One-Year Cardiovascular Event Rates in Outpatients With Atherothrombosis

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One-Year Cardiovascular Event Rates in Outpatients With Atherothrombosis

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Context Few data document current cardiovascular (CV) event rates in stable patients with atherothrombosis in a community setting. Differential event rates for patients with documented coronary artery disease (CAD), cerebrovascular disease (CVD), or peripheral arterial disease (PAD) or those at risk of these diseases have not been previously evaluated in a single international cohort.

Objective To establish contemporary, international, 1-year CV event rates in outpatients with established arterial disease or with multiple risk factors for atherothrombosis.

Design, Setting, and Participants The Reduction of Atherothrombosis for Continued Health (REACH) Registry is an international, prospective cohort of 68 236 patients with either established atherosclerotic arterial disease (CAD, PAD, CVD; n=55 814) or at least 3 risk factors for atherothrombosis (n=12 422), who were enrolled from 5587 physician practices in 44 countries in 2003-2004.

Main Outcome Measures Rates of CV death, myocardial infarction (MI), and stroke.

Results As of July 2006, 1-year outcomes were available for 95.22% (n=64 977) of participants. Cardiovascular death, MI, or stroke rates were 4.24% overall: 4.69% for those with established atherosclerotic arterial disease vs 2.15% for patients with multiple risk factors only. Among patients with established disease, CV death, MI, or stroke rates were 4.52% for patients with CAD, 6.47% for patients with CVD, and 5.35% for patients with PAD. The incidences of the end point of CV death, MI, or stroke or of hospitalization for atherothrombotic event(s) were 15.20% for CAD, 14.53% for CVD, and 21.14% for PAD patients with established disease. These event rates increased with the number of symptomatic arterial disease locations, ranging from 5.31% for patients with risk factors only to 12.58% for patients with 1, 21.14% for patients with 2, and 26.27% for patients with 3 symptomatic arterial disease locations ($P<.001$ for trend).

Conclusions In this large, contemporary, international study, outpatients with established atherosclerotic arterial disease, or at risk of atherothrombosis, experienced relatively high annual CV event rates. Multiple disease locations increased the 1-year risk of CV events.

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ATHEROTHROMBOSIS (CORONARY artery disease [CAD], cerebrovascular disease [CVD], and peripheral arterial disease [PAD]) is associated with the main causes of mortality on a worldwide scale. Recent US data have confirmed that despite a decrease in age-standardized national death rates, the absolute number of deaths from these conditions continues to increase,[1] and prevalence is sharply increasing in other parts of the world. Thus, atherothrombotic diseases are, and are projected still to be, the leading cause of death worldwide by 2020.[2]

Thus far, most of the information available on atherothrombosis risk has been derived from single regional locales (such as studies conducted in Europe or North America), often confined to a single subtype of patient (patients with CAD, previous stroke patients without PAD), and generally limited to hospitalized patients (as opposed to outpatients or individuals in primary care) or to patients in clinical trials (as opposed to patients in the community).

For editorial comment see p 1253.

The REACH (Reduction of Atherothrombosis for Continued Health) Registry has been established to circumvent these limitations by recruit-

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ing and following up a large cohort of outpatients with a history of, or who are at high risk of developing, atherothrombosis. The REACH Registry aims to study contemporary outpatient populations from various regions of the world to describe the demographic characteristics and management as well as to determine the risk of cardiovascular (CV) events in the global population and in each clinical subgroup. Additional aims were to assess the risk related to the overlap between the subgroups within the various symptomatic locations of atherothrombosis, compare outcomes within different patient profiles, and define predictors of risk for subsequent CV events.

This article describes the characteristics and outcomes of patients for whom 1-year follow-up data were available and reports the association between multiple symptomatic locations of atherothrombosis (ie, polyvascular disease) and CV event rates.

METHODS

The design, including the strategy for selecting physicians, collecting follow-up data, and ensuring data quality,[3] and the baseline description of the REACH Registry[4] have been published. Briefly, consecutive outpatients aged at least 45 years with established CAD, CVD, or PAD or patients with at least 3 atherothrombotic risk factors (multiple risk factors only) were enrolled by their physician over an initial 7-month recruitment period. The patients were from 5587 physician practices in 44 countries and were enrolled between December 2003 and June 2004. Due to regulatory requirements in Japan, enrollment in that country was delayed and occurred between August and December 2004.

The risk factors used for enrollment consisted of treated diabetes mellitus, diabetic nephropathy, ankle brachial index of less than 0.9, asymptomatic carotid stenosis of 70% or higher, carotid intima-media thickness more than 2 times adjacent sites, systolic blood pressure of at least 150 mm Hg despite therapy for at least 3 months, hypercholesterolemia treated with medication, current frequent smoking (≥15 cigarettes per day), and age 65 years or older (men) or 70 years or older (women). Patients already in a clinical trial or those who might have difficulty returning for a follow-up visit were excluded from enrollment. Patients with ongoing events were not enrolled and hospitalized patients were specifically excluded.

To ensure uniformity of the REACH Registry population, a site selection strategy was implemented at the national level, accounting for patient and physician profiles, type of health care environment, and medical practice, using the best available epidemiological data regarding the prevalence of atherothrombotic events and risk factors for the geographic distribution (urban vs suburban or local) and the types of physicians responsible for their management in each country. This protocol was submitted to the institutional review boards in each country according to local requirements and signed informed consent was required for all patients.

