Original Investigation

Prevalence of Anginal Symptoms and Myocardial Ischemia and Their Effect on Clinical Outcomes in Outpatients With Stable Coronary Artery Disease

Data From the International Observational CLARIFY Registry

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IMPORTANCE In the era of widespread revascularization and effective antianginals, the prevalence and prognostic effect of anginal symptoms and myocardial ischemia among patients with stable coronary artery disease (CAD) are unknown.

OBJECTIVE To describe the current clinical patterns among patients with stable CAD and the association of anginal symptoms or myocardial ischemia with clinical outcomes.

DESIGN, SETTING, AND PARTICIPANTS The Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease (CLARIFY) registry enrolled outpatients in 45 countries with stable CAD in 2009 to 2010 with 2-year follow-up (median, 24.1 months; range, 1 day to 3 years). Enrollees included 32 105 outpatients with prior myocardial infarction, chest pain, and evidence of myocardial ischemia, evidence of CAD on angiography, or prior revascularization. Of these, 20 291 (63.2%) had undergone a noninvasive test for myocardial ischemia within 12 months of enrollment and were categorized into one of the following 4 groups: no angina or ischemia (n = 13 207 [65.1%]); evidence of myocardial ischemia without angina (silent ischemia) (n = 3028 [14.9%]); anginal symptoms alone (n = 1842 [9.1%]); and angina and ischemia (n = 2214 [10.9%]).

EXPOSURES Stable CAD.

MAIN OUTCOME AND MEASURE The composite of cardiovascular (CV)–related death or nonfatal myocardial infarction.

RESULTS Overall, 4056 patients (20.0%) had anginal symptoms and 5242 (25.8%) had evidence of myocardial ischemia on results of noninvasive testing. Of 469 CV-related deaths or myocardial infarctions, 58.2% occurred in patients without angina or ischemia, 12.4% in patients with ischemia alone, 12.2% in patients with angina alone, and 17.3% in patients with both. The hazard ratios for the primary outcome relative to patients without angina or ischemia and adjusted for age, sex, geographic region, smoking status, hypertension, diabetes mellitus, and dyslipidemia were 0.90 (95% CI, 0.68-1.20; $P = .47$) for ischemia alone, 1.45 (95% CI, 1.08-1.95; $P = .01$) for angina alone, and 1.75 (95% CI, 1.34-2.29; $P < .001$) for both. Similar findings were observed for CV-related death and for fatal or nonfatal myocardial infarction.

CONCLUSIONS AND RELEVANCE In outpatients with stable CAD, anginal symptoms (with or without ischemia on noninvasive testing) but not silent ischemia appear to be associated with an increased risk for adverse CV outcomes. Most CV events occurred in patients without angina or ischemia.

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Major changes have occurred in the management of coronary artery disease (CAD), with increasing use of revascularization[1] and effective evidence-based secondary prevention therapies, such as lifestyle interventions, statins, angiotensin-converting enzyme inhibitors, and antiplatelet agents, and the availability of newer antianginals. These factors have dramatically changed the presentation, management, and prognosis among patients with stable CAD.[2]

Uncertainty remains concerning which factors determine the prognosis of patients with stable CAD (ie, patients with evidence of CAD but without recent acute myocardial infarction [MI]) in the modern era of widespread revascularization and effective medical treatments. Furthermore, as a consequence of improved treatments, the prevalence and severity of anginal symptoms and myocardial ischemia may have diminished. The present analysis aims to describe the prevalence of anginal symptoms and MI in patients with stable CAD and their association with clinical outcomes using data from a large prospective registry of outpatients with stable CAD.

Methods

Study Design and Patients

The Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease (CLARIFY) has enrolled 33 283 outpatients with stable CAD. The registry is observational, does not interfere with clinical management, and does not mandate any specific test, procedure, or treatment. The rationale and design of the registry have been published previously[3-6] and are available online at www.clarify-registry.com. Patients were enrolled in 45 countries in Africa, Asia, Australia, Europe, the Middle East, and North and South America but not in the United States.

To be eligible for enrollment, patients had to meet at least 1 of the following criteria: documented MI more than 3 months before enrollment; angiographic demonstration of coronary stenosis of more than 50%; chest pain with evidence of MI (on a stress electrocardiogram); or coronary artery bypass graft or percutaneous coronary intervention more than 3 months before enrollment. We excluded patients with hospital admission for cardiovascular (CV) reasons (including revascularization) in the past 3 months, planned revascularization, or conditions hampering participation or 5-year follow-up (eg, limited cooperation, limited legal capacity, serious non-CV disease or conditions interfering with life expectancy [eg, cancer or substance abuse], or other severe CV disease [eg, advanced heart failure, severe valve disease, and history of valve repair/replacement]).

