Preventing Cardiovascular Disease: Implications for Business and Industry

BY PAUL A. SOMMERS, PH.D.

Cardiovascular disease (CVD) claims more lives each year than the next four leading causes of death combined—more than the total of cancer, lower respiratory disease, accidents, and diabetes mellitus. The prevalence of CVD in the U.S. population in 2010 has been estimated by the American Heart Association (AHA) at 81.1 million individuals. Every day more than 2,300 die of CVD, which is an average of 1 person every 38 seconds and 1 of every 2.9 deaths. The estimated total direct and indirect costs of CVD to the American economy in 2010 will be $503.2 billion, up from $475.3 billion in 2009, according to the AHA.

Prevention-based worksite screening and health improvement programs are needed throughout business and industry.

The 2009 Towers Perrin survey data shows that total healthcare costs have increased by 33% since 2004, with the employee share increasing by 42 percent during the same period. (see Figure 1). CMS developed a 10-year projection (2009–2019) of the average annual health spending growth (6.1 percent) to outpace an average annual growth in the overall economy (4.4 percent). By 2019, national health spending is expected to reach $4.5 trillion and comprise 19.3 percent of GDP. Public spending is projected to grow faster on average than private spending (7.0 percent versus 5.2 percent, respectively) for 2009 through 2019. As a result of more rapid growth in public spending, the public share of total healthcare spending is expected to rise from 47 percent in 2008, exceed 50 percent by 2012, and then reach nearly 52 percent by 2019.

Prevention-based worksite screening and health improvement programs are needed throughout business and industry to quell the skyrocketing costs of health care for “preventable conditions” such as CVD. Although this need is not new, many efforts heretofore have failed to produce a more significant ROI because of the lack of a systematic evidence-based process used to identify candidates with early CVD who would benefit the most from intervention. The highest ROI occurs when health improvement programs include participants with the earliest evidence of CVD. In the past, many programs have selected participants based on symptoms as a reason to participate, and not the root causes of CVD.

Managing the risk factors associated with CVD does not get the job done. Instead, prevention programs that identify the earliest evidence of the disease, followed by direct intervention to stabilize or reverse it, are a top priority. The preventive medical literature is...
replete with company study after study demonstrating the significant health, emotional, and financial gains made by businesses from almost all sectors where worksite screening, wellness, and prevention programs have been established. To achieve the highest ROI possible, a goal should be to include a screening process that insures the identification and participation of individuals with early evidence of CVD.

As reported and summarized in 2008 by Don R. Powell, president of the American Institute for Preventive Medicine, the significant return on investment (ROI) results of worksite screening, wellness, and prevention-based programs span many manufacturing and service industries.5

Examples of the effects of worksite screening, wellness, and prevention-based programs vary by industry, where ROI ranges from $3 to $15 for each dollar spent, as seen in Table 1.

Powell further notes that researchers have looked at a large number of employee populations to determine the most common health risks. On the average, for every 100 workers in this country, 27 have cardiovascular disease, 24 have high blood pressure, 50 or more have high cholesterol, 26 are classified as being obese, 26 smoke, 10 are heavy drinkers, 50 don’t get adequate exercise, and 44 suffer from excessive levels of stress.6

Research conducted at the University of Michigan has shown that low-risk employees (those with one or two CVD risk factors) have lower costs for short-term disability, workers’ compensation, absence, and health care services, whereas high-risk employees (with five or more risk factors) have higher costs.7 (See Table 2.)

**Benefits of Early CVD Identification and Treatment**

The estimated prevalence of CVD by age and gender is illustrated by company personnel totals based upon the National Health and Nutrition Examination Survey (NHANES III) in Table 3.8

Burden of illness (BOI) costs include both direct medical and non-medical expenses related to any defined illness and need to be considered when measuring the effects of cardiovascular events. A case study was conducted by a health plan serving an employer group with 13,811 employees based in Minneapolis and St. Paul Minnesota.9 The purpose was to determine how healthcare expenses were being allocated as part of the employee benefit program and the impact of CVD classifications on total expenses.