Data were collected centrally via use of a standardized international case report form, completed at the study visit. *Body mass index* (BMI) was defined as weight in kilograms divided by height in meters squared. Patients were considered to be overweight if their BMI ranged from 25 to 29 or obese if it were 30 or higher. Patients were also classified as obese if their waist circumference was more than 40 in (>102 cm) in men or more than 35 in (>88 cm) in women. *Current smoking* was defined as at least 5 cigarettes per day on average within the last month before enrollment; former smoking was defined as stopping more than a month before enrollment. Polyvascular disease was defined as coexistent established, clinically recognized arterial disease in 2 or 3 arterial territories (coronary, cerebral, lower extremity, or all 3).

Follow-up

At 12 months (plus or minus 3 months) after enrollment, data were collected from participating physicians regarding patients' clinical outcomes, vascular endovascular procedures, employment status, weight, and current smoking status, as well as whether patients were taking medications regularly since baseline for long-term disease. The current report is based on a database lock of July 21, 2006, for analysis of the 1-year follow-up. Events were not adjudicated; however, reports of ischemic stroke and transient ischemic attack had to be sourced from a neurologist or hospital to ensure a reliable diagnosis.

Cardiovascular death included fatal stroke, fatal myocardial infarction (MI), and other cardiovascular death. *Other cardiovascular death* included other death of cardiac origin; pulmonary embolism; any sudden death, including unobserved and unexpected death (eg, while sleeping) unless proven otherwise by autopsy; death following a vascular operation, vascular procedure, or amputation (except for trauma or malignancy); 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 MI or stroke followed by death, whatever the cause, in the subsequent 28 days was considered as a fatal MI or fatal stroke.

This report was prepared in compliance with the STROBE checklist (version 3, accessible at http://www.strobe-statement.org).[5]

Statistical Analysis

Continuous variables are expressed as mean (SD). Categorical variables are expressed as frequencies and percentages. Event rates are reported as annualized event rates. All event rates are reported after adjustment for age and sex. This adjustment was accomplished through the corrected group prognosis method in the Cox proportional hazards model previously

described.[6] Only patients with complete outcome and covariate information for a given end point were included in calculating the rates for that end point. Three additional sets of analyses—which adjusted incrementally for age and sex, on risk factors, ethnicity/race, and BMI—provided very similar results.

Cumulative incidence curves were constructed for selected end points (nonfatal stroke; CV death; nonfatal MI; and CV death, MI, or stroke) using the Kaplan-Meier approach. The differences in incidence rates for selected end points (nonfatal stroke; CV death; nonfatal MI; CV death, MI, or stroke; and CV death, MI, stroke, or hospitalization) according to the number of atherothrombosis disease locations were tested using the test for trend in the Cox proportional hazards model. Statistical analysis was performed using SAS v8 software (SAS Institute Inc, Cary, NC).

RESULTS

Of the 68 375 patients enrolled in the REACH Registry, 68 236 entered the follow-up phase, with 139 (0.20%) patients withdrawing consent early. As of the database lock on July 21, 2006, 1-year follow-up was available for 64 977 (95.22%) of the patients who had entered the follow-up stage. Of those who withdrew, 2338 patients (3.43%) did so because of missed site visits and 910 (1.33%) because their enrolling physicians had withdrawn from the registry. Among the reasons for physician withdrawal were because their clinical sites had been destroyed by the 2004 tsunami in Asia or by Hurricane Katrina in the southern United States; because these physicians had died, retired, or decided to withdraw from the

Table 1. Baseline Characteristics of Patients in 1-Year Follow-up Analysis by Geographic Distribution

	Percentage of Population								
	Total (n = 64 977)	North America (n = 25 999)	Latin America (n = 1835)	Western Europe (n = 17 142)	Eastern Europe (n = 5622)	Middle East (n = 840)	Asia (n = 5671)	Australia (n = 2847)	Japan (n = 5021)
Age, mean (SD), y	69 (10)	70 (10)	67 (10)	69 (10)	63 (9)	66 (10)	65 (10)	73 (9)	70 (9)
Men	63.77	58.09	61.58	69.41	65.51	71.62	65.05	65.07	69.25
Diabetes	43.88	50.64	44.03	39.07	27.57	52.38	47.35	30.31	45.77
Hypertension	81.71	86.40	78.04	79.13	83.74	80.69	78.98	77.63	70.88
Hypercholesterolemia	72.05	82.70	61.47	72.32	55.10	82.38	61.04	77.56	46.43
Overweight (BMI 25-<30)	39.96	36.30	45.90	45.90	46.20	46.10	37.47	43.09	29.36
Obese (BMI ≥30)	29.84	41.47	23.89	28.08	28.87	29.88	8.82	29.20	4.00
Former smoker	41.74	43.73	41.47	44.05	30.80	31.20	29.29	53.96	45.18
Current smoker	15.19	14.38	8.64	17.00	20.93	14.80	12.80	6.82	16.86
Previous history of atherosclerotic disease*									
CAD	59.41	60.67	56.89	58.06	70.58	68.21	51.90	73.59	44.85
Stable angina with documented CAD	30.02	27.58	21.57	30.01	50.97	32.28	25.45	35.99	23.59
Unstable angina with documented CAD	12.70	11.28	18.12	12.09	21.54	19.25	13.82	11.74	8.38
MI	31.67	31.73	33.94	32.92	39.25	39.08	23.26	37.62	22.53
PCI	25.16	27.76	25.14	24.98	15.86	30.50	22.63	24.91	24.85
CABG	20.44	26.91	20.59	18.02	10.75	23.72	10.37	30.10	11.32
CVD	27.72	21.00	31.93	26.36	38.83	25.71	42.71	23.39	39.08
TIA	13.04	12.41	12.93	15.19	15.89	11.65	11.84	12.63	7.54
Stroke	20.27	13.97	25.08	16.99	30.21	18.06	37.50	14.91	35.19
PAD	12.18	9.16	11.88	19.75	12.49	6.67	5.43	9.03	12.01
Claudication and ABI <0.9	13.83	9.14	12.44	21.88	15.52	8.11	7.90	3.63	20.70
Peripheral angioplasty, stenting, or surgery	6.54	5.37	5.01	10.75	4.00	2.38	1.92	6.88	7.41
Claudication and history of amputation	1.77	1.79	3.38	2.18	1.74	0.71	1.41	0.84	0.90
Any history of symptomatic atherothrombosis	81.89	74.97	86.76	84.05	95.02	84.88	86.97	89.32	83.45
Three risk factors only	18.11	25.03	13.24	15.95	4.98	15.12	13.03	10.68	16.55
Employment (n = 64 199)									
Full time	16.75	17.44	19.14	11.59	24.12	23.19	21.75	5.24	21.63
Part time	5.94	5.50	10.48	4.06	9.53	14.25	8.55	6.53	4.23
Unemployed	6.62	3.18	9.16	3.18	3.69	18.84	15.41	0.57	30.95
Retired	62.53	66.62	33.92	74.67	53.84	38.16	41.76	82.66	35.24
Incapacitated for work	5.21	6.15	8.77	3.79	7.88	1.93	4.96	3.07	2.89
Other employment	2.94	1.11	18.53	2.71	0.95	3.62	7.56	1.93	5.06