Participating physicians were cardiologists, office-based primary care physicians, and physicians based in hospitals with outpatient clinics. These physicians were selected on the basis of geographic distribution, location (ie, urban, suburban, or rural areas), and specialty to obtain an epidemiologically representative data set in each country. Each physician was requested to recruit 10 to 15 consecutive outpatients. Each country had a predefined national target of 25 patients per million inhabitants (range, 12.5-50 except for China). Patient enrollment was restricted during a brief period to achieve near-consecutive enrollment. The first patient was enrolled in November 2009 and recruitment was completed in June 2010. The study was conducted in accordance with the Declaration of Helsinki, and local ethical approval was obtained before recruitment. All patients gave written informed consent.

Data Collection

Data were captured by standardized electronic case report forms completed at baseline and at annual patient visits. For patients who missed visits, telephone contact with the patient, a designated relative or representative, or the patient's physician was attempted. Where applicable, registries could be used to retrieve vital status.

To ensure data quality, on-site audits of 100% of the data were performed in 1% of randomly selected centers per annum; regular telephone contact was maintained with investigators; and electronic case report forms underwent centralized verification for completeness, consistency, and accuracy. At baseline, data were collected on patient characteristics, risk factors, lifestyle, medical history, physical condition, vital signs, current symptoms, and treatments. Angina or equivalent symptoms were ascertained by each physician, defined as necessitating occasional or long-term use of antianginals and categorized according to the Canadian Cardiovascular Society (CCS) classification (class I indicates angina only during strenuous or prolonged physical activity; class II, slight limitation, with angina only during vigorous physical activity; class III, symptoms with everyday activities of daily living; and class IV, inability to perform any activity without angina or angina at rest).[7] Symptoms of congestive heart failure were defined as signs and symptoms of right or left ventricular failure or both, confirmed by noninvasive or hemodynamic measurements and categorized according to the New York Heart Association classification. Class I indicates patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. Class II indicates patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. Class III indicates patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest, but less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. Class IV indicates patients with cardiac disease resulting in inability to perform any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased (patients with New York Heart Association class IV symptoms were not enrolled).[8] Available results of invasive and noninvasive tests were collected, but no test was mandated by the study, and no standardized measurement of left ventricular ejection fraction was performed. At each visit, clinical outcomes occurring during the previous 12 months were recorded. The performance of a noninvasive test for myocardial ischemia during the prior 12 months was collected, including stress electrocardiogram, stress echocardiogram, or nuclear imaging, regardless of the protocol. In addition, patients with any positive test result that did not lead to revascularization were defined as having evidence of myocardial ischemia on noninvasive testing (regardless of

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the extent and severity of ischemia and the level of exercise or stress achieved). Results of tests that were positive for myocardial ischemia that had led to revascularization before entry into the registry were not considered in this analysis.

For the purpose of this analysis, we predefined the main outcome as the composite of CV-related death or MI. Additional outcomes of interest were the triple composite of CV-related death, MI, or stroke, each of the components of these composite outcomes, all-cause mortality, and major bleeding (defined as bleeding leading to hospitalization or blood transfusion). Events were accepted as reported by physicians and were not adjudicated. However, all events were verified at the source during the audits.

Statistical Analysis

Baseline characteristics for the whole population and by subgroup (in **Table 1** and eTable 1 in the Supplement) are presented using descriptive statistics with mean (SD) or median (25th and 75th quartiles) for continuous variables, depending on the distribution of the data, and counts and percentages for categorical variables. Baseline values were compared between groups using 1-way analysis of variance or the Kruskal-Wallis test for continuous variables, depending on the distribution of the data, and χ^2 tests for categorical variables. Individual and composite clinical outcomes were analyzed based on the time to first event. The data were analyzed using Cox proportional hazards regression models to calculate hazard ratios (HRs), corresponding 95% confidence intervals, and *P* values, first for those who underwent testing for ischemia compared with those who did not, and second among those who underwent testing for ischemia comparing those who had ischemia and no angina, angina and no ischemia, or angina and ischemia with those who did not have angina or ischemia. Adjusted analyses were performed in which clinical outcomes data were adjusted for baseline differences (age, sex, geographical region, smoking status, hypertension, diabetes mellitus, and dyslipidemia). Additional analyses also involved adjustments for other elements of medical history or for the Reduction of Atherothrombosis for Continued Health (REACH) risk score for recurrent events in atherothrombosis.[9] As sensitivity analyses, we examined clinical outcomes in the subgroup of patients with diabetes mellitus and then extended the model to formally test for an interaction between diabetes mellitus and the combined angina and ischemia variable. The unadjusted model results were also examined in the male and female subpopulations, and this comparison was extended to include a test for interaction between sex and the combined angina and ischemia variable in the total population from a further Cox proportional hazards regression model, which also included these variables as main effects. Statistical analysis was performed at the Robertson Centre for Biostatistics at the University of Glasgow using a commercially available statistical program (SAS, version 9.2; SAS Institute, Inc).

