposition of calcium may play a less important, independent role in the incidence of hypertension than do other changes in the endothelium that affect function or structure of arteries. However, it is also possible that vascular calcium is an important contributor to hypertension only at much higher levels than those observed in MESA.

Our study is novel in that it includes different techniques to measure subclinical cardiovascular disease (ultrasound, MRI, and pulse contour analysis), which significantly

### Table 3. Association of Common Carotid Intima-Media Thickness (mm) With Incident Hypertension Among MESA Participants, United States, 2000–2007

<table>
<thead>
<tr>
<th>Baseline Group of Maximum Common Carotid Intima-Media Thickness, mm&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No.</th>
<th>No. of Cases</th>
<th>Incidence Rate&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Model 1&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IRR</td>
<td>IRR</td>
</tr>
<tr>
<td>0.44–0.67</td>
<td>508</td>
<td>50</td>
<td>2.2</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>0.67–0.75</td>
<td>502</td>
<td>66</td>
<td>2.9</td>
<td>1.21 0.85, 1.73</td>
<td>1.10 0.77, 1.56</td>
</tr>
<tr>
<td>0.75–0.83</td>
<td>496</td>
<td>96</td>
<td>4.5</td>
<td>1.73 1.24, 2.43</td>
<td>1.33 0.95, 1.87</td>
</tr>
<tr>
<td>0.83–0.93</td>
<td>490</td>
<td>142</td>
<td>6.9</td>
<td>2.48 1.79, 3.42</td>
<td>1.78 1.28, 2.46</td>
</tr>
<tr>
<td>0.93–2.16</td>
<td>498</td>
<td>185</td>
<td>9.4</td>
<td>2.93 2.10, 4.08</td>
<td>1.80 1.28, 2.53</td>
</tr>
<tr>
<td>Per 1 SD</td>
<td>2,494</td>
<td>539</td>
<td>5.0</td>
<td>1.36 1.24, 1.48</td>
<td>1.22 1.12, 1.32</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; MESA, Multi-Ethnic Study of Atherosclerosis; SD, standard deviation.

<sup>a</sup> Categories overlap because all values were rounded to 2 decimal places.

<sup>b</sup> Per 100 person-years.

<sup>c</sup> Adjusted for age, gender, and race/ethnicity.

<sup>d</sup> Adjusted for age, race/ethnicity, gender, income, education, diabetes, body mass index, ln(C-reactive protein), ln(albumin/creatinine ratio), cystatin C, and baseline systolic blood pressure.
Table 4. Association of Functional Vascular Measures With Incident Hypertension Among MESA Participants, United States, 2000–2007