Abbreviations: ABI, ankle brachial index; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CVD, cerebrovascular disease; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.
*Patients can have multiple histories of atherosclerotic disease.

registry; or because their patients had withdrawn consent late (n = 11). Comparison of baseline demographics of patients for whom 1-year follow-up data were and were not available were similar in age, risk factors for atherosclerosis, previous history of CV disease, and use of medications (TABLE 1 and TABLE 2).

The registry patients with 1-year follow-up were a mean (SD) age of 68.6 (10.1) years and were predominantly male (63.77%). The majority were either overweight or obese, were former or current smokers, and had a history of CAD (Table 1). Overall, 36.55% of patients were enrolled and followed up by family and general practitioners. The percentages of the remaining specialties are listed in Table 2 and detailed baseline characteristics of patients in the various geographic regions are shown in Table 1.

All-cause mortality was 2.58% overall at 1 year, with 2.81% of patients having established arterial disease compared with 1.51% of patients having multiple risk factors only (with ≥3 risk factors; TABLE 3). A total of 63.95% of those deaths were from CV causes. The overall combined CV death, MI, or stroke rate at 1 year was 4.24% (95% confidence interval [CI], 3.97%-4.51%), ranging from 2.15% (95% CI, 1.84%-2.46%) of patients with multiple risk factors only to 6.47% (95% CI, 5.96%-6.97%) of patients enrolled with CVD. Cardiovascular event rates for the total population, for each of the CAD, CVD, and PAD subsets, and for those with only multiple risk factors are shown in Table 3. Kaplan-Meier event curves as a function of time from enrollment for the triple end point of CV death, MI, or stroke and each of its com-

Table 2. Baseline Medication and Physician Profile in 1-Year Follow-up Analysis by Geographic Distribution

	Percentage of Population								
	Total (n = 64 977)	North America (n = 25 999)	Latin America (n = 1835)	Western Europe (n = 17 142)	Eastern Europe (n = 5622)	Middle East (n = 840)	Asia (n = 5671)	Australia (n = 2847)	Japan (n = 5021)
Medication use									
≥1 Antiplatelet agent	78.65	77.14	87.02	77.96	86.37	90.71	81.61	74.75	73.91
Aspirin	67.29	71.39	76.72	62.13	75.06	83.57	63.59	64.45	54.51
Other antiplatelet agent	24.63	20.02	29.75	27.28	26.11	25.06	30.78	19.78	31.65
Aspirin and other antiplatelet agent	13.15	14.19	19.43	11.12	14.77	17.87	12.75	9.48	12.25
Oral anticoagulants	12.30	14.23	7.95	12.28	11.47	8.01	6.51	12.46	12.45
NSAIDs	11.54	18.24	6.07	7.63	4.48	8.15	4.14	23.38	2.93
≥1 Lipid-lowering agent	75.11	83.78	67.87	75.36	62.34	85.24	67.08	80.33	50.81
Statins	69.30	77.06	63.56	69.95	57.63	82.50	60.85	78.89	44.05
Other lipid-lowering agents	11.95	18.04	9.89	7.85	6.99	7.50	9.37	2.49	9.88
≥1 Cardiovascular agent	91.28	93.80	88.11	90.76	95.11	95.12	89.83	88.34	79.55
Calcium channel blockers	34.00	32.75	31.11	30.43	27.16	37.23	39.95	30.49	55.98
β-Blockers	47.52	50.56	39.15	50.61	63.23	59.86	40.47	37.32	18.60
Nitrates	24.45	19.08	16.72	23.72	42.44	31.45	28.16	31.49	27.46
Diuretics	40.32	48.10	36.65	42.41	47.15	40.24	23.45	28.41	12.65
ACE inhibitors	45.21	47.07	42.74	45.93	72.77	54.07	32.36	42.11	18.10
Angiotensin II receptor blocker	22.80	25.37	21.83	21.07	3.79	18.73	27.80	22.82	32.01
Other antihypertensives	9.39	11.40	4.88	8.93	8.07	12.83	8.43	8.40	4.82
Peripheral arterial claudication medications	6.54	4.75	7.26	8.76	13.87	4.93	5.07	0.18	5.28
≥1 Antidiabetic agent	39.71	46.20	42.64	35.41	23.45	48.81	44.93	26.80	37.86
Insulin	11.78	14.15	11.20	12.19	6.55	13.13	7.88	6.74	11.25
Biguanides	18.46	22.17	21.21	16.49	9.11	30.35	25.50	17.50	6.15
Sulfonylureas	19.72	22.89	22.90	14.87	10.95	27.39	28.63	12.63	21.33
Thiazolidinedione	7.74	15.76	3.28	2.01	0.48	3.25	5.38	0.67	3.05
Other	5.01	4.01	3.99	4.79	3.19	4.09	7.11	0.56	13.46
Physician profile (n = 64 346)									
Family or general practitioner	36.55	43.55	3.05	45.78	5.25	37.02	8.98	100.00	11.97
Internist	32.99	44.80	29.59	27.48	34.29	12.62	18.94		29.89
Cardiologist	13.95	7.38	35.15	12.03	27.32	29.76	30.51		17.59
Angiologist	1.15	0	1.58	2.77	1.32	0	0.51		2.63
Vascular surgeon	2.21	0.25	6.70	2.78	2.90	2.38	2.73		8.33
Neurologist	9.40	0.98	16.68	7.19	27.89	12.26	29.38		18.38
Endocrinologist	2.99	2.11	6.43	1.60	0.71	1.19	8.89		8.78
Other	0.77	0.93	0.82	0.36	0.32	4.76	0.07		2.43

