Prevalences of Anginal Symptoms and Myocardial Ischemia and their Impact on Clinical Outcomes in Stable Outpatients with Coronary Artery Disease Data from the International Observational CLARIFY registry.

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Importance: In the era of widespread revascularization and effective anti-anginal agents, the prevalence and prognostic impact of anginal symptoms and myocardial ischemia among patients with stable coronary artery disease are unknown.

Objective: To describe the current clinical patterns of patients with stable coronary artery disease and the association of anginal symptoms or myocardial ischemia with clinical outcomes.

Design: The CLARIFY registry enrolled outpatients with stable CAD during 2009/2010 and followed them up for 2 years (median, 24.1 months, range 1 day to 3 years)

Setting: Outpatients in 45 countries.

Participants: 32 396 outpatients with any of: prior myocardial infarction, chest pain and evidence of myocardial ischemia, evidence of coronary artery disease on angiography, or prior revascularization. Of these, 20 402 (63.0%) had undergone a non-invasive test for myocardial ischemia within 12 months of enrolment, and were categorized into four groups: neither angina nor ischemia (n = 13 283; 65.1%); evidence of myocardial ischemia without angina (silent ischemia: n = 3060; 15.0%); anginal symptoms alone (n = 1843; 9.0%); and both angina and ischemia (n = 2216; 10.9%).

Main Outcome and Measure: The primary outcome was the composite of cardiovascular death and non-fatal myocardial infarction.

Results: Overall, 4059 patients (19.9%) had anginal symptoms and 5276 (25.9%) had evidence of myocardial ischemia on non-invasive testing. Of 470 cardiovascular deaths or myocardial infarctions, 58.3% occurred in patients without angina or ischemia, 12.3% in patients with ischemia alone, 12.1% in patients with angina alone, and 17.2% in patients with both. The hazard ratios and 95% confidence intervals for the primary outcome, relative to patients with neither angina nor ischemia, adjusted for age, sex, geographic region, smoking status, hypertension, diabetes, and dyslipidemia, were 0.89 (0.67-1.19) (*P*=.44), 1.46 (1.09-1.95) (*P*=.01), and 1.76 (1.34-2.30) (*P*<.001) for ischemia alone,

angina alone, and both, respectively. Similar findings were observed for cardiovascular death and for fatal or non-fatal myocardial infarction.

Conclusions and Relevance: In stable coronary artery disease outpatients, anginal symptoms (with or without ischemia on non-invasive testing), but not silent ischemia, appear associated with an increased risk of adverse cardiovascular outcomes. The majority of cardiovascular events occurred in patients with neither angina nor ischemia.

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

There is uncertainty over what factors determine the prognosis of patients with stable CAD (i.e. patients with evidence of coronary artery disease but without recent acute myocardial infarction) 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 current analysis aims to describe the prevalence of anginal symptoms and myocardial ischemia in patients with stable CAD, and their association with clinical outcomes, using data from the large prospective CLARIFY registry in outpatients with stable CAD.

METHODS

Study Design and Patients

The prospe**C**tive observational **L**ongitudin**A**l **R**eg**I**stry o**F** patients with stable coronary arter**Y** disease (CLARIFY) is a prospective longitudinal registry of 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 the Americas, but not in the United States.

To be eligible for enrollment, patients had to meet at least one of the following criteria: documented myocardial infarction >3 months before enrollment; angiographic demonstration of coronary stenosis >50%; chest pain with evidence of myocardial ischemia (stress electrocardiogram); or coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) >3 months before enrolment.

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 (such as limited cooperation, limited legal capacity, serious non-CV disease or conditions interfering with life expectancy [eg, cancer or drug abuse], or other severe CV disease [eg, advanced heart failure, severe valve disease, history of valve repair/replacement]) were excluded.

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, in order to obtain an epidemiologically representative dataset in each country. Each physician was requested to recruit 10-15 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 over 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 is being conducted in accordance with the Declaration of Helsinki and local ethical approval was obtained prior to recruitment. All patients gave written informed consent. The study is registered (ISRCTN43070564).