<table>
<thead>
<tr>
<th>Baseline Group*</th>
<th>No.</th>
<th>No. of Cases</th>
<th>Incidence Rateb</th>
<th>Model 1c</th>
<th>Model 2d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IRR 95% CI</td>
<td>IRR 95% CI</td>
</tr>
<tr>
<td>Aortic distensibility, mm Hg⁻¹ x 10³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.05–24.2</td>
<td>289</td>
<td>26</td>
<td>1.9</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2.29–3.05</td>
<td>289</td>
<td>41</td>
<td>3.2</td>
<td>1.41</td>
<td>0.87, 2.28</td>
</tr>
<tr>
<td>1.72–2.29</td>
<td>289</td>
<td>60</td>
<td>4.8</td>
<td>1.99</td>
<td>1.26, 3.14</td>
</tr>
<tr>
<td>1.24–1.71</td>
<td>289</td>
<td>67</td>
<td>5.4</td>
<td>1.95</td>
<td>1.22, 3.09</td>
</tr>
<tr>
<td>0–1.24</td>
<td>290</td>
<td>95</td>
<td>8.1</td>
<td>2.61</td>
<td>1.65, 4.15</td>
</tr>
<tr>
<td>Per −1 SD</td>
<td>1,446</td>
<td>289</td>
<td>4.6</td>
<td>1.53</td>
<td>1.25, 1.88</td>
</tr>
<tr>
<td>Large artery elasticity, mL/mm Hg x 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.0–55.8</td>
<td>467</td>
<td>72</td>
<td>3.4</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>15.8–19.0</td>
<td>467</td>
<td>69</td>
<td>3.3</td>
<td>1.04</td>
<td>0.76, 1.43</td>
</tr>
<tr>
<td>13.3–15.8</td>
<td>467</td>
<td>84</td>
<td>4.1</td>
<td>1.22</td>
<td>0.90, 1.65</td>
</tr>
<tr>
<td>10.8–13.3</td>
<td>467</td>
<td>116</td>
<td>5.7</td>
<td>1.67</td>
<td>1.24, 2.24</td>
</tr>
<tr>
<td>3.3–10.8</td>
<td>468</td>
<td>166</td>
<td>9.0</td>
<td>2.25</td>
<td>1.67, 3.03</td>
</tr>
<tr>
<td>Per −1 SD</td>
<td>2,336</td>
<td>507</td>
<td>5.0</td>
<td>1.34</td>
<td>1.17, 1.54</td>
</tr>
<tr>
<td>Small artery elasticity, mL/mm Hg x 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.86–17.32</td>
<td>467</td>
<td>35</td>
<td>1.6</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>5.67–7.86</td>
<td>467</td>
<td>87</td>
<td>4.2</td>
<td>2.48</td>
<td>1.70, 3.62</td>
</tr>
<tr>
<td>4.06–5.67</td>
<td>467</td>
<td>116</td>
<td>5.8</td>
<td>3.17</td>
<td>2.19, 4.60</td>
</tr>
<tr>
<td>2.70–4.06</td>
<td>467</td>
<td>123</td>
<td>6.2</td>
<td>3.34</td>
<td>2.28, 4.87</td>
</tr>
<tr>
<td>0.81–2.70</td>
<td>468</td>
<td>146</td>
<td>7.8</td>
<td>3.68</td>
<td>2.52, 5.38</td>
</tr>
<tr>
<td>Per −1 SD</td>
<td>2,336</td>
<td>507</td>
<td>5.0</td>
<td>1.57</td>
<td>1.40, 1.75</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; MESA, Multi-Ethnic Study of Atherosclerosis; SD, standard deviation.

a Some categories overlap because all values were rounded to 2 decimal places.
b Rate per 100 person-years.
c Adjusted for age, gender, and race/ethnicity.
d Adjusted for age, race/ethnicity, gender, income, education, diabetes, body mass index, ln(C-reactive protein), ln(albumin:creatinine ratio), cystatin C, and baseline systolic blood pressure.

strengthens our conclusions and reduces the bias that may occur from using only one technique. Moreover, these measures have been associated with adverse events. For example, common carotid intima-media thickness has been shown to predict adverse cardiovascular events (18, 25), and lower arterial elasticity has been found to be associated with cardiovascular risk factors in healthy adults (26), with early kidney dysfunction (20), and with cardiovascular disease (27). In addition, this large, multiethnic cohort is fairly representative of the US population, free of cardiovascular disease at baseline. To minimize noise from those close to the threshold, we also included only those participants with blood pressures of <130/80 mm Hg.

Our study has certain limitations. We did not have invasive measures of endothelial function. We used pulse contour analysis to estimate large and small arterial elasticity. This method makes certain assumptions about the arterial tree when using the modified Windkessel model of circulation. Although some studies have suggested low reliability of the estimates, which may reduce the validity of the methodology (28), this method has been shown to correlate with invasive measures of arterial compliance, and it has high reproducibility (10, 11). Moreover, lower elasticity by this measure has been associated with higher prevalence of cardiovascular risk factors among young adults (26), with early kidney dysfunction (20), and reported adverse cardiovascular events in one US cohort (27). We ascertained some cases by the use of a newly prescribed antihypertensive medication, which may result in misclassification due to other indications for some of these medications, including the report of subclinical abnormalities to treating physicians. Misclassification may also have occurred if a participant started and then stopped using a medication before a follow-up visit. However, our sensitivity analyses reclassifying diabetics, those with kidney disease, or those who had an adverse cardiovascular event during follow-up showed similar results.