Abbreviations: ACE, angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drug.

ponents are shown in FIGURE 1 and demonstrate linearity.

Event rates were consistently and markedly lower for patients with multiple risk factors only than for patients with established arterial disease. Patients with PAD had the highest CV mortality; CAD patients had the highest nonfatal MI rate, and the highest nonfatal stroke rate was seen among patients with CVD. The end points of CV death/MI/stroke or hospitalization for atherothrombotic event(s) were 12.81% (95% CI, 12.38%-13.23%) in the total patient population, 14.41% (95% CI, 13.93%-14.89%) in the population with established arterial disease, and 5.31% (95% CI, 4.86%-5.75%) in the population with multiple risk factors only. In the overall stable population with established arterial disease, approximately 1 in 7 patients had a major event (CV death, MI, and stroke) or was hospitalized for a CV event or revascularization procedure within a year of enrollment.

Data for other CV outcome events leading to hospitalization for such reasons as unstable angina (overall yearly rate, 4.26%) and congestive heart failure leading to hospitalization (which occurred in 3.42% of the overall population and in 3.77% of symptomatic patients) are shown in Table 3. Bleeding leading to hospitalization or transfusion occurred in 0.91% of the patients with established disease vs 0.55% of the patients with multiple risk factors only. The CV revascularization rate was approximately 5% for patients with CAD, predominantly via percutaneous coronary intervention in three quarters of those cases (Table 3). More than 1% of patients with CVD underwent surgery or angioplasty (with or without

Table 3. One-Year CV Event Rates for the Total Population and Main Subsets, Adjusted for Sex and Age*

	Percentage of Population With Event (95% Confidence Interval)					
CV Event	Total (n = 64 977)	Total Established Disease (n = 53 390)	Total CAD† (n = 38 602)	Total CVD† (n = 18 013)	Total PAD† (n = 8581)	Multiple Risk Factor Only (n = 11 766)
All-cause mortality	2.58 (2.37-2.79)	2.81 (2.57-3.04)	2.89 (2.63-3.15)	3.14 (2.80-3.47)	3.76 (3.27-4.25)	1.51 (1.24-1.77)
Major CV events						
CV death	1.65 (1.48-1.82)	1.84 (1.65-2.03)	1.93 (1.71-2.14)	2.05 (1.78-2.33)	2.51 (2.10-2.92)	0.75 (0.56-0.93)
Nonfatal MI	1.14 (1.00-1.28)	1.22 (1.06-1.38)	1.44 (1.25-1.64)	0.99 (0.80-1.18)	1.29 (1.01-1.58)	0.76 (0.57-0.95)
Nonfatal stroke	1.66 (1.49-1.84)	1.86 (1.66-2.06)	1.38 (1.21-1.55)	3.70 (3.27-4.13)	1.92 (1.56-2.27)	0.80 (0.61-0.99)
CV death, MI, or stroke	4.24 (3.97-4.51)	4.69 (4.39-5.00)	4.52 (4.19-4.84)	6.47 (5.96-6.97)	5.35 (4.77-5.97)	2.15 (1.84-2.46)
CV death, MI, stroke, or hospitalization for atherothrombotic event‡	12.81 (12.38-13.23)	14.41 (13.93-14.89)	15.20 (14.67-15.73)	14.53 (13.89-15.16)	21.14 (20.17-22.09)	5.31 (4.86-5.75)
Other CV outcomes leading to hospitalization						
Unstable angina	4.26 (3.99-4.53)	4.94 (4.63-5.25)	6.44 (6.03-6.85)	3.34 (3.02-3.66)	4.47 (3.97-4.97)	1.17 (0.96-1.38)
TIA	1.40 (1.24-1.56)	1.58 (1.40-1.76)	1.25 (1.09-1.42)	3.22 (2.82-3.60)	1.88 (1.54-2.23)	0.61 (0.45-0.76)
Other ischemic arterial event	1.35 (1.20-1.50)	1.52 (1.35-1.70)	1.47 (1.29-1.66)	1.58 (1.34-1.82)	3.91 (3.36-4.46)	0.54 (0.39-0.69)
Congestive heart failure	3.42 (3.18-3.66)	3.77 (3.49-4.04)	4.64 (4.30-4.98)	3.40 (3.07-3.73)	4.36 (3.86-4.86)	1.89 (1.61-2.16)
Bleeding	0.85 (0.72-0.97)	0.91 (0.78-1.05)	0.90 (0.76-1.04)	0.93 (0.75-1.11)	1.31 (1.01-1.61)	0.55 (0.39-0.70)
Worsening of claudication and hospitalization	1.18 (1.03-1.32)	1.35 (1.18-1.52)	1.06 (0.91-1.21)	1.01 (0.83-1.19)	6.43 (5.62-7.24)	0.35 (0.23-0.47)
New diagnosis of claudication and hospitalization	0.40 (0.32-0.48)	0.42 (0.33-0.51)	0.42 (0.32-0.52)	0.49 (0.35-0.62)	0.77 (0.54-1.01)	0.30 (0.18-0.42)
New diagnosis/worsening of claudication	1.40 (1.25-1.56)	1.58 (1.40-1.76)	1.31 (1.14-1.47)	1.28 (1.08-1.49)	6.58 (5.79-7.36)	0.55 (0.40-0.70)
CV surgical outcomes						
Coronary angioplasty or stenting	2.59 (2.38-2.80)	2.93 (2.69-3.18)	3.77 (3.46-4.09)	1.52 (1.31-1.74)	2.38 (2.01-2.74)	0.89 (0.70-1.08)
CABG	1.02 (0.89-1.15)	1.12 (0.97-1.27)	1.40 (1.20-1.59)	0.74 (0.59-0.89)	0.99 (0.75-1.23)	0.54 (0.39-0.70)
Carotid angioplasty or stenting	0.28 (0.21-0.35)	0.30 (0.22-0.38)	0.30 (0.22-0.39)	0.36 (0.24-0.47)	0.56 (0.36-0.77)	0.17 (0.08-0.25)
Carotid surgery	0.46 (0.37-0.55)	0.48 (0.39-0.58)	0.42 (0.32-0.51)	0.72 (0.55-0.89)	0.97 (0.70-1.23)	0.33 (0.21-0.46)
Peripheral artery bypass graft	0.71 (0.60-0.82)	0.81 (0.68-0.94)	0.62 (0.51-0.73)	0.51 (0.39-0.64)	3.66 (3.04-4.28)	0.21 (0.12-0.30)
PAD angioplasty or stenting	1.05 (0.91-1.18)	1.18 (1.03-1.34)	0.98 (0.84-1.13)	0.88 (0.71-1.05)	5.01 (4.30-5.70)	0.40 (0.27-0.52)
Amputation	0.34 (0.26-0.42)	0.35 (0.27-0.43)	0.25 (0.18-0.32)	0.28 (0.18-0.37)	1.63 (1.22-2.04)	0.27 (0.16-0.39)