Results

Of the initial 32 954 patients available for analysis at baseline, 196 withdrew and 653 had no current follow-up data available for other reasons, resulting in a study population 32 105 patients (**Figure 1**). Median follow-up was 24.1 months (range, 1 day to 3 years; mean, 23.6 months). Among the 32 105 patients included in this analysis, 20 291 (63.2%) had undergone testing for myocardial ischemia in the 12 months before enrollment. Patients who did not undergo testing differed markedly from patients who had for almost all baseline characteristics (eTable 1 in the Supplement); they were younger, more frequently female, and had a more recent diagnosis of CAD, a more frequent history of MI, and more frequent symptoms of angina and congestive heart failure. They more frequently received aspirin, thienopyridines, and β-blockers and less frequently received drugs to lower lipid levels, including statins. The rate of use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers was similar between groups.

At the 2-year follow-up, the adjusted HR for the primary outcome was lower among patients who had undergone a noninvasive test for ischemia before enrollment compared with patients who did not (HR, 0.70 [95% CI, 0.60-0.82]; $P < .001$). In addition, adjusted HRs for CV-related death, all-cause death, and MI risks were also lower in patients who underwent testing (eFigure 1 in the Supplement).

Patients who had undergone a test for myocardial ischemia were categorized into 4 groups according to the presence or absence of myocardial ischemia on results of noninvasive testing and the presence or absence of anginal symptoms (CCS class, >0) (Figure 1). The largest group consisted of patients without angina or ischemia (**Figure 2**). Overall, 4056 patients (20.0%) had anginal symptoms (with or without ischemia) and 5242 (25.8%) had evidence of myocardial ischemia on results of noninvasive testing (with or without angina). The baseline characteristics of these 4 groups are summarized in Table 1. Important differences were found between groups. In particular, compared with patients without angina, patients with angina were slightly younger, more frequently female, had a slightly higher weight, a less frequent history of percutaneous coronary intervention or coronary artery bypass graft, and a more frequent history of stroke, asthma/chronic obstructive pulmonary disease, treated hypertension, or peripheral arterial disease. They also had more frequent symptoms of heart failure, higher systolic and diastolic blood pressure, higher plasma levels of low-density lipoprotein cholesterol, and less frequent coronary angiography than patients without angina.

Unadjusted clinical outcomes for the 4 groups are described in **Table 2**; adjusted outcomes are shown in **Figure 3**. Given the larger size of the group without angina or ischemia, 58.2% of all CV-related deaths and MIs occurred in this group, whereas 12.4% occurred in patients with ischemia alone, 12.2% in those with angina alone, and 17.3% in those with angina and ischemia. Therefore, 70.4% of events occurred in patients without evidence of ischemia. Using the group without angina or ischemia as a reference and after adjustment for age, sex, geographic region, smoking status, hypertension, diabetes mellitus, and dyslipidemia, the primary outcome of CV-related death or nonfatal MI was not more frequent in patients with ischemia alone (adjusted HR, 0.90 [95% CI, 0.68-1.20]; $P = .47$) (Figure 3). Conversely, the risk for the primary outcome was

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Table 1. Baseline Characteristics of Patients According to Presence or Absence of Angina and Ischemia