In summary, we found that structural and functional measures of subclinical vascular disease are independent predictors of incident hypertension in a multiethnic cohort and that small arterial elasticity is the earliest predictor. Our findings are an important step in elucidating possible
pathways for the development of idiopathic hypertension. Future studies should focus on elucidating whether these measures may be cost-effective in identifying persons at risk of hypertension and who may benefit from earlier treatment.

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Conflict of interest: none declared.

REFERENCES


Most attempts to identify individuals at risk for cardiovascular morbid events have involved screening for risk factors. These traditional risk factors do not identify the underlying atherosclerotic disease nor assess the severity of disease in individual patients. The goal for identifying a marker or markers for early cardiovascular disease that could serve as a surrogate for disease progression and ultimate morbid events is to improve the precision for early detection and treatment. The authors utilize a variety of techniques, which consist of 7 vascular tests (large and small artery elasticity, resting blood pressure and exercise blood pressure response, optic fundus photography, carotid intimal-media thickness, and microalbuminuria) and 3 cardiac tests [electrocardiography, [N-terminal pro-] B-type natriuretic peptide, and left ventricular ultrasonography]. Each test is individually scored, and the total disease score is the sum of all the test scores. A study is ongoing to compare the new disease score vs the classical Framingham risk estimate in the prediction of cardiovascular events.


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Atherosclerosis is a devastating disease because it is the most frequent cause of myocardial infarction, stroke, renal failure, peripheral vascular disease, and perhaps even dementia. Thus, the complications of atherosclerosis have a profound impact on quality of life, life expectancy, and health care costs. Most attempts to identify individuals at risk for cardiovascular (CV) morbid events have involved screening for risk factors. These risk factors have included smoking, blood pressure (BP), cholesterol elevation, obesity, physical inactivity, and other well-established targets for intervention. They are not disease markers, but rather phenomena statistically associated with disease. Data from epidemiologic studies and intervention trials support the benefit on morbid events of aggressive attempts to modify these risk factors. When dealing with a healthy population, however, the efficacy of these interventions may be modest and the number needed to treat to prevent a morbid event is considerable.

EARLY VASCULAR DISEASE DETECTION

By identifying individuals with evidence of early CV disease (CVD) before the occurrence of symptoms or morbid events, one should be able to identify a population far more likely to progress than the general population who may have no early disease. By aggressive intervention in this population, first morbid events may potentially be delayed or prevented and the result should be a healthier, asymptomatic population who can anticipate a normal life expectancy. This approach may be viewed as a variation of secondary prevention, because it is designed to identify disease before it becomes clinically manifested and to intervene before symptoms occur.

The fact that morbidity and mortality events do not serve as a sensitive or specific guide to
disease progression renders surrogate markers an important potential contributor to understanding the natural history of disease and its response to therapeutic intervention. Some potential surrogate markers progress with time; therefore, an alteration in the surrogate may be a slowing of the time-dependent progression rather than necessarily a normalization of the surrogate. This concept of progression and the trajectory of time-dependent structural or functional measures as predictors of subsequent events are important in understanding the value of certain surrogate markers.\textsuperscript{11,12}

Atherosclerotic disease is usually viewed as the development of lesions in the wall of conduit arteries that lead to obstruction to blood flow and/or clot formation that impedes perfusion. The term atherothrombotic disease has recently evolved to clarify the mechanistic understanding that lipid-containing plaques and thrombotic events go hand in hand and the underlying process is endothelial dysfunction.\textsuperscript{13-15}

**DIAGNOSTIC TESTS**

In considering the ways to identify functional and structural abnormalities of the vasculature and heart, we use a variety of techniques that are complimentary. This allows us to establish an individual's absolute CVD score.\textsuperscript{16,17}

**Vascular Tests**

**Large and Small Artery Elasticity.** BP is one of the major determinants of CV risk. In clinical practice, 2 specific and arbitrary points of the BP curve, peak systolic and end-diastolic BP, are used to define CV risk. Traditionally, the BP curve has been considered to contain a steady component, mean BP, and a pulsatile component, the pulse pressure. The growing importance of pulsatile pressure indices paralleled the notion that not only increases in systemic vascular resistance but also increases in arterial stiffness are important in the pathophysiology of hypertension.\textsuperscript{18} Information about the interaction between the left ventricle and the physical impact of the arterial circulation can be derived by the descriptive and quantitative analysis of the arterial pressure pulse waveform.\textsuperscript{19}