Abbreviations: CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CV, cardiovascular; CVD, cerebrovascular disease; MI, myocardial infarction; PAD, peripheral arterial disease; TIA, transient ischemic attack.

*Calculated on the basis of the sample of patients with nonmissing outcomes and nonmissing covariates. Two hundred twenty-eight patients had covariates missing, precluding adjustment: EAD, 185; CAD, 145; CVD, 53; PAD, 41; and multiple risk factors only, 43.

†These subsets overlap each other.

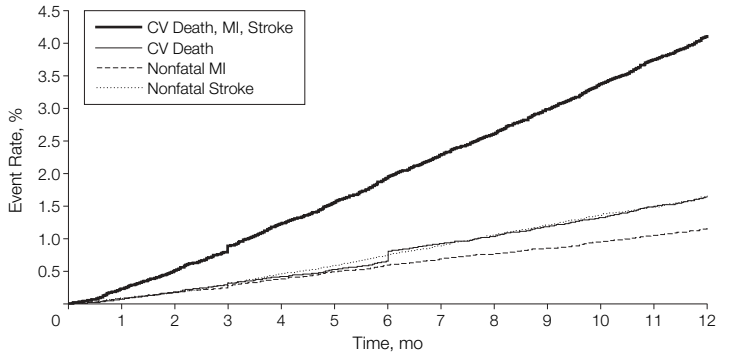
‡TIA, unstable angina, or worsening of PAD.

stenting) of the carotid artery, and more than 10% of patients with PAD underwent a lower-extremity revascularization procedure or an amputation, with a yearly lower-limb amputation rate of 1.63%. Notably, because of the overlap between groups, significant proportions of the CVD and PAD populations, 1.52% and 2.38%, respectively, also underwent coronary angioplasty.

There is a substantial overlap between the various locations of the atherosclerotic disease, such that patients with multiple arterial beds affected are counted in several groups (eg, a PAD patient with CAD is counted in the PAD group and in the CAD group). To further explore the relative risk of an acute ischemic event in an arterial bed that was not included as a qualifying condition (hereafter called the "cross-risk"), event rates are also reported as observed for predefined cohorts with either a single symptomatic arterial bed or multiple arterial beds (polyvascular disease; TABLE 4). Overall major CV event rates were approximately doubled in patients with polyvascular disease compared with patients with a single symptomatic arterial bed (Table 4). In an analysis of event rates as a function of the number of symptomatic arterial beds affected (FIGURE 2), counting patients with multiple risk factors only as 0 symptomatic beds, event rates increased in stepwise fashion with the number of symptomatic vascular beds, with the end point of CV death, MI, stroke, or hospitalization for a CV event ranging from 5.31% of patients with risk factors only to 12.58% with 1, 21.14% with 2, and 26.27% with 3 disease locations ($P<.001$ for trend).

