

Comparative Determinants of 4-Year Cardiovascular Event Rates in Stable Outpatients at Risk of or With Atherothrombosis

Deepak L. Bhatt, MD, MPH

Kim A. Eagle, MD

E. Magnus Ohman, MD

Alan T. Hirsch, MD

Shinya Goto, MD, PhD

Elizabeth M. Mahoney, ScD

Peter W. F. Wilson, MD

Mark J. Alberts, MD

Ralph D'Agostino, PhD

Chiau-Suong Liao, MD, PhD

Jean-Louis Mas, MD

Joachim Röther, MD

Sidney C. Smith Jr, MD

Geneviève Salette, PharmD, MSc

Charles F. Contant, PhD

Joseph M. Massaro, PhD

Ph. Gabriel Steg, MD

for the REACH Registry Investigators

PATIENTS WITH ATHEROTHROMBOSIS are at elevated risk of ischemic events but, depending on their specific manifestations of atherothrombosis, may have varying degrees of future risk for ischemic events. Accurate knowledge of the major determinants of subsequent ischemic risk would be extremely useful, both for clinical and investigational purposes.

Several recent clinical trials of new agents in acute coronary syndromes, stable atherosclerosis, and diabetes mellitus have reported event rates lower than initially projected.¹⁻⁶ The ability to identify patients at highest risk of cardiovascular events would allow trials of novel therapies to focus on those patients most likely to derive benefit. For clinicians, the ability to

Context Clinicians and trialists have difficulty with identifying which patients are highest risk for cardiovascular events. Prior ischemic events, polyvascular disease, and diabetes mellitus have all been identified as predictors of ischemic events, but their comparative contributions to future risk remain unclear.

Objective To categorize the risk of cardiovascular events in stable outpatients with various initial manifestations of atherothrombosis using simple clinical descriptors.

Design, Setting, and Patients Outpatients with coronary artery disease, cerebrovascular disease, or peripheral arterial disease or with multiple risk factors for atherothrombosis were enrolled in the global Reduction of Atherothrombosis for Continued Health (REACH) Registry and were followed up for as long as 4 years. Patients from 3647 centers in 29 countries were enrolled between 2003 and 2004 and followed up until 2008. Final database lock was in April 2009.

Main Outcome Measures Rates of cardiovascular death, myocardial infarction, and stroke.

Results A total of 45 227 patients with baseline data were included in this 4-year analysis. During the follow-up period, a total of 5481 patients experienced at least 1 event, including 2315 with cardiovascular death, 1228 with myocardial infarction, 1898 with stroke, and 40 with both a myocardial infarction and stroke on the same day. Among patients with atherothrombosis, those with a prior history of ischemic events at baseline (n=21 890) had the highest rate of subsequent ischemic events (18.3%; 95% confidence interval [CI], 17.4%-19.1%); patients with stable coronary, cerebrovascular, or peripheral artery disease (n=15 264) had a lower risk (12.2%; 95% CI, 11.4%-12.9%); and patients without established atherothrombosis but with risk factors only (n=8073) had the lowest risk (9.1%; 95% CI, 8.3%-9.9%) ($P < .001$ for all comparisons). In addition, in multivariable modeling, the presence of diabetes (hazard ratio [HR], 1.44; 95% CI, 1.36-1.53; $P < .001$), an ischemic event in the previous year (HR, 1.71; 95% CI, 1.57-1.85; $P < .001$), and polyvascular disease (HR, 1.99; 95% CI, 1.78-2.24; $P < .001$) each were associated with a significantly higher risk of the primary end point.

Conclusion Clinical descriptors can assist clinicians in identifying high-risk patients within the broad range of risk for outpatients with atherothrombosis.

JAMA. 2010;304(12):1350-1357

www.jama.com

identify rapidly the major determinants of risk among patients with atherosclerosis would be useful to triage novel preventive therapies toward those at the higher end of the risk spectrum. Thus, the international Reduction of Atherothrombosis for Continued Health (REACH) Registry, a contemporary data set comprising patients with various manifestations of atherosclerosis, spanning from asymptomatic adults with risk factors, to patients

with stable atherosclerosis, to those with prior ischemic events, would be potentially useful to establish the risk of future ischemic events. Herein, the 4-year results of the REACH Registry are presented.

Author Affiliations are listed at the end of this article. A complete list of the REACH Registry Investigators was published in *JAMA*. 2006;295(2):180-189.

Corresponding Author: Deepak L. Bhatt, MD, MPH, VA Boston Healthcare System, 1400 VFW Parkway, Boston, MA 02132 (dlbhattmd@post.harvard.edu).

METHODS

The methods of the REACH Registry have been published in detail previously.⁷⁻¹⁰ This protocol was submitted to institutional review boards in each country according to the local requirements and signed informed consent was required for all patients. Briefly, patients at least 45 years old with 3 or more risk factors for atherosclerosis and patients with established coronary artery disease, peripheral arterial disease, or cerebrovascular disease were enrolled. The multiple risk factors category consisted of diabetes, diabetic nephropathy, ankle-brachial index less than 0.9, asymptomatic carotid stenosis of 70% or more, carotid intima media thickness at least 2 times that at adjacent sites, systolic blood pressure of 150 mm Hg or higher despite treatment, hypercholesterolemia treated with medication, current smoking of 15 or more cigarettes per day, and age 65 years and older for men or 70 years and older for women.

Documented coronary artery disease consisted of 1 or more of the following: stable angina, history of unstable angina, history of percutaneous coronary intervention, history of coronary artery bypass grafting, or previous myocardial infarction. Documented cerebrovascular disease consisted of a neurologist report or hospital report with the diagnosis of ischemic stroke or transient ischemic attack. Documented peripheral artery disease consisted of current intermittent claudication with ankle-brachial index of less than 0.9 and/or a history of intermittent claudication together with a previous intervention, such as angioplasty, stenting, atherectomy, peripheral arterial bypass grafting, or other vascular interventions, including amputations. Diabetes was defined as any history of diabetes or current diabetes (diagnosed by at least 2 fasting blood glucose measures >126 mg/dL; to convert to mmol/L, multiply by 0.0555) treated with medication, lifestyle, or both.