Although the large conduit arteries are the target for atherosclerotic plaque formation, the endothelial dysfunction, which precedes such plaque development, involves the small arteries as well as the conduit arteries. In the setting of endothelial dysfunction, a reduction in nitric oxide bioactivity will result in a reduction in caliber of the small arteries and an increase in their tone. From the vascular standpoint, the reduction in caliber may lead to an increase in systemic vascular resistance; the alteration in tone alters the oscillations or reflected waves generated in the arterial bed that influence the contour of the arterial pressure waveform.\textsuperscript{20} By noninvasively assessing the waveform, one can identify this alteration in the small artery function or structure by an alteration in the diastolic pressure decay. This pulse contour analysis methodology has now been applied to a wide range of patient groups and can be considered as a potential marker for the risk of future CV events.\textsuperscript{21}

Conduit artery disease exists long before symptoms develop or morbid events occur. Aging and atherosclerosis exert their conduit artery effects by thickening the wall as well as eventually inducing luminal plaques. Measurements of arterial stiffness provide useful information regarding the health of the arterial vasculature. Large artery stiffness, as assessed by pulse pressure and pulse wave velocity, is age-dependent and reflects structural alterations in the conduit arteries that are accelerated by hypertension and atherosclerosis. Methodology is now available to use arterial stiffness as a marker for premature disease and to track changes in stiffness as a guide to progression of disease and the impact of therapy.\textsuperscript{22}

**Sitting BP.** BP is a well-established risk marker.\textsuperscript{23} An important number of CV events that occur in our society, however, are experienced in individuals whose BP is not above the normal range. The evidence that BP is linearly related to the risk of morbid CV events is remarkably strong.\textsuperscript{18}

The relationship between BP and stroke is more pronounced than it is with ischemic heart disease and other vascular events. Because the risk and benefit appear to be linear, the absolute BP level at which treatment should be instituted remains controversial. Recent guidelines that emphasize BPs >120/80 mm Hg as a risk (prehypertension) reflect evolving and differing views.\textsuperscript{24} The choice of what phase of the pulsatile pressure to focus on and on what conditions (rest or stress) should exist at the time the measurements are made remain controversial.

The value of BP as a marker for risk and as a target for therapy in large population studies does not address its possible inadequate precision in monitoring individual patients. More precision in methodology and better means of separating high-risk from low-risk individuals may be necessary to make BP a more useful tool in clinical practice. Whether the ultimate screening tool will be resting BP, stress-induced pressure, or some additional...
measure of vascular health, to augment data from the BP readings will require further study.

Treadmill Exercise BP. During exertion, a rise in cardiac output is buffered by a reduction in systemic vascular resistance that modulates the rise in BP. In the setting of endothelial dysfunction with an increase in vascular tone, the reduction in systemic vascular resistance may be impaired or delayed, thus resulting in an accelerated rise in BP during exertion. This mechanistic possibility has provided the opportunity to monitor the BP rise during a fixed treadmill workload for 3 minutes as a guide to the functional integrity of the CV system. Early data suggest that the rise in BP and its ultimate maximum provide more insight than resting BP alone in identifying early vascular disease. Abnormal BP response to exercise has been related to an increased risk of developing hypertension and also to a higher risk of stroke. Moreover, exercise-induced hypertension is associated with decreased CV event-free survival.

Optic Fundus Photography. Visualizing the vasculature of the retina provides opportunities for a direct assessment of the small arteries. Funduscopic examination provides a window into the small vessels. Changes in the arteriovenous crossings in the retina can reveal the effect of thickening of the arteriolar wall and impact on the associated venule. These changes in arteriovenous crossing can then help to identify the early vascular disease that may eventually lead to morbid events. New nonmydriatic cameras facilitate collection of digital images that allow rigorous assessment of the arterial/venous crossings and arterial architecture.