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**Case Study Data**

<table>
<thead>
<tr>
<th>Burden of Illness Factors</th>
<th>Annual Costs (Millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Care Insurance Costs</td>
<td>$47.00 (56.00%)</td>
</tr>
<tr>
<td>Workers Compensation</td>
<td>5.10 (6.30%)</td>
</tr>
<tr>
<td>Long-term Disability</td>
<td>1.80 (2.20%)</td>
</tr>
<tr>
<td>Short-term Disability</td>
<td>0.24 (0.03%)</td>
</tr>
<tr>
<td>Dental Care Insurance Costs</td>
<td>3.90 (4.80%)</td>
</tr>
<tr>
<td>Employee Assistance Program (EAP)</td>
<td>36 (0.04%)</td>
</tr>
<tr>
<td>FTE Replacement</td>
<td>7.00 (8.60%)</td>
</tr>
<tr>
<td>Sick Leave</td>
<td>16.00 (20.00%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$81.40</strong></td>
</tr>
</tbody>
</table>

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**FIGURE 1**

**Healthcare Costs per Individual**

Total employee/employer health care costs: 2004 vs. 2009 (All plan types)

2004 Total Cost = $7,284

2009 Total Cost = $9,660

Source: Towers Perrin 2009 Health Care Cost Survey

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**Case Study (1997-1998)**

**Employer:** a Minneapolis/St. Paul area healthcare organization with 13,811 employees

**Total employer annual healthcare expenses:** $81,396,000 ($5,894 per employee)

**Direct medical and dental costs:** 62.8%

**Non-medical costs:** 37.2%

**Insurer:** At the time of study, insurer was part of the corporate healthcare organization

See “Case Study Data” for financial data.
The company’s wholly-owned insurance company managed the claims processing function. The cost of cardiovascular disease was measured in claims paid for CVD billing classifications—including heart attacks, strokes, heart failure, kidney failure, peripheral vascular disease, aneurysms, high blood pressure, and high cholesterol—totaled $70 million (19,223 cases at $3,641 per case). Health plan member compliance with physician office visits was retroactively measured and compared to actuarial tables demonstrating “best practice patient compliance” for each CVD diagnosis. The difference between best practice patient compliance and actual patient/employee compliance was compared to the number and costs of documented CVD events, i.e., acute MI; coronary revascularization; angina (documented); stroke; heart failure; and peripheral vascular disease. The analysis was based upon the assumption that increased office visits to reach the best practice patient compliance standards equate to less utilization of more-expensive hospital and emergency room services related to CVD events.

Follow-up evaluation indicated that early diagnosis, proper management, and consistent patient compliance reflected by keeping physician appointments could have minimally avoided at least 10 percent of the cardiovascular disease identified, conservatively saving $7 million annually.10

The Rasmussen Center Approach

Early Identification

Risk markers such as age, elevated BP, abnormal lipid profile, elevated glucose level, and abnormal level of inflammatory markers may correlate with the risk of cardiovascular events,11-14 much as the barometer may predict the likelihood of rain, but the first few raindrops are a far more sensitive and specific marker for raising the umbrella. Since potent interventions are now available to slow the progression of CVD,15-17 the need has increased for techniques that can detect the earliest evidence rather than the risk. This is the purpose of the Rasmussen Center service.

The Rasmussen Center for Cardiovascular Disease Prevention at the University of Minnesota in Minneapolis has, since 2000, sponsored a primary care, early detection/prevention service for individuals who have not been diagnosed with CVD but are concerned about the presence or risk of early-stage cardiovascular disease such as myocardial infarction, heart failure, or stroke.18-20 A global model has been developed for assessing vascular and cardiac health and identifying early-stage disease. Asymptomatic individuals screened to date include those with a family history of cardiovascular disease, cholesterol elevations, diabetes, high blood pressure, or questions and concerns about cardiovascular fitness and aging. At the center, patients learn how to prevent a cardiovascular event such as a heart attack, stroke, or peripheral vascular disease. A separate risk-reduction program is available for those who have known cardiovascular disease.

