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Angina and Future Cardiovascular Events in Stable Patients with Coronary Artery Disease: Insights from the REACH registry

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Abstract

Background: The extent to which angina is associated with future cardiovascular (CV) events in patients with coronary artery disease (CAD) has long been debated.

Methods and Results: Included were outpatients with established CAD who were enrolled in the REACH registry and were followed for 4 years. Angina at baseline was defined as necessitating episodic or permanent anti-anginal treatment. The primary endpoint was the composite of CV death, myocardial infarction (MI), or stroke. Secondary endpoints included heart failure (HF), CV 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 CAD, 13,619 (52%) had angina at baseline. Compared with patients without angina, patients with angina were more likely to be older, female, had more HF, and polyvascular disease (P<0.001 for each). Compared with patients without angina, patients with angina had higher rates of first primary endpoint event (14.2% vs. 16.3%, unadjusted HR 1.19, CI 1.11-1.27, P<0.001; adjusted HR 1.06, CI 0.99-1.14, P=0.11), and total primary endpoint events (adjusted RR 1.08, CI 1.01-1.16, P=0.03). Patients with angina

were at increased risk for HF (adjusted OR 1.17, CI 1.06-1.28, P=0.002), CV hospitalizations (adjusted OR 1.29, CI 1.21-1.38,P<0.001), and coronary revascularization (adjusted OR 1.23, CI 1.13-1.34, P<0.001).

Conclusions: Patients with stable CAD and angina have higher rates of future CV events compared with patients without angina. After adjustment, angina was only weakly associated with CV death, MI, or stroke, but significantly associated with HF, CV hospitalization and coronary revascularization.

Key words: angina, coronary artery disease, cardiovascular events

Introduction

Stable angina affects more than 8 million people in the United States each year [1]. Patients with stable angina have reduced quality of life and utilize greater health care resources [2]. The extent to which angina is independently associated with future cardiovascular (CV) events or is just a marker of disease severity has long been debated [3-12]. While several studies have demonstrated that angina is independently associated with CV outcome including CV death and myocardial infarction (MI) [6-9], others have not found a compelling association between angina and 'hard' CV endpoints [10, 12]. 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 [13]. Furthermore, in outpatients with stable coronary artery disease (CAD), most CV events actually occur in patients without prior angina [9]. We therefore aimed to examine the independent association between angina at baseline and future CV 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 [14, 15]. 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 post baseline follow-up visit and were enrolled at centers that participated in the 4-year REACH follow-up study [16]. CAD was defined as having one 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 ≤ 1 year prior to baseline or > 1 year prior to baseline.

Clinical endpoints

Data regarding events were collected locally and forwarded to the central research organization. The primary endpoint was a composite of CV death, MI, or stroke. The rate of each endpoint was calculated and stratified by angina status at baseline. Endpoints were not adjudicated. CV death included fatal stroke, fatal MI, or other CV death. Other CV death included other death of cardiac origin; pulmonary embolism; any sudden death including unobserved and unexpected death (e.g., 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 endpoints included all cause death, heart failure, UAP, CV hospitalizations, and coronary revascularization. Heart failure was defined as symptoms of heart failure leading to hospitalization. CV 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 endpoints have been previously described [15].

The total number of the primary endpoint events (total CV death, MI, or stroke), as well as the total CV 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± standard deviation (SD), and categorical variables as frequencies and percentages. Cumulative incidence for CV death, MI, or stroke was examined using the Kaplan-Meier approach. Cox proportional hazard models were used to examine whether angina is associated with CV death, MI, or stroke. All cause death was also examined using the Kaplan-Meier approach. Incidence of heart failure, UAP, CV hospitalizations, and coronary revascularizations are presented as crude rates at 45 months. Logistic regression models were used to examine the association between angina and heart failure, UAP, CV hospitalizations, and coronary revascularizations. The variables included in all multivariate models were based on the previously validated REACH model for recurrent CV events [17]. This model included the following variables: age, sex, current smoker, history of diabetes, body mass index less than 20 (calculated as weight in kg/m^2), ischemic event (≤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 [i.e., only CAD]), congestive heart failure, atrial fibrillation/flutter, aspirin (at baseline), statins (at baseline), and Eastern Europe and Middle East, or Japan vs. 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 CV death, MI, or stroke, as well as CV 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% confidence intervals 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 CV events [17]. This model includes traditional risk factors, burden of disease, lack of treatment, and geographic location [17], 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 CV death, MI, or stroke in the different risk-groups. Hazard ratios 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 less than 0.05. Statistical analyses were performed using SAS version 9 (SAS Institute, Cary, North Carolina).