Detailed information was collected at baseline, with subsequent annual follow-up at 1, 2, 3, and 4 years.^{7,9} Patients were enrolled between 2003 and 2004 and followed up until 2008. Final database lock

was in April 2009. The initial follow-up was planned for up to 2 years and shortly before that point, an additional 2-year extension was proposed. Not all countries and sites that were in the 2-year follow-up cohort elected to continue participation in the registry, largely for financial reasons, although the majority did elect to continue. Countries and sites that decided not to participate in the 4-year follow-up were excluded from the results.

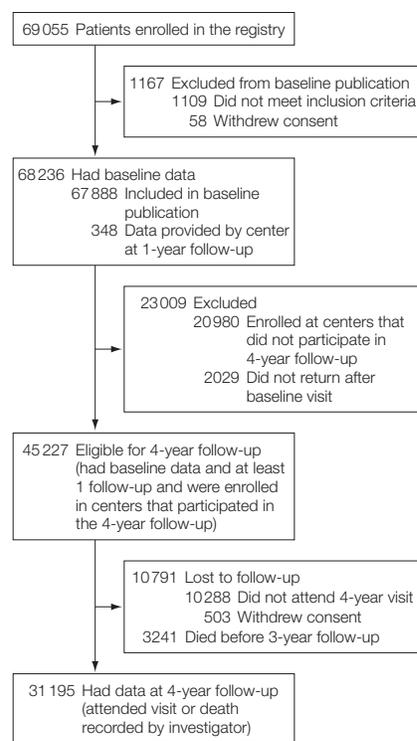
Event rates of cardiovascular death, myocardial infarction, stroke, and cardiovascular hospitalization were calculated. End points were not adjudicated. Cardiovascular death included fatal stroke, fatal myocardial infarction, or other cardiovascular death. Other cardiovascular death included other death 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.

Groups based on the enrollment criteria of risk factors only (for example, diabetic patients without established disease), stable atherosclerosis (without prior myocardial infarction or stroke but with atherosclerosis established objectively, for example, patients with a history of revascularization), or prior ischemic events (myocardial infarction or stroke) were compared. On the case report form, the time of previous ischemic event was re-

corded as 1 year or less or longer than 1 year; no specific date of event was recorded. For the purposes of comparing event rates, patients were also classified as having diabetes or polyvascular disease at baseline. Polyvascular disease was defined as having atherosclerosis in 2 or 3 arterial beds (coronary, peripheral, cerebrovascular) at baseline.

All analyses were performed on patients eligible for the 4-year follow-up study, defined as all patients who completed at least 1 postbaseline follow-up visit and who were enrolled at centers that agreed to participate in the 4-year follow-up study. Continuous variables are expressed as mean (standard deviation), and categorical variables are expressed as frequencies and percentages. Cumulative incidence

Figure 1. Flow Diagram of Study Participants



Complete baseline data were available for 67 888 patients at time of baseline publication. Complete 1-year follow-up data were available for 64 977 patients (lost to follow-up were 3248 patients who did not attend 1-year visit and 11 who withdrew consent). At the 3-year follow-up, 48 050 patients were eligible. Complete 3-year follow-up data were available for 36 608 patients (2301 died before the 2-year follow-up; lost to follow-up were 8712 who did not attend 3-year visit and 429 who withdrew consent).

rates are reported after adjustment for age and sex. Multivariable analysis was performed to determine the predictors of 4-year cardiovascular death, myocardial infarction, or stroke; the variables entered in the Cox model were sex; age; current smoker; history of diabetes; body mass index less than 20 (calculated as weight in kilograms divided by height in meters squared); ischemic event (≤ 1 year, > 1 year, or no ischemic event); vascular disease status (polyvascular disease, single vascular disease, or risk factors only); congestive heart failure; atrial fibrillation/flutter; statins (at base-

line); aspirin (at baseline); and Eastern Europe, Middle East, or Japan vs other regions. Geographic regions were collapsed into higher (Eastern Europe and Middle East) and lower (Japan) risk locations.

Candidate variables considered in that model that were not significant included systolic and diastolic blood pressure at baseline, cholesterol levels at baseline, and blood pressure treatment. No method was used to impute missing values or adjust the model for the presence of missing data, as the frequency of baseline missing data was very low (under 1% or 2% for most

variables). Deaths due to noncardiovascular causes were censored. Four-year event rates as a function of different baseline risk features were generated using the corrected group prognosis method.¹¹ This method provides an alternative form for estimating survival rates from the Cox model. The cumulative incidence curves for cardiovascular death, myocardial infarction, or stroke were constructed using the Kaplan-Meier approach. Statistical significance was considered as a 2-sided probability of less than .05. Statistical analyses were performed using SAS version 9 (SAS Institute, Cary, North Carolina).