Measurement of Carotid Intima-Media Thickness. Considerable data exist on the rate of increase of intimal-media thickness (IMT) in the carotid artery with age and its abnormality with disease states. Early studies confirm that this methodology can be employed in a screening mode and that it has the power to detect disease long before symptoms develop. Carotid IMT is a direct measure of the status of the vascular wall; abnormalities are not a surrogate but a direct measure of atherosclerotic and arteriosclerotic processes. The degree of carotid disease that appears to be of prognostic value is much subtler, requiring meticulous and detailed measurements of IMT through B-mode ultrasound. Carotid atherosclerosis has been correlated with risk factors associated with the development of atherosclerosis in any vascular bed. Prevalence of coronary artery disease, cerebrovascular disease, and peripheral vascular disease increased in parallel with increasing IMT. Accordingly, the finding of a significant association between a quantitative abnormality of the carotid IMT and evidence of established coronary artery disease is reassuring and is concordant with the principle that atherosclerosis is a diffuse disease. Detection in one bed implies a high likelihood of association with atherosclerosis in a different bed. Even more compelling is evidence showing that carotid atheroma is a predictor of vascular events and that it is useful for risk stratification. It is clear that IMT is sex- and age-related. The establishment of standards for performance and interpretation of carotid IMT is critical for further utilization of this technique. A normal age-dependent range for quantitative assessment must be established for geographic, sex, and ethnic groups.

Microalbuminuria. Microalbuminuria has been recognized as a marker for small artery disease in the kidneys that results in leakage of albumin into the urine. This measurement has provided an additional marker for early vascular disease and appears to be sensitive in identifying high-risk patients who have not yet sustained morbid events. The appearance of trace amounts (microalbuminuria, 30-300 mg/d) and larger amounts (frank proteinuria, >1 g/d) of albumin are associated with an increased risk of renal failure, heart disease, stroke, and CV mortality. Albumin excretion is best expressed as a function of creatinine or as a clearance. Timed 24-hour urine collection has been the gold standard for quantifying urinary protein excretion but is limited by poor compliance and a cumbersome collection technique. Modifications of 24-hour collection to include shorter collection time (12- or 4-hour collection after a standard water load or first morning void) have yielded to the simplicity of measuring a spot protein/creatinine ratio. Ultimately, the spot protein/creatinine ratio provides an approximation of the level of proteinuria. Any standard laboratory will perform this analysis.

Cardiac Tests

Electrocardiography. Electrocardiography (ECG) is still considered a screening tool for arrhythmias, conduction abnormalities, myocardial ischemia, old myocardial infarction, and left ventricular hypertrophy (LVH). The best-documented ECG-LVH criteria are Sokolow-Lyon and Cornell Voltage Duration Product. It has been demonstrated that
Table. Rasmussen Disease Score With the Scoring of Each Individual Test

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal (Score = 0)</th>
<th>Borderline (Score = 1)</th>
<th>Abnormal (Score = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large artery elasticity</td>
<td>Age- and sex-dependent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small artery elasticity</td>
<td>Age- and sex-dependent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting BP, mm Hg</td>
<td>SBP &lt;130 and DBP &lt;85</td>
<td>SBP 130–139 or DBP 80–89</td>
<td>SBP ≥140 or DBP ≥90</td>
</tr>
<tr>
<td>Exercise BP, mm Hg</td>
<td>SBP rise &gt;30 and SBP ≤169</td>
<td>SBP rise 130–179 or SBP 170–179</td>
<td>SBP rise ≥40 or SBP ≥180</td>
</tr>
<tr>
<td>Retinal vasculature</td>
<td>A/V ratio &gt;3:5</td>
<td>A/V ratio ≤3:5 or mild A/V crossing</td>
<td>A/V ratio ≤1.2 or A/V nicking crossing</td>
</tr>
<tr>
<td>Carotid IMT</td>
<td>Age- and sex-dependent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microlbaminuria, mg/mmol</td>
<td>≤0.60</td>
<td>0.61–0.99</td>
<td>≥1.00</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>No abnormalities</td>
<td>Non-specific abnormalities</td>
<td>Diagnostic abnormalities</td>
</tr>
<tr>
<td>LV ultrasonography, LV mass</td>
<td>≤120 g/m²</td>
<td>120–129 g/m²</td>
<td>≥130 g/m²</td>
</tr>
<tr>
<td>index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP, pg/dL</td>
<td>≤50</td>
<td>50–99</td>
<td>≥100</td>
</tr>
</tbody>
</table>