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 (IQR 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 26159 patients with CAD, 13619 (52%) have had angina prior to baseline and 12540 (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 CV events

During follow-up, the rate of the composite primary endpoint of CV death, MI, or stroke was 16.3% in patients with angina and 14.2% in patients without angina (unadjusted hazard ratio [HR] 1.19, 95% confidence interval (CI) 1.11-1.27, P<0.001; Figure 1). In a landmark analysis, this difference in the rate of the primary endpoint between patients with vs. 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 endpoint was also higher among patients with angina (Table 2). After adjusting for multiple variables (Table 2, Table 3), the association between angina and the composite of CV 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 endpoint events (RR 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 CV causes (Table 2). Compared with patients without angina, patients with angina had higher rates of heart failure (8.0% vs. 11.0%, P<0.001), CV hospitalization (21.0% vs. 26.9%, P<0.001), and coronary revascularization (10.0% vs. 11.4%, P<0.001). After adjusting for multiple variables, the association between angina and each of these endpoints 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 CV 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 CV hospitalizations, as well as the total number of coronary revascularizations (Table 4).

No significant difference in the association between angina and the primary endpoint 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 endpoint by polyvascular disease status (adjusted HR 0.99, 95% CI 0.88-1.12, in patients with polyvascular disease; adjusted HR 1.13, 95% 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 endpoint by diabetes status (adjusted HR 0.99, 95% CI 0.89-1.10, in patients with diabetes; adjusted HR 1.13, 95% CI 1.02-1.25, in patients without diabetes; P-interaction= 0.08).

No association was observed between angina and the primary endpoint 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 endpoint 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 endpoint was 16.5% (adjusted HR angina vs. 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 CV events [17], patients in higher quartiles had higher rates of the primary endpoint of CV death, MI, or stroke (Figure 3). Interestingly, angina was associated with the primary endpoint in lower-risk patients (unadjusted HR angina vs. 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 endpoint in patients at higher-risk for recurrent CV events (unadjusted HR angina vs. 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=21344), consistent qualitative results for the association between angina and future CV events were obtained (adjusted HR for the primary endpoint 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 CV diseases, and medications use, from patients without angina. Second, patients with angina have higher rates of future CV events, including CV death

and MI. Third, the independent association between angina and CV events was attenuated after a rigorous adjustment for baseline co-morbidities. Specifically, angina was only weakly associated with CV death, MI, or stroke, but the association with heart failure, CV hospitalization and coronary revascularizations remained significant after multivariable adjustment. Finally, stratifying the patients by their risk for recurrent CV events, angina seemed to be associated with CV death, MI, or stroke in lower-risk patients, but not in high-risk patients.

In patients with CAD included in the REACH registry, prior CV 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 CV endpoints, even more so than traditional atherosclerotic risk factors [18, 19] (Table 3). Indeed, several prior studies have examined angina associated risk with CV events after adjusting solely for traditional risk factors such as diabetes, hypertension, and hyperlipidemia and thus their results might be different based on the degree of multivariable modeling [6-8]. Our results are consistent with findings from several prior studies such as the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial (BARI 2D) [10] and the Heart and Soul study [12], in which angina was not or was very weakly associated with future CV death, MI, or stroke. Nevertheless, a recent analysis from the CLARIFY registry [9] demonstrated a consistent association between angina, with or without ischemia, and CV 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 two-fold annual rate of the composite endpoint of CV 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` CV 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 for recurrent CV events, we indeed demonstrated that angina might be associated with `hard` CV 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 CV death, MI, or stroke, in several lower-risk groups such as patients without diabetes and without other vascular beds involved besides CAD. Nevertheless, the complex association between angina and `hard` CV endpoints 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 [2]. Nevertheless, stable angina includes other less common presentations such as microvascular angina, vasospastic angina, and angina caused by ischemic cardiomyopathy [2]. In each of these conditions, myocardial ischemia is present, albeit each with a different burden and mechanism. The association between angina, ischemia, and CV 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 CV events [10]. These results are consistent with our findings in diabetic patients in whom angina by itself was not predictive of CV death, MI, or stroke. Interestingly, in the CLARIFY registry, patients who had only ischemia without angina had adjusted risk for CV outcomes comparable to patients without both, whereas, patients who had both angina and ischemia had the worst outcome [9]. Interestingly, more than half of the CV death and MI events in the CLARIFY study occurred in patients without detectable ischemia or angina at 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 CV 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 CV death or MI [13, 20, 21]. Thus, the relationship between angina, ischemia, and future CV events remain an area of debate [22- 24]. 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 endpoints 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 during 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 endpoints since the exact time of event was not available for all subjects.