Table 1. Baseline Characteristics of the Patients in the 4-Year Analysis and Medication Use at the 4-Year Visit^a

Baseline characteristic	Patients With 4-Year Follow-up			
	All (n = 45 227)	Prior Ischemic Event at Baseline (n = 21 890)	Stable Atherosclerosis Without Prior Ischemic Event at Baseline (n = 15 264)	Risk Factors Only (n = 8073)
Age, mean (SD), y	68.4 (10.0)	67.8 (10.1)	68.9 (9.9)	69.2 (9.7)
Men, %	64.7	70.1	64.8	49.8
Cardiovascular risk factors, %				
Hypertension	81.3	79.3	79.7	89.6
Hypercholesterolemia	70.4	67.3	69.6	80.2
Diabetes mellitus	43.6	36.5	37.3	74.7
Obesity (body mass index ≥ 30) ^b	28.4	25.0	27.1	40.0
Current smoker at baseline	15.6	14.4	15.4	19.2
Heart failure	13.6	17.9	11.7	5.8
Atrial fibrillation	10.3	11.9	10.2	6.2
Vascular disease status, %				
CAD at baseline	58.4	70.8	71.4	0
CVD at baseline	28.3	45.9	18.1	0
PAD at baseline	13.0	9.6	24.7	0
Medication use at 4 y, %	(n = 31 195)	(n = 15 146)	(n = 10 591)	(n = 5458)
≥ 1 Antithrombotic drug	88.0	93.2	91.2	67.5
Diabetic patients with ≥ 1 antidiabetic drug	87.0	83.8	86.0	91.7
≥ 1 Lipid-lowering drug	77.1	76.0	77.6	79.0
Statin	72.6	72.6	72.9	72.2
ACE inhibitor or ARB	69.4	69.8	65.4	76.0
Aspirin alone	56.0	56.6	57.2	51.8
β -Blocker	51.4	56.4	53.0	34.6
Diuretic	43.9	42.0	42.8	51.4
ACE inhibitor	43.3	46.1	40.2	41.7
Calcium-channel blocker	37.9	35.6	39.0	41.8
ARB	29.3	26.4	28.2	39.4
Nitrate or other antiangina medication	23.0	27.2	26.0	5.5
Other antiplatelet drug alone	13.2	14.6	14.6	6.4
Oral anticoagulant drug	12.6	14.5	12.4	7.5
Aspirin + another antiplatelet drug	11.2	13.4	12.0	3.7
Other antihypertensive	8.9	8.0	8.6	11.5

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor antagonist; CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease.

^aDenominators may vary due to missing data. Ischemic events were defined as myocardial infarction or stroke.

^bCalculated as weight in kilograms divided by height in meters squared.

RESULTS

Of the 68 236 patients enrolled in the REACH Registry who had baseline data, 45 227 who were enrolled at 3647 centers in 29 countries were eligible for inclusion in the 4-year follow-up study and contributed 4-year outcomes data (20 980 patients enrolled at centers that did not participate in 4-year follow-up; 2029 patients did not return after baseline visit) (FIGURE 1).

The countries included were Austria (n = 1458), Belgium (n = 316), Brazil (n = 331), Canada (n = 1975), Chile (n = 244), China (n = 679), Taiwan (n = 764), Finland (n = 297), France (n = 3904), Germany (n = 4508), Greece (n = 610), Hong Kong (n = 171), Hungary (n = 926), Israel (n = 314), Japan (n = 5073), Malaysia (n = 417), Mexico (n = 801), the Netherlands (n = 305), Philippines (n = 985), Portugal (n = 209), Romania (n = 2005), Russia (n = 999), Spain (n = 1886), Switzerland (n = 632), Thailand (n = 506), United Arab Emirates (n = 150), Ukraine (n = 596), the United Kingdom (n = 496), and the United States (n = 13 670).

The baseline characteristics of the 45 227 patients and the medication use at 4 years in the 31 195 patients who had data at the 4-year follow-up are shown in TABLE 1. The patients' mean age was 68.4 years and approximately two-thirds were men. Hypertension (81.3%) and hypercholesterolemia (70.4%) were very common; diabetes

was present in 43.6% of patients. Polyvascular disease was present in 15.9% of patients; 48.4% had prior ischemic events, with 28.1% of those having an ischemic event within the previous year. A majority of patients were treated with antiplatelet and lipid-lowering therapies.

During the follow-up period, a total of 5481 patients experienced at least 1 event, including 2315 with cardiovascular death, 1228 with myocardial infarction, 1898 with stroke, and 40 with both a myocardial infarction and stroke reported on the case report form as occurring on the same day. TABLE 2 lists the multivariable predictors of cardiovascular death, myocardial infarction, or stroke at 4 years. The *c* statistic for this model was 0.68 (95% confidence interval [CI], 0.67-0.69). Bootstrap validation of the *c* statistic yielded a value of 0.67, only minimally different from the observed value of 0.68. The risk of the triple ischemic end point over time in this population was essentially constant (FIGURE 2). The model described in Table 2 was refit using a 3-level factor for region: North America/Western Europe, Japan, and all other regions. Two-way interactions were fit between re-

gion and the 2 components of the diagnosis: duration of ischemia (3 levels: ≤ 1 year, > 1 year, no ischemia) and type of disease (3 levels: polyvascular, single disease, risk factors only). Neither of these 2-way interactions was significant ($P = .76$ for duration of ischemia; $P = .63$ for type of disease). These results indicate that for the diagnosis variable, there was no evidence that the

effect of this variable on cardiovascular death, myocardial infarction, or stroke differed by region.

FIGURE 3 shows the event rates for patients with risk factors only (9.1%; 95% CI, 8.3%-9.9%), stable atherosclerosis without prior ischemic events (12.2%; 95% CI, 11.4%-12.9%), and those with prior ischemic events (18.3%; 95% CI, 17.4%-19.1%), and the

Table 2. Multivariable Predictors of Cardiovascular Death, Myocardial Infarction, or Stroke From the Cox Regression Model

