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# Angina and Future Cardiovascular Events in Stable Patients With Coronary Artery Disease: Insights From the Reduction of Atherothrombosis for Continued Health (REACH) Registry

Alon Eisen, MD; Deepak L. Bhatt, MD, MPH; P. Gabriel Steg, MD; Kim A. Eagle, MD; Shinya Goto, MD; Jianping Guo, MS; Sidney C. Smith, MD; E. Magnus Ohman, MD; Benjamin M. Scirica, MD, MPH; on Behalf of the REACH Registry Investigators\*

**Background**—The extent to which angina is associated with future cardiovascular events in patients with coronary artery disease has long been debated.

**Methods and Results**—Included were outpatients with established coronary artery disease who were enrolled in the REACH registry and were followed for 4 years. Angina at baseline was defined as necessitating episodic or permanent antianginal treatment. The primary end point was the composite of cardiovascular death, myocardial infarction, or stroke. Secondary end points included heart failure, cardiovascular hospitalizations, and coronary revascularization. The independent association between angina and first/total events was examined using Cox and logistic regression models. Out of 26 159 patients with established coronary artery disease, 13 619 (52%) had angina at baseline. Compared with patients without angina, patients with angina were more likely to be older, female, and had more heart failure and polyvascular disease ( $P<0.001$  for each). Compared with patients without angina, patients with angina had higher rates of first primary end-point event (14.2% versus 16.3%, unadjusted hazard ratio 1.19, CI 1.11–1.27,  $P<0.001$ ; adjusted hazard ratio 1.06, CI 0.99–1.14,  $P=0.11$ ), and total primary end-point events (adjusted risk ratio 1.08, CI 1.01–1.16,  $P=0.03$ ). Patients with angina were at increased risk for heart failure (adjusted odds ratio 1.17, CI 1.06–1.28,  $P=0.002$ ), cardiovascular hospitalizations (adjusted odds ratio 1.29, CI 1.21–1.38,  $P<0.001$ ), and coronary revascularization (adjusted odds ratio 1.23, CI 1.13–1.34,  $P<0.001$ ).

**Conclusions**—Patients with stable coronary artery disease and angina have higher rates of future cardiovascular events compared with patients without angina. After adjustment, angina was only weakly associated with cardiovascular death, myocardial infarction, or stroke, but significantly associated with heart failure, cardiovascular hospitalization, and coronary revascularization. (*J Am Heart Assoc.* 2016;5:e004080 doi: 10.1161/JAHA.116.004080)

**Key Words:** angina • cardiovascular events • coronary artery disease

Stable angina affects more than 8 million people in the United States each year.<sup>1</sup> Patients with stable angina have reduced quality of life and utilize greater healthcare resources.<sup>2</sup> The extent to which angina is independently associated with future cardiovascular events or is just a

marker of disease severity has long been debated.<sup>3–11</sup> While several studies have demonstrated that angina is independently associated with cardiovascular outcome including cardiovascular death and myocardial infarction (MI),<sup>6–9</sup> others have not found a compelling association between angina and

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An accompanying Appendix S1 is available at <http://jaha.ahajournals.org/content/5/10/e004080/DC1/embed/inline-supplementary-material-1.pdf>

\*The members of the REACH Registry Investigators are given in Appendix S1.

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“hard” cardiovascular end points.<sup>10,12</sup> In addition, large-scale trials have shown that the alleviation of anginal symptoms by pharmacological treatment or by coronary revascularization improves quality of life measures but does not tend to decrease the rates of future MI or mortality.<sup>13</sup> Furthermore, in outpatients with stable coronary artery disease (CAD), most cardiovascular events actually occur in patients without prior angina.<sup>9</sup> We therefore aimed to examine the independent association between angina at baseline and future cardiovascular events in patients with stable CAD who were included in a large international outpatient registry.

## Methods

### Study Design

The design of the Reduction of Atherothrombosis for Continued Health (REACH) registry has been previously published.<sup>14,15</sup> In brief, REACH is an outpatient registry of patients with either stable symptomatic vascular disease (CAD, cerebrovascular disease, or peripheral artery disease) or with multiple atherosclerotic risk factors. Patients from 3647 centers in 29 countries were enrolled between 2003 and 2004 and treated according to best judgment and practices of their primary care physicians. Detailed information was collected at baseline, with subsequent annual follow-up on a longitudinal outpatient basis at 1, 2, 3, and 4 years. Final database lock was in April 2009. In each country, 10% of all sites underwent data control audits and were monitored for source documentation and accuracy of all case report forms. The protocol was approved by local institutional review boards, and each enrolled patient was required to provide a signed informed consent.

In the current analysis, we included patients with documented CAD at baseline who completed at least 1 postbaseline follow-up visit and were enrolled at centers that participated in the 4-year REACH follow-up study.<sup>16</sup> CAD was defined as having 1 or more of the following: stable angina, history of unstable angina (UAP), previous MI, history of percutaneous coronary intervention (PCI), or history of coronary artery bypass graft surgery (CABG). Patients without CAD at baseline were excluded from the current analysis. A sensitivity analysis included only patients who had a previous MI, history of PCI, or a history of CABG.

### Stable Angina

Patients were stratified by the presence of stable angina symptoms at baseline. Stable angina at baseline was documented by the treating physician using the case report form and was defined as angina necessitating episodic or permanent medication use. The last episode of angina was

documented in the case report form as either occurring  $\leq 1$  year prior to baseline or  $>1$  year prior to baseline.