Conclusion

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

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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
>75y	3788 (27.9)	3094 (24.8)	6882 (26.4)	<0.001

Characteristic	Angina (n=13,619)	No Angina (n=12,540)	Total (n=26,159)	P value
Men	9061 (66.6)	9449 (75.4)	18510 (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	11316 (83.1)	9541 (76.1)	20857 (79.7)	<0.001
Hypercholesterolemia	10076 (74.0)	9666 (77.1)	19742 (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)	15340 (59.3)	<0.001
Prior MI	6010 (44.6)	7933 (63.7)	13943 (53.8)	<0.001
Prior PCI	5015 (37.1)	5975 (47.9)	10990 (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

Characteristic	Angina (n=13,619)	No Angina (n=12,540)	Total (n=26,159)	P value
≥1 Antithrombotic drug	8334 (92.2)	7612 (94.8)	15946 (93.4)	<0.001
≥1 Lipid-lowering drug	7271 (80.6)	6850 (85.3)	14121 (82.8)	<0.001
Medication at 4 years:				
Statins	6879 (76.4)	6562 (81.9)	13441 (79.0)	<0.001
ACE inhibitor or ARB	6348 (70.3)	5670 (70.7)	12018 (70.5)	<0.001
Beta Blocker	5875 (65.1)	5265 (65.7)	11140 (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 *	3642 (40.5)	2194 (27.6)	5836 (34.4)	<0.001
Any beta blockers, calcium channel blocker, nitrate or other antianginal	7941 (87.9)	6769 (84.3)	14710 (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.

‡ Percentages are for each region except for the total population. P value is calculated using Chi-square.

*Nitrate as a chronic treatment and not if given episodically. Treatment could have been prescribed for other indications (eg. heart failure). Other antianginal include molsidomine, and nicorandil.

ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, basal mass index; CABG, coronary artery bypass graft; CVD, cerebrovascular disease; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SD, standard deviation.

Table 2: Clinical endpoints by angina status at baseline.

Endpoint	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
CV death, 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
CV death	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
CV death, 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 †	1498 (11.0)	1006 (8.0)	1.42 (1.30-1.54)	<0.001	1.17 (1.06-1.28)	0.002
CV death, or heart failure †	2167 (15.9)	1578 (12.6)	1.31 (1.23-1.41)	<0.001	1.08 (1.00-1.17)	0.06
Unstable angina †	2073 (15.2)	1334 (10.6)	1.51 (1.40-1.62)	<0.001	1.40 (1.29-1.52)	<0.001
CV hospitalization †	3664 (26.9)	2637 (21.0)	1.38 (1.31-1.46)	<0.001	1.29 (1.21-1.38)	<0.001
Coronary Revascularization †	1547 (11.4)	1258 (10.0)	1.15 (1.06-1.24)	0.001	1.23 (1.13-1.34)	<0.001

*Adjusted for age, sex, current smoker, history of diabetes, 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.

† Event rates are crude rates at 45 months. Logistic regression models were used. Data presented are Odds ratio (95% CI).

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction

Table 3: Cox-proportional hazard model for predictors of cardiovascular death, myocardial infarction, or stroke.

Variable	Adjusted HR (95% CI)	Chi square	P value
Age, per 1-year 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
Poly vascular disease vs. single vascular disease	1.52 (1.41-1.64)	118.5	<0.001
History of diabetes, yes vs. no	1.44 (1.34-1.56)	100.6	<0.001
Ischemic event<=1 year vs. no ischemic event	1.67 (1.50-1.85)	87.7	<0.001
Ischemic event>1 year 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
Body mass index<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

Table 4: *Total events* during 4 years by angina status at baseline.