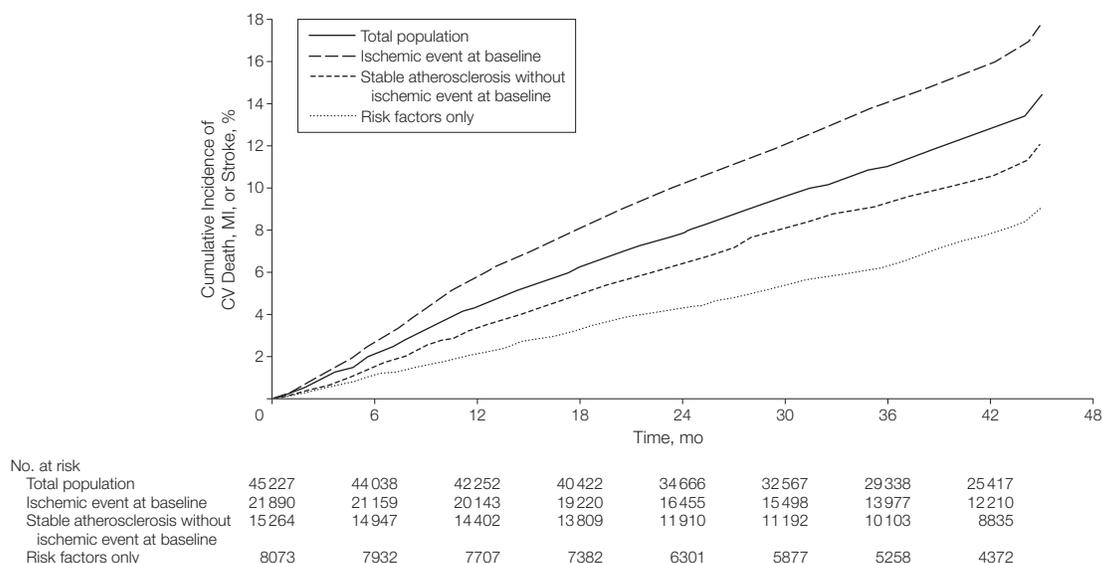
Variable	HR (95% CI)	Estimate	P Value
Polyvascular disease vs risk factors only	1.99 (1.78-2.24)	0.69	<.001
Congestive heart failure, yes vs no	1.71 (1.60-1.83)	0.54	<.001
Ischemic event ≤ 1 y vs no ischemic event	1.71 (1.57-1.85)	0.53	<.001
History of diabetes, yes vs no	1.44 (1.36-1.53)	0.37	<.001
Ischemic event > 1 y vs no ischemic event	1.41 (1.32-1.51)	0.34	<.001
Single vascular territory disease vs risk factors only	1.39 (1.25-1.54)	0.33	<.001
Body mass index < 20 , yes vs no ^a	1.30 (1.14-1.49)	0.26	<.001
Smoker, current vs former or never	1.30 (1.20-1.41)	0.26	<.001
Eastern Europe and Middle East vs other regions ^b	1.28 (1.19-1.39)	0.25	<.001
Atrial fibrillation/flutter, yes vs no	1.28 (1.18-1.38)	0.25	<.001
Sex, male vs female	1.14 (1.07-1.21)	0.13	<.001
Age, per 1-year increase	1.04 (1.03-1.04)	0.03	<.001
Aspirin, yes vs no	0.93 (0.87-0.98)	-0.08	.01
Statins, yes vs no	0.73 (0.69-0.77)	-0.31	<.001
Japan vs other regions ^b	0.70 (0.63-0.77)	-0.36	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aCalculated as weight in kilograms divided by height in meters squared.

^bOther regions were North America, Latin America, Western Europe, and Asia.

Figure 2. Kaplan-Meier Cumulative Incidence Curves for the Composite End Point of Cardiovascular Death, Myocardial Infarction, or Stroke in the Entire Population With 4-Year Follow-up and Key Subgroups



Only first events are included. CV indicates cardiovascular; MI, myocardial infarction.

additional risk of diabetes (hazard ratio [HR], 1.44; 95% CI, 1.36-1.53; $P < .001$) or polyvascular disease (HR, 1.99; 95% CI, 1.78-2.24; $P < .001$) at baseline. From the lowest-risk subgroup to the highest-risk subgroup, the primary end point event rates ranged from 7.1% to 25%.

TABLE 3 shows the event rates for patients with risk factors only, stable atherosclerosis without prior ischemic events (single/polyvascular disease), and prior ischemic events (single/polyvascular disease). The total number of patients represents those eligible for the 4-year follow-up. The rates

of the primary end point and its components are shown. The majority of deaths were due to cardiovascular causes in this population. Rates of cardiovascular hospitalization were high. The cumulative rate of cardiovascular death, myocardial infarction, stroke, or cardiovascular hospitalization ranged from 16.6% in the risk factor-only group to 47.1% in the patients with a baseline history of prior ischemic events and polyvascular disease.

FIGURE 4 illustrates the additional risk of having an ischemic event during the year prior to enrollment vs more remotely in those patients with a his-

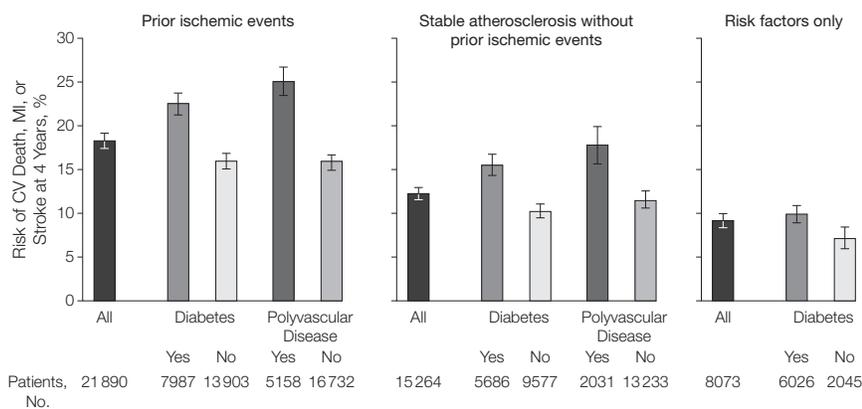
tory of an ischemic event at baseline. Those with a prior ischemic event in the past year had a significantly higher rate of cardiovascular death, myocardial infarction, or stroke than those with no ischemic event (HR, 1.71; 95% CI, 1.57-1.85; $P < .001$).