Abbreviations: A/V, arteriovenous; BNP, B-type natriuretic peptide; BP, blood pressure; DBP, diastolic BP; IMT, intima-media thickness; LV, left ventricular; SBP, systolic BP.

nonspecific (minor) ST-segment depression and/or T-wave abnormalities have a long-term prognostic impact for coronary heart disease and CVD death in middle-aged women and men and can be considered markers of heightened coronary heart disease and CVD risk.37

Left Ventricular Ultrasonography. Cardiac screening is aimed at a different chain of events. Asymptomatic left ventricular dysfunction may exist before the clinical syndrome of heart failure appears. As a risk indicator for future CV events, LVH is strong and independent and second only to age in predictive power. Finally, there is documentation for both ECG-LVH and echocardiographic LVH that reversal has an independent prognostic value, independent of therapy and BP.38 BP lowering with all of the available antihypertensive agents, except vasodilators, has resulted in reversal of LVH. That LVH has become a validated surrogate end point for the treatment of hypertension has clinical implications. Many new diagnostic advances, however, may further refine this valuable tool.

(N-Terminal Pro-) B-Type Natriuretic Peptide. The plasma level of this cardiac hormone has emerged as a sensitive and specific guide to the presence of heart failure in symptomatic patients and to left ventricular dysfunction in asymptomatic patients. The concentration is a determinant of adverse outcome in heart failure and appears to correlate with a favorable therapeutic effect on outcome. As such, plasma (N-terminal pro-) B-type natriuretic peptide may ultimately prove to be a reliable surrogate marker for the severity of left ventricular remodeling and perhaps a sensitive and specific marker for the progression of cardiac disease in ischemic and nonischemic forms of cardiomyopathy.39

EARLY CVD SCORE VS RISK SCORE
We have developed a global model that consists of composite disease markers called the Rasmussen Disease Score, named for the benefactor of the Rasmussen Center for Cardiovascular Disease Prevention. The history, physical examination, and laboratory testing in the center are carried out by a nurse practitioner and a medical technologist. The total duration of the center visit is confined to 2 hours: 1 hour dedicated to extensive history, CV examination, and lifestyle discussion; and 1 hour to the testing procedures. The entire 2-hour screening takes place in one room, where all the necessary equipment is installed for the different measurements.

A cardiologist oversight includes chart and data review, report generation, and direct patient contact, only when indicated. Screening consists of modifiable disease contributor assessment. Our strategy has been to use a combination of 7 vascular and 3 cardiac tests to better define the presence of early disease. The basis for selecting the 10 tests has been discussed above. This approach requires a scoring system for the biological detection of early disease. The Table summarizes the Rasmussen Disease Score and the scoring of each test. Each of the 10 tests is scored as follows: 0 for normal, 1 for borderline abnormal, and 2 for abnormal. The total score for any individual may therefore range from 0 to 20.8 The additional information from the "risk contributors" assessment is then used to design a management strategy. We have now screened 1500 patients. One-third of this population has a Rasmussen Disease Score between 0
and 2 (low risk), one-third between 3 and 5, and one-third 6 and above, which is considered high risk. Tracking of events is also in process to evaluate this personalized disease score compared with the classical CV risk scores. At present, there is no proof that this type of screening will improve outcome over and above treating known risk factors; however, we are performing a study to compare the new disease score vs the classical Framingham risk estimate in the prediction of long-term CV events.

COST

The cost of testing in the Rasmussen Center has been reimbursed by private insurers, based on the current procedural terminology codes for individual tests. The reimbursement rate will likely vary depending on local reimbursement policies and specific insurance coverage.

CONCLUSIONS

Most attempts to identify individuals at risk for CV morbid events have involved screening for risk factors that are statistically associated with future cardiac and cerebrovascular events. This approach has resulted in several risk factor assessment scales that can identify groups with higher risk but may provide limited information about individual risk. Since the risk factors used are not necessarily disease markers, however, this approach does not provide insight as to how the risk factors are impacting the biologic target organs, the vasculature, and the heart. Screening tests, which identify early vascular and cardiac functional and structural abnormalities, may identify abnormalities in asymptomatic individuals without obvious risk factors for CVD. Bringing these techniques to so-called asymptomatic individuals who have not yet sustained CV events represents the challenge for the 21st century.

