Background and Purpose—We developed a model to estimate the costs incurred by ineffective primary and secondary prevention in terms of excess cardiovascular disease (CVD) mortality in a nationally representative sample of the US population.

Methods—Cox proportional hazards analyses were used to examine the effect of inadequate risk factor control on the incidence of fatal stroke and myocardial infarction (MI) during a follow-up period of 13.4±3.6 years after adjusting for differences in age, gender, and ethnicity in a national cohort of 9252 adults who participated in the Second National Health and Nutrition Examination Survey (NHANES) Mortality Follow-up Study. Inadequate risk factor modification was defined by presence of either blood pressure >140/90 mm Hg, serum cholesterol >200 mg/dL, or active cigarette smoking. Using the data from 4115 adults screened in the NHANES 1999 to 2000, population attributable risk (PAR) percent and associated cost incurred (expressed as proportion of total 1-year cost incurred for CVD mortality in year 2001) was estimated.

Results—CVD mortality risk increased in a stepwise manner for persons with no previous MI or stroke and ≥2 inadequately controlled risk factors (2×); and previous history of MI and stroke and adequately controlled risk factors (2.6×), 1 inadequately controlled risk factor (4.3×), and ≥2 inadequately controlled risk factors (5.7×). The PAR was 14% (estimated cost incurred $13.2 billion) among persons with ≥2 inadequately controlled risk factors without previous MI or stroke (estimated 17% of total US population). Among persons with previous MI or stroke, the PAR was 7% (cost incurred $6.2 billion) and 8% (cost incurred $7.4 billion) for 1 inadequately controlled risk factor and ≥2 inadequately controlled risk factors, respectively. An excess of cost of $13.6 billion was spent on 4% of the total population (persons with inadequate secondary prevention).

Conclusions—The model demonstrates the differential risk of mortality from inadequately controlled cardiovascular risk factors in primary and secondary prevention settings. The large financial cost incurred by inadequate primary and secondary prevention justifies intensive efforts directed toward detection and treatment of cardiovascular risk factors.

Key Words: cigarette smoking ▪ hypercholesterolemia ▪ hypertension ▪ mortality ▪ primary prevention ▪ secondary prevention
of uncontrolled hypertension was made on the basis of average blood pressure >140/90 mm Hg derived from 3 consecutive readings. This criterion is based on threshold for defining hypertension in previous studies. Uncontrolled hypercholesterolemia was defined on the basis of serum cholesterol >200 mg/dL. The definition was chosen to represent value considered elevated by the Adult Treatment Panel II guidelines. Current smoking status was determined based on self-report.

NHANES II Mortality Follow-Up Study: Incident Cardiovascular Mortality

Mortality follow-up was conducted for the cohort of 9252 NHANES II participants who were aged 30 years or older at the time of enrollment through ascertainment of the vital status of each participant through December 31, 1992 by matching data with deaths recorded in the National Death Index and the Social Security Administration Death Master File 9. Underlying cause of death according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) code was recorded. Events of ischemic stroke, intracerebral hemorrhage, and MI were determined by death certificate diagnoses that included 1 or more of the following ICD-9 CM codes: 433, 434, 436, 437.0, or 437.1 (for ischemic stroke); 431 to 432 (for intracerebral hemorrhage); and 410 to 414 (for MI). Subarachnoid hemorrhage was not included because of the small number of events (n=3) observed in NHANES II participants.

Calculation of Relative Risk of Incident Cardiovascular Mortality

Cox proportional hazards analyses were used to estimate the relative risks (RR) and 95% CIs for all CVDs including stroke and MI in the following 6 categories of persons according to adequacy of risk factor control: (1) No inadequately controlled risk factors and no previous history of stroke or MI (reference group); (2) 1 inadequately controlled risk factor and no previous history of stroke or MI; (3) 2 or more inadequately controlled risk factors and no previous history of stroke or MI; (4) 4 adequately controlled risk factors and a previous history of stroke or MI; (5) 1 inadequately controlled risk factor and a previous history of stroke or MI; and (6) 2 or more inadequately controlled risk factors and a previous history of stroke or MI. The analysis was adjusted for differences in age, gender, and ethnicity.