The 10-test assessment effectively identifies the approximately 30 percent of the asymptomatic population in need of treatment. These individual tests were selected based on their ability to predict cardiovascular morbidity and mortality.21 The focus of analysis is on the systems where cardiovascular disease presents itself and where evidence of the disease can be quantified. Three primary cardiovascular disease systems and related organs serve as the target of analysis for the 10 tests:

Large Arteries
- Large artery elasticity
- Carotid intimal-medial thickness/abdominal aortic wall thickness

Small Arteries
- Small artery elasticity
- Retinal artery changes
- Microalbumin in urine
- Resting blood pressure
- Blood pressure response to three-minute normal walking exercise

Left Ventricle
- Heart structure and function
- Left ventricle size
- Brain Natriuretic Peptide level

Screening consists of seven vascular and three cardiac functional and structural tests performed in one hour by a technician in a single room. The seven vascular tests are: large and small artery elasticity (compliance), sitting BP, BP response during a moderate treadmill exercise test, optic fundus photography, measurement of carotid intimal-media thickness, and microalbuminuria. The three cardiac tests are: electrocardiogram, left ventricular (LV) ultrasonography for LV volume and mass, and determination of blood N-terminal pro-B-type natriuretic peptide level.22

All tests used are FDA approved and use standard CPT, ICD-9, and HCPCS codes. Laboratory services are certified by the Clinical Laboratory Improvement Amendments (CLIA).

Screening Process

The patient history, physical examination, and laboratory testing at the Rasmussen Center are carried out by a nurse practitioner and a medical technologist. The total duration of the center visit is limited to two hours, one hour dedicated to extensive history, cardiovascular examination, and lifestyle discussion and one hour to the testing procedures. Physician oversight includes chart and data review, report generation and, when indicated, direct patient contact.

The screening process consists of two phases: (1) early disease assess-
### Table 1

**Effects of Screening, Wellness, and Prevention-Based Programs**

<table>
<thead>
<tr>
<th>Company</th>
<th>Prevention Costs/Savings</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Northeast Utilities      | Prevention/Well Aware Program:  
  * $1.4 million decrease in behavioral claims  
  * 21% decrease in smoking  
  * 25% decrease in inactivity  
  * 16% decrease in mental health risk  
  * 11% decrease in cholesterol risk.  
| Florida Power & Light    | Employee prevention program:  
  * 30% decrease in healthcare costs  
  * 38% cost decrease per worker compensation claim  
  * 82% of employees reported personal health improvements | Wellness Councils of America, The Cost Benefit of Worksite Wellness, 2002 |
| Motorola                | Prevention program participants:  
  * 2.4% increase in healthcare costs  
  Non-participants:  
  * 18% increase in healthcare costs  
| Xerox Corporation        | Prevention program participants:  
  * 5.6% of prevention participants filed claims with an average cost of $6,566 per injury  
  * 8.9% of non-wellness participants filed claims with an average cost of $9,482 per injury | University of Michigan Health Management Research Center, 2001 |
| Union Pacific Railroad   | Company's preventive wellness program produced a $53 million reduction in healthcare costs in one year. | U.S. Dept. of Health and Human Services, Prevention Makes Common Cents, 2003 |
| Citibank                | Comprehensive health/disease prevention and management program showed reduced healthcare costs  
  The Impact of the Citibank, NA, Health Management Program on Changes in Employee Health Risks Over Time.  
  * Journal of Occupational & Environmental Medicine, 42(5): 502-511. |
| Wisconsin Educational Insurance Group | Preventive medical self-care program and health education materials led to a reduction in the number and size of health care claims  
  ROI: $4.75: $1 | Internal company study |
| Washoe County School District | Prevention program participants averaged three fewer missed workdays than those who did not participate in the program  
  ROI of $15.60: $1 | Internal company study referenced in Preventive Medicine, 40: 131-137 |
| Caterpillar             | Participants in the preventive Healthy Balance Program who completed the Health Risk Assessment had:  
  * 17% fewer doctor visits  
  * 20% fewer inpatient days | Wellness Councils of America, The Cost Benefit of Worksite Wellness, 2002 |
| Manufacturing Company    | Six-year prevention-based wellness program including 2,596 participants saved $23,040 due to reductions in days missed due to disability  
  Influence of Participation in a Worksite Health Promotion Program on Disability Days.  
  * Journal of Occupational & Environmental Medicine, 44(6): 776-780. |
| DuPont                  | 45,000 blue-collar workers in worksite prevention program vs. non-participants:  
  * 41% decrease among participating workers  
  * 5.8% decline among non-participating workers  
  ROI: $1.42: $1 due to reductions in absenteeism | Wellness Councils of America, The Cost Benefit of Worksite Wellness, 2002 |
| Large Company           | Worksite prevention program compared 13,048 participants who filled out a Health Risk Appraisal (HRA) with 13,363 non-participants.  
  Participants using the HRA had an average of $212 per year less in medical costs than non-participants | S.A. Sexner, D.B. Gold, J.J. Grossmeier, and D.R. Anderson, 2003.  
  The Relationship Between Health Promotion Program Participation and Medical Costs: A Dose Response.  
  * Journal of Occupational & Environmental Medicine, 45(11): 1196-1200. |
| Johnson & Johnson       | Four-year worksite prevention program involving 18,331 employees.  
  $8.5 million annually in reduced healthcare costs ($225 savings per employee per year) | Internal company study |
The Prevention Payoff
Investment in the Rasmussen testing series:

- Two-hour screening per employee (Most insurance plans have paid Rasmussen Center charges in the past. Some health plans require referrals. Co-pays and deductibles continue to apply.)

Return on Investment:
- ROI of $3 to $15 for each $1 spent on employee CVD screening and corrective follow-up programs to improve cardiovascular health.
- Reducing and stabilizing employer premiums for employee medical insurance and related non-medical expenses associated with cardiovascular events, e.g., heart attacks, strokes, heart failure, kidney failure, peripheral vascular disease, aneurysms, dementia, and sudden death.
- Reducing BOI expenses incurred by employer groups, which will directly decrease costs of workers compensation, short- and long-term disability, EAPs, FTE replacement, and sick leave.
- Extending employee longevity and enhancing quality of life while reducing employee out-of-pocket expenses associated with cardiac rehabilitation and cardiovascular health recovery. Assuring employees that by avoiding CVD that they will be living and working longer and with better health with an average net worth 20 to 30 percent greater than those with CVD.
- Reducing self-insurance reserves by 10 to 20 percent at the end of 12 months following initial Rasmussen Center screening and subsequent implementation of individual cardiovascular health improvement plans. These savings are estimated at 20 to 30 percent by the end of years two and three following Rasmussen Center screening and implementation of

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**TABLE 2**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Low Risk (N=671)</th>
<th>Medium Risk (N=504)</th>
<th>High Risk (N=396)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term disability</td>
<td>$120</td>
<td>$216</td>
<td>$333</td>
</tr>
<tr>
<td>Worker's compensation</td>
<td>$228</td>
<td>$224</td>
<td>$496</td>
</tr>
<tr>
<td>Absence</td>
<td>$245</td>
<td>$341</td>
<td>$527</td>
</tr>
<tr>
<td>Medical and pharmacy</td>
<td>$1,158</td>
<td>$1,487</td>
<td>$3,696</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$1,751</strong></td>
<td><strong>$2,288</strong></td>
<td><strong>$5,052</strong></td>
</tr>
</tbody>
</table>


ment and (2) modifiable disease contributor assessment. Early disease assessment is accomplished by measuring arterial elasticity, resting blood pressure, blood pressure response to exercise, and albumin concentration in the urine. A photograph of the eye retina enables visual examination of the small arteries. An ultrasound is used to measure the size of the left ventricle, the thickness of the carotid artery, and the condition of the abdominal aorta. A blood sample is obtained for measurement of B-type natriuretic peptide. A patent-pending, proprietary scoring method is used to calculate a composite score from the individual tests known as the Rasmussen Disease Score. Modifiable disease contributors are determined from a blood sample tested for level of cholesterol (total cholesterol or TC; low-density cholesterol or LDL; high-density cholesterol (HDL); triglycerides (TG); blood glucose concentration; Hs C-reactive protein; and brain natriuretic peptide (BNP).