REFERENCES

Complementary Diagnostic Tests to Identify Individuals at Risk for Morbid CVD Events

- C1-Large and C2-Small Artery Stiffness
  - markers for disease, progression of disease, and impact of therapy
- Resting BP
- ECG
- Treadmill Exercise BP
- Optic Fundus Photography
- Measurement of Carotid IMT
- Microalbuminuria
- Left Ventricular Ultrasonography
- (N-Terminal Pro- ) B-Type Natriuretic Peptide

Duprez D, Cohn JN; Identifying Early Cardiovascular Disease to Target Candidates for Treatment, The Journal of Clinical Hypertension, 2008;10:226-231, (U of M) Ref: 284
Complementary
CVD Diagnostic Testing

- Resting BP
- Cholesterol (total, HDL, LDL, triglycerides)
- Fasting blood sugar
- hsCRP
- Microalbuminuria
- Homocysteine
- HbA1c
- BNP
- C1/C2
- ECG
- Exercise stress test
- BP response to treadmill exercise
- Holter monitoring
- ABPM
- IMT
- NICO
- Optic Fundus Photograph
- Echocardiogram
- Cardiac Autonomic Dysfunction
CARDIO 101/ 4-TEST PROCEDURE: EXAM ROOM

Introduction

1. Collect patient packet:
   a. Intake form: make sure you can read contact information.
   b. CV Early Detection sheet (Score sheet)
   c. Elasticity measurement sheet.
   d. Light blue file folder/ patient permanent file
   e. Blue file folder.
2. Greet patient and introduce yourself.
   a. Ask them to follow you to the scale.
   b. Show them the chair or countertop where they may place personal items.
   c. They may take off their shoes. If barefoot-disinfect scale before next patient.
   d. ** Make sure scale is set for pounds not kilograms.
   e. Have patient face away from scale to get height.

Exam Room Procedure

1. Bring patient to the exam room.
   a. Show them where to place their personal items (chair).
   b. Close curtain/ door to exam room.
   c. Pull out the stepstool (if applicable) and ask client to sit on exam table.
2. Explain testing procedure.
   a. Tell them you will be taking a series of 6 to 7 blood pressure readings.
   b. 1 to 2 will be while sitting.
   c. 2 will be while lying down.
      - The first blood pressure, I will be attaching the sensor/transducer.
      - Show sensor/transducer and tell them there are no needles.
      - Tell them it is placed over the radial artery in the wrist.
      - The next blood pressure will be taken as the sensor measures artery elasticity.
   d. 3 blood pressures will be part of the treadmill test.
      -one while standing.
      -one while exercising on the treadmill for 3 to 4 minutes.
      - one will be taken 1 minute post exercise.
   e. Tell patients they will get copies of their results and explanation before leaving.

CVProfilor

1. Apply appropriate size blood pressure cuff (b.p.) while patient is sitting.
   a. Make sure artery marker is over the brachial artery according to manufacturer’s recommendations.
b. Use proper sized cuff. See measurement markers on cuff.
   c. Wrap cuff firmly around upper arm and secure. Make sure 2 fingers can fit
      between the cuff and patient's arm.
2. Ask patient to place left arm on top of the bolster and pillow. Have palm facing up.
   a. Tell the patient to relax.
   b. Reach over and push the Measure Blood Pressure button on the screen.
   c. Push Start button to begin measurement.
   d. Record the b.p. result in the initial HR(heart rate) and BP(blood pressure) area on
      the CV HeartDetection Score sheet. (See sample sheet at end A).
3. Ask patient to lie down and get comfortable.
   a. If they have back problems, offer to get a pillow for under their legs.
   b. Make sure they relax and don't cross their legs.
4. On CVProfile screen, push Perform CV Profile.
   a. Type in Patient ID #__________ push next on screen.
   b. First Name ____________ push next on screen.
   c. Last Name ______________ push next on screen.
   d. Gender: choose male or female. Push next on screen.
   e. Birthdate: month, date, year. Record age on back of CV score sheet for later.
      **** Ask patient to verify their birthdate**** push next on screen.
   f. Record weight and push next on screen.
   g. Type in height and push next on screen.
   h. Push Finished to proceed to the next screen.