Characteristic	Patient Group[a]				*P* Value[b]
	No Angina or Ischemia (n = 13 207)	Ischemia and No Angina (n = 3028)	Angina and No Ischemia (n = 1842)	Angina and Ischemia (n = 2214)	
Age, mean (SD), y	64.8 (10.3)	64.9 (10.1)	64.4 (10.0)	63.3 (10.3)	<.001
Men	10 689 (80.9)	2402 (79.3)	1325 (71.9)	1576 (71.2)	<.001
BMI, median (25th, 75th quartiles)	27.5 (25.1, 30.4)	27.7 (25.1, 30.6)	28.4 (25.7, 31.6)	28.1 (25.6, 31.2)	<.001
Weight, median (25th, 75th quartiles), kg	80 (70, 89)	80 (70, 89)	82 (72, 92)	80 (71, 90)	<.001
Ethnicity					
White	9059 (68.6)	2118 (69.9)	1519 (82.5)	1702 (76.9)	<.001
South Asian	653 (4.9)	186 (6.1)	110 (6.0)	163 (7.4)	
Chinese	149 (1.1)	82 (2.7)	24 (1.3)	65 (2.9)	
Japanese/Korean	234 (1.8)	49 (1.6)	6 (0.3)	4 (0.2)	
Hispanic	721 (5.5)	207 (6.8)	36 (2.0)	85 (3.8)	
Black/African American	127 (1.0)	30 (1.0)	33 (1.8)	18 (0.8)	
Unknown	2264 (17.1)	356 (11.8)	114 (6.2)	177 (8.0)	
Time since first CAD diagnosis, median (25th, 75th quartiles), y	5 (2, 10)	5 (2, 10)	6 (3, 12)	5 (2, 10)	<.001
Medical history					
MI	7442 (56.3)	1658 (54.8)	1040 (56.5)	1159 (52.3)	.003
PCI	8322 (63.0)	1707 (56.4)	928 (50.4)	844 (38.1)	<.001
CABG	3667 (27.8)	806 (26.6)	444 (24.1)	438 (19.8)	<.001
Hospitalization for CHF	385 (2.9)	179 (5.9)	108 (5.9)	166 (7.5)	<.001
Stroke	382 (2.9)	107 (3.5)	77 (4.2)	120 (5.4)	<.001
Asthma/COPD	954 (7.2)	258 (8.5)	192 (10.4)	236 (10.7)	<.001
Family history of premature CAD	3858 (29.2)	941 (31.1)	694 (37.7)	860 (38.8)	<.001
Treated hypertension	9037 (68.4)	2259 (74.6)	1435 (77.9)	1782 (80.5)	<.001
Diabetes mellitus	3638 (27.5)	998 (33.0)	540 (29.3)	724 (32.7)	<.001
Dyslipidemia	10 312 (78.1)	2460 (81.2)	1519 (82.5)	1819 (82.2)	<.001
PAD	1270 (9.6)	350 (11.6)	233 (12.6)	353 (15.9)	<.001
Smoking status[c]					
Current	1355 (10.3)	336 (11.1)	244 (13.3)	303 (13.7)	<.001
Former	6589 (49.9)	1369 (45.2)	862 (46.9)	879 (39.7)	
Never	5263 (39.9)	1323 (43.7)	733 (39.9)	1032 (46.6)	
CHF symptoms including NYHA class[c]					
No CHF	12 394 (93.9)	2724 (90.0)	1360 (73.8)	1455 (65.7)	<.001
CHF NYHA Class II	721 (5.5)	250 (8.3)	400 (21.7)	613 (27.7)	
CHF NYHA Class III	90 (0.7)	54 (1.8)	82 (4.5)	146 (6.6)	
HbA_{1C}, mean (SD), %	6.8 (2.1)	6.8 (1.3)	7.2 (3.9)	6.9 (1.4)	.002
Creatinine level, median (25th, 75th quartiles), mg/dL	1.0 (0.9, 1.1)	1.0 (0.9, 1.2)	1.0 (0.8, 1.1)	1.0 (0.9, 1.2)	<.001
Total cholesterol level, median (25th, 75th quartiles), mg/dL	162 (139, 185)	166 (139, 193)	174 (147, 205)	185 (154, 216)	<.001
HDL-C level, median (25th, 75th quartiles), mg/dL	46 (39, 54)	46 (39, 54)	46 (39, 54)	46 (39, 54)	.17
LDL-C level, median (25th, 75th quartiles), mmol/L	89 (73, 108)	89 (73, 112)	97 (77, 124)	100 (77, 127)	<.001
Fasting triglyceride level, median (25th, 75th quartiles), mg/dL	115 (88, 159)	124 (88, 168)	133 (97, 177)	133 (97, 186)	<.001
Palpation heart rate, mean (SD), beats/min	66.5 (10.2)	68.1 (10.4)	68.1 (10.6)	70.2 (11.2)	<.001
ECG heart rate, mean (SD), beats/min	65.5 (10.9)	67.3 (11.3)	67.2 (11.4)	69.7 (12.0)	<.001
Systolic BP, mean (SD), mm Hg	130.5 (16.0)	130.4 (16.1)	132.8 (17.3)	134.3 (17.2)	<.001
Diastolic BP, mean (SD), mm Hg	76.6 (9.4)	76.6 (9.6)	77.8 (10.6)	79.7 (10.8)	<.001
LVEF, mean (SD), %[d]	57.4 (10.8)	55.8 (11.4)	56.1 (10.3)	55.8 (10.4)	<.001
Coronary angiography					
Not done	1033 (7.8)	383 (12.7)	350 (19.0)	742 (33.5)	<.001
No or minimal vessel disease	411 (3.1)	98 (3.2)	102 (5.5)	96 (4.3)	<.001
Single vessel disease	4991 (37.8)	864 (28.6)	544 (29.5)	452 (20.4)	
Multivessel disease	6760 (51.2)	1677 (55.5)	846 (45.9)	922 (41.7)	