Data Collection

Data were captured by standardized electronic case report forms (eCRFs) completed at baseline and at annual patient visits. For patients who missed visits, telephone contact with the patient, a designated relative or contact, or his/her 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 eCRFs 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 permanent use of antianginal drugs and categorized according to the Canadian Cardiovascular Society (CCS) classification (class I indicates angina only during strenuous or prolonged physical activity; class II indicates slight limitation, with angina only during vigorous physical activity; class III indicates symptoms with everyday activities of daily living; class IV indicates inability to perform any activity without angina, or angina at rest).[7] Congestive heart failure symptoms were defined as signs and symptoms of either right or left ventricular failure, or both, confirmed by non-invasive or hemodynamic measurements and categorized according to the New York Heart Association (NYHA) 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. 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. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. Class IV indicates patients with cardiac disease resulting in inability to carry on 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 class IV NYHA were not enrolled).[8] Available results of invasive and non-invasive tests were collected, but no test was mandated by the study and there was no standardized measurement of left ventricular ejection fraction. At each visit, clinical outcomes occurring during the previous 12 months were recorded. The performance of a non-invasive test for myocardial ischemia during the prior 12 months was collected, regardless of whether this was a stress electrocardiogram

(ECG), stress echocardiogram, or nuclear imaging, and regardless of the protocol. In addition, patients with any positive test that did not lead to revascularization were defined as having evidence of myocardial ischemia on non-invasive testing (regardless of the extent and severity of ischemia and the level of exercise or stress achieved). Importantly, positive tests 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 pre-defined the main outcome as the composite of CV death and myocardial infarction (MI). Additional outcomes of interest were the triple composite of CV 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 source-verified during the audits.

Statistical Analysis

Baseline characteristics for the whole population and by subgroup (in Table 1 and eTable 1) are presented using descriptive statistics with mean (standard deviation [SD]) or median (25^{th}, 75^{th} quartiles) for continuous variables, depending on the distribution of the data, and counts and percents for categorical variables. Baseline values were compared between groups using one-way Analysis of Variance or the Kruskal-Wallis test for continuous variables, depending on the distribution of the data; and chi-squared tests for categorical variables. Individual and composite clinical outcomes were analyzed on a time-to-first event basis. The data were analyzed using Cox proportional hazards models to calculate hazard ratios (HRs), corresponding 95% confidence intervals (CIs) and *P* values, firstly for those who had a test for ischemia compared to those who did not, and secondly among those with a test for ischemia comparing those who had ischemia and no angina, angina and no ischemia, or both 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, 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. The unadjusted model results were also examined in two subpopulations, males and females, and this

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 model, which also included these variables as main effects. Statistical analysis was performed at the Robertson Centre for Biostatistics at the University of Glasgow, UK, using the SAS (version 9.2, Cary, NC, USA) statistical program.

RESULTS

Of the 33 283 patients who were available for analysis at baseline, 196 withdrew and 691 currently have no follow-up data available for another reason, resulting in 32 396 being available for analysis (**FIGURE 1**). Median follow-up was 24.1 months (range, 1 day to 3 years; mean, 23.4 months). Among the 32 396 patients included in this analysis, 20 402 (63.0%) had undergone a test for myocardial ischemia in the 12 months prior to enrollment. Patients without a test differed markedly from patients who had undergone a test, for almost all baseline characteristics (eTable 1): they were younger, more frequently female, had a more recent diagnosis of CAD, more frequent history of MI, and more frequent anginal and congestive heart failure (CHF) symptoms. They more frequently received aspirin, thienopyridines, and beta-blockers, and less frequently received lipid-lowering drugs, including statins. The rate of use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers was similar between groups.

At 2-year follow-up, the adjusted HR for the primary outcome was lower in patients who had undergone a non-invasive test for ischemia before enrollment compared to patients who did not (HR, 0.70; 95% CI, 0.60-0.81; *P*<.001). In addition, CV death, all-cause death, and MI risks were also lower in patients with a test (eFigure 1).