Medical History Screen

1. Inform the patient that you are required to ask the same questions again that they
   filled out on the intake form, but there will be one new one.
2. If they ask why, tell them that question #1, people can sometimes interpret that to
   mean family history, not pertaining to them personally.
   a. After each question, push next when done.
   b. Push finished when done with screen

*** If you key something incorrectly, use the arrow keys, or previous item to correct mistakes.
Push cancel only if you wish to start over. ***

Diagnostic Screen

1. Push continue to get the baseline blood pressure reading. Write results in the Lying
   Down Blood Pressure section on the CV score sheet.
2. Apply splint, sensor/transducer to patient's right arm, and adjust waveform and
   strength.
3. Explain to patient, they may blink, swallow, and breathe, but "no talking, or moving-
   just relax." Push the continue button.
4. Testing may take up to 5 minutes
5. Using patient's age, find where the C1 (large) and C2 (small) artery results fall on the
   Arterial Elasticity Measurement Chart.
   a. Run the test once if the results are normal, run 2 to 3 times if abnormal.
b. Average results together, if 2 or more runs done. Write in Arterial Elasticity section of score sheet.
c. When done, remove sensor and splint.
d. Have patient sit up, then remove blood pressure cuff.

_Treadmill Test_

1. Have the patient stand next to the treadmill. Place mobile/manual bp cuff on.
2. Take initial bp reading and pulse. Write results in the walking blood pressure response (pre-exercise) portion of the score sheet.
3. Ask patient to stand on the side rails of the treadmill.
4. Have patient attach clip end of safety line to their shirt, pocket, belt loop.
5. Explain that they will be walking at 2.3 mph at 7% incline. Ask if they want quick Speed or dial it up manually?
6. Tell them that at 2 minutes and 30 seconds, technician will position stethoscope chest piece in the antecubital space below the cuff.
7. At 2 minutes and 45 seconds, you will be pumping up the bp cuff to 200mmHg in order to read bp. at 3 minutes. Take manual pulse (may have to stop treadmill).
8. Record results in the exercise portion in the treadmill test.
9. Tell patient you are going to press ‘stop’ and the treadmill will slow down fast.
10. Disconnect safety line, and have patient stand right next to the treadmill. Time 1 Minute and take last bp and pulse.
11. Record on the score sheet under post-exercise.
12. Let patient know they can gather their things, wait in the waiting room and you will finish scoring their results.

13. Clean room, treadmill, replace exam paper and fill in paper work. Sanitize hands.
14. Take paperwork to administrative assistant and have them copy the following:
   a. CV Early Detection Score Sheet
   b. CV Profile report
   c. Place copies in patient take home pocket folder.
   d. Place originals in patient folder.
15. The Nurse Practitioner or Physician will explain the results.
16. Technician explains results in the absence of a Nurse Practitioner or Physician.
**CVProfile™ Report**

**ID#:**

**Name:**

**SSN:**

**Date:**

**Time:**

**Age:**

**Gender:**

**Height:**

**Weight:**

**BSArea:**

**Body Mass Index:**

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### Average Blood Pressure Waveform

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### PARAMETER | VALUE

| Systolic Blood Pressure  (mmHg) |
| Diastolic Blood Pressure  (mmHg) |
| Mean Arterial Blood Pressure  (mmHg) |
| Pulse Pressure  (mmHg) |
| Pulse Rate  (beats/min) |
| C1 – Large Artery Elasticity Index  (ml/mmHg x 10) |
| (Capacitive Arterial Compliance) |
| C2 – Small Artery Elasticity Index  (ml/mmHg x 100) |
| (Oscillatory or Reflective Arterial Compliance) |

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### MEDICAL HISTORY

| CV Disease: |
| CV Medications: |
| Diabetes: |
| Relatives CV Disease: |
| Tobacco: |
| Race: |

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### CLINICAL COMMENTS: