Background: Atherosclerosis begins in childhood and progresses through young adulthood to form the lesions that cause coronary heart disease. These preclinical lesions are associated with coronary heart disease risk factors in young persons.

Methods: The Pathobiological Determinants of Atherosclerosis in Youth study collected arteries and samples of blood and other tissues from persons aged 15 to 34 years who died of external causes and underwent autopsy in forensic laboratories. We measured the coronary heart disease risk factors and atherosclerotic lesions in the coronary arteries (CAs) (n=1117) and the abdominal aorta (n=1458).

Results: We developed risk scores, normalized so that a 1-unit increase was equivalent to a 1-year increase in age, to estimate the probability of advanced atherosclerotic lesions in the CAs and the abdominal aorta from age, sex, serum lipoprotein concentrations, smoking, hypertension, obesity, and hyperglycemia. Odds ratios for a 1-unit increase in the risk scores were 1.18 (95% confidence interval, 1.14-1.22) for the CAs and 1.29 (95% confidence interval, 1.23-1.35) for the abdominal aorta. These risk scores had good discrimination (c-indexes: 0.78 for the CAs and 0.84 for the abdominal aorta) and were calibrated. The presence of abdominal aortic lesions increased the likelihood of having CA lesions.

Conclusion: Risk scores calculated from traditional coronary heart disease risk factors provide a tool for identifying young individuals with a high probability of having advanced atherosclerotic lesions.

Arch Intern Med. 2005;165:883-890

IN 1953, ENOS ET AL.1 PUBLISHED A landmark article that described a high frequency of advanced coronary atherosclerosis in young Korean War casualties.2 Fifty years of study have reinforced this finding of atherosclerosis in young Americans.3 Between 1987 and 1994, approximately 1 in 20 men aged 25 to 29 years and 1 in 5 men aged 30 to 34 years had an advanced atherosclerotic lesion that caused stenosis of 40% or more in the proximal left anterior descending coronary artery (LADCA).4 Furthermore, the risk factors for adult coronary heart disease (CHD) were associated with the prevalence and severity of atherosclerosis in autopsied young people decades before the occurrence of CHD.4,8 The same risk factors were associated with atherosclerosis in living young people whose arteries were evaluated by noninvasive imaging.9-15 These results from autopsied and living individuals indicate that dyslipidemia, hypertension, smoking, hyperglycemia, and obesity damage arteries during youth and suggest that long-range prevention of CHD should begin early in life. A public health strategy for population-based prevention will require decades to accomplish. During the intervening time, physicians have the opportunity to promote risk factor control among their young patients.14,15 Risk factor modification to prevent CHD is now accepted practice in adults,16 but evidence based on randomized clinical trials for similar intervention in young persons is not available except for those with familial hypercholesterolemia.17 Currently, physicians who care for young people must be guided by observational evidence. The lack of clinical trial results, together with the difficulty in perceiving atherosclerosis as a decades-long process beginning in adolescence, has hampered intervention to modify risk factors in young individuals to prevent progression of atherosclerosis.

When the clinical manifestations of a disease do not appear until several de-
cades later, motivation for patients to make lifestyle changes is weak. Even objective evidence of advanced coronary artery (CA) atherosclerosis in the form of radiographic images of CA calcification did not motivate young adults to modify their risk factor status. In contrast, intensive case management compared with usual care resulted in improved risk factor status after 1 year, and improvement was independent of radiographic findings. These results show that physicians’ concern about long-term CHD risk in young persons is critical to current preventive efforts.

We analyzed data from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study to determine whether a risk score derived from CHD risk factor measurements in young persons aged 15 to 34 years predicts the probability of advanced atherosclerotic lesions in the CAs and the abdominal aorta (AA) just as a risk score in older adults predicts the probability of clinical CHD. The results indicate that such a risk score can identify young people with advanced atherosclerotic disease who consequently are at high long-term risk of CHD.

**METHODS**

**STUDY DESIGN**

Fifteen cooperating medical centers followed standardized procedures to collect specimens and data and to submit them to central laboratories. Study subjects were persons aged 15 through 34 years who died of external causes (accidents, homicides, and suicides) within 72 hours of injury and underwent autopsy within 48 hours of death in a cooperating forensic laboratory. The institutional review board of each participating medical center approved this study.

