

# An International Model to Predict Recurrent Cardiovascular Disease

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## ABSTRACT

**BACKGROUND:** Prediction models for cardiovascular events and cardiovascular death in patients with established cardiovascular disease are not generally available.

**METHODS:** Participants from the prospective REduction of Atherothrombosis for Continued Health (REACH) Registry provided a global outpatient population with known cardiovascular disease at entry. Cardiovascular prediction models were estimated from the 2-year follow-up data of 49,689 participants from around the world.

**RESULTS:** A developmental prediction model was estimated from 33,419 randomly selected participants (2394 cardiovascular events with 1029 cardiovascular deaths) from the pool of 49,689. The number of vascular beds with clinical disease, diabetes, smoking, low body mass index, history of atrial fibrillation, cardiac failure, and history of cardiovascular event(s) <1 year before baseline examination increased risk of a subsequent cardiovascular event. Statin (hazard ratio 0.75; 95% confidence interval, 0.69-0.82) and acetylsalicylic acid therapy (hazard ratio 0.90; 95% confidence interval, 0.83-0.99) also were significantly associated with reduced risk of cardiovascular events. The prediction model was validated in the remaining 16,270 REACH subjects (1172 cardiovascular events, 494 cardiovascular deaths). Risk of cardiovascular death was similarly estimated with the same set of risk factors. Simple algorithms were developed for prediction of overall cardiovascular events and for cardiovascular death.

**CONCLUSIONS:** This study establishes and validates a risk model to predict secondary cardiovascular events and cardiovascular death in outpatients with established atherothrombotic disease. Traditional risk factors, burden of disease, lack of treatment, and geographic location all are related to an increased risk of subsequent cardiovascular morbidity and cardiovascular mortality.

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**KEYWORDS:** Acute coronary syndromes; Cardiovascular disease; Cerebrovascular disease/stroke; Coronary disease; Mortality; Peripheral vascular disease; Risk factors

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The prediction of atherothrombotic events (coronary artery disease, cerebrovascular disease, and peripheral arterial disease) in the outpatient setting has focused on the occurrence of first events,<sup>1-3</sup> and Framingham Heart Study data or similar observational study data have been used to predict vascular disease risk in people. Less cardiovascular prediction research has focused on patients with existing coronary artery disease.<sup>4</sup> The estimation of vascular disease risk among people known to have atherothrombotic disease at baseline would facilitate efforts by patients, clinicians, and public health officials to prevent these morbid and mortal events in a real-world setting. Multi-variable analysis of risk for recurrent cardiovascular events could provide the underpinnings of an individualized risk scoring system and help to identify individuals at higher risk for more intensive investigation, treatment, and follow-up.

Largely, risk-assessment scores for initial cardiovascular event prediction have been developed from specific geographic regions, such as the US,<sup>1,5,6</sup> Germany,<sup>7</sup> Italy,<sup>8</sup> and the UK.<sup>9</sup> Projects that have tested the applicability of risk assessment scores across large regions such as the US<sup>10</sup> or Europe<sup>11</sup> have been undertaken as post hoc analyses. The REduction of Atherothrombosis for Continued Health (REACH) Registry was established in 2003 to recruit and follow a large cohort of outpatients with known atherothrombotic disease or at high risk of developing atherothrombosis.<sup>12</sup> This design provides a contemporary data set that includes individuals across the world and allows the assessment of risk for cardiovascular events, including investigation of the potential role of vascular disease burden, protective effect of specific treatments, and effects according to geographic region.

The purpose of this report is to identify the determinants of secondary vascular ischemic events and cardiovascular death in the study participants, to develop a vascular disease risk algorithm from this experience, and to develop a robust risk prediction model that has been internally validated.

## METHODS

The study design, selection of physicians,<sup>12</sup> and baseline and follow-up experience of participants in the REACH Registry<sup>13-15</sup> have been published previously. The current study included outpatients aged  $\geq 45$  years with established coronary artery disease, cerebrovascular disease, or peripheral arterial disease, with enrollment by their physician over a 7-month period on a worldwide basis between December 2003 and June 2004. Documented coronary artery disease

consisted of one or more of the following criteria: stable angina with documented coronary artery disease, history of unstable angina with documented coronary artery disease, history of percutaneous coronary intervention, history of coronary artery bypass graft surgery, or previous myocardial infarction. Documented cardiovascular disease consisted of a hospital or neurologist report with the diagnosis of transient ischemic attack or ischemic stroke. Documented peripheral artery disease consisted of one or both of the following criteria: current intermittent claudication with ankle-brachial index of  $<0.9$  or a history of intermittent claudication together with a previous and related intervention such as angioplasty, stenting, atherectomy, peripheral arterial bypass graft, or other vascular intervention, including amputation.

Data were collected using a standardized, international case report form that was completed

at the study visit. Body mass index was defined as weight (kilograms) divided by the square of the height (meters), and subjects were categorized using commonly used definitions of obesity and overweight. Current smoking was defined as  $\geq 5$  cigarettes per day on average within the last month before entry into the Registry, and former smoking was defined as  $\geq 5$  cigarettes per day on average more than 1 month before entry into the Registry. Cholesterol levels were transcribed from the clinical record and lipids were not measured in a standard manner in the registry participants. Because of differences in high-density lipoprotein cholesterol measurement methods around the world, and lack of standardization for this assay in many locales, information concerning high-density lipoprotein cholesterol levels was not obtained.

Physician selection was performed at the country level in collaboration with the respective national coordinators, and was designed to provide a representative distribution across specialties, geographic regions, types of practice (office-based, public or private hospital-based, dispensary only, multiple, or other structures), and locations (urban, suburban, or rural). Each physician recruited a maximum of 15 patients (20 patients in the US).

In each country, 10% of the investigator sites that enrolled at least one patient underwent quality control assessment. Six percent of these sites were chosen randomly, and an additional 4% were chosen in response to queries about missing data requests. For each of the sites undergoing monitoring, 100% of case report forms for patients enrolled at that site were monitored for source documentation and accuracy and information related to risk factor levels, med-

## CLINICAL SIGNIFICANCE

- Risk of recurrent cardiovascular disease in survivors of myocardial infarction can be estimated from outpatient clinic information.
- The key determinants of recurrent cardiovascular disease are age, male sex, current smoking, diabetes mellitus, low body mass index, number of vascular beds involved, CVD event in the past year, history of heart failure, atrial fibrillation, not taking statins, and not taking anti-platelet therapy.

ical history items, medication use, and cardiovascular diagnoses.

### Follow-up

Participants were followed for the development of a subsequent cardiovascular event and were invited to a baseline clinical examination and follow-up evaluation at 12 and 24 months after the baseline. At the follow-up visits, data were collected regarding interim development of clinical outcomes according to self-report and medical records available, vascular and endovascular procedures, employment status, weight and current smoking status, and medications used since baseline. The current report is based on a database lock of June 15, 2007 for analysis of the 2-year follow-up. This follow-up interval was used for the development of multivariable risk estimation because of the high participation rate at this time and because only a single baseline examination was available in the study. Model performance was assessed at 20 months to avoid unstable predictions occurring at the very end of follow-up.

### Statistical Analysis

A large sample was available, and we desired to validate the results of prediction models. A priori we randomly split the cohort 2:1 and developed the predictive models in two thirds of the participants and validated it in the remaining one third.

Risk analyses were performed using Cox proportional-hazard regression.<sup>16</sup> Model development included clinical judgment and careful consideration of well-accepted traditional variables for vascular disease risk assessment. Stepwise selection models were run with age, sex, and geographic region forced into the model. Treating each region as a separate stratum did not improve model performance, and we collapsed geographic region membership into higher (Eastern Europe and Middle East), intermediate (North America/Western Europe—referent), and lower (Japan or Australia)-risk locations. Separate analyses were performed for the cardiovascular event and cardiovascular death end points, and significance levels were set at 0.05 to identify candidate risk factors. In an effort to retain the same variables in both models, we included only variables that were significant in both models. Pair-wise interactions with sex and age were assessed at the 0.01 level to account for multiple testing and to avoid weak interaction signals that would not transport well with application of the function to new cohorts.

The traditional candidate variables considered for this analysis included systolic and diastolic blood pressure, blood pressure treatment, cholesterol level, diabetes mellitus, current smoking, and body mass index modeled as a continuous variable as well as in categories ( $<20$  kg/m<sup>2</sup>, 20–30 kg/m<sup>2</sup>,  $>30$  kg/m<sup>2</sup>). Variables that characterized the vascular disease burden of participants at baseline included information concerning the number of vascular beds affected, occurrence of a cardiovascular event in the year

before the baseline evaluation, history of congestive heart failure, and history of atrial fibrillation. Treatment with acetylsalicylic acid and statins also was included, but information on the type or dose of statin or the dose of acetylsalicylic acid was not available. To assess the role of previously diagnosed vascular disease, we used ordinal variables to test for the effects of 1, 2, or 3 vascular beds involved. Only data from subjects with complete outcome and covariate information for a given end point were used to obtain the rates for that end point. Statistical analysis was performed using SAS Version 9 software (SAS Institute Inc., Cary, NC).

Discrimination was assessed using C-statistics calculated for each of these models; the error associated with C-statistic estimates was estimated using published methods.<sup>17</sup> Calibration was assessed using decile plots of mean predicted and observed risks, and D'Agostino and Nam<sup>18</sup> modified Hosmer-Lemeshow chi-squared statistics with 9 degrees of freedom. Performance was assessed at 20 months of follow-up (95<sup>th</sup> percentile of follow-up for events) on both development and validation data sets. Simplified risk calculator was developed for 20-month risk prediction for cardiovascular death and next cardiovascular event using methods described by Sullivan et al.<sup>19</sup>

Event rates of cardiovascular death, myocardial infarction, stroke, and cardiovascular hospitalization were calculated. End points were not adjudicated. Cardiovascular death included fatal stroke, fatal myocardial infarction, or other cardiovascular death. Other cardiovascular death included other death of cardiac origin; pulmonary embolism; any sudden death including unobserved, and unexpected death (eg, death while sleeping) unless proven otherwise by autopsy, death following a vascular operation, vascular procedure, or amputation; death attributed to heart failure; death following a visceral or limb infarction; and any other death that could not be definitely attributed to a nonvascular cause or hemorrhage. Any myocardial infarction or stroke followed by a death, whatever the cause, in the next 28 days, was considered to be a fatal myocardial infarction or fatal stroke. Cardiovascular hospitalization consisted of hospitalization for unstable angina, transient ischemic attack, worsening of claudication related to peripheral artery disease, other ischemic arterial event, coronary artery bypass grafting, coronary angioplasty/stenting, carotid surgery, carotid angioplasty/stenting, amputation affecting lower limbs, peripheral bypass graft, or angioplasty/stenting for peripheral artery disease.<sup>13</sup>

### RESULTS

The baseline characteristics of the participants are shown in **Table 1**. Participants were followed for a maximum of 24 months, with mean follow-up of 19 and median of 21 months. There were 55,814 persons in the REACH Study who were eligible for these data analyses, and approximately 89% ( $n = 49,689$ ) from the 5473 participating study sites in 44 countries had full information on covariates at

**Table 1** Baseline Characteristics of Participants in the Development and Validation Cohorts

| Characteristic                              | Development Cohort<br>(n = 33,419) | Validation Cohort<br>(n = 16,270) |
|---------------------------------------------|------------------------------------|-----------------------------------|
| Traditional risk factors                    |                                    |                                   |
| Male, %                                     | 66.9                               | 66.8                              |
| Age, y, mean $\pm$ SD                       | 68.4 $\pm$ 10.1                    | 68.3 $\pm$ 10.2                   |
| Current smoking, %                          | 14.6                               | 13.8                              |
| Diabetes, %                                 | 36.9                               | 36.5                              |
| Body mass index                             | 27.7 $\pm$ 5.4                     | 27.7 $\pm$ 5.3                    |
| Body mass index $>30$ kg/m <sup>2</sup> , % | 27.2                               | 27.0                              |
| Body mass index $<20$ kg/m <sup>2</sup> , % | 3.8                                | 3.5                               |
| Blood pressure, mm Hg, mean $\pm$ SD        |                                    |                                   |
| Systolic                                    | 136.8 $\pm$ 19.3                   | 136.6 $\pm$ 19.5                  |
| Diastolic                                   | 78.2 $\pm$ 11.2                    | 78.2 $\pm$ 11.2                   |
| Cholesterol level, mg/dL                    | 191.4 $\pm$ 45.9                   | 191.9 $\pm$ 46.7                  |
| Atrial fibrillation, %                      | 11.7                               | 11.4                              |
| Cardiovascular burden, %                    |                                    |                                   |
| Coronary artery disease                     | 72.4                               | 72.5                              |
| Cerebrovascular disease                     | 33.8                               | 33.7                              |
| Peripheral arterial disease                 | 14.9                               | 14.5                              |
| Number of vascular beds: 1, 2, or 3         | 80.8, 17.2, 2.0                    | 81.1, 17.1, 1.8                   |
| Cardiovascular event in past year*          | 31.5                               | 32.3                              |
| Congestive heart failure*                   | 15.2                               | 15.5                              |
| Cardiovascular treatment, %                 |                                    |                                   |
| Statins                                     | 69.2                               | 68.5                              |
| Hypertension treatment                      | 91.0                               | 91.1                              |
| Acetylsalicylic acid                        | 71.5                               | 71.4                              |
| Geographic Region                           |                                    |                                   |
| North America                               | 36.4                               | 36.3                              |
| Latin America                               | 3.1                                | 3.1                               |
| Western Europe                              | 26.6                               | 26.6                              |
| Eastern Europe                              | 10.4                               | 10.9                              |
| Middle East                                 | 1.3                                | 1.3                               |
| Asia                                        | 9.4                                | 9.6                               |
| Australia                                   | 4.6                                | 4.6                               |
| Japan                                       | 8.2                                | 7.6                               |

\*Based on information obtained at baseline evaluation.

baseline and complete follow-up. By random selection, two thirds of the participants were assigned to a developmental cohort (n = 33,419), and the remaining one third were assigned to the validation cohort (n = 16,270). The baseline characteristics for these participants are shown in **Table 1**. The study participants were predominantly male (67%), and the mean age was 68 years at entry. Approximately 53% lived in Europe or Western Europe; 21% lived in Australia, Japan, or other parts of Asia, and 12% lived in Eastern Europe or the Middle East. Geographic clusters were determined according to proximity of the regions and similarities

in cardiovascular disease incidence reported within the REACH Registry over 1 year of follow-up.<sup>13</sup>

Approximately 72% had coronary artery disease, 34% had cerebrovascular disease, and 14% had peripheral artery disease. Overall, 81% of the participants had vascular disease affecting one arterial bed, 17% had 2 arterial beds involved, and 2% had 3 arterial beds involved. The occurrence of a cardiovascular event in the year before entry into the registry was common, and 32% of the participants were affected. A history of congestive heart failure at entry was less frequent, and affected 15%. Treatment with statins or acetylsalicylic acid was reported in 71% of the participants, and hypertension therapy was reported in 91%.

Among the 33,419 participants with vascular disease at baseline, there were 2394 cardiovascular events, and 1029 of these were cardiovascular deaths. Traditional risk factors (sex, age, smoking, diabetes, systolic blood pressure level, diastolic blood pressure level, low body mass index), the cardiovascular disease burden at baseline (number of vascular beds affected, cardiovascular event in the past year, history of congestive heart failure, and history of atrial fibrillation), cardiovascular treatment (hypertension therapy, statin use, acetylsalicylic acid use), and 3 geographic regions (1 – North America or Western Europe, 2 – Eastern Europe or Middle East, 3 – Japan or Australia) were evaluated for inclusion in the stepwise prediction models. The variables selected in our stepwise models included age, diabetes, smoking status, number of vascular beds affected, history of atrial fibrillation, cardiac failure, history of cardiovascular event(s)  $<1$  year before the baseline examination, body mass index  $<20$  kg/m<sup>2</sup>, geographic region, statin use, and acetylsalicylic acid therapy. The results of the multivariable prediction of recurrent cardiovascular events and cardiovascular death with the hazard ratios and statistical significance are shown in **Table 2**. All variables in the table were significant at  $P < .05$  level in both models. Candidate variables in the stepwise regression model that did not make it to final model included systolic blood pressure, diastolic blood pressure, and cholesterol level.

To test the ability of the prediction model to discriminate the risk of recurrent cardiovascular events in other regions, we used a validation set of 16,270 REACH participants who had not been included in the developmental data set. These participants met the same entry criteria and had the same duration of follow-up for CV events. In the validation data set, there were 1172 recurrent cardiovascular events and 494 cardiovascular deaths during the follow-up interval. The C-statistic for the prediction of a next cardiovascular event was 0.67 (95% confidence interval [CI], 0.66-0.68) for both the developmental and the validation datasets. The corresponding C-statistic for the prediction of cardiovascular death was 0.74 (95% CI, 0.73-0.76) for the developmental dataset and 0.75 (95% CI, 0.73-0.77) for the internal validation dataset. The D'Agostino and Nam<sup>18</sup> chi-squared value was 15.14 in the validation set for prediction of next cardiovascular events, indicating good calibration for this outcome. The corresponding