### Clinical End Points

Data regarding events were collected locally and forwarded to the central research organization. The primary end point was a composite of cardiovascular death, MI, or stroke. The rate of each end point was calculated and stratified by angina status at baseline. End points were not adjudicated. Cardiovascular death included fatal stroke, fatal MI, 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 MI or stroke followed by a death whatever the cause in the next 28 days was considered to be a fatal MI or fatal stroke.

Secondary end points included all-cause death, heart failure, UAP, cardiovascular hospitalizations, and coronary revascularization. Heart failure was defined as symptoms of heart failure leading to hospitalization. Cardiovascular hospitalization consisted of hospitalization for UAP, transient ischemic attack, worsening of claudication related to peripheral artery disease, other ischemic arterial event, coronary revascularization (PCI or CABG), carotid surgery, carotid angioplasty/stenting, amputation affecting lower limbs, peripheral bypass graft, or angioplasty/stenting for peripheral artery disease. Complete definitions of other clinical end points have been previously described.<sup>15</sup>

The total number of the primary end-point events (total cardiovascular death, MI, or stroke), as well as the total cardiovascular hospitalizations and total coronary revascularizations during follow-up, were also examined and stratified by angina status at baseline.

### Statistical Analysis

Continuous variables are presented as mean  $\pm$  SD, and categorical variables as frequencies and percentages. Cumulative incidence for cardiovascular death, MI, or stroke was examined using the Kaplan–Meier approach. Cox proportional hazard models were used to examine whether angina is associated with cardiovascular death, MI, or stroke. All-cause death was also examined using the Kaplan–Meier approach. Incidence of heart failure, UAP, cardiovascular hospitalizations, and coronary revascularizations are presented as crude rates at 45 months. Logistic regression models were used to

**Table 1.** Baseline Characteristics

Characteristic	Angina (n=13 619)	No Angina (n=12 540)	Total (n=26 159)	P-Value
Age, y—mean (SD)	68.5 (10.0)	67.5 (10.0)	68.0 (10.0)	<0.001
>75 y	3788 (27.9)	3094 (24.8)	6882 (26.4)	<0.001
Men	9061 (66.6)	9449 (75.4)	18 510 (70.8)	<0.001
Region*				<0.001
North America	4430 (47.6)	4881 (52.4)	9331 (35.7)	
Latin America	286 (37.2)	483 (62.8)	769 (2.9)	
Western Europe	4367 (51.6)	4102 (48.4)	8469 (32.4)	
Eastern Europe	2276 (71.4)	912 (28.6)	3188 (12.2)	
Middle East	147 (44.8)	181 (55.2)	328 (1.2)	
Asia Pacific	2113 (51.6)	1981 (48.4)	4094 (15.7)	
Hypertension	11 316 (83.1)	9541 (76.1)	20 857 (79.7)	<0.001
Hypercholesterolemia	10 076 (74.0)	9666 (77.1)	19 742 (75.5)	<0.001
Diabetes mellitus	5308 (39.0)	4526 (36.1)	9834 (37.6)	<0.001
Obesity (BMI ≥30)	3974 (29.4)	3391 (27.3)	7365 (28.4)	<0.001
Current smoker at baseline	1778 (13.5)	1605 (13.2)	3383 (13.3)	<0.001
Prior ischemic event	7042 (52.4)	8298 (66.7)	15 340 (59.3)	<0.001
Prior MI	6010 (44.6)	7933 (63.7)	13 943 (53.8)	<0.001
Prior PCI	5015 (37.1)	5975 (47.9)	10 990 (42.2)	<0.001
Prior CABG	3790 (28.0)	4579 (36.6)	8369 (32.1)	<0.001
Heart failure	3016 (22.5)	2007 (16.2)	5023 (19.5)	<0.001
Atrial fibrillation	1780 (13.3)	1304 (10.5)	3084 (12.0)	<0.001
CVD at baseline	2732 (20.1)	1670 (13.3)	4402 (16.8)	<0.001
PAD at baseline	1633 (12.0)	1183 (9.4)	2816 (10.8)	<0.001
Polyvascular disease	3888 (28.6)	2622 (20.9)	6510 (24.9)	<0.001
Aortic valve stenosis	588 (4.5)	411 (3.4)	999 (4.0)	<0.001
≥1 Antithrombotic drug	8334 (92.2)	7612 (94.8)	15 946 (93.4)	<0.001
≥1 Lipid-lowering drug	7271 (80.6)	6850 (85.3)	14 121 (82.8)	<0.001
<b>Medication at 4 y</b>				
Statins	6879 (76.4)	6562 (81.9)	13 441 (79.0)	<0.001
ACE inhibitor or ARB	6348 (70.3)	5670 (70.7)	12 018 (70.5)	<0.001
β-Blocker	5875 (65.1)	5265 (65.7)	11 140 (65.4)	<0.001
Diuretic	4197 (46.7)	3359 (42.1)	7556 (44.5)	<0.001
Calcium channel blocker	3530 (39.3)	2620 (32.8)	6150 (36.3)	<0.001
Nitrate or other antianginal <sup>†</sup>	3642 (40.5)	2194 (27.6)	5836 (34.4)	<0.001
Any β-blockers, calcium channel blocker, nitrate, or other antianginal	7941 (87.9)	6769 (84.3)	14 710 (86.2)	<0.001
Aspirin+another antiplatelet drug	1248 (13.8)	1110 (13.8)	2358 (13.8)	<0.001
Oral anticoagulant drug	1206 (13.3)	1113 (13.8)	2319 (13.6)	<0.001

Data shown are n (%) unless otherwise indicated. ACE indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CVD, cerebrovascular disease; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

\*Percentages are for each region except for the total population. P-value is calculated using  $\chi^2$ .