National Health and Nutrition Survey 1999 to 2000: Recent Evaluation of Prevalence of Inadequately Controlled Risk Factors

The model for calculation of financial cost incurred with inadequately controlled cardiovascular risk factors is dependent on the proportion of the population in each subset stratified by adequacy of risk factor control. The baseline data for the NHANES II data were between 1976 and 1980. Since then, physician’s practices may have been modified based on the educational activities to develop and implement guidelines for treatment of elevated cholesterol by the National Cholesterol Education Program (NCEP) and recent studies documenting the benefits of antihypertensive treatment in patients with isolated systolic hypertension and hypertension among diabetic patients. The most recent nationally representative sample of 4115 US adults was screened in 1999 and 2000 as part of the continuous NHANES (1999 to 2000). We determined the proportion of patients in strata based on previous history of MI or stroke and adequacy of risk factor control to estimate population attributable risk (PAR) as described below. Statistical analysis was carried out using WesVar (version 4.2; Westat). Variance estimation was calculated using the delete 1 jackknife method. The calculated proportions of the population exposed to inadequate control of risk factor were representative of US population in 1999 to 2000.

Population Attributable Risk

To estimate the impact of inadequately controlled risk factors on incident fatal CVD, we calculated the population-attributable risk percent (PAR) expressing the proportion of cardiovascular mortality that would be reduced if that risk category were eliminated (calculated as PAR). We performed sensitivity analyses by calculating the cost for the upper and lower limit (based on 95% CIs) of both the RR of fatal cardiovascular events and cost estimates from the regression model and US life tables for 2001. We performed Cox proportional hazards analyses to estimate the RR and 95% CI for all cause mortality in 6 categories of persons according to adequacy of risk factor control, and report the range of results in each of the 6 categories of persons according to adequacy of risk factor control. For example, the lowest possible estimate for cost incurred in any category is based on PAR% derived from lower values of 95% CI of the RR and Pe. These analyses were performed to analyze the impact of relevant assumptions and statistical variations on cost estimates.

Effect of Inadequately Controlled Risk Factors on Years of Life Lost

We performed Cox proportional hazards analyses to estimate the RR and 95% CI for all cause mortality in 6 categories of persons according to adequacy of risk factor control. We used the coefficients from the regression model and US life tables for 2001 (http://www.cdc.gov/nchs/data/nvss/nvss52/nvss52_14.pdf) to estimate the years of life lost as described previously. The number of
years lost was the difference in expected ages between the 5 categories of persons with various risk factor control status and expected age of the person without a previous history of MI or stroke and adequately controlled risk factors.

Results

Table 1 demonstrates the baseline characteristics of 9252 participants enrolled in the NHANES II Mortality Follow-up Study according to previous history of MI or stroke. A total of 691 fatal cardiovascular events were observed; 565 were MI and 126 were stroke during a mean follow-up period of 13.4 years.

The results of the analysis are shown in Table 2. Compared with persons without a previous history of MI or stroke and adequate risk factor control, the risk of incident cardiovascular mortality increased in a stepwise manner for persons with a previous history of MI and stroke and (1) adequately controlled risk factors (2.6), (2) 1 inadequately controlled risk factor (4.3), and (3) ≥2 inadequately controlled risk factors (5.7). The RR for all-cause mortality is presented in Table 2. The years of life lost ranged from 1.9 years for persons with no previous MI or stroke and 1 inadequately controlled risk factor to 8.9 years for persons with a previous history of MI and stroke and ≥2 inadequately controlled risk factors.

The PAR was 14% for persons with 2 or more inadequately controlled risk factors in the absence of previous MI or stroke (17% of the US population; Table 3). Among persons with previous MI or stroke, the PAR was 4% in the absence of any inadequately controlled risk factor and increased to 7% and 8% in the presence of 1 and ≥2 risk factors, respectively. Another way to interpret the results is that 14% of the incident cardiovascular mortality in the population is related to inadequate control of multiple risk factors in persons without previous MI or stroke. The estimated annual cost incurred, or that which could be saved in this category because of cardiovascular mortality, is estimated to be $13.2 billion. Among persons with previous MI or stroke (2% of the US population), ≥2 inadequately controlled risk factors accounted for 8% of the incident cardiovascular mortality (total cost incurred is $7.4 billion; Table 3). An estimated 7% of incident cardiovascular mortality is related to 1 inadequately controlled risk factor among persons with previous MI or stroke (2% of the US population) leading to a total incurring of $6.2 billion.

Sensitivity analyses estimated the cost incurred ranging from $5.5 to $22.1 billion for persons with 2 or more inadequately controlled risk factors in the absence of previous MI or stroke.