(continued)

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Table 1. Baseline Characteristics of Patients According to Presence or Absence of Angina and Ischemia (continued)

Characteristic	Patient Group[a] No Angina or Ischemia (n = 13 207)	Ischemia and No Angina (n = 3028)	Angina and No Ischemia (n = 1842)	Angina and Ischemia (n = 2214)	*P* Value[b]
Treatments at baseline					
Aspirin	11 408 (86.4)	2639 (87.2)	1612 (87.5)	1963 (88.7)	.02
Thienopyridine	3447 (26.1)	752 (24.8)	399 (21.7)	511 (23.1)	<.001
β-Blocker	9816 (74.3)	2248 (74.2)	1410 (76.5)	1692 (76.4)	.04
ACEI and/or ARB	9853 (74.6)	2349 (77.6)	1438 (78.1)	1787 (80.7)	<.001
Drug to lower lipid levels	12 382 (93.8)	2796 (91.4)	1713 (93.0)	2026 (91.5)	<.001
Statin	11 135 (84.3)	2457 (81.1)	1569 (85.2)	1811 (81.8)	<.001
REACH risk score, mean (SD)	10.8 (3.1)	11.2 (3.2)	11.3 (3.1)	11.5 (3.3)	<.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; REACH, Reduction of Atherothrombosis for Continued Health.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; creatinine to millimoles per liter, multiply by 88.4; HbA_{1c} to a proportion of 1.0, multiply by 0.01; triglyceride to millimoles per liter, multiply by 0.0113.

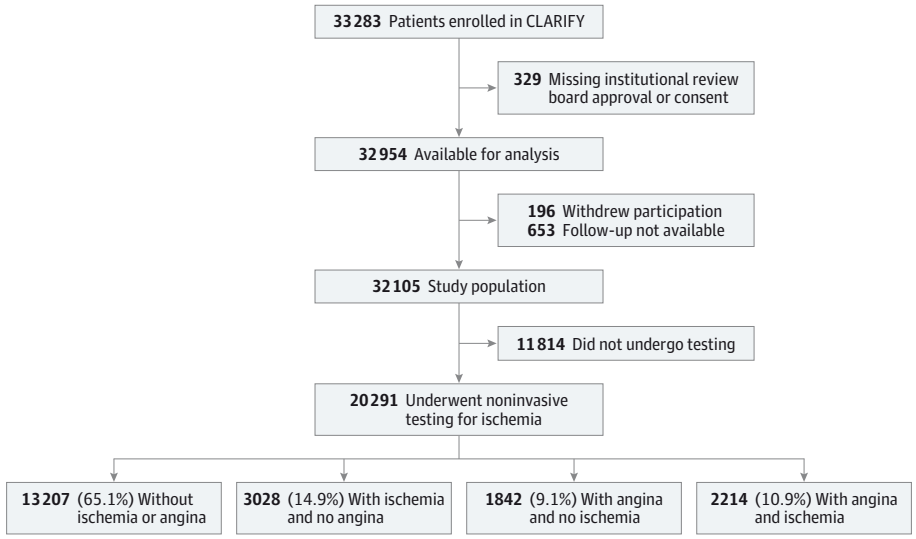
[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and might not total 100.

[b] Pertains to the overall comparison among the 4 groups.

[c] Some data were missing for these variables.

[d] Available in 14 890 patients.