**ARTERRIES AND LESIONS**

The PDAY study investigators prepared opened, flattened, and Sudan IV–stained gross specimens of the right CA (RCA) and the AA. They prepared Gomori trichrome–stained and Oil Red-O–stained microscopic sections of a standard site in the perfusion-fixed LADCA. This site was known to be highly susceptible to advanced atherosclerosis. Three pathologists (R.E.T., J.P.S., and another pathologist) blindly and independently estimated the extent of plaques in the RCA and the AA, and 2 pathologists (A.W.Z. and H.C.M.) blindly and independently evaluated LADCA sections according to the American Heart Association grading system.

**TARGET LESIONS**

We defined a case as positive for CA target lesions if there were lesions of a specified size or quality in the LADCA, the RCA, or both. For the LADCA, we selected American Heart Association grade 4 or 5 lesions as target lesions. A grade 4 lesion contains numerous macrophage foam cells and a well-defined core of extracellular lipid covered by normal intima. A grade 5 lesion shows a similar lipid core plus a reactive fibrous cap, vascularization, or calcification. Lesions with these characteristics are susceptible to rupture and thrombosis. For the RCA, we defined raised lesions covering 9% or more of the intimal surface as the target. This cutoff point was selected to yield a prevalence similar to that of grade 4 or 5 lesions in the LADCA of 30- to 34-year-old men. The International Atherosclerosis Project showed a positive relation between CHD among populations and the average extent of raised lesions in the CAs above a threshold of approximately 10%, approximately equal to the RCA target lesion definition of 9% extent involvement used in this study. For the AA, we selected a cutoff point of 15% surface area involvement with raised lesions to yield a prevalence similar to that of grade 4 or 5 lesions in the LADCA in 30- to 34-year-old men.

**RISK FACTOR MEASUREMENTS**

Methods for measuring the risk factors are described in previous publications. Briefly, we measured concentrations of total serum cholesterol and high-density lipoprotein (HDL) cholesterol (after precipitation of other lipoproteins) using a cholesterol oxidase method, and we calculated non-HDL cholesterol concentration by subtraction. We constructed categories of non-HDL cholesterol by adding 30 mg/dl (0.78 mmol/L) to the cutoff points for low-density lipoprotein cholesterol recommended by the National Cholesterol Education Program, and we used the HDL cholesterol categories as recommended by the same group. A serum thiocyanate level of 5 mg/L or more (≥90 μmol/L) defined a smoker. Hypertension was identified when the intimal thickness of small renal arteries indicated a mean blood pressure of 110 mm Hg or greater. This classification resulted in a hypertension prevalence similar to that reported for sex, race, and age groups by the National Health and Nutrition Examination Survey II. A body mass index (calculated as weight in kilograms divided by the square of height in meters) greater than 30 indicated obesity, and a red blood cell glycated hemoglobin value of 8% or greater indicated hyperglycemia.

**STATISTICAL ANALYSIS**

For each artery, a prediction model was developed using maximum likelihood logistic regression. Appropriate models included the effects of sex, linear trend with 5-year age group, linear trend with non-HDL cholesterol category, linear trend with HDL cholesterol category, hypertension, smoking, obesity, and hyperglycemia. The numbers of predictors (9 for the CAs and 8 for the AA) were consistent with recommendations. The models were assessed by residual analysis, goodness-of-fit tests, and comparison with second-order models (including race, quadratic terms, and interactions).

The c-index, equivalent to the area under the receiver operating characteristic curve, was used as a global measurement of discrimination, defined as the ability of a prediction model to separate individuals with target lesions from those without target lesions. The c-index is the proportion of all pairs of subjects, 1 with and 1 without target lesions, in which the subject with the lesions has the higher predicted probability of lesions. A value of 0.5 for the c-index indicates no discrimination (noninformative test), and a value of 1.0 indicates perfect discrimination. Bootstrapping (1000 samples) was used for internal validation of the c-index and to estimate shrinkage. Calibration was assessed by using graphical displays and goodness-of-fit statistics.
A higher risk score was used as a single predictor in a logistic regression analysis to predict the probability of lesions.