Total endpoint	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
CV death, MI, or stroke	2176	1649	1.21 (1.12-1.29)	<0.001	1.08 (1.01-1.16)	0.03
CV hospitalization	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

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; RR, rate ratio

*Adjusted for age, sex, current smoker, history of diabetes, 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.

Table 5: Sensitivity analysis- Clinical endpoints by angina status at baseline of patients with previous MI, history of PCI or CABG.

Endpoint	Angina (n=9,415) 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
CV death, 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
CV death	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
CV death, 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 †	1063 (11.3)	953 (8.0)	1.47 (1.34-1.61)	<0.001	1.18 (1.06-1.31)	0.002
CV death, or heart failure †	1534 (16.3)	1492 (12.5)	1.36 (1.26-1.47)	<0.001	1.12 (1.02-1.22)	0.02
Unstable angina †	1573 (16.7)	1175 (9.9)	1.84 (1.69-1.99)	<0.001	1.68 (1.54-1.83)	<0.001
CV hospitalization †	2704 (28.7)	2432 (20.4)	1.57 (1.48-1.68)	<0.001	1.48 (1.39-1.59)	<0.001
Coronary Revascularization †	1258 (13.4)	1198 (10.0)	1.38 (1.27-1.50)	<0.001	1.39 (1.27-1.52)	<0.001

*Adjusted for age, sex, current smoker, history of diabetes, 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.

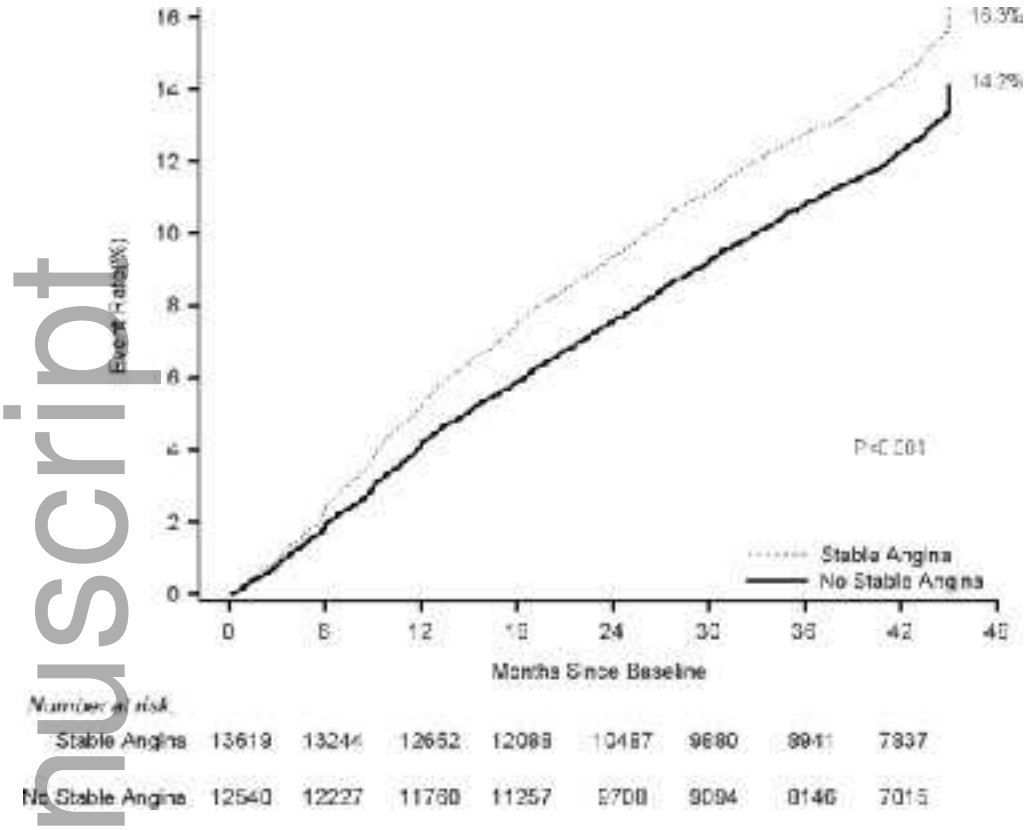
† Event rates are crude rates at 45 months. Logistic regression models were used. Data presented are Odds ratio (95% CI).