### Table 1. Baseline Characteristics of Patients Screened in the National Health and Nutrition Survey II (1976 to 1980)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No Previous Myocardial Infarction or Stroke, n=8521 (%)</th>
<th>Previous Myocardial Infarction or Stroke, n=731 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean±SD</td>
<td>53±13</td>
<td>63±8</td>
</tr>
<tr>
<td>Men</td>
<td>3903 (46)</td>
<td>446 (61)</td>
</tr>
<tr>
<td>Women</td>
<td>4618 (54)</td>
<td>285 (40)</td>
</tr>
<tr>
<td>White</td>
<td>7454 (87)</td>
<td>637 (87)</td>
</tr>
<tr>
<td>African-Americans</td>
<td>910 (11)</td>
<td>88 (12)</td>
</tr>
<tr>
<td>Other</td>
<td>157 (2)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Inadequately controlled hypertension</td>
<td>3128 (37)</td>
<td>355 (49)</td>
</tr>
<tr>
<td>Inadequately controlled hyperlipidemia</td>
<td>5768 (68)</td>
<td>549 (75)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2781 (33)</td>
<td>204 (28)</td>
</tr>
</tbody>
</table>

*α P<0.05 by χ² method.

### Table 2. Relative Risk of Cardiovascular and All-Cause Mortality During the Mortality Follow-Up Study Among Patients Included in the National Health and Nutrition Survey II (1980 to 1992)

<table>
<thead>
<tr>
<th>Person Strata</th>
<th>Total Persons</th>
<th>Fatal Cardiovascular Events (%)</th>
<th>All-Cause Mortality (%)</th>
<th>Relative Risk (95% CI) for Cardiovascular Death†</th>
<th>Relative Risk (95% CI) for All-Cause Mortality†</th>
<th>Years of Life Lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous history of MI or stroke (candidates for primary prevention)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequately controlled risk factors</td>
<td>1207</td>
<td>37 (3)</td>
<td>138 (11)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>1 inadequately controlled risk factor</td>
<td>3545</td>
<td>143 (4)</td>
<td>599 (17)</td>
<td>1.0 (0.7–1.5)</td>
<td>1.2 (1.0–1.5)</td>
<td>1.9</td>
</tr>
<tr>
<td>2 or more inadequately controlled risk factors</td>
<td>3769</td>
<td>318 (8)</td>
<td>985 (26)</td>
<td>2.0 (1.4–2.8)</td>
<td>1.7 (1.4–2.1)</td>
<td>5.3</td>
</tr>
<tr>
<td>Previous history of MI or stroke (candidates for secondary prevention)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequately controlled risk factors</td>
<td>57</td>
<td>10 (18)</td>
<td>26 (46)</td>
<td>2.6 (1.3–5.1)</td>
<td>2.0 (1.3–3.0)</td>
<td>5.7</td>
</tr>
<tr>
<td>1 inadequately controlled risk factor</td>
<td>298</td>
<td>75 (25)</td>
<td>151 (51)</td>
<td>4.3 (2.9–6.3)</td>
<td>2.5 (2.0–3.2)</td>
<td>7.5</td>
</tr>
<tr>
<td>2 or more inadequately controlled risk factors</td>
<td>376</td>
<td>108 (29)</td>
<td>204 (54)</td>
<td>5.7 (3.9–8.3)</td>
<td>3.1 (2.5–3.9)</td>
<td>8.9</td>
</tr>
</tbody>
</table>

†Adjusted for age, sex, and ethnicity.
$0.5 to $8.9 billion for persons with adequately controlled risk factors and $3.2 to $11.1 billion for persons with 1 inadequately controlled risk factor among persons with previous MI or stroke. Among persons with previous MI or stroke, ≥2 inadequately controlled risk factors accounted for incurred cost ranging between $4.1 to 12.2 billion.

Discussion

Salient Findings of the Study
We have developed a model that defines the population attributable mortality risk associated with failure to control modifiable risk factors. When the excess risk and cost incurred is computed, persons with inadequate secondary prevention efforts incur a cost of cardiovascular mortality estimated at $13.6 billion ($6.2 billion and $7.4 billion for persons with 1 and 2 or more inadequately controlled risk factors, respectively). This is almost the same as the cost incurred by inadequate primary prevention efforts estimated at $13.2 billion (Table 3). The total cost of $30.1 (range $13.3 to $54.4) billion incurred by inadequate primary and secondary prevention of CVDs represents ~3% of the $1.3 trillion spent on health care in the United States in 2001 (http://www.cms.hhs.gov/). Our results call for major efforts directed toward primary and secondary prevention in subsets of the population at highest risk for cardiovascular events.