Major CV end points were also examined by geographic region (TABLE 5). Although the adjusted rates reported show overall consistency across geographic regions, with extremes of CV death rates ranging from 0.74% in Japan to 2.90% in Eastern Europe, there

Figure 1. Event Curves for CV Death, Nonfatal Myocardial Infarction, and Stroke From Enrollment to 1 Year



No. at Risk

CV Death, MI, Stroke	64 692	64 296	63 642	62 196	60 265	50 706	23 538
CV Death	64 749	64 555	64 194	63 029	61 339	51 798	24 099
Nonfatal MI	64 723	64 471	64 045	62 702	61 122	51 577	23 983
Nonfatal Stroke	64 718	64 466	63 979	62 576	60 910	51 360	23 889

CV indicates cardiovascular; MI, myocardial infarction.

Table 4. One-Year CV Outcomes Among Patients With Established Atherosclerotic Disease as a Function of Single Arterial or Polyvascular Diseases, Adjusted for Sex and Age*

	Percentage of Population (95% Confidence Interval)†								
Event	Overall Single Disease Bed (n = 42 716)	CAD Alone (n = 28 867)	CVD Alone (n = 10 603)	PAD Alone (n = 3246)	CAD+CVD (n = 5339)	CAD+PAD (n = 3264)	CVD+PAD (n = 939)	CAD+CVD+PAD (n = 1132)	Overall Polyvascular Disease (n = 10 674)
All-cause mortality	2.45 (2.23-2.68)	2.42 (2.17-2.68)	2.55 (2.18-2.91)	2.39 (1.82-2.96)	3.61 (3.05-4.17)	4.58 (3.75-5.40)	3.58 (2.34-4.80)	5.37 (3.98-6.73)	4.08 (3.61-4.55)
CV death	1.58 (1.39-1.76)	1.58 (1.38-1.79)	1.62 (1.32-1.91)	1.37 (0.93-1.81)	2.40 (1.93-2.85)	3.23 (2.52-3.93)	2.15 (1.19-3.09)	3.93 (2.72-5.12)	2.78 (2.39-3.18)
Nonfatal MI	1.12 (0.97-1.28)	1.37 (1.17-1.57)	0.51 (0.35-0.67)	1.00 (0.61-1.39)	1.72 (1.31-2.13)	1.49 (1.02-1.95)	1.08 (0.34-1.81)	1.83 (0.98-2.67)	1.60 (1.30-1.90)
Nonfatal stroke	1.54 (1.36-1.73)	0.86 (0.72-1.00)	3.60 (3.10-4.09)	0.81 (0.49-1.14)	3.54 (2.93-4.14)	1.24 (0.79-1.69)	4.93 (3.42-6.42)	4.39 (3.03-5.74)	3.07 (2.63-3.51)
CV death, MI, or stroke	4.07 (3.78-4.36)	3.64 (3.34-3.94)	5.54 (4.98-6.09)	3.06 (2.41-3.71)	7.35 (6.53-8.17)	5.54 (4.64-6.42)	7.76 (5.93-9.55)	9.21 (7.38-11.01)	7.05 (6.42-7.67)
CV death, MI, stroke, or hospitalization for atherothrombotic event(s)‡	12.58 (12.12-13.04)	13.04 (12.52-13.57)	9.87 (9.24-10.50)	17.44 (16.10-18.75)	19.81 (18.66-20.94)	23.11 (21.63-24.56)	21.95 (19.43-24.40)	26.29 (23.80-28.70)	21.68 (20.76-22.59)

Abbreviations: CAD, coronary artery disease; CV, cardiovascular; CVD, cerebrovascular disease; MI, myocardial infarction; PAD, peripheral arterial disease.
*Calculated on the basis of the sample of patients with nonmissing outcomes and nonmissing covariates.
†Covariates missing precluding adjustment: 138 were missing from the total cohort; 103, CAD alone; 19, CVD alone; 16, PAD alone; 22, CAD plus CVD; 13, CAD plus PAD; 5, CVD plus PAD; 7, CAD plus CVD plus PAD; and 47, overall polyvascular disease.
‡Transient ischemic attack, unstable angina, or worsening of PAD.

are some differences. Japan has the lowest rates of CV death and of nonfatal MI but higher rates of nonfatal stroke compared with North America, Western Europe, and Australia. The observed combined rates of CV death, MI, or stroke ranged from 3.13% in Australia to 7.62% in Eastern Europe. Patients from Japan experienced low rates for all end points, which were lower than those of other Asian countries. In all geographic regions, the rate of the triple end point of CV death, MI, or stroke exceeded the anticipated 3% event rate (Table 5).

These CV ischemic events were associated with changes in the employment of participating patients. Among 14 406 patients for whom part- or full-time employment had been documented at baseline (Table 1), 50.34% of those who experienced an event were no longer working at 1 year vs 29.79% of those without an event.

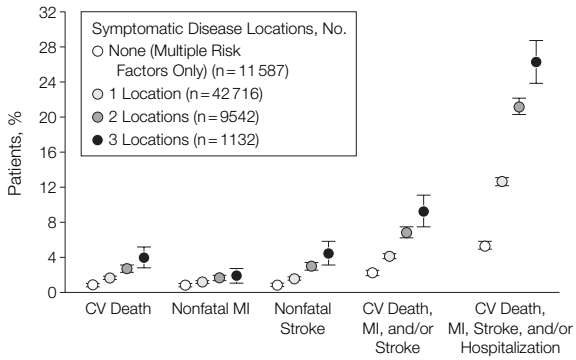
COMMENT

In this large, international study of a stable outpatient population with established atherothrombosis or at high risk of disease and receiving contemporary risk-reduction therapies, 1-year event rates are high and accrued almost linearly over time. This sustained event rate, observed in each region internationally, contrasts with the early steep increase in event rates followed by a plateau that is routinely observed in patients discharged from the hospital after acute events.