Patients who had undergone a test for myocardial ischemia were categorized according to the presence or absence of myocardial ischemia on non-invasive testing and the presence or absence of anginal symptoms (CCS class >0) into four groups (**FIGURE 1**). The largest group was patients with neither angina nor ischemia (**FIGURE 2**). Overall, 4059 patients (19.9%) had anginal symptoms (with or without ischemia) and 5276 (25.9%) had evidence of myocardial ischemia on non-invasive testing (with or without angina). The baseline characteristics of these four groups are summarized in **TABLE 1**. There were important differences between groups. In particular, compared to patients without angina, patients with angina were slightly younger, more frequently female, had a slightly higher weight, less

frequent history of either PCI or CABG, but more frequent history of stroke, asthma/chronic obstructive pulmonary disease (COPD), treated hypertension, or peripheral arterial disease (PAD). They also more frequently had symptoms of heart failure, higher systolic and diastolic blood pressure, higher plasma low-density lipoprotein cholesterol and less frequently underwent coronary angiography than patients without angina.

Unadjusted clinical outcomes for the four groups are described in **TABLE 2**; adjusted outcomes are shown in **FIGURE 3**. Given the larger size of the group with neither angina nor ischemia, 58.3% of all CV deaths and MIs occurred in this group, whereas 12.3% occurred in patients with ischemia alone, 12.1% in those with angina alone, and 17.2% in those with both angina and ischemia. Therefore, 70.4% of events occurred in patients without evidence of ischemia. Using the group with neither angina nor ischemia as a reference, and after adjustment for age, sex, geographic region, smoking status, hypertension, diabetes, and dyslipidemia, the primary outcome of CV death or non-fatal MI was not more frequent in patients with ischemia alone (adjusted HR, 0.89; 95% CI, 0.67-1.19; *P*=.44; **FIGURE 3**). Conversely, the risk of the primary outcome was greater in patients with anginal symptoms and no evidence of ischemia (adjusted HR, 1.46; 95% CI, 1.09-1.95; *P*=.01) and in those with both anginal symptoms and evidence of ischemia (adjusted HR, 1.76; 95% CI, 1.34-2.30; *P*<.001; **FIGURE 3**). The four-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, and dyslipidemia). Similar observations were made for various secondary outcome measures (including the triple composite outcome of CV death, myocardial infarction, or stroke), except for stroke and major bleeds, in which there were no statistically significant difference between groups (**FIGURE 3**).

Sensitivity analyses were performed to ensure the robustness of the results. Firstly, there was no statistically significant interaction with sex or diabetes for each of the outcomes analyzed. Specifically, the *P*-values obtained from the tests for interaction in the Cox Proportional Hazards Models indicate that there is no evidence of any statistically significant differences between males and females (eTables 2 to 4). Secondly, the effects of angina and ischemia on CV 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/COPD, stroke, PAD, and diabetes,

256 further adjusted for the type of practice (hospital based or not, primary care or not), or adjusted for the
257 REACH score of recurrent events (eTable 5). Finally, a sensitivity analysis for the primary outcome
258 was performed in the subset of patients with diabetes mellitus (n = 5942) and its findings were
259 directionally consistent with the overall results (eFigure 2), although there was no statistically
260 significant increase in adjusted event rates in the group with angina alone.
261 Since anginal symptoms appeared to be a major determinant of the risk of CV death and MI,
262 we examined the relationship between angina CCS class and outcomes. Relative to patients without
263 angina (n = 16 343, 80.1%), those with CCS class I angina (n = 1252; 6.1%) had an adjusted HR for
264 the primary outcome of 1.86 (95% CI, 1.36-2.53; *P*<.001), whereas it was 1.47 (95% CI 1.11-1.95;
265 *P*=.007) for patients with CCS class II (n = 2153; 10.6%) and 1.76 (95% CI, 1.15-2.71; *P*=.009) for
266 patients with CCS class III or IV (n = 651; 3.2%).
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DISCUSSION

The main findings of this analysis are that the vast majority of outpatients with stable CAD have neither anginal symptoms nor evidence of myocardial ischemia. Among patients who had undergone a test for myocardial ischemia, approximately 20% suffered from anginal symptoms and 25% 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 non-invasive testing, whereas ischemia alone was not.