<sup>†</sup>Nitrate as a chronic treatment and not if given episodically. Treatment could have been prescribed for other indications (eg, heart failure). Other antianginal includes molsidomine and nicorandil.

examine the association between angina and heart failure, UAP, cardiovascular hospitalizations, and coronary revascularizations. The variables included in all multivariate models were based on the previously validated REACH model for recurrent cardiovascular events.<sup>17</sup> This model included the following variables: age, sex, current smoker, history of diabetes mellitus, body mass index  $<20$  (calculated as weight in  $\text{kg}/\text{m}^2$ ), ischemic event ( $\leq 1$  year,  $>1$  year, or no ischemic event), vascular disease status (polyvascular disease defined as CAD with concomitant cerebrovascular disease/peripheral artery disease, or single vascular disease [ie, only CAD]), congestive heart failure, atrial fibrillation/flutter, aspirin (at baseline), statins (at baseline), and Eastern Europe and Middle East, or Japan versus other regions (geographic regions were collapsed into higher [Eastern Europe and Middle East] and lower [Japan] risk locations). The total event counts of the composite of cardiovascular death, MI, or stroke, as well as cardiovascular hospitalization and coronary revascularization were fitted by the negative binomial regression model after accounting for varying lengths of individual's total follow-up time as an offset parameter as well as other baseline confounding factors. Results are reported in terms of adjusted incidence rate ratio (RR) and corresponding 95% CI from this model. Similar statistical methods were performed in the sensitivity analysis.

Patients were further stratified to 4 risk-groups according to the REACH model for recurrent cardiovascular events.<sup>17</sup> This model includes traditional risk factors, burden of disease, lack of treatment, and geographic location,<sup>17</sup> whereas angina status was not a candidate variable in the derivation of the REACH model. Cox proportional hazard models were used to examine whether angina is associated with cardiovascular death, MI, or stroke in the different risk-groups. Hazard ratios (HRs) are reported as unadjusted given the stratification by the REACH model, which already includes the adjustment variables.

Statistical significance was considered as a 2-sided probability of  $<0.05$ . Statistical analyses were performed using SAS version 9 (SAS Institute, Cary, NC).

## Results

### Patient Population

Of the 45 227 patients who were included in the REACH 4-year follow-up study, 44 736 patients had data on angina status at baseline. Of these, 18 577 patients without CAD were excluded from the current analysis. Thus, 26 159 patients with CAD were included and were followed for a median of 43.5 months (interquartile range 31.3–45.0). The patients' mean age was 68 years (SD 10) and 70.8% were men. Hypertension (79.7%) and hypercholesterolemia (75.5%)

were very common. More than half of the patients had a prior MI, a quarter had polyvascular disease, and a fifth of the patients had prior heart failure (Table 1).

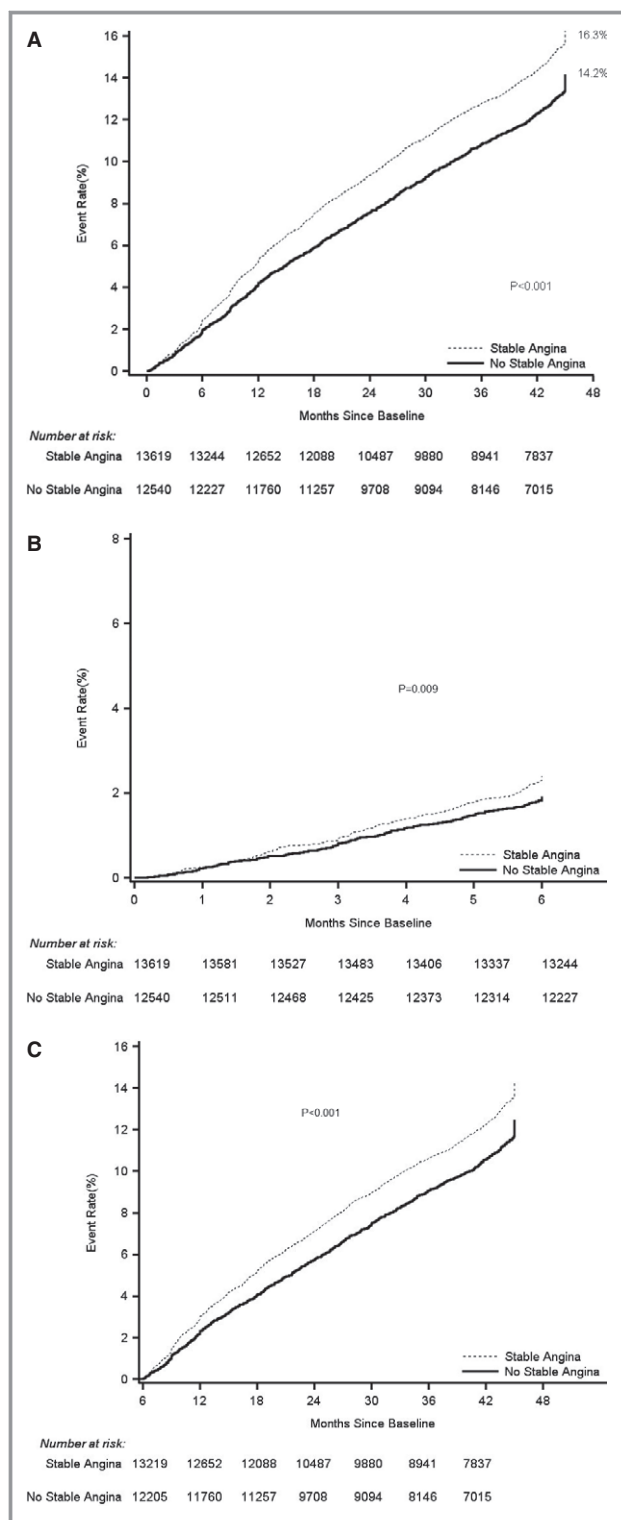
Out of the 26 159 patients with CAD, 13 619 (52%) have had angina prior to baseline and 12 540 (48%) did not have angina prior to baseline. Compared with patients without angina, patients with angina were more likely to be older, female, had more heart failure and polyvascular disease, but had fewer ischemic events and coronary revascularization procedures (PCI or CABG) prior to baseline ( $P<0.001$  for each; Table 1). Angina was more commonly reported in Eastern Europe and less in Latin America (Table 1). Patients with angina at baseline were more likely to be treated with either  $\beta$ -blockers, calcium channel blockers, or nitrates at 4 years of follow-up, but less likely to be treated with statins ( $P<0.001$  for each; Table 1).

### Angina and Cardiovascular Events

During follow-up, the rate of the composite primary end point of cardiovascular death, MI, or stroke was 16.3% in patients with angina and 14.2% in patients without angina (unadjusted HR 1.19, 95% CI 1.11–1.27,  $P<0.001$ ; Figure 1). In a landmark analysis, this difference in the rate of the primary end point between patients with versus without angina became statistically significant after 6 months from baseline and it remained significant at 4 years (Figure 1). The rate of each individual component of the composite primary end point was also higher among patients with angina (Table 2). After adjusting for multiple variables (Tables 2 and 3), the association between angina and the composite of cardiovascular death, MI, or stroke was attenuated (adjusted HR 1.06, 95% CI 0.99–1.14,  $P=0.11$ ), and so was the association between angina and each of the individual components (Table 2). An analysis of the total number of events during follow-up demonstrated that angina was significantly, albeit weakly, associated with the total number of the primary end-point events (rate ratio 1.08, 95% CI 1.01–1.16,  $P=0.03$ ; Table 4).

During follow-up, nearly a quarter of the patients were hospitalized due to cardiovascular causes (Table 2). Compared with patients without angina, patients with angina had higher rates of heart failure (8.0% versus 11.0%,  $P<0.001$ ), cardiovascular hospitalization (21.0% versus 26.9%,  $P<0.001$ ), and coronary revascularization (10.0% versus 11.4%,  $P<0.001$ ). After adjusting for multiple variables, the association between angina and each of these end points remained significant. Compared with patients without angina, patients with angina had a 17% higher relative risk for heart failure ( $P=0.002$ ), a 29% higher relative risk for cardiovascular hospitalization ( $P<0.001$ ), and a 23% higher relative risk for coronary revascularization ( $P<0.001$ ; Table 2). In addition, angina was associated with the total number of cardiovascular





**Figure 1.** Kaplan–Meier rates of the primary composite end point of cardiovascular death, MI, or stroke by presence of angina at baseline in the overall period (A), and landmark analysis during the first 6 months (B) and during 6 months to 4 years (C). The Kaplan–Meier curves demonstrate a higher rate of the composite primary end point of cardiovascular death, MI, or stroke in patients with angina, as compared to patients without angina. MI indicates myocardial infarction.

hospitalizations, as well as the total number of coronary revascularizations (Table 4).

No significant difference in the association between angina and the primary end point was observed in subgroups by age, sex, time from ischemic event, current smoking, heart failure, or prior coronary revascularization (PCI or CABG) (Figure 2). However, a significant interaction was observed between angina and the primary end point by polyvascular disease status (adjusted HR 0.99, 95% CI 0.88–1.12, in patients with polyvascular disease; adjusted HR 1.13, 95% CI 1.03–1.24, in patients without polyvascular disease; *P*-interaction=0.015). In addition, a marginal interaction was observed between angina and the primary end point by diabetes mellitus status (adjusted HR 0.99, 95% CI 0.89–1.10, in patients with diabetes mellitus; adjusted HR 1.13, 95% CI 1.02–1.25, in patients without diabetes mellitus; *P*-interaction=0.08).

No association was observed between angina and the primary end point by the time of last angina episode. In patients who had anginal symptoms during ≤1 year prior to baseline (*n*=4085), the rate of the primary end point was 16.1%, whereas in patients who have had the last anginal symptoms >1 year prior to baseline (*n*=9534), the rate of the primary end point was 16.5% (adjusted HR angina versus no angina 1.06, 95% CI 0.96–1.18, *P*=0.26; 1.06, 95% CI 0.98–1.15, *P*=0.14, respectively).