Figure Legends:

Figure 1: Kaplan Meier rates of the primary composite endpoint of CV 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-4 years (c). .
The Kaplan-Meier curves demonstrate a higher rate of the composite primary endpoint of CV death, MI, or stroke in patients with angina, as compared to patients without angina.

Figure 2: Rates and adjusted hazard ratios (95% CI) of the primary composite endpoint of CV death, MI, or stroke, in patients with and without angina at baseline by subgroups.
Adjustment variables: age, sex, current smoker, history of diabetes, 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 endpoint 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 status.

Figure 3: Kaplan Meier rates and unadjusted hazard ratios (95% CI) of the primary composite endpoint of CV death, MI, or stroke in patients with and without angina, stratified by patients' risk according to the REACH risk-score for recurrent CV events [17]. Data were available for 24,315 patients.
Stratifying the patients to quartiles according to the REACH risk score for recurrent CV events, patients in higher quartiles had higher rates of the primary endpoint of CV death, MI, or stroke. Angina was associated with the primary endpoint in lower-risk patients, whereas, it was not associated with the primary endpoint in patients at higher-risk for recurrent CV events.



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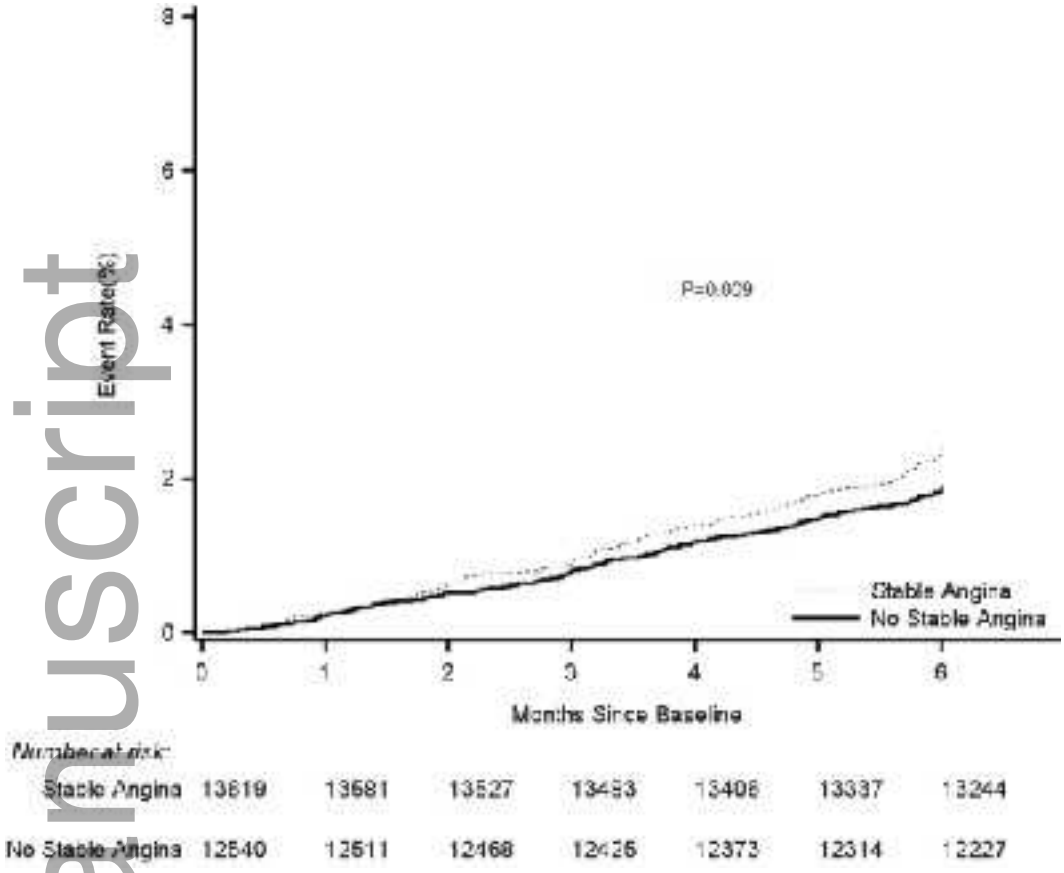