The 1-year hard event rates (CV death, MI, or stroke) increased markedly with the number of symptomatic arterial disease locations, ranging from 2.2% (in patients with risk factors only) to 9.2% (in patients with symptomatic disease in all 3 locations). Although this finding has been previously reported,[7] the additive risk is well defined in this data set, as well as the specific risk of each symptomatic arterial location, alone and in combination. The totality of risk appeared defined not only by arterial bed initially affected but also by the extent of disease (the overlap between symptomatic locations). The current report may in fact underestimate the impact of polyvascular disease because the database only addresses diagnosed symptomatic polyvascular disease.

Patients with PAD are usually regarded as a group that is at particu-

Figure 2. One-Year CV Event Rates as a Function of Number of Symptomatic Disease Locations



All *P* values <.001. CV indicates cardiovascular; MI, myocardial infarction. Patients with at least 3 factors but no symptoms are counted as 0, even in the presence of asymptomatic carotid plaque or reduced ankle brachial index. Error bars represent 95% confidence intervals.

Table 5. Geographic Variation of 1-Year CV End Points in the REACH Registry, Adjusted for Sex and Age*

	Percentage of Population (95% Confidence Interval)†								
Event	Global Population (n = 64 977)	North America (n = 25 999)	Latin America (n = 1835)	Western Europe (n = 17 142)	Eastern Europe (n = 5622)	Middle East (n = 840)	Asia (n = 5671)	Australia (n = 2847)	Japan (n = 5021)
All-cause mortality	2.58 (2.37-2.79)	2.51 (2.26-2.77)	3.30 (2.41-4.19)	2.68 (2.37-3.00)	3.63 (2.96-4.30)	3.07 (1.66-4.44)	2.95 (2.38-3.52)	2.40 (1.64-3.16)	1.48 (1.07-1.88)
CV death	1.65 (1.48-1.82)	1.50 (1.30-1.70)	2.23 (1.48-2.98)	1.75 (1.49-2.01)	2.90 (2.28-3.52)	2.71 (1.39-4.00)	2.04 (1.56-2.52)	1.41 (0.84-1.97)	0.74 (0.44-1.04)
Nonfatal MI	1.14 (1.00-1.28)	1.29 (1.09-1.49)	0.96 (0.47-1.45)	1.07 (0.87-1.27)	1.25 (0.91-1.60)	2.66 (1.44-3.87)	0.82 (0.53-1.11)	0.91 (0.56-1.27)	0.80 (0.43-1.17)
Nonfatal stroke	1.66 (1.49-1.84)	1.18 (1.01-1.35)	2.74 (1.89-3.58)	1.53 (1.28-1.77)	3.78 (3.10-4.45)	2.21 (1.01-3.39)	2.60 (2.06-3.13)	0.94 (0.59-1.29)	1.80 (1.36-2.25)
CV death, MI, or stroke	4.24 (3.97-4.51)	3.70 (3.40-4.01)	5.76 (4.57-6.93)	4.14 (3.74-4.53)	7.62 (6.70-8.53)	6.99 (5.01-8.92)	5.27 (4.53-6.01)	3.13 (2.39-3.86)	3.22 (2.59-3.84)
CV death, MI, stroke, or hospitalization for atherothrombotic event(s)‡	12.81 (12.38-13.23)	11.64 (11.13-12.15)	13.09 (11.56-14.58)	14.15 (13.52-14.77)	21.68 (20.54-22.81)	18.07 (15.59-20.47)	10.11 (9.28-10.93)	10.96 (9.82-12.08)	6.33 (5.66-7.00)

Abbreviations: CV, cardiovascular; MI, myocardial infarction.
*Calculated on the basis of the sample of patients with nonmissing outcomes and nonmissing covariates.
†Covariates missing precluding adjustment: 228 were missing from the global population; 126, North America; 9, Latin America; 75, Western Europe; 2, Eastern Europe; 6, the Middle East; 9, Asia; 1, Australia; and 0, Japan.
‡Transient ischemic attack, unstable angina, or worsening of peripheral arterial disease.

larly high risk of proximate cardiac ischemic events, yet PAD is commonly both underdiagnosed and undertreated.[8-10] The REACH Registry findings support these concepts, with PAD patients experiencing the highest rates of CV death and major CV events due to an atherothrombotic event. Many clinically relevant morbid limb ischemic events are known to be common and relevant for individuals with PAD (such as critical limb ischemia, abdominal aortic aneurysm rupture, or peripheral embolism) but were not captured individually in the REACH Registry. Thus, these data potentially underestimate the apparent clinical effect of PAD event rates. Interestingly, these higher event rates may be driven by a larger proportion of patients with PAD (approximately 60%) having polyvascular disease than the CAD cohorts (25%) or CVD cohorts (40%).

When focusing on patients with disease of a single arterial bed, patients with PAD alone were observed to experience lower CV death and CV death, MI, or stroke rates than patients with CAD or CVD. The event rates in patients with PAD alone were lower than those for PAD in combination with any other arterial disease location. PAD patients also required a large number of lower-extremity revascularization procedures: more than 10% underwent peripheral procedures after a year, with a 1.6% annual lower-limb amputation rate. Overall, these findings support the need for increased awareness among physicians and patients of the amount of cross-risk that is related to overlap between the various locations of atherothrombosis[11,12] and the value of actively seeking out the presence of multicirculation atherosclerotic arterial disease if individual risk is to be more precisely assessed.[8,13-15]

Important advances have been made in the demonstration of the benefits of aggressive risk reduction using lifestyle and pharmacological interventions for preventing initial and recurrent CV events in patients at high risk of, or with, established atherothrombosis.[16,17] Evidence stems mostly from large-scale clinical trials, which have provided the framework for recommendations regarding prevention. Yet there is evidence that in primary and secondary prevention—even in affluent geographic environments, such as Western Europe and North America—there is underuse of evidence-based preventive therapies across and among patients with various arterial beds affected by atherothrombosis.[4] Although there were some regional variations in risk factors, ethnicity, and BMI, the prevalence of risk factors, including overweight or obesity, in the REACH population was remarkably high. To provide actual event rates, we computed event rates after adjusting for age and sex but did not adjust for risk factors, which may remove variables that are presumably in the causal pathway for the events. Likewise, we chose not to adjust for BMI or ethnicity. Interestingly, in 3 additional sets of analyses, with incremental adjustments on risk factors, BMI, and ethnicity, such adjustment did not substantially affect most of the point estimates for event rates.