Stratifying the patients to quartiles according to the REACH risk score for recurrent cardiovascular events,<sup>17</sup> patients in higher quartiles had higher rates of the primary end point of cardiovascular death, MI, or stroke (Figure 3). Interestingly, angina was associated with the primary end point in lower-risk patients (unadjusted HR angina versus no angina 1.17, 95% CI 0.98–1.41, *P*=0.09 in quartile I; 1.21, 95% CI 1.02–1.43, *P*=0.03 in quartile II), whereas it was not associated with the primary end point in patients at higher risk for recurrent cardiovascular events (unadjusted HR angina versus no angina 0.95, 95% CI 0.84–1.09, *P*=0.47 in quartile III; 0.98, 95% CI 0.87–1.10, *P*=0.69 in quartile IV; Figure 3).

In a sensitivity analysis that included only patients with previous MI, history of PCI, or CABG (*n*=21 344), consistent qualitative results for the association between angina and future cardiovascular events were obtained (adjusted HR for the primary end point 1.08, 95% CI 1.00–1.17, *P*=0.07; Table 5).

## Discussion

This study from a large international registry demonstrates several observations. First, patients with stable CAD who have angina substantially differ in their baseline characteristics, atherosclerotic risk factors, concomitant cardiovascular

**Table 2.** Clinical End Points by Angina Status at Baseline

End Point	Angina (n=13 619) 4-Y KM Rate, n (%)	No Angina (n=12 540) 4-Y KM Rate, n (%)	Unadjusted HR (95% CI)	P-Value	Adjusted HR* (95% CI)	P-Value
CVD, MI, or stroke	1911 (16.3)	1479 (14.2)	1.19 (1.11–1.27)	<0.001	1.06 (0.99–1.14)	0.11
CVD	964 (8.4)	781 (7.6)	1.12 (1.02–1.23)	0.02	0.95 (0.86–1.05)	0.33
MI	541 (4.8)	428 (4.2)	1.16 (1.02–1.31)	0.03	1.14 (1.00–1.31)	0.06
Stroke	606 (5.4)	406 (4.1)	1.37 (1.21–1.55)	<0.001	1.19 (1.04–1.37)	0.01
Any-cause death	1473 (12.6)	1260 (12.1)	1.06 (0.99–1.15)	0.11	0.93 (0.85–1.01)	0.07
CVD, or MI	1429 (12.3)	1156 (11.1)	1.13 (1.04–1.22)	0.002	1.01 (0.93–1.10)	0.83
Heart failure <sup>†</sup>	1498 (11.0)	1006 (8.0)	1.42 (1.30–1.54)	<0.001	1.17 (1.06–1.28)	0.002
CVD, or heart failure <sup>†</sup>	2167 (15.9)	1578 (12.6)	1.31 (1.23–1.41)	<0.001	1.08 (1.00–1.17)	0.06
Unstable angina <sup>†</sup>	2073 (15.2)	1334 (10.6)	1.51 (1.40–1.62)	<0.001	1.40 (1.29–1.52)	<0.001
CVH <sup>†</sup>	3664 (26.9)	2637 (21.0)	1.38 (1.31–1.46)	<0.001	1.29 (1.21–1.38)	<0.001
Coronary revascularization <sup>†</sup>	1547 (11.4)	1258 (10.0)	1.15 (1.06–1.24)	0.001	1.23 (1.13–1.34)	<0.001

CAD indicates coronary artery disease; CVD, cardiovascular death; CVH, cardiovascular hospitalization; HR, hazard ratio; KM, Kaplan–Meier; MI, myocardial infarction.

\*Adjusted for age, sex, current smoker, history of diabetes mellitus, body mass index <20, ischemic event ≤1 year, ischemic event >1 year, polyvascular disease (CAD+ cerebrovascular disease/peripheral arterial disease), congestive heart failure, atrial fibrillation/flutter, aspirin (at baseline), statins (at baseline), and region.

<sup>†</sup>Event rates are crude rates at 45 months. Logistic regression models were used. Data presented are odds ratio (95% CI).

diseases, and medications use from patients without angina. Second, patients with angina have higher rates of future cardiovascular events, including cardiovascular death and MI. Third, the independent association between angina and cardiovascular events was attenuated after a rigorous adjustment for baseline comorbidities. Specifically, angina was only weakly associated with cardiovascular death, MI, or stroke,

but the association with heart failure, cardiovascular hospitalization, and coronary revascularizations remained significant after multivariable adjustment. Finally, stratifying the patients by their risk of recurrent cardiovascular events, angina seemed to be associated with cardiovascular death, MI, or stroke in lower-risk patients, but not in high-risk patients.

**Table 3.** Cox-Proportional Hazard Model for Predictors of Cardiovascular Death, Myocardial Infarction, or Stroke

Variable	Adjusted HR (95% CI)	$\chi^2$	P-Value
Age, per 1-y increase	1.035 (1.031–1.039)	284.3	<0.001
Congestive heart failure, yes vs no	1.75 (1.62–1.89)	191.1	<0.001
Polyvascular disease vs single vascular disease	1.52 (1.41–1.64)	118.5	<0.001
History of diabetes mellitus, yes vs no	1.44 (1.34–1.56)	100.6	<0.001
Ischemic event ≤1 y vs no ischemic event	1.67 (1.50–1.85)	87.7	<0.001
Ischemic event >1 y vs no ischemic event	1.48 (1.36–1.61)	85.6	<0.001
Statins, yes vs no	0.74 (0.68–0.80)	57.0	<0.001
Japan vs other regions	0.61 (0.53–0.72)	39.6	<0.001
Current smoker vs former or never	1.37 (1.24–1.52)	35.9	<0.001
Eastern Europe and Middle East vs other regions	1.27 (1.16–1.40)	23.1	<0.001
Atrial fibrillation/flutter, yes vs no	1.24 (1.13–1.36)	19.4	<0.001
Sex, male vs female	1.12 (1.03–1.21)	7.7	0.005
BMI <20, yes vs no	1.28 (1.06–1.54)	6.8	0.009
Aspirin, yes vs no	0.93 (0.86–1.01)	3.0	0.08
History of stable angina vs no history of stable angina	1.06 (0.99–1.14)	2.6	0.11

BMI indicates body mass index; HR indicates hazard ratio.