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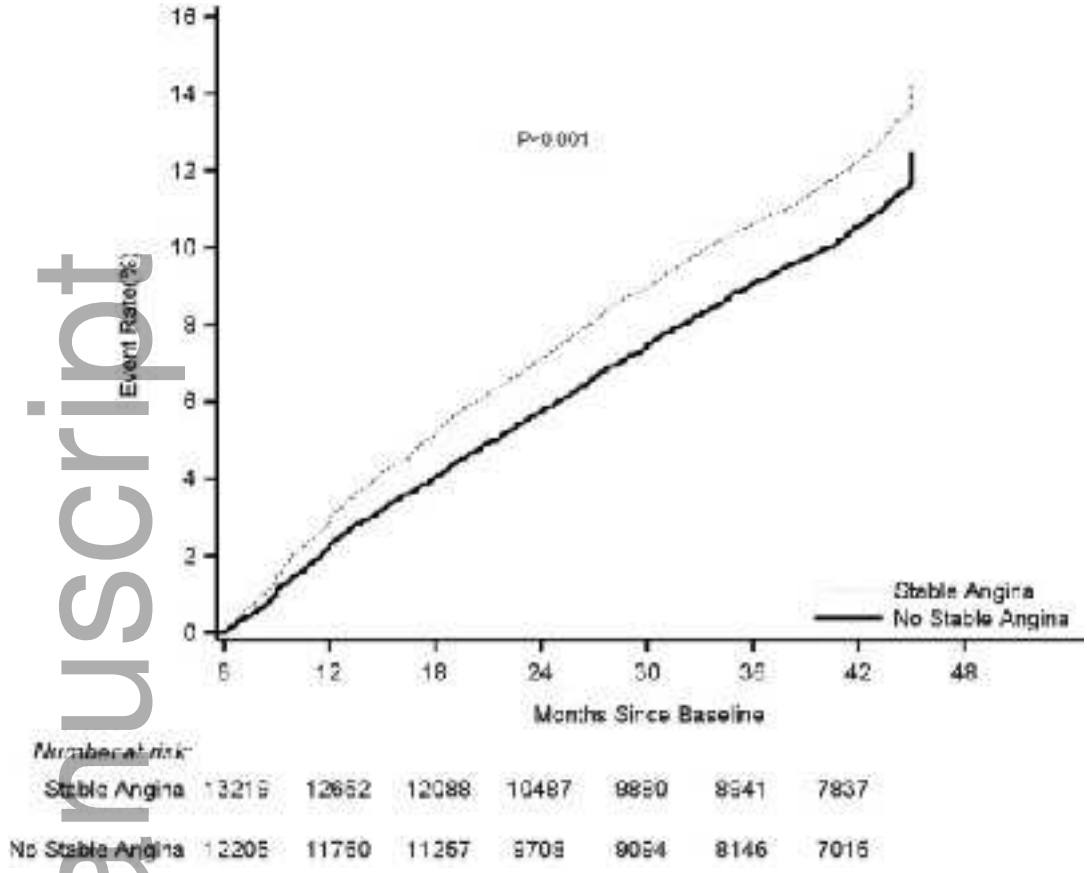