COMMENT

This analysis of a large international registry demonstrates that there are simple clinical predictors of future ischemic events in patients at various stages along the atherosclerotic continuum. Over the course of 4 years, easily demarcated subgroups of atherothrombotic patients had widely varying risks, ranging from 7% in nondiabetic patients with other risk factors for atherothrombosis to 25% in patients with polyvascular disease and prior ischemic events. This greater than 3-fold gradient in cumulative risk for cardiovascular death, myocardial infarction, or stroke illustrates that not all atherothrombosis is equal—an observation that the broad array of clinicians caring for these types of patients may find clinically relevant.

Patients with prior ischemic events at baseline were at higher risk than patients with stable atherosclerosis but without a history of ischemic events, who in turn were at higher risk than those patients with multiple risk factors only (with no evidence of established atherothrombosis). Among pa-

Figure 3. Risk of Ischemic Events in the Subsequent 4 Years of Follow-up in Patients According to Baseline Risk Category



Ischemic events were defined as myocardial infarction (MI) or stroke. Diabetes status was missing for 3 patients: 2 patients in the category risk factors only and 1 patient in the category stable atherosclerosis without prior ischemic events. Error bars indicate 95% confidence intervals for each event rate; CV indicates cardiovascular.

Table 3. Four-Year Hazard Rates in Patients With a History at Enrollment of Prior Ischemic Events, Stable Atherosclerosis Without Prior Ischemic Events, or Risk Factors for Atherosclerosis Without Established Disease^a

Event	Hazard Rate, % (95% CI)				
	Prior Ischemic Event at Baseline		Stable Atherosclerosis Without Prior Ischemic Event at Baseline		Risk Factors Only (n = 8073)
	Single Vascular Disease (n = 16 732)	Polyvascular Disease (n = 5158)	Single Vascular Disease (n = 13 233)	Polyvascular Disease (n = 2031)	
All-cause mortality	12.05 (11.23-12.86)	17.65 (16.26-19.00)	10.28 (9.36-11.18)	15.39 (13.42-17.31)	8.34 (7.56-9.11)
CV death	7.57 (6.89-8.24)	12.69 (11.42-13.94)	5.80 (5.09-6.51)	9.42 (7.78-11.03)	4.34 (3.76-4.92)
Nonfatal MI	4.13 (3.62-4.64)	6.01 (5.07-6.94)	2.92 (2.39-3.45)	4.45 (3.20-5.68)	2.26 (1.83-2.68)
Nonfatal stroke	5.92 (5.32-6.52)	10.74 (9.49-11.97)	3.79 (3.20-4.37)	6.70 (5.20-8.18)	3.35 (2.83-3.87)
CV hospitalization	20.70 (19.71-21.67)	35.48 (33.66-37.25)	24.91 (23.65-26.15)	38.12 (35.40-40.73)	10.70 (9.89-11.51)
CV death, MI, and stroke	15.72 (14.80-16.63)	25.02 (23.35-26.65)	11.50 (10.52-12.46)	17.69 (15.52-19.81)	9.10 (8.29-9.91)
CV death, MI, stroke, and CV hospitalization	29.89 (28.79-30.97)	47.14 (45.35-48.88)	31.11 (29.79-32.41)	45.01 (42.35-47.54)	16.64 (15.64-17.62)

Abbreviations: CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.
^aIschemic events were defined as myocardial infarction or stroke.

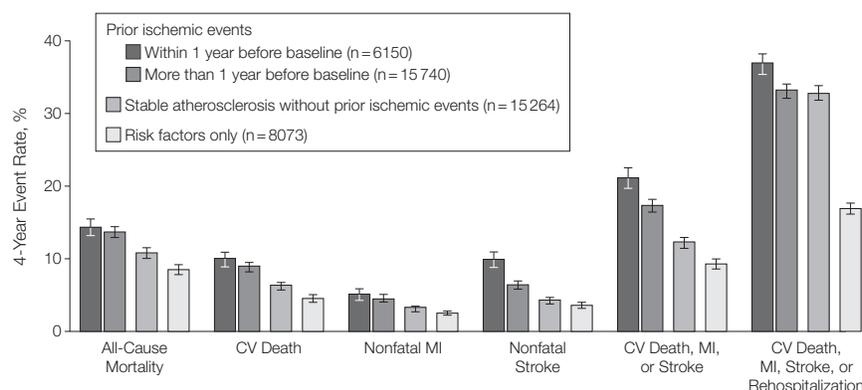
tients with a history of ischemic events, the occurrence of an ischemic event in the year before enrollment was a stronger predictor of future ischemic events than an ischemic event more than a year before enrollment in the registry. Notably, the effects of these factors on event rates within this registry were consistent for all geographic regions included without significant variation, and therefore these findings may be broadly applicable.

Among all categories of patients, diabetes substantially increased the risk of future ischemic events. In those with established atherosclerosis, polyvascular disease was a particularly strong independent risk factor, even stronger than diabetes. These 2 factors were associated with significantly increased risk of the composite end point of cardiovascular death, myocardial infarction, or stroke as well as the individual components of this composite; in addition, they were associated with a significant increase in the risk of cardiovascular hospitalization. When included in the composite end point, cardiovascular hospitalization was associated with nearly doubling of the event rate in all subpopulations analyzed and tracked well with the more objective triple ischemic end point.