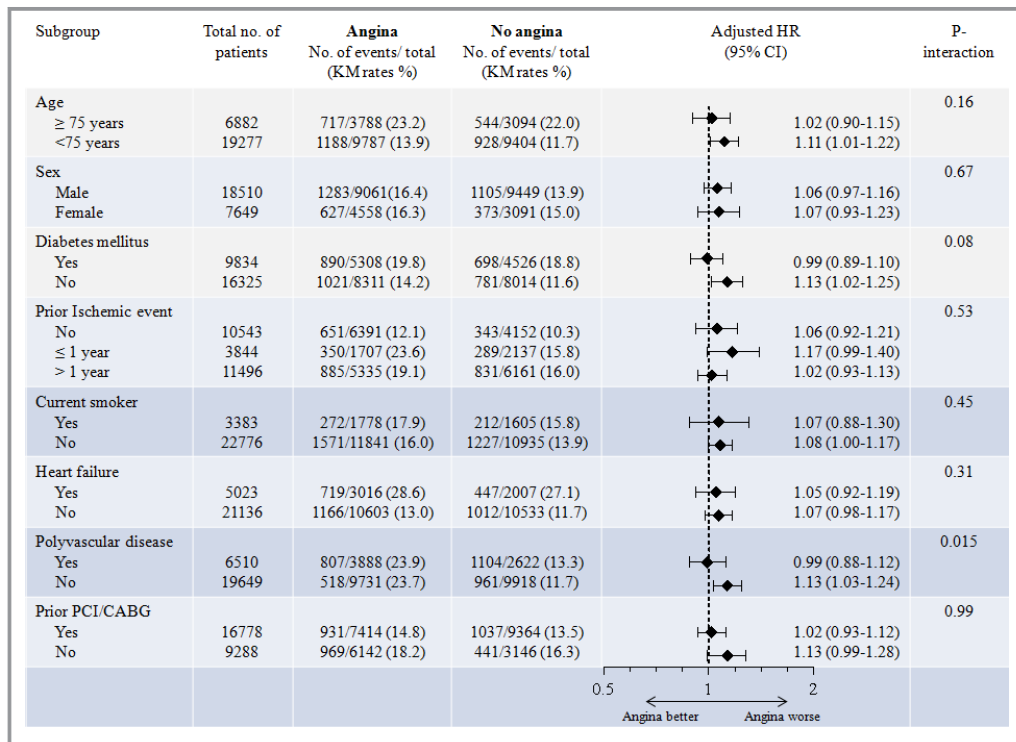
**Table 4.** Total Events During 4 Years by Angina Status at Baseline

Total End Point	Angina (n=13 619) Total Events, n	No Angina (n=12 540) Total Events, n	Unadjusted RR (95% CI)	P-Value	Adjusted RR* (95% CI)	P-Value
CVD, MI, or stroke	2176	1649	1.21 (1.12–1.29)	<0.001	1.08 (1.01–1.16)	0.03
CVH	7488	5065	1.36 (1.28–1.44)	<0.001	1.27 (1.20–1.35)	<0.001
Coronary revascularization	1814	1499	1.11 (1.03–1.20)	0.006	1.19 (1.10–1.29)	<0.001

BMI indicates body mass index; CAD, coronary artery disease; CVD, cardiovascular death; CVH, cardiovascular hospitalization; MI, myocardial infarction; RR, rate ratio.  
 \*Adjusted for age, sex, current smoker, history of diabetes mellitus, BMI <20, ischemic event (≤1 year, ischemic event >1 year), polyvascular disease (CAD+ cerebrovascular disease/peripheral arterial disease), congestive heart failure, atrial fibrillation/flutter, aspirin (at baseline), statins (at baseline), and region.