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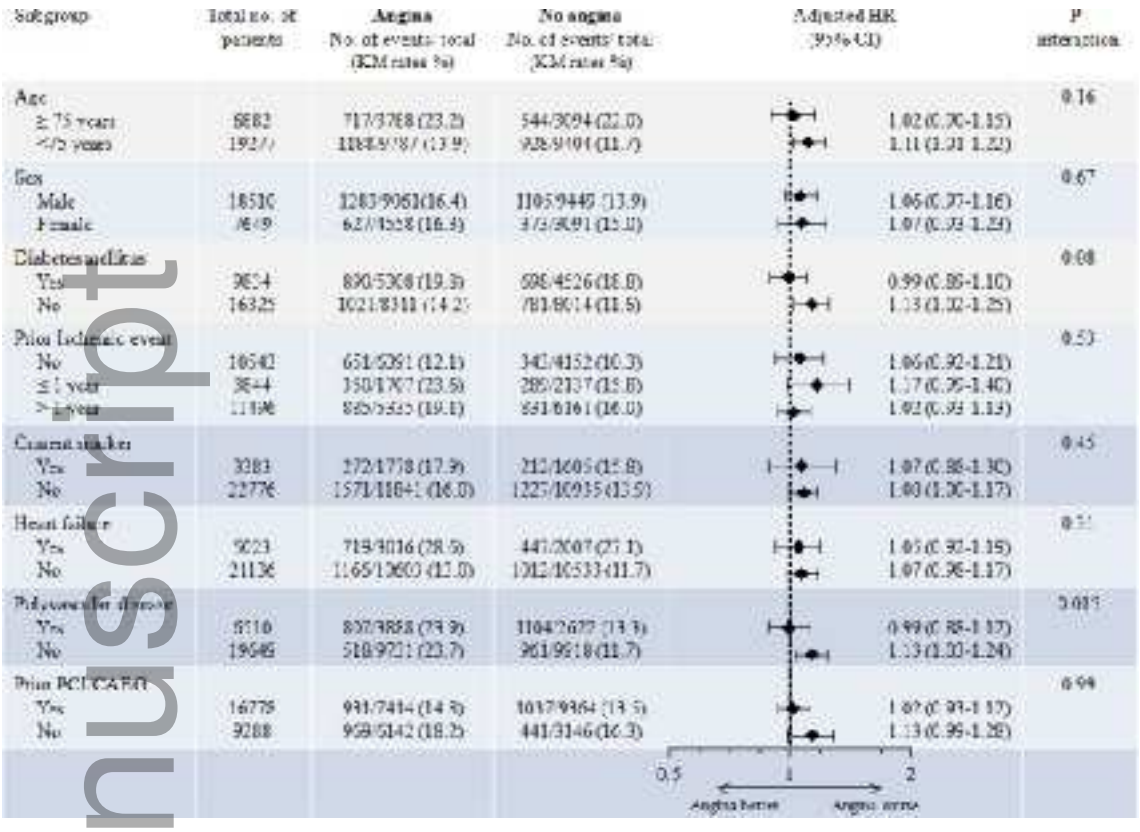

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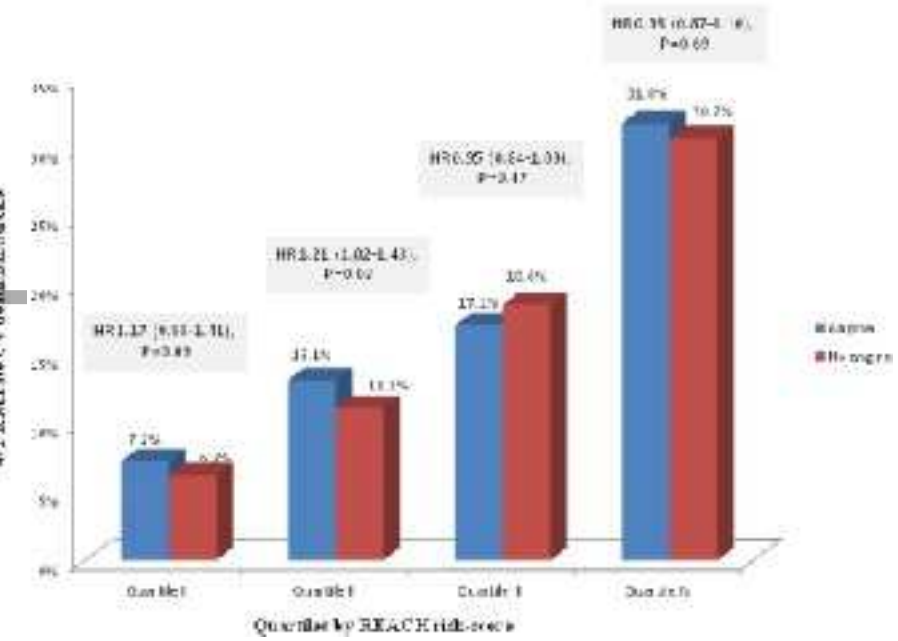

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