Figure 1. Description of the Study Population



CLARIFY indicates Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease.

greater in patients with anginal symptoms and no evidence of ischemia (adjusted HR, 1.45 [95% CI, 1.08-1.95]; *P* = .01) and in those with anginal symptoms and evidence of ischemia (adjusted HR, 1.75 [95% CI, 1.34-2.29]; *P* < .001) (Figure 3). The 4-way variable presence of angina and/or ischemia was a highly statistically significant predictor of the primary outcome (*P* < .001 after adjustment for age, sex, geographic region, smoking status, hypertension, diabetes mellitus, and dyslipidemia). Similar observations were made for various secondary outcome measures (including the triple composite outcome of CV-related death, MI, or stroke) except for stroke and major bleeding, in which no statistically significant difference was noted between groups (Figure 3).

We performed sensitivity analyses to ensure the robustness of the results. First, we found no statistically significant interaction with sex for each of the outcomes analyzed. Specifically, the *P* values obtained from the tests for interaction in the Cox proportional hazards regression models indicate no evidence of any statistically significant differences between male and female patients (eTables 2 to 4 in the Supplement). Second, the effects of angina and ischemia on CV-related death or MI relative to the group of patients with neither were assessed after various adjustment methods. Results were similar regardless of whether event rates were unadjusted; adjusted for age, sex, geographical region, and smoking status; further adjusted for hypertension, MI, asthma/chronic ob-

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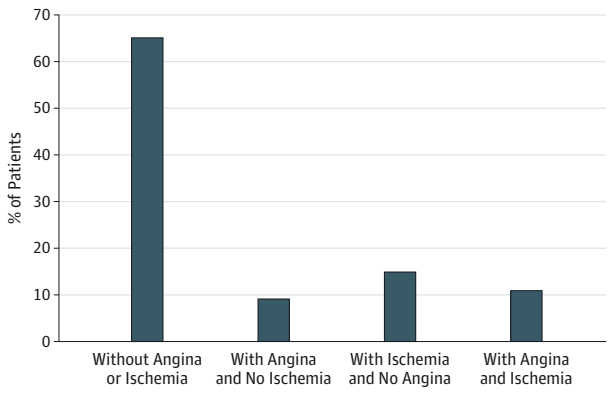
structive pulmonary disease, stroke, peripheral arterial disease, and diabetes mellitus; further adjusted for the type of practice (hospital based or not, primary care or not); or adjusted for the REACH score of recurrent events (eTable 5 in the Supplement). Finally, a sensitivity analysis for the primary outcome was performed in the subset of patients with diabetes mellitus (n = 5901), and its findings were directionally consistent with the overall results (eFigure 2 in the Supplement), although we found no statistically significant increase in adjusted event rates in the group with angina alone. A formal test of interaction between diabetes mellitus and the combined angina-ischemia variable confirmed the absence of any statistically significant interaction.

Because anginal symptoms appeared to be a major determinant of the risk for CV-related death and MI, we examined the relationship between angina CCS class and outcomes. Relative to patients without angina (n = 16 235 [80.0%]), those with CCS class I angina (n = 1251 [6.2%]) had an adjusted HR for the primary outcome of 1.85 (95% CI, 1.36-2.53; $P < .001$), whereas it was 1.47 (95% CI, 1.11-1.95; $P = .008$) for patients with CCS class II angina (n = 2151 [10.6%]) and 1.76 (95% CI, 1.15-2.69; $P = .01$) for patients with CCS class III or IV angina (n = 651 [3.2%] (data were missing for some variables).

Figure 2. Clinical Patterns of Stable Coronary Artery Disease



Patterns are based on the presence of anginal symptoms and evidence of myocardial ischemia on results of noninvasive testing in the Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease (CLARIFY) population.

Discussion

The main findings of this analysis are that most of the outpatients with stable CAD did not have anginal symptoms or evidence of myocardial ischemia. Among patients who had undergone a test for myocardial ischemia, 20.0% had anginal symptoms and 25.8% had evidence of myocardial ischemia. After 2 years of follow-up, the presence of anginal symptoms was associated with worse clinical outcomes regardless of the presence of myocardial ischemia on noninvasive testing, whereas ischemia alone was not.