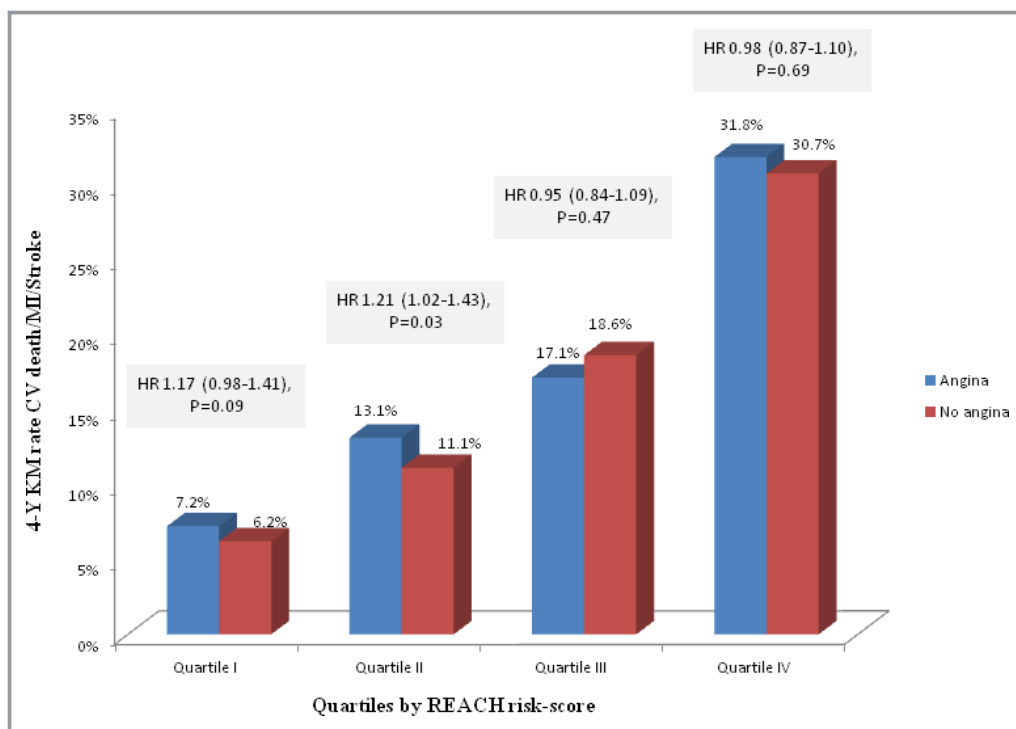
In patients with CAD included in the REACH registry, prior cardiovascular disease, particularly prior ischemic events, heart failure, cerebrovascular disease, and peripheral artery disease were common and found to be robust and independent markers of subsequent cardiovascular end points, even more so than traditional atherosclerotic risk factors<sup>18,19</sup> (Table 3). Indeed, several prior studies have examined angina-associated risk with cardiovascular events after adjusting solely for traditional risk factors such as diabetes mellitus,

hypertension, and hyperlipidemia and thus their results might be different based on the degree of multivariable modeling.<sup>6–8</sup> Our results are consistent with findings from several prior studies such as the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial (BARI 2D)<sup>10</sup> and the Heart and Soul study,<sup>12</sup> in which angina was not or was very weakly associated with future cardiovascular death, MI, or stroke. Nevertheless, a recent analysis from the CLARIFY registry<sup>9</sup> demonstrated a consistent association between angina, with



**Figure 2.** Rates and adjusted hazard ratios (95% CI) of the primary composite end point of cardiovascular death, MI, or stroke, in patients with and without angina at baseline by subgroups. Adjustment variables: age, sex, current smoker, history of diabetes mellitus, body mass index <20, ischemic event (≤1 year, ischemic event >1 year), polyvascular disease (CAD+ cerebrovascular disease/peripheral arterial disease), congestive heart failure, atrial fibrillation/flutter, aspirin (at baseline), statins (at baseline), and region. No significant interaction in the association between angina and the primary end point was observed in subgroups by age, sex, time from ischemic event, current smoking, heart failure, or prior PCI/CABG. However, a significant interaction was observed by polyvascular disease status and a marginal interaction was observed by diabetes mellitus status. CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; HR, hazard ratio; KM, Kaplan–Meier; MI, myocardial infarction; PCI, percutaneous coronary intervention.





**Figure 3.** Kaplan–Meier rates and unadjusted hazard ratios (95% CI) of the primary composite end point of CVD, MI, or stroke in patients with and without angina, stratified by patients’ risk according to the REACH risk score for recurrent Cardiovascular events.<sup>17</sup> Data were available for 24 315 patients. Stratifying the patients to quartiles according to the REACH risk score for recurrent Cardiovascular events, patients in higher quartiles had higher rates of the primary end point of CVD, MI, or stroke. Angina was associated with the primary end point in lower-risk patients, whereas it was not associated with the primary end point in patients at higher risk of recurrent Cardiovascular events. CVD indicates cardiovascular death; HR, hazard ratio; KM, Kaplan–Meier; MI, myocardial infarction.

or without ischemia, and cardiovascular death or MI, even after adjusting for the REACH risk score. Interestingly, compared with CLARIFY, the patients included in this analysis from REACH had a higher-risk profile and had a 2-fold annual rate of the composite end point of cardiovascular death, MI, or stroke and of each of the individual components. Thus, it is not clear whether angina has different prognostication according to the patient’s risk: While it may be independently associated with “hard” cardiovascular events in patients at lower risk, it is perhaps only a surrogate for more advanced disease in patients at higher risk. Interestingly, by stratifying the patients by their risk of recurrent cardiovascular events, we indeed demonstrated that angina might be associated with “hard” cardiovascular events only in patients at lower risk and not in patients at higher risk. In addition, our subgroup analysis also demonstrated that angina was independently associated with cardiovascular death, MI, or stroke, in several lower-risk groups such as patients without diabetes mellitus and without other vascular beds involved besides CAD. Nevertheless, the complex association between angina and “hard” cardiovascular end points should be further delineated in future research.