There are several important clinical implications of these findings. Firstly, anginal symptoms alone, even without evidence of myocardial ischemia, were associated with high event rates and identify a group of patients at high risk of CV death or MI. It is well known that there can be an important disconnect between anginal symptoms and evidence of myocardial ischemia.[10] Conversely, our findings should not be interpreted as detracting from the value of treating ischemia, as our patients were treated, and there is clear evidence 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, ISCHEMIA (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, the majority of CV deaths and MIs occurred in patients with neither angina nor ischemia, emphasizing the importance of implementing optimal medical therapy and preventive measures regardless of symptoms or ischemia. Approximately 70% of events occurred in patients with no evidence of myocardial ischemia on non-invasive 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. Firstly, ischemia was present in approximately 25% of patients of a stable CAD population 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 with no angina or ischemia or patients with silent ischemia. The presence of anginal symptoms was more frequent in women than in men, was associated with an increased risk of CV outcomes, consistent with the wealth of evidence documenting the prognostic impact of angina,[20] including among outpatients,[21] both in men and women.[22,23] It is, however, somewhat unexpected that patients with anginal symptoms in daily life but no evidence of inducible ischemia were at higher risk than patients

with asymptomatic ischemia. These findings appear at odds with results from the Heart and Soul Study,[19] where myocardial ischemia rather than anginal symptoms appeared key in determining clinical prognosis, as well as with those from the BARI-2D trial in a diabetic population,[24] where angina presence or severity did not appear to affect mortality and cardiovascular outcomes, prompting the conclusion that "ischemia dictates outcome, not symptoms".[25] Of note, the prevalence of anginal symptoms was very high in the BARI-2D population,[24] with 82% of patients being characterized as having angina or angina equivalents (compared to approximately 20% in the present study). There are several potential explanations for why patients with anginal symptoms but no evidence of myocardial ischemia on non-invasive testing may fare worse than patients with silent ischemia. Firstly, 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 non-invasive testing. 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. It is conceivable that what is interpreted by patients and physicians as anginal symptoms may really be related to heart failure. Note, however, that despite the major differences in baseline characteristics between the four groups in the current study, adjustment of outcomes on the REACH risk score did not modify the results. Finally, not all datasets 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]

Strengths and Limitations

There are some important limitations to the present analysis. Firstly, 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 to angina observed during a calibrated stress test, but as such may reflect routine clinical practice where such questionnaires are rarely, if ever, used. The non-invasive tests performed prior to enrolment to categorize the presence or absence of myocardial ischemia were not standardized in terms of

background medical therapy, type of test or protocol for the test, and time elapsed between performance of the test and enrollment. However, conversely, this enhances the clinical applicability of our results, as 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] There is inception variability in this cohort, with a mean follow-up of approximately 2 years, while the median time since diagnosis was 5 years. It is conceivable that 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 revascularization may be either too sick to be revascularized (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 "non-inception cohort" may represent a selected group of high-risk patients, although this was accounted in part by adjusting for risk factors at entry. Lastly, while the cohort studied is large and has broad geographic representation, no patients were enrolled in the United States.

There are also important strengths in the present analysis: 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.

CONCLUSION

The majority of stable CAD outpatients have neither angina nor ischemia. The presence of anginal symptoms in daily life appears associated with a higher risk of CV death or MI than ischemia alone. Presence of both is associated with the worst outcomes.

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

Study concept and design: Steg, Ferrari, Ford, Fox, Tardif, Tendera.

Acquisition of data: Al-Zaibag, Dayi Hu, Dorian, Fox, Ferrari, Shalnova, Sokn, Steg, Tardif, Tendera.

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Drafting of the manuscript: Steg.

Critical revision of the manuscript for important intellectual content: Al-Zaibag, Dayi Hu, Dorian, Fox, Ferrari, Shalnova, Sokn, Tardif, Tendera.

Statistical analysis: Greenlaw, Ford.

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Figure Legends

Figure 1. Description of the Population Studied

Figure 2. Clinical Patterns of Stable CAD Based Upon Presence of Anginal Symptoms and Evidence of Myocardial Ischemia on Non-Invasive Testing in the CLARIFY Stable CAD Population

CAD, coronary artery disease.

