






# Long-term outcomes of chronic coronary syndrome worldwide: insights from the international CLARIFY registry

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## Aims

Over the last decades, the profile of chronic coronary syndrome has changed substantially. We aimed to determine characteristics and management of patients with chronic coronary syndrome in the contemporary era, as well as outcomes and their determinants.

## Methods and results

Data from 32 703 patients (45 countries) with chronic coronary syndrome enrolled in the prospective observational CLARIFY registry (November 2009 to June 2010) with a 5-year follow-up, were analysed. The primary outcome [cardiovascular death or non-fatal myocardial infarction (MI)] 5-year rate was 8.0% [95% confidence interval (CI) 7.7–8.3] overall [male 8.1% (7.8–8.5); female 7.6% (7.0–8.3)]. A cox proportional hazards model showed that the main independent predictors of the primary outcome were prior hospitalization for heart failure, current smoking, atrial fibrillation, living in Central/South America, prior MI, prior stroke, diabetes, current angina, and peripheral artery disease. There was an interaction between angina and prior MI ( $P=0.0016$ ); among patients with prior MI, angina was associated with a higher primary event rate [11.8% (95% CI 10.9–12.9) vs. 8.2% (95% CI 7.8–8.7) in patients with no angina,  $P<0.001$ ], whereas among patients without prior MI, event rates were similar for patients with [6.3% (95% CI 5.4–7.3)] or without angina [6.4% (95% CI 5.9–7.0)],  $P>0.99$ . Prescription rates of evidence-based secondary prevention therapies were high.

## Conclusion

This description of the spectrum of chronic coronary syndrome patients shows that, despite high rates of prescription of evidence-based therapies, patients with both angina and prior MI are an easily identifiable high-risk group who may deserve intensive treatment.

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## Introduction

Over the last decades, the management and prognosis of chronic coronary syndrome has improved considerably and consequently cardiovascular mortality has declined steadily.<sup>1</sup> Outcomes following acute myocardial infarction (MI) have improved following the advent of reperfusion therapy with thrombolysis or primary angioplasty<sup>2</sup> and widespread implementation of evidence-based secondary prevention medications,<sup>3</sup> including aspirin and other antiplatelet agents,<sup>4,5</sup> statins,<sup>6</sup> beta-blockers,<sup>7</sup> and renin–angiotensin antagonists.<sup>8,9</sup> In addition, the profile of these patients has changed with the use of coronary revascularization, particularly percutaneous coronary intervention (PCI) as well as the improved survival of patients experiencing an acute coronary syndrome (ACS). Whereas in the past, patients with chronic coronary syndrome were largely defined as patients with 'stable angina',<sup>10–12</sup> today these patients are a heterogeneous group encompassing patients with or without symptoms of angina pectoris, with or without a history of coronary revascularization, and with or without a history of prior and often remote ACS.<sup>13,14</sup> While there is a wealth of information regarding the acute and short-term outcomes of ACS patients, less is known regarding the contemporary characteristics, management, and long-term prognosis of the broad chronic coronary syndrome population.

The CLARIFY registry (Prospective observational Longitudinal Registry of patients with stable coronary artery disease; ISRCTN 43070564) was established to provide information regarding the profile and prognosis of chronic coronary syndrome in clinical practice, across a broad range of geographic regions.

The aim of the present study was to describe the characteristics and management of chronic coronary syndrome patients and to establish the determinants of their long-term prognosis with a focus on assessing the relative importance of angina and a history of MI.

## Methods

### Study design and participants

The rationale, design, and preliminary baseline characteristics of the CLARIFY registry have been described in detail previously.<sup>13,15,16</sup> Briefly, between 26 November 2009 and 30 June 2010, 32 703 chronic coronary syndrome patients were enrolled in 45 countries (Supplementary material online, Table S1), encompassing patients from high/middle/low-income countries organized in six geographical areas: Western/Central Europe, Eastern Europe, Middle East, Asia, Central/South America, and some Commonwealth countries (Australia/Canada/South Africa/UK).

Patients were eligible for enrolment if they fulfilled  $\geq 1$  of the following criteria (not mutually exclusive): documented MI for more than 3 months before enrolment, coronary artery bypass grafting (CABG) or PCI for more than 3 months before enrolment, chest pain with proven myocardial ischaemia, or previous coronary angiography showing at least one coronary stenosis of more than 50%. Exclusion criteria were

hospitalization for cardiovascular disease within the previous 3 months, planned revascularization, and conditions interfering with 5-year follow-up, including severe heart failure (HF). Severe HF was left to the investigator opinion without providing an left ventricular ejection fraction (LVEF) threshold (which would not take into account HF with preserved ejection fraction), or New York Heart Association class (which can transiently improve).

Patients were enrolled over a brief period to minimize the risk of selection bias and were followed-up yearly for up to 5 years. Medical care was at the discretion of each physician. Outcomes were not adjudicated, but investigators were provided with definitions for each outcome in case report forms. Yearly, 1% of sites were randomly selected for onsite audit of 100% of the data.

CLARIFY was conducted in accordance with the Declaration of Helsinki and local ethical approval was obtained in each country. All patients gave informed consent.

### Outcomes

The primary outcome was the composite of cardiovascular death or non-fatal MI. Secondary outcomes were cardiovascular death, non-cardiovascular death, all-cause death, the triple composite of cardiovascular death, non-fatal MI or non-fatal stroke, fatal MI, fatal stroke, non-fatal MI, non-fatal stroke, hospitalization for HF, coronary angiography, PCI, and CABG.