## RESULTS

### LESION PREVALENCE

<table>
<thead>
<tr>
<th>Sex and Age, y</th>
<th>Patients, No. (n = 1117)</th>
<th>Either or Both LADCA and RCA</th>
<th>LADCA</th>
<th>RCA</th>
<th>Patients, No. (n = 1458)</th>
<th>Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-19</td>
<td>201</td>
<td>2.5</td>
<td>2.0</td>
<td>0.5</td>
<td>243</td>
<td>0.4</td>
</tr>
<tr>
<td>20-24</td>
<td>226</td>
<td>5.3</td>
<td>3.5</td>
<td>2.2</td>
<td>285</td>
<td>1.4</td>
</tr>
<tr>
<td>25-29</td>
<td>226</td>
<td>9.7</td>
<td>5.8</td>
<td>6.2</td>
<td>312</td>
<td>5.1</td>
</tr>
<tr>
<td>30-34</td>
<td>182</td>
<td>23.3</td>
<td>17.3</td>
<td>18.3</td>
<td>245</td>
<td>18.8</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-19</td>
<td>56</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>20-24</td>
<td>69</td>
<td>2.9</td>
<td>2.9</td>
<td>0</td>
<td>94</td>
<td>2.1</td>
</tr>
<tr>
<td>25-29</td>
<td>86</td>
<td>10.5</td>
<td>5.8</td>
<td>5.8</td>
<td>119</td>
<td>7.6</td>
</tr>
<tr>
<td>30-34</td>
<td>71</td>
<td>12.7</td>
<td>7.0</td>
<td>9.9</td>
<td>89</td>
<td>24.7</td>
</tr>
</tbody>
</table>

*Abbreviations: AA, abdominal aorta; LADCA, left anterior descending coronary artery; RCA, right coronary artery.*

### PREDICTION OF LESIONS

#### Multivariable Analysis

Odds ratios (ORs) from the logistic regression analyses are given in Table 2. Each OR is adjusted for the other variables in the model. The relationship to lesions was different in the CAs and the AA for sex, smoking, and obesity, and the association of obesity with CA lesions was different in men and women. The reasons for these differences are unknown.

The goodness-of-fit statistics (CAs: $\chi^2=2.59; P=.96$; AA: $\chi^2=7.11; P=.52$) indicated agreement between the observed and predicted probabilities. The mean (SD) bootstrap-validated c-index for the CAs was 0.78 (0.01) and for the AA was 0.84 (0.01). The estimate of shrinkage was 0.91 for the CAs and 0.94 for the AA. The estimates of shrinkage (both $>0.85$) did not indicate model overfitting and suggested that the models will be useful in other groups of patients.

#### Risk Scores Based on Risk Factors

Table 3 gives the points, derived from the logistic regression models, assigned to each risk factor. The points for each risk factor are added to calculate the risk score. The ORs for a 1-unit increase in the risk score were 1.18 (95% confidence interval, 1.14-1.22) for the CAs and 1.29 (95% confidence interval, 1.23-1.35) for the AA. For an individual patient, the estimated probability of lesions (absolute risk) can be obtained for the risk score as shown in Figure 1. For the CAs and the AA, high risk scores are associated with substantial probabilities of lesions.

The cumulative effects of modifiable risk factors (non-HDL cholesterol, HDL cholesterol, smoking, hypertension, obesity, and hyperglycemia) can result in individuals having substantially increased risk relative to others in their age and sex group. Figure 2 shows the risk due to combinations of only modifiable risk factors. These ORs compare the odds of a CA target lesion in an individual who has a specified risk score due only to the modifiable risk factors with the odds of a target lesion in an individual of the same sex and 5-year age group who has no modifiable risk factors.

### Risk Scores Based on Risk Factors and Aortic Lesions

Including the presence of AA target lesions with the CA risk score in a logistic regression model indicated in...
Including the presence of AA lesions with the CA risk score yielded a mean (SD) c-index of 0.80 (0.01). The large OR for the presence of AA target lesions did not result in a large increase in the c-index because of the low prevalence of AA target lesions and because the c-index is based on rank order.