Figure 3. HRs, 95% CIs and *P* Values for the Primary Outcome and Various Composite Outcomes, for Patients With Ischemia and No Angina, Angina and No Ischemia, and Both Angina and Ischemia, all Relative to Those With Neither Angina nor Ischemia

Outcomes are adjusted for age, sex, geographical region, smoking status, hypertension, dyslipidemia, and diabetes. *Fatal or non-fatal. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

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

	Neither Angina nor Ischemia (n = 13 283)	Ischemia and no Angina (n = 3060)	Angina and no Ischemia (n = 1843)	Both Angina and Ischemia (n = 2216)	*P* Value[a]
Age, mean (SD), y	64.8 (10.3)	64.9 (10.1)	64.4 (10.0)	63.3 (10.3)	<.001
Men, No. (%)	10 747 (80.9)	2427 (79.3)	1326 (71.9)	1576 (71.2)	<.001
BMI, median (Q1, Q3), kg/m^2	27.4 (25.1, 30.4)	27.6 (25.0, 30.6)	28.4 (25.7, 31.6)	28.1 (25.5, 31.2)	<.001
Weight, median (Q1, Q3), kg	80 (70, 89)	79 (70, 89)	82 (72, 92)	80 (71, 90)	<.001
Ethnicity					
Caucasian	9088 (68.4)	2123 (69.4)	1519 (82.4)	1702 (76.8)	
South Asian	695 (5.2)	213 (7.0)	111 (6.0)	165 (7.4)	
Chinese	153 (1.2)	82 (2.7)	24 (1.3)	65 (2.9)	
Japanese/Korean	234 (1.8)	49 (1.6)	6 (0.3)	4 (0.2)	<.001
Hispanic	721 (5.4)	207 (6.8)	36 (2.0)	85 (3.8)	
Black/African	128 (1.0)	30 (1.0)	33 (1.8)	18 (0.8)	
Unknown	2264 (17.0)	356 (11.6)	114 (6.2)	177 (8.0)	
Time since first CAD diagnosis, median (Q1, Q3), y	5 (2, 10)	5 (2, 10)	6 (3, 12)	5 (2, 10)	<.001
Medical history, No. (%)					
Myocardial infarction	7464 (56.2)	1664 (54.4)	1040 (56.4)	1159 (52.3)	.003
PCI	8375 (63.1)	1728 (56.5)	929 (50.4)	844 (38.1)	<.001
CABG	3685 (27.7)	818 (26.7)	444 (24.1)	438 (19.8)	<.001
Hospitalization for CHF	389 (2.9)	182 (5.9)	108 (5.9)	166 (7.5)	<.001
Stroke	383 (2.9)	108 (3.5)	77 (4.2)	120 (5.4)	<.001
Asthma/COPD	955 (7.2)	258 (8.4)	192 (10.4)	236 (10.6)	<.001
Family history of premature CAD	3870 (29.1)	950 (31.0)	694 (37.7)	860 (38.8)	<.001
Treated hypertension	9072 (68.3)	2279 (74.5)	1435 (77.9)	1784 (80.5)	<.001
Diabetes	3664 (27.6)	1012 (33.1)	541 (29.4)	725 (32.7)	<.001
Dyslipidemia	10 361 (78.0)	2486 (81.3)	1519 (82.4)	1821 (82.2)	<.001
Peripheral artery disease	1271 (9.6)	350 (11.4)	233 (12.6)	353 (15.9)	<.001
Smoking status, No. (%)					
Current	1360 (10.2)	338 (11.0)	244 (13.3)	303 (13.7)	
Former	6611 (49.8)	1379 (45.1)	862 (46.8)	879 (39.7)	<.001
Never	5312 (40.0)	1343 (43.9)	734 (39.9)	1034 (46.7)	
CHF symptoms including NYHA class, No. (%)					
No CHF	12 469 (93.9)	2755 (90.0)	1361 (73.9)	1457 (65.7)	
CHF NYHA Class II	722 (5.4)	251 (8.2)	400 (21.7)	613 (27.7)	<.001
CHF NYHA Class III	90 (0.7)	54 (1.8)	82 (4.4)	146 (6.6)	