These findings have several important clinical implications. First, anginal symptoms alone, even without evidence of myocardial ischemia, were associated with high event rates and identified a group of patients at high risk for CV-related death or MI. The possibility of an important disconnect between anginal symptoms and evidence of myocardial ischemia is well known.[10] Conversely, our findings should not be interpreted as detracting from the value of treating ischemia because our patients were treated, and clear evidence suggests that the presence and severity of myocardial ischemia are important correlates of prognosis in stable CAD[11-14] and possibly of the benefit of revascularization.[15-18] A large international trial, the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (clinicaltrials.gov identifier NCT01471522), is exploring whether angiography with a view to revascularization in addition to optimal medical management is superior to optimal medical management alone in patients with myocardial ischemia. Finally, most CV-related deaths and MIs occurred in patients without angina or ischemia, emphasizing the importance of implementing optimal medical therapy and preventive measures regardless of symptoms or ischemia. Approximately 70% of events occurred among patients with no evidence of myocardial ischemia on results of noninvasive testing. Therefore, focusing management of stable CAD solely on the prevention or treatment of ischemia does not address the risks incurred by these patients.

Some of our findings are expected. First, ischemia was present in 25.8% of patients of a population with stable CAD who had undergone stress testing, a proportion similar to that seen in a previous study.[19] Also, patients with symptomatic ischemia were at higher risk than patients without angina or ische-

Table 2. Unadjusted 2-Year Event Percentages for the 4 Patient Groups

Outcome	Patient Group, %				*P* Value[a]
	No Angina or Ischemia (n = 13 207)	Ischemia and No Angina (n = 3028)	Angina and No Ischemia (n = 1842)	Angina and Ischemia (n = 2214)	
CV-related death or MI[b]	2.11	1.94	3.13	3.72	<.001
CV death, MI, or stroke	2.75	2.54	3.89	4.41	<.001
CV-related death	1.17	1.03	1.36	2.07	.004
MI[c]	1.35	1.27	2.36	2.34	<.001
Stroke[c]	0.82	0.73	1.04	1.06	.46
All-cause death	2.62	2.84	2.93	3.52	.10
Major bleeding	0.87	0.74	0.67	0.65	.62

Abbreviations: CV, cardiovascular; MI, myocardial infarction.

[a] Pertains to the overall comparison among the 4 groups from an unadjusted Cox proportional hazards regression model.

[b] Indicates primary outcome.

[c] Includes fatal and nonfatal.

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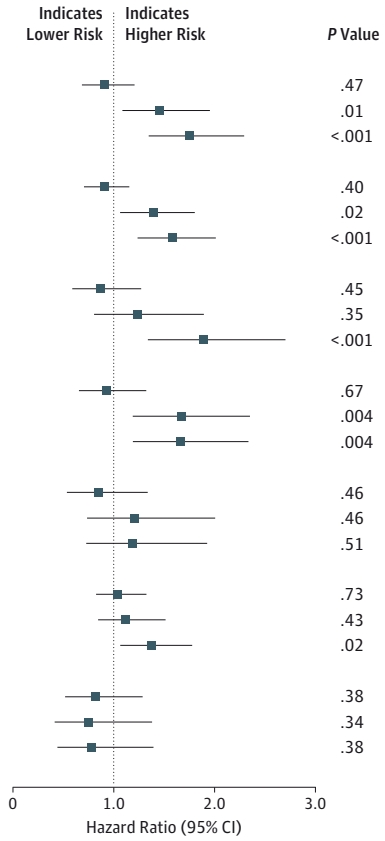
Figure 3. Primary Outcome and Various Composite Outcomes for Patient Groups

Outcome by Patient Group	HR (95% CI)	P Value
CV-related death, nonfatal MI		
Ischemia only	0.90 (0.68-1.20)	.47
Angina only	1.45 (1.08-1.95)	.01
Both	1.75 (1.34-2.29)	<.001
CV-related death, nonfatal MI, or stroke		
Ischemia only	0.90 (0.70-1.15)	.40
Angina only	1.38 (1.06-1.80)	.02
Both	1.57 (1.23-2.01)	<.001
CV-related death		
Ischemia only	0.86 (0.58-1.27)	.45
Angina only	1.23 (0.80-1.89)	.35
Both	1.89 (1.33-2.70)	<.001
MI[a]		
Ischemia only	0.93 (0.65-1.32)	.67
Angina only	1.67 (1.18-2.35)	.004
Both	1.66 (1.18-2.33)	.004
Stroke[a]		
Ischemia only	0.84 (0.53-1.33)	.46
Angina only	1.21 (0.73-2.00)	.46
Both	1.18 (0.72-1.92)	.51
All-cause death		
Ischemia only	1.04 (0.82-1.32)	.73
Angina only	1.12 (0.84-1.51)	.43
Both	1.37 (1.06-1.78)	.02
Major bleeding		
Ischemia only	0.81 (0.51-1.29)	.38
Angina only	0.74 (0.41-1.37)	.34
Both	0.77 (0.43-1.39)	.38



Hazard ratios (HRs) and 95% CIs are given for patients with ischemia and no angina, angina and no ischemia, and angina and ischemia relative to patients without angina or ischemia. Outcomes are adjusted for age, sex, geographic region, smoking status, hypertension, dyslipidemia, and diabetes mellitus. CV indicates cardiovascular; MI, myocardial infarction.