### Comment

We developed risk scores that use traditional CHD risk factors to predict the probability of advanced atherosclerotic lesions in the CAs and the AA of young persons 15 to 34 years of age. Discrimination is similar to that obtained for the prediction of CHD events in Framingham, a result indicating that the PDAY formulas predict the risk of advanced preclinical atherosclerosis in young people years before CHD just as the Framingham formulas predict the risk of CHD events in older people. The weighting of risk factors differs between the 2 formulas because risk factors may contribute to atherogenesis and clinical CHD in different ways. For example, a risk factor that promotes lipid deposition (such as hypercholesterolemia) may not contribute to plaque rupture and thrombosis (such as smoking), and vice versa. The PDAY risk score reflects the slow but steady progression of atherosclerosis with age in young people. In contrast, the Framingham formula includes a large negative contribution to the score for individuals aged 30 to 34 years, and no information is given for younger people.

### Calculation and Application of Risk Scores

The risk scores are calculated by adding the points for each risk factor given in Table 3. For example, a man (0 points) aged 25 to 29 (10 points) with a non-HDL cholesterol concentration of 160 to 189 mg/dL (4.14-4.90 mmol/L) (4 points) who smokes (1 point), is obese (6 points), and has no other risk factors has a CA risk score of 21, with 11 of the points due to modifiable risk factors. Figure 1 indicates that this individual has approximately a 25% probability of having a target CA lesion. For ease of interpretation, the risk scores are normalized so that a 1-unit increase is equivalent to a multiplicative change in the odds (an additive change in the logarithm of the odds) due to a 1-year increase in age. Thus, the points due to the modifiable risk factors are equivalent to 11 years. The documented presence of a target AA lesion, which can be determined by current imaging techniques, increases the probability of an advanced CA lesion in this example to 48% (Figure 3).

### Comparison with Cohort Studies

The PDAY study results are strongly supported by findings from 5 cohort studies, all reported during the past 3 years, of the relation of cardiovascular risk factors to markers for atherosclerosis in living persons. Three studies assessed risk factors in adolescents or young adults and then measured carotid artery intimal- medial thickness in the same individuals 12 to 22 years later. In all
of these studies, 1 or more of the risk factors were associated with the carotid intimal-medial thickness of adults. Another study found a similar association between CA calcification and risk factors measured 10 years earlier. A fifth study found strong associations between current risk factors and carotid intimal-medial thickness in young adults.

RISK FACTORS IN YOUNGER INDIVIDUALS

In younger persons, the contribution of the modifiable risk factors to long-term risk has increased importance because risk factors not only persist with time (track) but also typically worsen with age. At age 15 to 19 years, a moderate risk score such as 10 due entirely to modifiable risk factors (non–high-density lipoprotein cholesterol, high-density lipoprotein cholesterol, smoking, hypotension, obesity, and hyperglycemia) predicts a probability of only 5% of advanced lesions. This 5% probability is composed of a probability of 1% for a man of that age group along with an OR of approximately 5 due to the modifiable risk factors (Figure 2). The same modifiable risk factors at age 30 to 34 years result in a predicted probability of advanced lesions of almost 40%. This probability results from the OR of 5 combined with a probability of 11% for a 30- to 34-year-old man with no risk factors.

Although at increased risk relative to their age group, the probability of lesions in young persons (aged 15-19 years) may remain low (Figure 1) even for those with several modifiable risk factors and carotid intimal-medial thickness in young adults.

This 5% probability is composed of a probability of 1% for a man of that age group along with an OR of approximately 5 due to the modifiable risk factors (Figure 2). The same modifiable risk factors at age 30 to 34 years result in a predicted probability of advanced lesions of almost 40%. This probability results from the OR of 5 combined with a probability of 11% for a 30- to 34-year-old man with no risk factors.

Although at increased risk relative to their age group, the probability of lesions in young persons (aged 15-19 years) may remain low (Figure 1) even for those with several modifiable risk factors. In older persons, when contributions of age are included with risk due to similar values of the modifiable risk factors, the probability of lesions is greatly increased. High relative risk at a young age will likely be transformed into high absolute risk later in life. Two of the previously cited cohort studies reported that the risk factors measured in adolescence predicted adult lesions better than the risk factors measured at the time of imaging, a result further emphasizing the importance of risk factors at young ages.
Figure 4. Receiver operating characteristic curves for the prediction of target lesions in the coronary arteries (A) and the abdominal aorta (B). The numbers are the corresponding risk score cutoff points.