512

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

	Neither Angina nor Ischemia (n = 13 283)	Ischemia and no Angina (n = 3060)	Angina and no Ischemia (n = 1843)	Both Angina and Ischemia (n = 2216)	*P* Value[a]
$HbA1_C$, mean (SD), %	6.8 (2.1)	6.8 (1.3)	7.2 (3.9)	6.9 (1.4)	.002
Creatinine concentration, median (Q1, Q3), mmol/L	0.088 (0.076, 0.101)	0.088 (0.075, 0.101)	0.088 (0.078, 0.103)	0.089 (0.078, 0.105)	<.001
Total cholesterol, median (Q1, Q3), mmol/L	4.2 (3.6, 4.8)	4.3 (3.6, 4.9)	4.5 (3.8, 5.3)	4.8 (4.0, 5.6)	<.001
HDL, median (Q1, Q3), mmol/L	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)	.16
LDL, median (Q1, Q3), mmol/L	2.3 (1.9, 2.8)	2.3 (1.9, 2.9)	2.5 (2.0, 3.2)	2.6 (2.0, 3.3)	<.001
Fasting triglycerides, median (Q1, Q3), mmol/L	1.3 (1.0, 1.8)	1.4 (1.0, 1.9)	1.5 (1.1, 2.0)	1.5 (1.1, 2.1)	<.001
Heart rate (palpation), mean (SD), bpm	66.6 (10.2)	68.2 (10.5)	68.1 (10.7)	70.2 (11.2)	<.001
Heart rate (ECG), mean (SD), bpm	65.5 (10.9)	67.3 (11.3)	67.2 (11.4)	69.7 (12.0)	<.001
Systolic BP, mean (SD), mmHg	130.5 (16.0)	130.4 (16.2)	132.8 (17.3)	134.3 (17.2)	<.001
Diastolic BP, mean (SD), mmHg	76.6 (9.4)	76.6 (9.6)	77.8 (10.6)	79.7 (10.8)	<.001
LVEF[b], mean (SD), %	57.4 (10.8)	55.8 (11.4)	56.1 (10.3)	55.8 (10.4)	<.001
Coronary angiography, No. (%)					
Not done	1038 (7.8)	386 (12.6)	350 (19.0)	744 (33.6)	<.001
No or minimal vessel disease	411 (3.4)	98 (3.7)	102 (6.8)	96 (6.5)	
Single vessel disease	5027 (41.1)	872 (32.7)	545 (36.5)	452 (30.7)	<.001
Multivessel disease	6795 (55.5)	1698 (63.6)	846 (56.7)	922 (62.7)	
Treatments at baseline, No. (%)					
Aspirin	11 464 (86.3)	2668 (87.2)	1612 (87.5)	1964 (88.6)	.02
Thienopyridine	3486 (26.3)	765 (25.0)	400 (21.7)	513 (23.2)	<.001
Beta-blocker	9865 (74.3)	2271 (74.2)	1411 (76.6)	1693 (76.4)	.04
ACEi and/or ARB	9891 (74.5)	2366 (77.3)	1439 (78.1)	1789 (80.7)	<.001
Lipid-lowering drug	12 451 (93.7)	2826 (92.4)	1714 (93.0)	2028 (91.5)	<.001
Statin	11 199 (84.3)	2487 (81.3)	1570 (85.2)	1812 (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; BP, blood pressure; bpm, beats per minute; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; Cx, circumflex; ECG, electrocardiogram; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LAD, left anterior descending; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RCA, right coronary artery; SD, standard deviation; Q1, first quartile; Q3, third quartile.

[a] *P* values pertain to the overall comparison between the four groups.

[b] LVEF measurement available in 14 968 patients.