These findings should provide clinicians with improved estimates of their patients' future cardiovascular risk and thus enable more effective identification of patients who should be targeted for more intensive follow-up and therapy. Because the majority of patients in this registry would be candidates for basic secondary prevention, such as with statin therapy, future novel therapies may be optimally directed at those with higher levels of risk.¹²

Thus, even in secondary prevention, simple risk stratification may be incrementally useful, especially as a host of new anti-atherosclerotic and antithrombotic therapies are being developed. New antiplatelet, anticoagulant, anti-atherosclerotic, and anti-inflammatory agents will probably be expensive and may have additional adverse effects; thus, the ability to target

Figure 4. Risk of Ischemic Events in the Subsequent 4 Years of Follow-up in Patients With History at Enrollment of Prior Ischemic Events, Either Within Year Prior to Enrollment or More Remotely



Ischemic events were defined as myocardial infarction (MI) or stroke. Error bars indicate 95% confidence intervals for each event rate; CV indicates cardiovascular.

these therapies to patients at highest ischemic risk will be desirable and likely would be cost-effective. Although other risk prediction tools have been developed that are effective in the setting of acute coronary syndromes, acute heart failure, or primary prevention, the ability to further risk-stratify patients for advanced secondary prevention will likely be of increasing importance in the future.¹³⁻¹⁵

These findings also have potential implications for sample size determination for future clinical trials of therapies for atherosclerosis by helping identify those patients at highest risk who are most likely to benefit. For example, the discrepancy between diabetes trials targeting cardiovascular events and the low event rates in those trials illustrates the potential utility of the simple risk enrichment strategies found in the current analysis.⁶ Planned trials of diabetic patients specifically designed to assess cardiovascular safety may find such simple enrichment strategies particularly useful to avoid low event rates that then create clinical uncertainty over whether diabetic agents provide cardiovascular benefit or harm.¹⁶

The presence of established atherosclerosis was found to be a more potent predictor of risk than diabetes in patients with multiple risk factors, so

it is not entirely the case that diabetes is an atherosclerosis risk equivalent, as older studies had suggested.^{17,18} Among patients with atherosclerosis, a history of ischemic events is a stronger predictor than diabetes or stable atherosclerosis, or the combination. Thus, in this analysis, the strongest predictor of future ischemic risk is a history of ischemic events, particularly in the prior year. The concomitant presence of diabetes or polyvascular disease in those patients further identifies an extremely high-risk population.^{7,9,19,20} The risk model in this analysis has a modest *c* statistic of 0.68, although this is not dissimilar from some other published cardiovascular risk scores that are in use.¹³ Regardless, the main purpose of this analysis was to identify simple clinical descriptors of risk that clinicians could easily apply. Risk scores, despite being endorsed by professional society guidelines, are often not used in real-world practice, perhaps due to their perceived complexity with multiple variables.²¹

The high rate of hospitalization for cardiovascular causes during follow-up is notable, especially due to the attendant economic costs generated.²² Although high hospitalization rates have been recognized as a major problem for medical conditions such as heart failure, the present analysis highlights

that patients with a history of, or with several risk factors for, atherothrombosis also have a high hospitalization rate. Even though the majority of patients attending their 4-year visit were treated with antithrombotic therapy and lipid-lowering therapy, the overall rates were not improved compared with the rates at baseline.⁷ This persistent treatment gap may have contributed in part to their high hospitalization rates and may represent an opportunity to improve care.

Limitations to this analysis are those inherent to registries.²³ The follow-up of the initial cohort enrolled was incomplete because some centers and sites were unable to continue in the registry for financial reasons. Nevertheless, there was no evidence that the sites that dropped out were preferentially those with higher or lower ischemic risk, and therefore, there is no reason to think that the overall findings regarding event rates would have been significantly influenced. In fact, the primary end point event rate at 1 year was not significantly different in those with only 1-year follow-up vs those with 1-year and 4-year follow-up. An additional limitation is that end points were not adjudicated, although that is not unusual in a registry.

In conclusion, this analysis of a contemporary, international cohort of patients at various stages of atherothrombosis shows that there is a whole spectrum of ischemic risk in patients with risk factors or with established cardiovascular disease and that easily ascertainable clinical characteristics are the prominent factors associated with a high risk of future ischemic events. Polyvascular disease is the strongest predictor of future ischemic events; a history of previous ischemic events, particularly if such events occurred in the prior 12 months, and a diagnosis of diabetes each are strongly associated with further risk elevation. These findings may help in the identification of high-risk populations who may deserve intensive preventive efforts with novel therapies and also in the planning of future clinical trials.

Published Online: August 30, 2010. doi:10.1001/jama.2010.1322

Author Affiliations: VA Boston Healthcare System, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts (Dr Bhatt); University of Michigan Cardiovascular Center, Ann Arbor (Dr Eagle); Division of Cardiology, Duke University, Durham, North Carolina (Dr Ohman); Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis (Dr Hirsch); Tokai University School of Medicine, Isehara, Japan (Dr Goto); Saint Luke's Mid America Heart Institute, Kansas City, Missouri (Dr Mahoney); Emory University School of Medicine, Atlanta, Georgia (Dr Wilson); Department of Neurology, Northwestern University Medical School, Chicago, Illinois (Dr Alberts); Statistics and Consulting Unit, Boston University, Boston, Massachusetts (Drs D'Agostino and Massaro); Buddhist Tzu Chi General Hospital, Taipei Branch, Taipei, Taiwan (Dr Liao); Paris-Descartes University, INSERM U894, Department of Neurology, Hôpital Sainte-Anne, Paris, France (Dr Mas); Department of Neurology, Asklepios Klinik Altona, Hamburg, Germany (Dr Röther); Center for Cardiovascular Science and Medicine, University of North Carolina at Chapel Hill (Dr Smith Jr); Sanofi-Aventis, Paris (Dr Salette); TIMI Study Group, Boston (Dr Contant); INSERM U698, Université Paris 7, and Hôpital Bichat, AP-HP, Paris (Dr Steg).

Author Contributions: Dr Bhatt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bhatt, Ohman, Hirsch, Wilson, Liao, Röther, Steg.