**Table 2** Multivariable Prediction of Recurrent Cardiovascular Events\* in the Development Cohort

| Factor                                      | Type of Cardiovascular Event                  |                                                    |
|---------------------------------------------|-----------------------------------------------|----------------------------------------------------|
|                                             | Cardiovascular Death<br>Hazard Ratio (95% CI) | Next Cardiovascular Event<br>Hazard Ratio (95% CI) |
| Traditional risk factors                    |                                               |                                                    |
| Male sex                                    | 1.28 (1.12-1.46)                              | 1.11 (1.02-1.21)                                   |
| Age, years                                  | 1.05 (1.04-1.06)                              | 1.03 (1.03-1.04)                                   |
| Smoking (current vs other)                  | 1.36 (1.13-1.64)                              | 1.27 (1.13-1.43)                                   |
| Diabetes (yes/no)                           | 1.59 (1.40-1.80)                              | 1.46 (1.34-1.58)                                   |
| BMI <20 kg/m <sup>2</sup>                   | 1.74 (1.34-2.24)                              | 1.37 (1.14-1.64)                                   |
| Cardiovascular disease burden at baseline   |                                               |                                                    |
| Number of vascular beds                     |                                               |                                                    |
| 1                                           | 1.00 (referent)                               | 1.00 (referent)                                    |
| 2                                           | 1.28 (1.15-1.43)                              | 1.35 (1.26-1.46)                                   |
| 3                                           | 1.64 (1.32-2.06)                              | 1.83 (1.58-2.13)                                   |
| Cardiovascular event* in past year (yes/no) | 1.31 (1.15-1.49)                              | 1.46 (1.35-1.59)                                   |
| Congestive heart failure (yes/no)           | 2.46 (2.15-2.82)                              | 1.68 (1.53-1.85)                                   |
| Atrial fibrillation (yes/no)                | 1.53 (1.32-1.78)                              | 1.30 (1.17-1.46)                                   |
| Cardiovascular treatment                    |                                               |                                                    |
| Statins (yes/no)                            | 0.80 (0.70-0.91)                              | 0.75 (0.69-0.82)                                   |
| Acetylsalicylic acid (yes/no)               | 0.84 (0.73-0.95)                              | 0.90 (0.83-0.99)                                   |
| Adjustment for geographic region            |                                               |                                                    |
| North America or Western Europe             | 1.00 (referent)                               | 1.00 (referent)                                    |
| Eastern Europe or Middle East               | 1.30 (1.07-1.57)                              | 1.32 (1.17-1.48)                                   |
| Japan or Australia                          | 0.52 (0.41-0.66)                              | 0.73 (0.64-0.84)                                   |

BMI = body mass index; CI = confidence interval.

\*A cardiovascular event is defined as an occurrence of myocardial infarction, cerebrovascular disease, or cardiovascular death.

D'Agostino and Nam<sup>18</sup> chi-squared for the prediction of cardiovascular death also was acceptable at 19.45. Decile-based calibration plots suggested satisfactory performance for both outcomes (**Figure 1**).

A risk score sheet for the development of the next cardiovascular event and for cardiovascular death in patients with clinically recognized atherothrombotic cardiovascular disease is shown in **Figure 2**. Using this approach, the patient information for age, current smoking, diabetes mellitus, number of vascular beds, cardiovascular event in the past year, congestive heart failure, statin therapy, and acetylsalicylic acid therapy are matched with the status for each variable, and the assigned number of points are then summed. The total number of points is then matched with the estimated 20-month risk. Using **Figure 2**, the number of risk points for a next cardiovascular event in a person with the following characteristics: man (+1), 62 years old (+8), nonsmoker (+0), diabetes present (+2), body mass index 25 kg/m<sup>2</sup> (+0), history of myocardial infarction in the past 3 months (+2 for one vascular bed, +2 for event in the past year), history of congestive heart failure (+3), no history of atrial fibrillation (+0), taking statins (−2), taking acetylsalicylic acid (−1), Eastern Europe residence (+2), and the sum is 17 points for a next cardiovascular event, which translates to an absolute risk of 11% over a 20-month interval. Similarly, the number of risk points for cardiovascular

death (1 + 8 + 0 + 2 + 0 + 2 + 2 + 3 + 0 − 2 − 1 + 1 + 2 = 18 points), corresponds to a 13% risk over a 20-month interval. Risk calculations can also be made using methods shown in the **Appendix**.

## DISCUSSION

This study uses multivariable Cox regression analysis to identify factors that contribute to the risk of secondary ischemic events in a large, contemporary registry of patients with established cardiovascular disease. The factors that were statistically significant in the analyses included traditional risk variables for initial cardiovascular disease events (age, smoking, diabetes mellitus, body mass index), variables related to cardiovascular disease burden (number of vascular beds involved, history of a cardiovascular event in the year before the baseline evaluation, history of congestive heart failure, and history of atrial fibrillation), and use of cardiovascular risk reduction treatments (current use of statins or acetylsalicylic acid). This is the first international, prospective study to establish a comprehensive risk model to predict subsequent cardiovascular events and cardiovascular death in outpatients with established atherothrombotic disease.