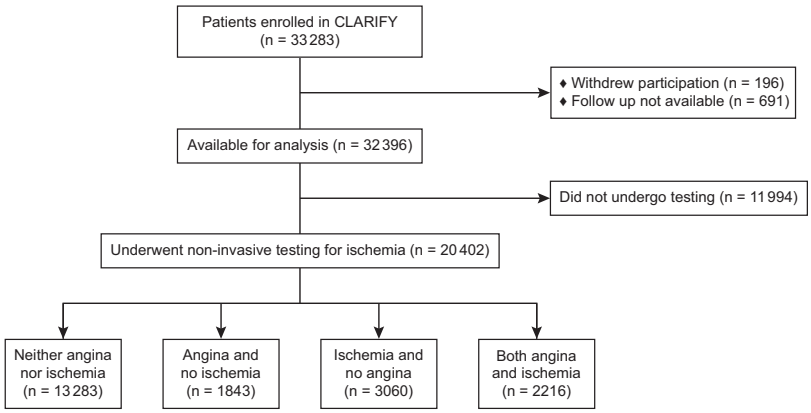
Table 2. Unadjusted 2-Year Event Percentages for the Four Patient Groups

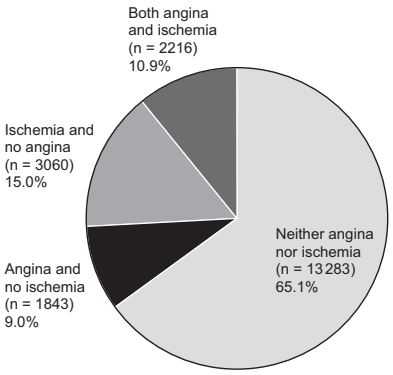
	Neither Angina nor Ischemia (n = 13 283)	Ischemia and no Angina (n = 3060)	Angina and no Ischemia (n = 1843)	Both Angina and Ischemia (n = 2216)	*P* Value[a]
Primary outcome: CV death or MI, %	2.10	1.92	3.12	3.72	<.001
CV death, MI, stroke, %	2.74	2.51	3.89	4.41	<.001
CV death, %	1.17	1.02	1.36	2.07	.003
MI,[b] %	1.34	1.26	2.36	2.34	<.001
Stroke,[b] %	0.81	0.73	1.04	1.06	.43
All-cause death, %	2.64	2.81	2.93	3.52	.12
Major bleed, %	0.86	0.77	0.66	0.65	.66

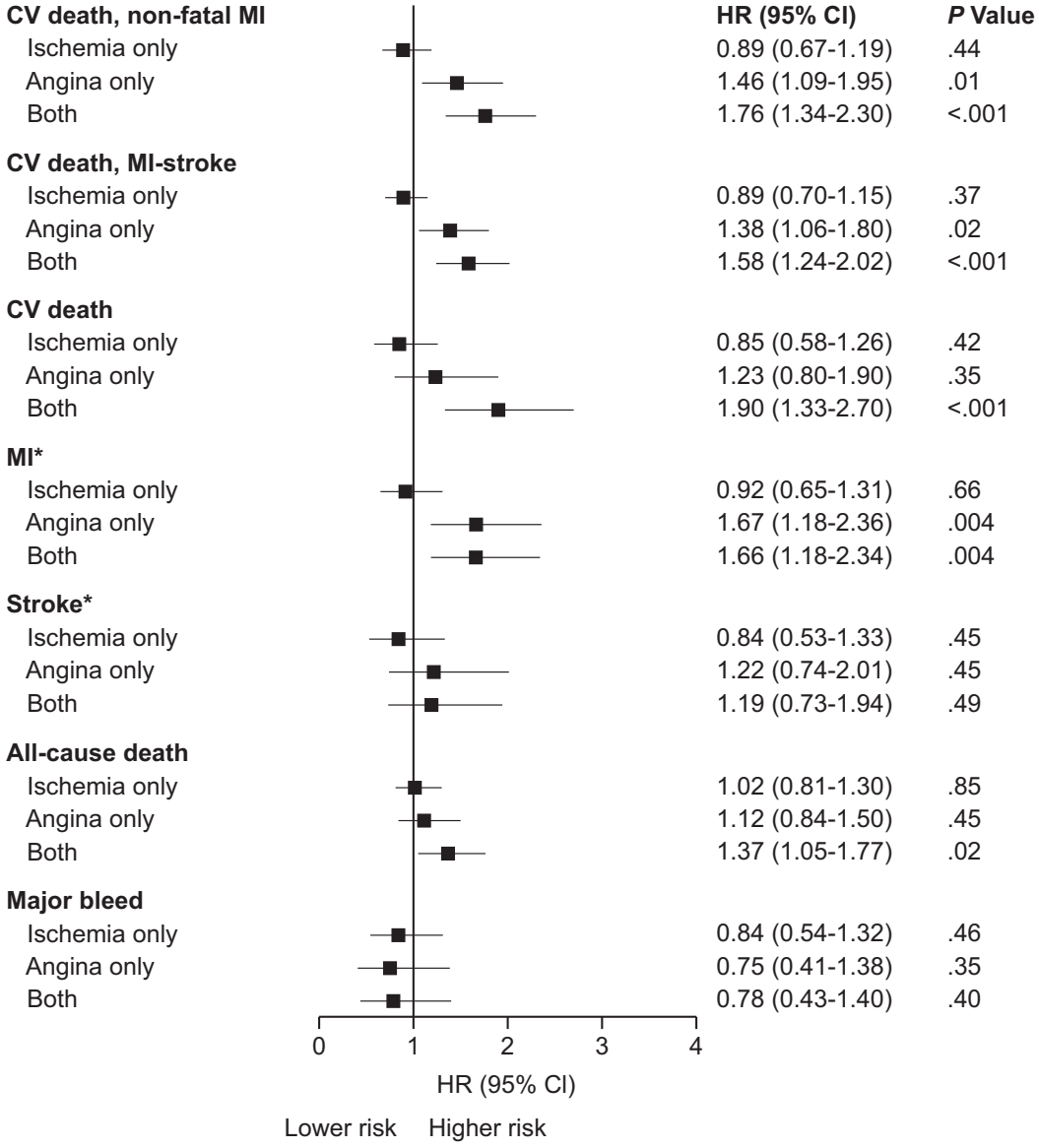
Abbreviations: CV, cardiovascular; MI, myocardial infarction; revasc.