The clinical diagnosis of stable angina has been linked historically to the classic chronic condition caused by epicardial coronary stenosis.<sup>2</sup> Nevertheless, stable angina includes other less common presentations such as microvascular angina, vasospastic angina, and angina caused by ischemic cardiomyopathy.<sup>2</sup> In each of these conditions, myocardial ischemia is present, albeit each with a different burden and mechanism. The association between angina, ischemia, and cardiovascular outcome is complex and is probably not consistent across all patients. In the BARI 2D trial, among patients with diabetes mellitus, myocardial ischemia, rather than anginal symptoms, appeared to be prognostic for future cardiovascular events.<sup>10</sup> These results are consistent with our findings in diabetic patients in whom angina by itself was not predictive of cardiovascular death, MI, or stroke. Interestingly, in the CLARIFY registry, patients who had only ischemia without angina had adjusted risk for cardiovascular outcomes comparable to patients without both, whereas patients who had both angina and ischemia had the worst outcome.<sup>9</sup> Interestingly, more than half of the cardiovascular death and MI events in the CLARIFY study occurred in patients without detectable ischemia or angina at

**Table 5.** Sensitivity Analysis—Clinical End Points by Angina Status at Baseline of Patients With Previous MI, History of PCI or CABG

End Point	Angina (n=9415) 4-Y KM Rate, n (%)	No Angina (n=11 929) 4-Y KM Rate, n (%)	Unadjusted HR (95% CI)	P-Value	Adjusted HR* (95% CI)	P-Value
CVD, MI, or stroke	1338 (16.6)	1401 (14.4)	1.21 (1.12–1.30)	<0.001	1.08 (1.00–1.17)	0.07
CVD	691 (8.7)	736 (7.5)	1.18 (1.06–1.30)	0.002	1.00 (0.90–1.12)	0.94
MI	427 (5.4)	415 (4.3)	1.30 (1.13–1.49)	<0.001	1.20 (1.04–1.38)	0.01
Stroke	366 (4.7)	379 (4.0)	1.22 (1.05–1.41)	0.007	1.11 (0.96–1.30)	0.17
Any-cause death	1048 (13.1)	1199 (12.1)	1.09 (1.01–1.19)	0.04	0.97 (0.89–1.06)	0.48
CVD, or MI	1056 (13.2)	1100 (11.1)	1.21 (1.11–1.32)	<0.001	1.06 (0.97–1.16)	0.19
Heart failure <sup>†</sup>	1063 (11.3)	953 (8.0)	1.47 (1.34–1.61)	<0.001	1.18 (1.06–1.31)	0.002
CVD, or heart failure <sup>†</sup>	1534 (16.3)	1492 (12.5)	1.36 (1.26–1.47)	<0.001	1.12 (1.02–1.22)	0.02
Unstable angina <sup>†</sup>	1573 (16.7)	1175 (9.9)	1.84 (1.69–1.99)	<0.001	1.68 (1.54–1.83)	<0.001
CVH <sup>†</sup>	2704 (28.7)	2432 (20.4)	1.57 (1.48–1.68)	<0.001	1.48 (1.39–1.59)	<0.001
Coronary revascularization <sup>†</sup>	1258 (13.4)	1198 (10.0)	1.38 (1.27–1.50)	<0.001	1.39 (1.27–1.52)	<0.001

CABG indicates coronary artery bypass graft surgery; CAD, coronary artery disease; CVD, cardiovascular death; CVH, cardiovascular hospitalization; HR, hazard ratio; KM, Kaplan–Meier; MI, myocardial infarction; PCI, percutaneous coronary intervention.

\*Adjusted for age, sex, current smoker, history of diabetes mellitus, body mass index <20, ischemic event (≤1 year, ischemic event >1 year), polyvascular disease (CAD+ cerebrovascular disease/peripheral arterial disease), congestive heart failure, atrial fibrillation/flutter, aspirin (at baseline), statins (at baseline), and region.

<sup>†</sup>Event rates are crude rates at 45 months. Logistic regression models were used. Data presented are odds ratio (95% CI).

baseline. In our study, ischemia status during follow-up was not available and could not be accounted for. Nevertheless, angina, regardless of ischemia status, was independently associated with more cardiovascular hospitalization and coronary revascularization procedures. Of interest, the association between angina and revascularization, although statistically significant, was not robust, perhaps reflecting the fact that the majority of patients with angina (70%) had their last angina symptoms >1 year prior to baseline, thus reducing the clinical impetus for revascularization. In addition, this may also reflect regional differences in the treatment of angina with revascularization.

Prior studies have demonstrated that the major benefit of optimal medical therapy or revascularization in patients with stable CAD is the relief of anginal symptoms rather than a reduction in cardiovascular death or MI.<sup>13,20,21</sup> Thus, the relationship between angina, ischemia, and future cardiovascular events remains an area of debate.<sup>22–24</sup> The ongoing International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA trial, NCT 01471522) might address this intricate relationship. Regardless, in this analysis from REACH, patients with angina have greater healthcare utilization with higher rates of total hospitalizations and revascularizations and therefore present an opportunity to improve care and reduce costs.

## Limitations

This analysis is based on a registry, which has inherent limitations. The end points in the study were not adjudicated. Analysis of patients with angina might have introduced a

selection bias. Angina was ascertained by the investigator's report in the electronic case report form at baseline, and patient self-reporting data were not available. Data regarding the exact date of last anginal episode, grading of angina severity, or change in angina over time were not available. In addition, data on the presence of objective coronary ischemia at baseline, or on left ventricular ejection fraction were also not available. Logistic regression models were used to examine the secondary end points since the exact time of event was not available for all subjects.

## Conclusions

Patients with stable CAD and angina have higher rates of future cardiovascular events compared with patients without angina. After accounting for baseline differences, angina was only weakly associated with cardiovascular death, MI, or stroke, but was significantly associated with heart failure, cardiovascular hospitalization, and coronary revascularization.

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# **SUPPLEMENTAL MATERIAL**



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