Although only a minority of patients in the REACH Registry were at target goals for blood pressure, glycemic control, cholesterol levels, body weight, and nonsmoking status, the overall rate of use of the main pharmacologic interventions recommended for secondary prevention[17] was relatively high. Approximately three quarters of patients in this registry received antiplatelet therapy, a similar proportion received either an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker therapy and approximately the same proportion received lipid-lowering therapy. In addition, approximately half of the patients were receiving β-blocker therapy. Yet, despite receiving contemporary evidence-based preventive drug therapy, these stable outpatients with established arterial disease and those with multiple risk factors for atherothrombosis both experienced high CV event rates, with a 4.7% yearly rate of hard events in the former group and 2.2% in the latter group. During the 1-year follow-up period, approximately 1 in 7 patients with established arterial disease experienced either a hard CV event or required hospitalization for an atherothrombotic event, with the associated health economic implications.

Patients with established arterial disease experienced 2 to 3 times higher event rates than patients with multiple risk factors only. Although there appears to be a continuum of risk among individuals,[16] the distinction between primary and secondary prevention remains valid from the standpoint of populations. This has important implications for designing large-scale preventive intervention trials.

The amount of cross-risk between arterial beds in patients with established disease has already been demonstrated in prior investigations,[18] with a high risk of recurrence of the baseline event[18] and of other manifestations of atherothrombosis.[13,19-23] The REACH data confirm that for patients with previous stroke, the risk of recurrent stroke exceeds the combined risks of MI and CV death. In addition, these data are consistent with findings from the Oxford Vascular Study, which have outlined the high rates of vascular events outside the coronary territory in a population-based study.[24] In the REACH Registry, among patients with established disease or at risk of disease, there were at least as many nonfatal strokes (excluding transient ischemic attacks) as nonfatal MIs at follow-up.

The clinical burden of atherothrombosis is compounded because in addition to the hard events of CV death, MI, or stroke, patients with established atherothrombosis required a large number of revascularization interventions (approximately 5% coronary artery bypass graft surgery or percutaneous coronary intervention in CAD patients, 10% peripheral interventions in PAD patients, 1% carotid stenting or surgery in CVD patients), bleeding that leads to hospitalization or transfusion occurred in 0.9% of patients, and hospitalization due to congestive heart failure was required in 3.4% of patients. The socioeconomic effect of this dis-

ease burden is reflected in the fact that approximately 50% of the patients who were employed at baseline but who experienced an ischemic event during follow-up were not working at the 1-year follow up (twice the rate of patients without events).

The REACH Registry provides high-quality data (with a large sample size and with systematic audits and quality checks) with high follow-up rates and from diverse patient types and environments. These data complement other large-scale global data sets designed to explore the epidemiology[25,26] or acute management of patients with atherothrombosis.[27-34] Despite the size, scope, and quality of the REACH data set, this analysis has several limitations. The external validity of the findings may be limited, as is often the case in non–population-based registries. It is possible that the mere acceptance of participation in the registry might result in selection of physicians and patients who are more adherent to guidelines and prevention than in the general population. However, this would likely result in underestimation of the degree of undertreatment and of the event rates.[4] In addition, the event rates observed in the multiple risk factor population are only applicable to similar patient populations but should probably not be extrapolated to the wider primary prevention setting.

Follow-up rates were high, particularly for a registry of this scope and size. However, approximately 5.0% of the patients missed visits and, thus, we cannot actually exclude a small margin of error in the estimation of event rates. However, the clinical characteristics of patients with and without follow-up appear quite similar and suggest no systematic bias. The findings in the REACH Registry complement a previous analysis[35] of several regional cohort studies that highlight the consistently high incidence of stroke throughout the world. The lower CV event rates in certain regions of the world, such as Japan, are important areas for future research.

CONCLUSIONS

The high event rates observed in this large, stable, contemporary outpatient cohort of patients with established atherosclerotic arterial disease or with multiple atherothrombotic risk factors indicate that continued efforts are needed to improve secondary prevention and clinical outcomes. Initiatives to improve adherence to evidence-based guidelines[36] and care are an important tool in this respect. In addition, the strong association of asymptomatic and symptomatic multiple locations of atherothrombosis with event rates suggests that atherothrombosis should be addressed as a global arterial disease in patients.

Author Contributions: Dr Steg 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.
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Acquisition of data: Steg, Liau, Ikeda, Goto.
Analysis and interpretation of data: Steg, Bhatt, Wilson, D'Agostino, Hirsch, Mas, Ikeda, Pencina, Goto.
Drafting of the manuscript: Steg, Bhatt, D'Agostino, Hirsch, Goto.
Critical revision of the manuscript for important intellectual content: Steg, Bhatt, Wilson, D'Agostino, Ohman, Röther, Liau, Hirsch, Mas, Ikeda, Pencina, Goto.
Statistical analysis: Bhatt, Wilson, D'Agostino, Pencina.
Obtained funding: Steg, Goto.
Administrative, technical, or material support: Steg, Röther, Goto.
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