Most of the research concerning prediction of cardiovascular disease has focused on first cardiovascular events, and has reported on the experience of apparently

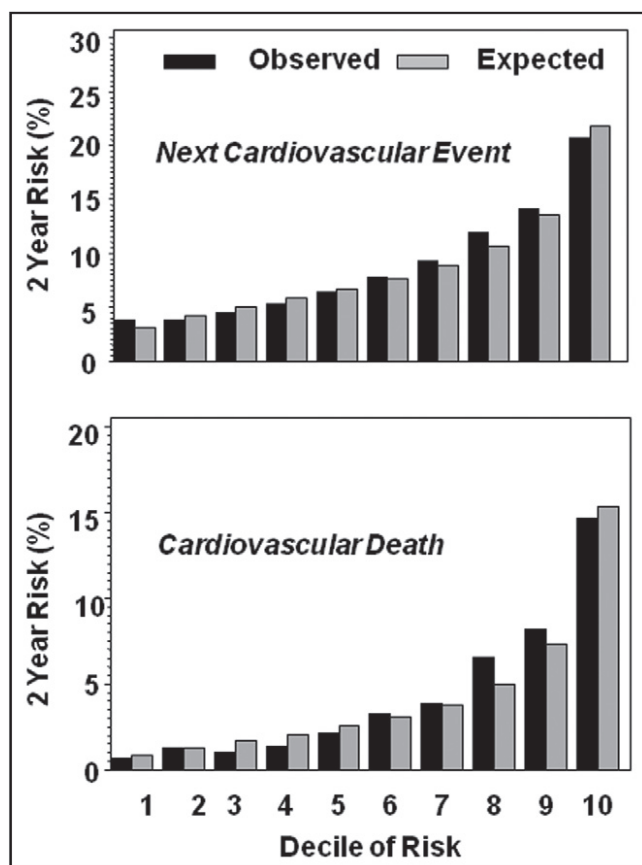


**Figure 1** Calibration by decile according to risk for next cardiovascular events and for cardiovascular death. Bars represent observed (Kaplan-Meier; black) and model-based predicted (decile specific means; gray) probabilities of a cardiovascular outcome over 20 months in deciles of model-based predicted probabilities.

healthy individuals who are “at risk.” With that approach the variables age, sex, cholesterol level, blood pressure, smoking, and diabetes mellitus have typically been used to predict events.<sup>1,5,7</sup> Over the past 3 decades, the treatment of first cardiovascular events has improved, survival has increased, and health care providers are increasingly required to provide effective long-term care for outpatients with established cardiovascular disease. It is helpful to identify, within this relatively large group of patients, those individuals at greatest short-term risk of a subsequent cardiovascular event or cardiovascular death in order to target them for more intensive follow-up, investigation, and treatment. Symptoms, traditional risk factors for initial vascular disease events, the burden of known vascular disease, and the results of specialized testing may affect risk for future vascular disease events.<sup>3</sup> In addition to increasing age and male sex, the key factors that have been associated with increased risk of cardiovascular events have been higher blood pressure, cholesterol, lower high-density lipoprotein cholesterol, diabetes mellitus, and cigarette smoking.<sup>1,3</sup>

The initial REACH analyses tested for associations between traditional risk factors used in formulations like the Framingham risk model for initial cardiovascular disease events,<sup>20</sup> and recurrent cardiovascular events included age, sex, systolic blood pressure, diastolic blood pressure, diabetes mellitus, and cigarette smoking.<sup>1</sup> From this list of variables, age was highly associated with recurrent cardiovascular disease, and in age-adjusted regression models that considered the variables individually, only current smoking and the presence of diabetes mellitus were associated with recurrent cardiovascular disease. As shown in the multivariable analysis presented in [Table 2](#), these variables (age, smoking, diabetes, and low body mass index) were significantly associated with recurrent cardiovascular events in the multivariable prediction model. An adverse effect of low body mass index on risk for future cardiovascular events has been noted for patients with cardiovascular disease and may represent poor nutrition and cachexia in severely ill patients.<sup>21</sup> The REACH registry is a global study and allowed for investigation of vascular disease risk according to where the participant resided. In multivariable analysis, risk for recurrent cardiovascular disease was lower in some regions (Japan, Australia) and higher in others (Eastern Europe, Middle East) in comparison with the other sites, where the referent was the combined experience of Europe and North America. Further investigation into the origins of these differences is merited, and public health experts have identified a need to prevent and manage chronic diseases throughout the world.<sup>22</sup>

Baseline levels of blood cholesterol, systolic pressure, and diastolic pressure were not related to the development of recurrent cardiovascular events. Part of the explanation for this finding may be that medications to treat these conditions were very commonly used at the baseline examination. As shown in [Table 1](#), current statin use at entry into the registry was reported for 74% of the participants. The survey form used in the study only queried whether the cholesterol level was >200 mg/dL, and information on the actual cholesterol level at baseline was not available for all participants.