Figure 5. Observed and estimated probability of target lesions by risk score in the coronary arteries for men (A) and women (C) and in the abdominal aorta for men (B) and women (D). Probabilities are for groups of 3 integer values of the risk score, with the highest category for each sex constructed to have at least 50 cases.
RISK SCORES COMBINED WITH NONINVASIVE IMAGING

Noninvasive imaging may have 2 potential roles in the future management of atherosclerosis in youth. The first is to separate individuals with high risk scores and atherosclerotic lesions from those with high risk scores but without atherosclerotic lesions.31-33 This information could make management decisions more precise. The second use is to monitor response to risk factor modification.34,35 Imaging of the AA could be used as a surrogate for CA atherosclerosis until CA imaging is routinely available.27,36 However, guidelines for the application of imaging currently are not available.

FUTURE STUDIES

The association of AA lesions with CA lesions beyond the expected relation due to similar associations with the CHD risk factors presumably reflects other factors that affect both lesion sites; this association suggests that including other risk factors will improve prediction. Cohort studies using noninvasive imaging, such as those already referenced, will be able to identify additional risk factors, refine the risk scores, and help develop guidelines for the clinical application of imaging and the age at which to measure the risk factors.

Clinical trials of lifestyle and, for extreme cases, pharmacologic intervention in adolescents and young adults likely to have advanced atherosclerotic lesions could be designed with noninvasive imaging techniques to show the value of treatment in limiting atherosclerosis progression, as has been demonstrated in middle-aged and elderly adults using noninvasive27 and invasive37 methods. Positive results from clinical trials would add a powerful impetus to the recommendation for risk factor control in youth.38

IMPLICATIONS

Previous PDAY studies showed that many young people have advanced atherosclerotic lesions, and these studies support the public health strategy of encouraging young people to adopt a healthy lifestyle. The present study shows that a risk score, based on simple and inexpensive measurements, has sufficient discrimination that physicians could identify and advise high-risk adolescents and young adults concerning their risk factors (hyperlipidemia, hypertension, smoking, obesity, and hyperglycemia) and their long-term risk of CHD.

Accepted for Publication: October 28, 2004.

Author Affiliations: Department of Pathology, The University of Texas Health Science Center at San Antonio (Drs McMahan and McGill); Outreach Services, Nemours Cardiac Center, Alfred I. duPont Hospital for Children, Wilmington, Del, and Department of Pediatrics, Jefferson Medical College, Philadelphia, Pa (Dr Gidding); Departments of Radiology and Medicine, Mount Sinai School of Medicine, New York, NY (Dr Fayad); Department of Pathology, Louisiana State University Health Sciences Center, New Orleans (Drs Zieske, Malcom, Tracy, and Strong); and the Department of Physiology and Medicine, Southwest Foundation for Biomedical Research, San Antonio (Dr McGill).

Correspondence: C. Alex McMahan, PhD, Department of Pathology, The University of Texas Health Science Center, 7703 Floyd Curl Dr, San Antonio, TX 78229-3900 (cmcman@uthscsa.edu).

Funding/Support: The PDAY study was supported by multiple grants from the National Heart, Lung, and Blood Institute, Bethesda, Md, to the following cooperating institutions: University of Alabama, Birmingham; Albany Medical College, Albany, NY; Baylor College of Medicine, Houston, Tex; University of Chicago, Chicago, Ill; The University of Illinois, Chicago; Louisiana State University Health Sciences Center, New Orleans; University of Maryland, Baltimore; Medical College of Georgia, Augusta; University of Nebraska Medical Center, Omaha; The Ohio State University, Columbus; Southwest Foundation for Biomedical Research, San Antonio, Tex; The University of Texas Health Science Center at San Antonio; Vanderbilt University, Nashville, Tenn; and West Virginia University Health Sciences Center, Morgantown. Dr Gidding was supported by grant 1 P20 RR020173-01 from the National Center for Research Resources, Bethesda.

REFERENCES

14. Olefsky MJ, Grundy SM. National Cholesterol Education Program recommen-