Relative Impact of Primary and Secondary Prevention on Survival
The years of life lost ranged from 1.9 years to 8.9 years for persons in various categories of inadequately controlled risk factors. Two prospective studies18 evaluated the long-term mortality for persons with low risk defined as serum cholesterol level <200 mg/dL, blood pressure ≤120/80 mm Hg, and no current cigarette smoking. Estimated greater life expectancy for low-risk groups ranged from 5.8 years to 9.5 years compared with those who had elevated cholesterol level, or blood pressure, or smoked. Grover et al19 compared the potential years of life saved between high-risk patients (presence of hyperlipidemia, cigarette smoking, and hypertension) and low-risk patients (presence of hypertension or hyperlipidemia). The forecasted benefits of lipid-lowering therapy were substantially greater among high-risk groups versus low-risk groups in primary prevention (4.7 years versus 2.5 years, respectively) but similar in secondary prevention group, (4.6 years versus 3.8 years, respectively). The results for hypertension therapy also demonstrated greater benefits for high-risk versus low-risk patients undergoing primary prevention therapy (1.3 years versus 0.9 years, respectively), and the forecasted benefits in secondary prevention were similar (1.3 years versus 1.0 year, respectively). The investigators concluded that the expected benefits of therapy among patients without cerebrovascular diseases are greatest in the presence of other risk factors.

Issue related to Data Interpretation
The definitions of MI and stroke used to identify participants with previous CVDs were based on self-reported physician diagnoses. Bergmann et al20 compared interview reports with hospitalization records in 10 523 participants from the NHANES I. A true positive rate of 83% was observed for the 294 self-reported MIs. O’Mahony et al21 validated the accuracy of assessing lifetime history of stroke in a random sample of 2000 persons aged ≥45 years in a mailed questionnaire. Participants were asked whether they ever had a stroke. Response accuracy was confirmed by medical records review. The question had a sensitivity and specificity of 95% and 96%, respectively.

We did not include diabetes mellitus as a modifiable cardiovascular risk factor in the analysis. Whether aggressive glucose control independently reduces the risk of cardiovascular events is debated.22 Certain other limitations of observational studies including selection bias, missing data, measurement errors, and lack of independent ascertainment of events need to be considered in the interpretation of data. We cannot rule out the possibility that mortality with CVDs estimated from NHANES II may be lower in 2001 because of improvement in treatment strategies independent of risk factor control and, therefore, the cost incurred may be lower than the estimated cost. We have provided the lowest and highest estimation of the cost incurred as mentioned above.

PAR is calculated from estimates of the relative risk and the prevalence of the risk factor.13,23 However, if the risk factors are clustered within individuals, PAR is an overestimate of the effect of a risk factor. Because cardiovascular risk factors do cluster within individuals, PAR may overestimate the effect of a single risk factor. In addition, adequate treatment of hypertension and hypercholesterolemia may not reduce the risk of CVDs to that observed in nonhypertensive

### TABLE 3. Population Attributable Risk and Economic Impact Using Prevalence Data From NHANES 1999 to 2000

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous history of MI or stroke (candidates for primary prevention)</td>
<td>Adequately controlled risk factors Reference 32% Reference 14% Not estimated</td>
<td>Not significant Not estimated</td>
<td>13.2</td>
<td></td>
</tr>
<tr>
<td>Adequately controlled risk factors Reference 32% Reference 14% Not estimated</td>
<td>1 inadequately controlled risk factor 1.04 (0.7–1.5) 44% Reference Not significant Not estimated</td>
<td>13.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 inadequately controlled risk factors Reference 32% Reference 14% Not estimated</td>
<td>2 or more inadequately controlled risk factors 2.0 (1.4–2.8) 17% Reference Not significant Not estimated</td>
<td>13.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous history of MI or stroke (candidates for secondary prevention)</td>
<td>Adequately controlled risk factors Reference 32% Reference 14% Not estimated</td>
<td>Not significant Not estimated</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Adequately controlled risk factors Reference 32% Reference 14% Not estimated</td>
<td>1 inadequately controlled risk factor 4.2 (2.9–6.3) 2% Reference Not significant Not estimated</td>
<td>13.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 inadequately controlled risk factors Reference 32% Reference 14% Not estimated</td>
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<td>13.2</td>
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</tbody>
</table>
persons with normal cholesterol. Therefore, the actual cost benefit may be lower than the estimated value.

**Conclusion**

The model demonstrates that the cost benefits with interventions to treat hyperlipidemia or hypertension or reduce cigarette smoking may be substantial, particularly when the combined benefits on fatal cerebrovascular and coronary events are considered together.

**References**

The Relative Impact of Inadequate Primary and Secondary Prevention on Cardiovascular Mortality in the United States
Adnan I. Qureshi, M. Fareed K. Suri, Jawad F. Kirmani and Afshin A. Divani

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