[a]*P* values pertain to the overall comparison between the four groups from an unadjusted Cox Proportional Hazards model.

[b]Fatal and non-fatal.


Patients enrolled in CLARIFY
(n = 33283)
♦ Withdrew participation (n = 196)
♦ Follow up not available (n = 691)
Available for analysis (n = 32396)
Did not undergo testing (n = 11994)
Underwent non-invasive testing for ischemia (n = 20402)
Neither angina
nor ischemia
(n = 13283)
Angina and
no ischemia
(n = 1843)
Ischemia and
no angina
(n = 3060)
Both angina
and ischemia
(n = 2216)


Both angina
and ischemia
(n = 2216)
10.9%
Ischemia and
no angina
(n = 3060)
15.0%
Angina and
no ischemia
(n = 1843)
9.0%
Neither angina
nor ischemia
(n = 13283)
65.1%


CV death, non-fatal MI
Ischemia only
Angina only
Both
CV death, MI-stroke
Ischemia only
Angina only
Both
CV death
Ischemia only
Angina only
Both
MI*
Ischemia only
Angina only
Both
Stroke*
Ischemia only
Angina only
Both
All-cause death
Ischemia only
Angina only
Both
Major bleed
Ischemia only
Angina only
Both
HR (95% CI)
P Value
0.89 (0.67-1.19)
.44
1.46 (1.09-1.95)
.01
1.76 (1.34-2.30)
<.001
0.89 (0.70-1.15)
.37
1.38 (1.06-1.80)
.02
1.58 (1.24-2.02)
<.001
0.85 (0.58-1.26)
.42
1.23 (0.80-1.90)
.35
1.90 (1.33-2.70)
<.001
0.92 (0.65-1.31)
.66
1.67 (1.18-2.36)
.004
1.66 (1.18-2.34)
.004
0.84 (0.53-1.33)
.45
1.22 (0.74-2.01)
.45
1.19 (0.73-1.94)
.49
1.02 (0.81-1.30)
.85
1.12 (0.84-1.50)
.45
1.37 (1.05-1.77)
.02
0.84 (0.54-1.32)
.46
0.75 (0.41-1.38)
.35
0.78 (0.43-1.40)
.40
0
1
2
3
4
HR (95% CI)
Lower risk
Higher risk