This study investigated the potential effect of the burden of cardiovascular disease on the risk of recurrent cardiovascular events. As described above for the traditional variables, the initial approach tested for age- and sex-adjusted associations between the cardiovascular burden variables (shown in [Table 1](#)) and cardiovascular death or recurrent cardiovascular disease. In an effort to summarize the potential risk associated with atherothrombotic disease involving multiple vascular beds, we used a composite variable “number of vascular beds affected by symptomatic vascular disease,” which was highly associated with recurrent ischemic events. In addition, the occurrence of a cardiovascular event in the year before the baseline examination and a positive history of congestive heart failure were associated with greater risk of recurrent atherothrombotic events. In the multivariable analyses shown in [Table 2](#), each of these

| Step | Factor                           | Next CV event:<br>factors and points                                                                                         | CV<br>event<br>points | CV death:<br>factors and points                                                                                              | CV<br>death<br>points |
|------|----------------------------------|------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| 1    | Sex                              | Man Woman<br>1 0                                                                                                             |                       | Man Woman<br>1 0                                                                                                             |                       |
| 2    | Age, years                       | 20-24 25-29 30-34 35-39 40-44 45-49 50-54<br>0 1 2 3 4 5 6<br>55-59 60-64 65-69 70-74 75-79 80-84 85-89<br>7 8 9 10 11 12 13 |                       | 20-24 25-29 30-34 35-39 40-44 45-49 50-54<br>0 1 2 3 4 5 6<br>55-59 60-64 65-69 70-74 75-79 80-84 85-89<br>7 8 9 10 11 12 13 |                       |
| 3    | Smoking                          | No Yes<br>0 2                                                                                                                |                       | No Yes<br>0 1                                                                                                                |                       |
| 4    | Diabetes mellitus                | No Yes<br>0 2                                                                                                                |                       | No Yes<br>0 2                                                                                                                |                       |
| 5    | BMI < 20 kg/m <sup>2</sup>       | No Yes<br>0 2                                                                                                                |                       | No Yes<br>0 2                                                                                                                |                       |
| 6    | Number of<br>vascular beds       | One Two Three<br>2 4 6                                                                                                       |                       | One Two Three<br>1 2 3                                                                                                       |                       |
| 7    | CV event in past<br>year         | No Yes<br>0 2                                                                                                                |                       | No Yes<br>0 1                                                                                                                |                       |
| 8    | Congestive heart<br>failure      | No Yes<br>0 3                                                                                                                |                       | No Yes<br>0 4                                                                                                                |                       |
| 9    | Atrial fibrillation              | No Yes<br>0 2                                                                                                                |                       | No Yes<br>0 2                                                                                                                |                       |
| 10   | Statin therapy                   | No Yes<br>0 -2                                                                                                               |                       | No Yes<br>0 -1                                                                                                               |                       |
| 11   | ASA therapy                      | No Yes<br>0 -1                                                                                                               |                       | No Yes<br>0 -1                                                                                                               |                       |
| 12   | Eastern Europe or<br>Middle East | No Yes<br>0 2                                                                                                                |                       | No Yes<br>0 1                                                                                                                |                       |
| 13   | Japan or Australia               | No Yes<br>0 -2                                                                                                               |                       | No Yes<br>0 -3                                                                                                               |                       |
| 14   |                                  | Next CV event points total                                                                                                   |                       | CV death points total                                                                                                        |                       |

**Figure 2** Score sheet to estimate the risk of the next cardiovascular event and of cardiovascular death over 20 months of follow-up, based on separate, multivariable, regression-estimating equations for each outcome. The sheet is used by assigning points for each factor, summing the points, and determining the percentage risk of either the next cardiovascular event or of cardiovascular death. CV = cardiovascular.

variables was associated with the development of recurrent cardiovascular disease.

Treatments for cardiovascular disease were considered as potential predictive factors in these analyses, and the

factors of blood pressure treatment, lipid-lowering therapy, and use of acetylsalicylic acid were considered. Almost all of the lipid-lowering medications being used were statins, which led to our using that single medica-