Acquisition of data: Bhatt, Goto, Wilson, Liao, Röther, Steg.

Analysis and interpretation of data: Bhatt, Eagle, Hirsch, Mahoney, Alberts, D'Agostino, Liao, Mas, Röther, Smith Jr, Salette, Contant, Massaro, Steg.

Drafting of the manuscript: Bhatt.

Critical revision of the manuscript for important intellectual content: Bhatt, Eagle, Ohman, Hirsch, Goto, Mahoney, Wilson, Alberts, D'Agostino, Liao, Mas, Röther, Smith Jr, Salette, Contant, Massaro, Steg.

Statistical analysis: D'Agostino, Salette, Contant, Massaro.

Obtained funding: Goto, Röther, Steg.

Administrative, technical, or material support: Bhatt, Ohman, Wilson.

Study supervision: Hirsch, Mas, Röther, Contant, Steg.

Financial Disclosures: Dr Bhatt reported having received institutional research support from AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Heartscape, Sanofi-Aventis, and The Medicines Company. Dr Eagle reported having received grant/research support from Bristol-Myers Squibb, Blue Cross Blue Shield of Michigan, the National Institutes of Health (NIH), Sanofi-Aventis, the Mardigan Foundation Varbedian Fund, GORE, and the Hewlett Foundation and being a consultant for the NIH National Heart, Lung, and Blood Institute, Sanofi-Aventis, and the Robert Wood Johnson Foundation. Dr Ohman reported receiving research grants from Bristol-Myers Squibb, CV Therapeutics, Daiichi Sankyo, Datascope, Eli Lilly, Marquet, Sanofi-Aventis, Schering-Plough, and The Medicines Company and providing consulting or other services for Abiomed, AstraZeneca, CV Therapeutics, Datascope, Gilead Sciences, Liposcience, Marquet, Northpoint Domain, Pozen, Response Biomedical, Sanofi-Aventis, The Medicines Company, and WebMD (theheart.org). Dr Hirsch reported having received research grants from Bristol-Myers Squibb, Sanofi-Aventis, and Abbott Vascular and served as a consultant to Roche, Cytokinetics, ev3, and Talcres. Dr Goto reported having received research grants from Pfizer, Sanofi-Aventis, Ono, Eisai, Otsuka, Sankyo, Daiichi, Takeda, Asters, Kowa, and AstraZeneca and hono-

raria from Sanofi-Aventis, Eisai, Otsuka, Daiichi-Sankyo, and Schering-Plough. Dr Mahoney reported having received grant support from Sanofi-Aventis, Bristol-Myers Squibb, Daiichi-Sankyo, and Eli Lilly and honoraria from Sanofi-Aventis and Bristol-Myers Squibb. Dr Wilson reported having received research grants from Sanofi-Aventis. Dr Alberts reported having received research support from AGA Medical, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, EKR, Sanofi-Aventis, and Schering-Plough; having participated in speakers' bureaus for Bristol-Myers Squibb, Boehringer Ingelheim, DiaDexus, Genentech, Medscape, and Sanofi-Aventis; having received honoraria from Bristol-Myers Squibb, Boehringer Ingelheim, DiaDexus, Genentech, Medscape, and Sanofi-Aventis; and having acted as a consultant or advisory board member for Bristol-Myers Squibb, Boehringer Ingelheim, EKR, Genentech, Merck, Pfizer, and Sanofi-Aventis. Dr D'Agostino reported having received honoraria from Sanofi-Aventis. Dr Liao reported no disclosures. Dr Mas reported having received research grants, honoraria, and consulting fees from Sanofi-Aventis, Bristol-Myers Squibb, and Servier and honoraria and consulting fees from Boehringer Ingelheim. Dr Röther reported having participated in speakers' bureaus for Boehringer-Ingelheim, Bristol-Myers Squibb, Sanofi-Aventis, and Lundbeck and having acted as a consultant or advisory board member for Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Sanofi-Aventis, and Lundbeck. Dr Smith Jr reported no disclosures. Dr Salette reported being an employee of Sanofi-Aventis. Dr Contant reported no disclosures. Dr Massaro reported having received honoraria from Sanofi-Aventis. Dr Steg reported having received research grants (to his institution) from Servier; participating in consultancy or advisory boards for Astellas, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, Daiichi-Sankyo-Lilly, GlaxoSmithKline, Medtronic, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, and The Medicines Company; and being a stockholder in Aterovax.

Funding/Support: The REACH Registry is sponsored by Sanofi-Aventis, Bristol-Myers Squibb, and the Wakman Foundation (Tokyo, Japan). The REACH Registry is endorsed by the World Heart Federation.

Role of the Sponsors: The design and conduct of the study were done by the academic executive committee in collaboration with the sponsors; the collection and management of the data were done by the sponsors under the direction of the academic executive committee; analysis was done by the sponsors and independently verified by an academic statistician (Dr Massaro) and those are the analyses presented in the article; the interpretation of the data was done solely by the authors; and the preparation of the first draft of the manuscript was done by Dr Bhatt. All authors reviewed and commented on the manuscript, and all authors gave approval of the submitted manuscript. The sponsors had the opportunity to review but not to approve.

Independent Statistical Analysis: Dr Massaro provided SAS data sets, the manuscript containing the statistical analytical plan and results, and a blank copy of the study annotated case report forms. Dr Massaro reviewed and regenerated the results of the statistical analysis on the end points in the tables and figures and independently verified the results and conclusions presented in the final manuscript. Those are the analyses and results presented in this article. Dr Massaro was not compensated for the independent statistical review.

REACH Registry Executive Committee: Deepak L. Bhatt, MD, MPH, VA Boston Healthcare System, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts (chair); Ph. Gabriel Steg, MD, Hôpital Bichat-Claude Bernard, Paris, France (chair); E. Magnus Ohman, MD, Duke University Medical Center, Durham, North Carolina;

Joachim Röther, MD, Department of Neurology, Asklepios Klinik Altona, Hamburg, Germany; Peter W. F. Wilson, MD, Emory University School of Medicine, Atlanta, Georgia.