**Scoring**

An abnormal test result is assigned a score of 2, a borderline abnormal test a score of 1, and a normal test a score of 0. Therefore, a maximum abnormal score is 20, and a perfectly normal score is zero. A total score of 6 or greater has been identified as indicative of significant CVD in need of therapy. It should be noted that the scoring system is not used to evaluate risk factors (weight, family history, cholesterol, and smoking, although this information is collected to provide a complete patient profile).

Treatment and cardiovascular health improvement recommendations based upon the Rasmussen Disease Score are:

- Score of 0–2: General lifestyle counseling and recheck in five years
- Score of 3–5: Specific, intensive lifestyle counseling and recheck in one to three years
- Score of 6 and above: Treatment of early CVD

**Results**

Heart attacks, strokes, heart failure, kidney failure, peripheral vascular disease, dementia and sudden death do not occur in the absence of an abnormality of the large arteries, the small arteries, or the heart. Preliminary data indicate that the Rasmussen Disease Score for early CVD detection is far more sensitive and specific for identifying the risk of future morbid events than the traditional risk factor assessment as quantified by the Framingham Score.
individual health improvement plans including medical intervention.

Discussion

Most CVD prevention efforts nationally have been devoted to risk factor modification in the asymptomatic population (primary prevention) or intervention in individuals who have sustained cardiovascular morbidity events (secondary prevention). Little attention has been directed to the recognition of early cardiovascular disease before organ involvement has occurred. Risk factor modification is aimed at preventing the progression of disease but can have no benefit in individuals who do not have vascular or cardiac disease and are not at risk for a premature cardiovascular event. Furthermore, cardiovascular disease often exists and progresses in the absence of the traditional risk markers yet its course can still be altered by intervention. Focusing on risk factor identification and management alone is prone to insensitivity and non-specificity in achieving risk reduction, whereas focusing on individuals with advanced disease will not accomplish the desired goal of symptomatic disease prevention and healthcare cost reduction.

Conclusion

The time has come to focus on early disease identification rather than risk factors. We now know how to identify and track arterial and cardiac disease that will eventually make people sick. In 2007, results of the DETECTIV (Detection and Treatment of Early Cardiovascular Disease Trial: Intervention with Valsartan) study demonstrated that the angiotensin II receptor blocker valsartan could reduce the Rasmussen Score in asymptomatic high-risk patients with pre-hypertension or BP controlled to 140/90 mm Hg.26 The TROPHY (Trial of Preventing Hypertension) trial suggests that development of arterial hyperten-

<table>
<thead>
<tr>
<th>TABLE 3</th>
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<tbody>
<tr>
<td><strong>Projected CVD in the Workplace</strong></td>
</tr>
</tbody>
</table>

The National Academy on an Aging Society indicates that 50 percent of Americans aged 45 to 64 with cardiovascular disease do not work. To avoid overestimating workforce CVD, the projected number of possible individuals in the labor force with cardiovascular disease in the 45-65 age bracket has been reduced by 50 percent as illustrated in table below (See age brackets 45-54 and 55-64).*