| Step 15 Calculation of risk from point score total |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |    |     |
|----------------------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|-----|
| Next CV event points                               | 0   | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  | 17 | 18  |
| 20-month risk of next CV event, %                  | <1  | 1   | 1.2 | 1.4 | 1.6 | 1.9 | 2.2 | 2.5 | 3   | 3.5 | 4   | 4.7 | 5.4 | 6.3 | 7.3 | 8.5 | 9.8 | 11 | 13  |
| Next CV event points                               | 19  | 20  | 21  | 22  | 23  | 24  | 25  | 26  | 27  | 28  | ≥29 |     |     |     |     |     |     |    |     |
| 20-month risk of next CV event, %                  | 15  | 17  | 20  | 23  | 26  | 30  | 34  | 38  | 43  | 48  | >50 |     |     |     |     |     |     |    |     |
| CV death points                                    | 0-8 | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  | 17  | 18  | 19  | 20  | 21  | 22  | 23  | 24  | 25 | ≥26 |
| 20-month risk of CV death, %                       | <1  | 1.1 | 1.4 | 1.8 | 2.3 | 3   | 3.8 | 4.9 | 6.2 | 7.9 | 10  | 13  | 16  | 20  | 25  | 30  | 37  | 45 | >50 |

Figure 2 Continued

tion as the lipid treatment variable. The use of antiplatelet medications other than acetylsalicylic acid was uncommon (<28%), and those data were not analyzed for potential associations with recurrent cardiovascular outcomes. Initial age- and sex-adjusted analyses showed no relation between blood pressure medication use and the development of recurrent cardiovascular events. On the other hand, both statin medications and acetylsalicylic acid use were associated with a significantly lower risk for recurrent cardiovascular events and cardiovascular death in the multivariable analyses (Table 2).

The strengths of this study include its large size, contemporary data collection, international scope, and consideration of several vascular disease event types. The study has limitations. A central laboratory for measurement of the lipid levels was not available, newer risk-factor variables such as inflammatory markers or natriuretic peptides were not included, and nonfatal ischemic event end points were not adjudicated. The risk prediction variables shown to be important determinants for recurrent cardiovascular disease and for cardiovascular death in patients who have already experienced at least one cardiovascular event should be investigated in other population samples. We have provided internally validated estimates of risk for recurrent cardiovascular disease and for cardiovascular death in patients who have already experienced a clinical vascular disease event. We encourage other research groups to use similar strategies to evaluate the risk of vascular disease events in this setting. The REACH Registry reflects the experience of outpatient clinics that were included as part of a research study, and the external validation of our research approach is of interest. We believe that investigating the components of vascular disease risk is probably more important than corroborating absolute risk estimates, which are likely to improve over time with more effective therapies for patients known to have clinical cardiovascular disease.

Future research endeavors should consider prognostic factors beyond traditional risk markers that have been used

to estimate risk for initial cardiovascular events. These factors include elements that identify the burden of ischemic atherothrombotic disease such as polyvascular disease, heart failure, a recent cardiovascular event, history of atrial fibrillation, and the salutary effects of medications such as statins and acetylsalicylic acid.

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## APPENDIX

**Table** Cox Model Coefficients for Calculation of 20-Month Risk of Recurrent Cardiovascular Events

| Factor                                      | Type of Cardiovascular Event    |                                      |
|---------------------------------------------|---------------------------------|--------------------------------------|
|                                             | Cardiovascular Death<br>$\beta$ | Next Cardiovascular Event<br>$\beta$ |
| Traditional risk factors                    |                                 |                                      |
| Male sex                                    | 0.24519                         | 0.10246                              |
| Age, years                                  | 0.04966                         | 0.03089                              |
| Smoking (current vs other)                  | 0.30925                         | 0.24121                              |
| Diabetes (yes/no)                           | 0.46141                         | 0.37824                              |
| BMI < 20 kg/m <sup>2</sup>                  | 0.55132                         | 0.31428                              |
| Cardiovascular disease burden at baseline   |                                 |                                      |
| Number of vascular beds                     | 0.24928                         | 0.30277                              |
| Cardiovascular event* in past year (yes/no) | 0.26681                         | 0.38168                              |
| Congestive heart failure (yes/no)           | 0.89976                         | 0.51873                              |
| Atrial fibrillation (yes/no)                | 0.42705                         | 0.26652                              |
| Cardiovascular treatment                    |                                 |                                      |
| Statins (yes/no)                            | -0.22296                        | -0.28332                             |
| Acetylsalicylic acid (yes/no)               | -0.17968                        | -0.10151                             |
| Aemsubstment for geographic region          |                                 |                                      |
| Eastern Europe or Middle East               | 0.25934                         | 0.27574                              |
| Japan or Australia                          | -0.65524                        | -0.31604                             |

BMI = body mass index.

\*The 20-month risk for cardiovascular death can be calculated as  $1-0.97749^{\exp(\sum \beta X - 4.03317)}$ , where  $\beta$  is the regression coefficient and X is the level for each risk factor; the risk for next cardiovascular event is given as  $1-0.93681^{\exp(\sum \beta X - 2.68845)}$ .

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