[a] Includes fatal or nonfatal.

mia or patients with silent ischemia. The presence of anginal symptoms was more frequent in women than in men and was associated with an increased risk for CV outcomes consistent with the wealth of evidence documenting the prognostic impact of angina,[20] including among outpatients,[21] in men and women.[22,23] However, the finding that patients with anginal symptoms in daily life but no evidence of inducible ischemia were at higher risk than patients with asymptomatic ischemia was somewhat unexpected. These findings appear to be at odds with results from the Heart and Soul Study,[19] in which myocardial ischemia rather than anginal symptoms appeared to be key in determining clinical prognosis, and those from the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial in a population with diabetes mellitus,[24] in which angina presence or severity did not appear to affect mortality and CV outcomes, prompting the conclusion that "ischemia dictates outcome, not symptoms".[25(p712)] Of note, the prevalence of anginal symptoms was very high in the Bypass Angioplasty Revascularization Investigation 2 Diabetes population,[24] with 82% of patients characterized as having angina or angina equivalents (compared with 20.0% in the present study). Several reasons may explain why patients with anginal symptoms but no evidence of myocardial ischemia on results of noninvasive testing may fare worse than patients with silent ischemia. First, because anginal symptoms may severely impair exercise capacity, these patients may not have achieved the same level of exercise as patients with silent ischemia. Thus, anginal symptoms may prevent completion of a full exercise test and, therefore, the identification of ischemia by noninvasive test results. Unfortunately, the CLARIFY registry did not collect information regarding the level of exercise reached during testing. Another explanation is that patients with anginal symptoms but no evidence of ischemia have substantially more symptoms of heart failure at baseline than patients with ischemia alone. Symptoms interpreted by patients and physicians as anginal may really be related to heart failure. However, despite the major differences in baseline characteristics among the 4 groups in the present study, adjustment of outcomes on the REACH risk score did not modify the results. Finally, not all data sets have found that asymptomatic myocardial ischemia is prognostic,[26] which is consistent with the fact that acute cardiac events often stem from rupture or erosion of plaques that are not severe enough to cause ischemia.[27,28]

The present analysis has several important limitations. First, the outcome events were not adjudicated but were based on investigator reporting. Angina was ascertained by physician evaluation as opposed to patient self-reporting of angina using standardized questionnaires[29] or angina observed during a calibrated stress test, but as such may reflect routine clinical practice where such questionnaires are rarely, if ever, used. The noninvasive tests performed before enrollment to categorize the presence or absence of myocardial ischemia were not

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standardized in terms of background medical therapy, type of test, protocol for the test, or time elapsed between performance of the test and enrollment. However, conversely, this nonstandardized assessment enhances the clinical applicability of our results because they pertain to the presence or absence of myocardial ischemia regardless of the test type, date, and protocol. Also, the CLARIFY registry did not collect information on the extent or severity of ischemia, which is an important correlate of prognosis.[30] Inception variability is a factor in this cohort, with a mean follow-up of approximately 2 years, whereas the median time since diagnosis was 5 years. Most patients with anginal symptoms and evidence of ischemia might have been offered revascularization before entry into the registry, and, therefore, CLARIFY patients who have angina despite having been considered for the procedure may be too sick to undergo revascularization (because of diffuse/severe disease and/or because of severe comorbidities) or may be those in whom revascularization has failed to cure symptoms. Therefore, patients with angina in this noninception cohort may represent a selected group of high-risk patients, although this was accounted for in part by adjusting for risk factors at entry. Last, although the cohort studied is large and has broad geographic representation, no patients were enrolled in the United States.

Important strengths in the present analysis are also apparent. The cohort is large and contemporary, the use of evidence-based therapies was high, and the results were robust and consistent regardless of the various adjustment methods and across several sensitivity analyses.

Conclusions

Most outpatients with stable CAD do not have angina or ischemia. The presence of anginal symptoms in daily life appears to be associated with a higher risk for CV-related death or MI than ischemia alone. The presence of angina and ischemia is associated with the worst outcomes.

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