<table>
<thead>
<tr>
<th>Company Size</th>
<th>Age 20-24</th>
<th>Age 25-34</th>
<th>Age 35-44</th>
<th>Age 45-54</th>
<th>Age 55-64</th>
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<tbody>
<tr>
<td><strong>5,000</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (M)</td>
<td>300</td>
<td>500</td>
<td>850</td>
<td>1,700</td>
<td>2,550</td>
</tr>
<tr>
<td>Women (W)</td>
<td>250</td>
<td>200</td>
<td>700</td>
<td>1,450</td>
<td>2,400</td>
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<tr>
<td><strong>4,000</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>240</td>
<td>400</td>
<td>680</td>
<td>1,360</td>
<td>2,940</td>
</tr>
<tr>
<td>Women</td>
<td>200</td>
<td>160</td>
<td>560</td>
<td>1,180</td>
<td>1,920</td>
</tr>
<tr>
<td><strong>3,000</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>180</td>
<td>300</td>
<td>510</td>
<td>1,020</td>
<td>1,530</td>
</tr>
<tr>
<td>Women</td>
<td>150</td>
<td>120</td>
<td>420</td>
<td>870</td>
<td>1,440</td>
</tr>
<tr>
<td><strong>2,000</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>120</td>
<td>200</td>
<td>340</td>
<td>680</td>
<td>1,020</td>
</tr>
<tr>
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<td>100</td>
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<td>280</td>
<td>580</td>
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<td>60</td>
<td>100</td>
<td>170</td>
<td>340</td>
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<td>40</td>
<td>140</td>
<td>290</td>
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<tr>
<td>Men</td>
<td>30</td>
<td>50</td>
<td>85</td>
<td>170</td>
<td>255</td>
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<td>20</td>
<td>70</td>
<td>145</td>
<td>240</td>
</tr>
<tr>
<td><strong>100</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>6</td>
<td>10</td>
<td>17</td>
<td>34</td>
<td>51</td>
</tr>
<tr>
<td>Women</td>
<td>5</td>
<td>4</td>
<td>14</td>
<td>29</td>
<td>48</td>
</tr>
<tr>
<td><strong>50</strong></td>
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</tr>
<tr>
<td>Men</td>
<td>3</td>
<td>5</td>
<td>9</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>Women</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>147</td>
<td>24</td>
</tr>
</tbody>
</table>

sion could be prevented if drug treatment were started earlier. It is important to seize the opportunity to identify asymptomatic individuals with CVD and treat it. This is something physicians can and should do. It would likely be more effective and understandable than the vague public health approaches we have advocated for the last generation and would lead to a more stable and productive workforce leading an improved quality of life. Longitudinal studies have documented the sensitivity and specificity of this approach and demonstrated that it can be distinctly beneficial to employers and employees alike.

Replication
The success of the Rasmussen Center led to the development of Cohn Prevention Center, a Minnesota LLC. Subsequently, new licensed centers have been established at the Institute for Advanced Medicine in the Sarasota Memorial Health Care System in Sarasota, Florida and as Coeur Health, LLC at the Lafayette Heart Clinic in Lafayette, Louisiana.

References
6. Ibid.
7. Ibid.
10. Ibid.

Paul A. Sommers, Ph.D., is co-founder of Cohn Prevention Center and previously administrator at the Rasmussen Center for Cardiovascular Disease Prevention, Department of Medicine, Cardiovascular Division, University of Minnesota Physicians, University of Minnesota.
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, 3.85; 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...
cohort. Understanding associations between subclinical measures of vascular changes and incident hypertension may suggest potential mechanisms of disease, may help in identifying persons at high risk, and may be important in developing prevention strategies.

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

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.
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 multidector 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 whether vessels 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., Eagan, 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 formulae 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 \(76.7 \times \text{cys C}^{-3.19}\) for cystatin C (16). Urine albumin and creatinine were measured by nephelometry and the rate Jaffé 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, 145 (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
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 mod-
eled 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 hy-
pertension 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 per-
formed 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 cardio-
vascular disease, chronic kidney disease, and increased mor-
tality (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 signifi-
cantly by vessel caliber, with the strongest associations
observed for the index relating to the pool of small arteries.
These findings suggest that subclinical vascular abnormali-
ies present before the onset of hypertension may be impor-
tant in the pathway of development of hypertension.

Our findings confirm prior findings that subclinical mea-
sures of central stiffness predict incident hypertension (7,
23, 24). Increased pulse wave velocity (a measure of central
stiffness) predicted hypertension among only those partici-
pants 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 co-
hort. Moreover, Liao et al. (24) found that arterial stiffness

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

* Median (interquartile range).

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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 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. of Cases</th>
<th>Incidence Rate</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1,593</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</td>
</tr>
<tr>
<td>30–99</td>
<td>216</td>
<td>63</td>
<td>7.0</td>
<td>1.35</td>
</tr>
<tr>
<td>100–399</td>
<td>238</td>
<td>67</td>
<td>7.0</td>
<td>1.35</td>
</tr>
<tr>
<td>≥400</td>
<td>111</td>
<td>41</td>
<td>9.7</td>
<td>1.59</td>
</tr>
<tr>
<td>Per doublingd</td>
<td>919</td>
<td>251</td>
<td>6.9</td>
<td>1.04</td>
</tr>
</tbody>
</table>

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

- a Per 100 person-years.
- b Adjusted for age, gender, and race/ethnicity.
- c 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.
- d Includes those with a baseline coronary artery calcification score of >0.