REACH Registry Global Publication Committee: Mark J. Alberts, MD, Northwestern University Medical School, Chicago, Illinois; Deepak L. Bhatt, MD, MPH, VA Boston Healthcare System, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts (chair); Ralph D'Agostino, PhD, Boston University, Boston; Kim A. Eagle, MD, University of Michigan, Ann Arbor; Shinya Goto, MD, PhD, Tokai University School of Medicine, Isehara, Japan; Alan T. Hirsch, MD, University of Minnesota School of Pub-

lic Health, Minneapolis; Chiau-Suong Liao, MD, PhD, Taiwan University Hospital and College of Medicine, Taipei, Taiwan; Jean-Louis Mas, MD, Centre Raymond Garcin, Paris, France; E. Magnus Ohman, MD, Duke University Medical Center, Durham, North Carolina; Joachim Röther, MD, Department of Neurology, Asklepios Klinik Altona, Hamburg, Germany; Sidney C. Smith Jr, MD, University of North Carolina at Chapel Hill; Ph. Gabriel Steg, MD, Hôpital Bichat-Claude Bernard, Paris (chair); Peter W. F. Wilson, MD, Emory University School of Medicine, Atlanta, Georgia.

Additional Contributions: The REACH Registry enforces a no ghost-writing policy. The manuscript was written and edited by the authors, who take full re-

sponsibility for its content. The first draft was written by Dr Bhatt. Sophie Rushton-Smith, PhD, and Rachel Spice, PhD, assisted with coordinating revisions and provided editorial help in preparing this manuscript, including editing, checking content and language, formatting, referencing, and preparing tables and figures; they received compensation from Sanofi-Aventis. Lucie Parent, an employee of Sanofi-Aventis, provided support for statistical analyses. Milan Novakovic, MD, Sanofi-Aventis, and Nihar Bhakta, MD, Bristol-Myers Squibb, provided support for the REACH Registry. Fang Ren, MS, Brigham and Women's Hospital and the TIMI Study Group, helped with statistical analyses.

REFERENCES

- Bhatt DL, Lincoff AM, Gibson CM, et al; CHAMPION PLATFORM Investigators. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med*. 2009;361(24):2330-2341.
- Harrington RA, Stone GW, McNulty S, et al. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med*. 2009;361(24):2318-2329.
- Sacco RL, Diener HC, Yusuf S, et al; PROFESS Study Group. Aspirin and extended-release dipyridamol versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359(12):1238-1251.
- Bhatt DL, Fox KA, Hacke W, et al; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354(16):1706-1717.
- Topol EJ, Bousser MG, Fox KA, et al; CRESCENDO Investigators. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. *Lancet*. 2010;376(9740):517-523.
- Home PD, Pocock SJ, Beck-Nielsen H, et al; RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes: an interim analysis. *N Engl J Med*. 2007;357(1):28-38.
- Bhatt DL, Steg PG, Ohman EM, et al; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006;295(2):180-189.
- Ohman EM, Bhatt DL, Steg PG, et al. The REDuction of Atherothrombosis for Continued Health (REACH) Registry: an international, prospective, observational investigation in subjects at risk for atherothrombotic events: study design. *Am Heart J*. 2006;151(4):786, e1-e10.
- Steg PG, Bhatt DL, Wilson PW, et al; REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA*. 2007;297(11):1197-1206.
- Alberts MJ, Bhatt DL, Mas JL, et al; REDuction of Atherothrombosis for Continued Health Registry Investigators. Three-year follow-up and event rates in the international REDuction of Atherothrombosis for Continued Health Registry. *Eur Heart J*. 2009;30(19):2318-2326.
- Chang LM, Gelman R, Pagano M. Corrected group prognostic curves and summary statistics. *J Chronic Dis*. 1982;35(8):669-674.
- Mehta C, Gao P, Bhatt DL, Harrington RA, Skerjanec S, Ware JH. Optimizing trial design: sequential, adaptive, and enrichment strategies. *Circulation*. 2009;119(4):597-605.
- Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*. 2000;284(7):835-842.
- Eagle KA, Lim MJ, Dabbous OH, et al; GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA*. 2004;291(22):2727-2733.
- Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ; ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA*. 2005;293(5):572-580.
- Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA*. 2007;298(10):1189-1195.
- Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339(4):229-234.
- Krempf M, Parhofer KG, Steg PG, et al; Reach Registry Investigators. Cardiovascular event rates in diabetic and nondiabetic individuals with and without established atherothrombosis (from the REDuction of Atherothrombosis for Continued Health [REACH] Registry). *Am J Cardiol*. 2010;105(5):667-671.
- Bhatt DL, Peterson ED, Harrington RA, et al; CRUSADE Investigators. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. *Eur Heart J*. 2009;30(10):1195-1202.
- Brilakis ES, Hernandez AF, Dai D, et al. Quality of care for acute coronary syndrome patients with known atherosclerotic disease: results from the Get With the Guidelines Program. *Circulation*. 2009;120(7):560-567.
- Müller-Riemenschneider F, Holmberg C, Rieckmann N, et al. Barriers to routine risk-score use for healthy primary care patients: survey and qualitative study. *Arch Intern Med*. 2010;170(8):719-724.
- Mahoney EM, Wang K, Cohen DJ, et al; REACH Registry Investigators. One-year costs in patients with a history of or at risk for atherothrombosis in the United States. *Circ Cardiovasc Qual Outcomes*. 2008;1(1):38-45.
- Bhatt DL. Advancing the care of cardiac patients using registry data: going where randomized clinical trials dare not. *JAMA*. 2010;303(21):2188-2189.