### 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</th>
<th>No. of Cases</th>
<th>Incidence Rate</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.44–0.57</td>
<td>508</td>
<td>50</td>
<td>2.2</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</td>
</tr>
<tr>
<td>0.75–0.83</td>
<td>496</td>
<td>96</td>
<td>4.5</td>
<td>1.73</td>
</tr>
<tr>
<td>0.83–0.93</td>
<td>490</td>
<td>142</td>
<td>6.9</td>
<td>2.48</td>
</tr>
<tr>
<td>0.93–2.16</td>
<td>498</td>
<td>185</td>
<td>9.4</td>
<td>2.93</td>
</tr>
<tr>
<td>Per 1 SD</td>
<td>2,494</td>
<td>536</td>
<td>5.0</td>
<td>1.36</td>
</tr>
</tbody>
</table>

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

- a Categories overlap because all values were rounded to 2 decimal places.
- b 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.
Table 4. Association of Functional Vascular Measures With Incident Hypertension Among MESA Participants, United States, 2000–2007

<table>
<thead>
<tr>
<th>Baseline Groupa</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>No.</td>
<td>Rate</td>
<td>IRR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Aortic distensibility, mm Hg ( \times 10^3 )</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>
</tr>
<tr>
<td>2.29–3.05</td>
<td>289</td>
<td>41</td>
<td>3.2</td>
<td>1.41</td>
</tr>
<tr>
<td>1.72–2.29</td>
<td>289</td>
<td>60</td>
<td>4.8</td>
<td>1.99</td>
</tr>
<tr>
<td>1.24–1.71</td>
<td>289</td>
<td>67</td>
<td>5.4</td>
<td>1.95</td>
</tr>
<tr>
<td>0–1.24</td>
<td>290</td>
<td>95</td>
<td>8.1</td>
<td>2.61</td>
</tr>
<tr>
<td>Per –1 SD</td>
<td>1,446</td>
<td>289</td>
<td>4.6</td>
<td>1.53</td>
</tr>
<tr>
<td>Large artery elasticity, mL/mm Hg ( \times 10 )</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>
</tr>
<tr>
<td>15.8–19.0</td>
<td>467</td>
<td>69</td>
<td>3.3</td>
<td>1.04</td>
</tr>
<tr>
<td>13.3–15.8</td>
<td>467</td>
<td>84</td>
<td>4.1</td>
<td>1.22</td>
</tr>
<tr>
<td>10.8–13.3</td>
<td>467</td>
<td>116</td>
<td>5.7</td>
<td>1.67</td>
</tr>
<tr>
<td>3.3–10.8</td>
<td>468</td>
<td>166</td>
<td>9.0</td>
<td>2.25</td>
</tr>
<tr>
<td>Per –1 SD</td>
<td>2,336</td>
<td>507</td>
<td>5.0</td>
<td>1.34</td>
</tr>
<tr>
<td>Small artery elasticity, mL/mm Hg ( \times 10 )</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>7.86–17.32</td>
<td>467</td>
<td>35</td>
<td>1.6</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>
</tr>
<tr>
<td>4.06–5.67</td>
<td>467</td>
<td>116</td>
<td>5.8</td>
<td>3.17</td>
</tr>
<tr>
<td>2.70–4.06</td>
<td>467</td>
<td>123</td>
<td>6.2</td>
<td>3.34</td>
</tr>
<tr>
<td>0.81–2.70</td>
<td>468</td>
<td>146</td>
<td>7.8</td>
<td>3.68</td>
</tr>
<tr>
<td>Per –1 SD</td>
<td>2,336</td>
<td>507</td>
<td>5.0</td>
<td>1.57</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 ascertainment some cases by the use of a newly prescribed antihypertensive medication, which may result in misclassification due to other indications for some of these medicines, 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


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