### Statistical analyses

Baseline characteristics were analysed according to history of MI and/or angina at baseline, using mean ( $\pm$ standard deviation) for continuous variables, and counts (and percentages) for categorical variables. Continuous and categorical variables were compared across groups using Student's and  $\chi^2$  tests, respectively. Baseline characteristics were also analysed across geographical areas and compared using analyses of variance and  $\chi^2$  tests, where appropriate.

Five-year rates with 95% confidence intervals (CIs) were estimated by Kaplan–Meier method in the total population, according to gender as well as in clinical subgroups (according to history of prior MI and/or angina status at baseline, independently or combined). Comparisons across subgroups were performed using the log-rank tests.

To determine the main predictors of cardiovascular death or non-fatal MI, an univariate and a multivariable analysis without selection (cause-specific Cox proportional hazards model) determined hazard ratios (HRs) and 95% CI, including as potential predictors: (i) cardiovascular risk factors [age, sex, diabetes, smoking status (current/former/never), and treated hypertension]; (ii) medical history [prior MI, PCI, CABG, or hospitalization for HF, asthma/chronic obstructive pulmonary disease, atrial fibrillation/flutter, prior stroke, cerebrovascular disease, peripheral artery disease (PAD)]; (iii) clinical parameters [current angina, blood pressure (BP)  $< 140/90$  mmHg]; (iv) treatments (aspirin, statins); and (v) geographical zones. Only factors showing a *P*-value of significance lower than 0.2 in univariate models were introduced in the multivariable model. The interaction between prior MI and angina status was assessed using unadjusted and adjusted Cox models. The effect of this interaction to the predictors of the primary outcome was assessed by adding the interaction between prior MI and angina in the previous multivariable model.

Analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA).

## Role of the funding source

The CLARIFY registry is supported by Servier. The sponsor had no role in the study design, data analysis and interpretation, or decision to submit the manuscript for publication, but assisted with the set-up, data collection, and management of the study in each country. The corresponding author had full access to all data and had the final responsibility for the decision to submit for publication.

## Results

A total of 33 299 patients were screened. Five hundred and ninety-six withdrew consent and/or did not meet the inclusion criteria and/or did not have baseline information available, leaving a study population of 32 703 participants with planned follow-up up to 5 years (median follow-up 5.0 years; interquartile range 4.8–5.1) ([Supplementary material online, Figure S1](#)).

Baseline characteristics of the entire CLARIFY population were previously described.<sup>13</sup> Briefly, patients had a mean age of  $64.2 \pm 10.5$  years, 22.4% were women, 71.0% had a history of hypertension. As expected from the inclusion criteria, prior MI (59.9%) and prior revascularization (PCI = 58.6%; CABG = 23.6%) were common.

A minority of the patients had angina (22.1%), HF symptoms (15.1%), or HF symptoms and LVEF  $\geq 50\%$  (10.2%). The prevalence of HF symptoms with LVEF  $\geq 50\%$  was higher in female (13.8%) than in male (9.0%),  $P < 0.001$ . Rates for use of secondary prevention therapies, such as antiplatelet agents, statins, beta-blockers, and renin-angiotensin system (RAS) inhibitors (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) were: 95.2%, 82.9%, 75.3%, and 76.3%, respectively ([Supplementary material online, Table S2](#)).

Compared with patients without prior MI, patients with a history of prior MI were younger, more often males and current or former smokers, had a lower prevalence of treated hypertension, a higher prevalence of family history of premature coronary disease, and history of PCI. They had more symptoms of angina or HF, and lower LVEF. They were more likely to receive guideline-recommended secondary prevention therapies ([Table 1](#)).

Compared with patients without angina, patients with angina were younger, more frequently females, had a higher prevalence of cardiovascular risk factors and history of hospitalization for HF, lower LVEF, higher rates of prior MI, lower extremity artery disease or cerebrovascular disease, and fewer prior coronary revascularization procedures. The use of medication was similar for single antiplatelet therapy and statins, but higher for antianginal drugs and RAS inhibitors in the angina subgroup. Rate of non-current smoking was lower in patients with angina ([Table 1](#)).

Baseline characteristics according to combined prior MI and angina status at study entry are reported in [Supplementary material online, Table S3](#).

Across geographical regions, substantial variations in clinical profiles were observed ([Supplementary material online, Table S4](#)). Patients enrolled in Eastern Europe were the youngest and had the lowest prevalence of diabetes, but the highest prevalence of treated hypertension, current smoking, prior MI, prior hospitalization for HF,

current angina, or HF symptoms, and the highest rate of RAS inhibitors use. In participating centres from the Middle East, patients had the lowest rate of current HF symptoms, the highest body mass index and the highest prevalence of diabetes. They had the lowest rate of lower extremity artery disease and family history of coronary disease. They had also the lowest LVEF. The overall use of secondary prevention therapy was the highest. Centres from Asia had the lowest prevalence of prior MI, the highest rate of prior PCI, but the lowest rate of CABG, the highest rate of stroke, and the smallest body mass index, and the lowest rate of use of statins and RAS inhibitors. Central/South America enrolled the highest proportion of females and the lowest rate of current smokers, prior stroke, or angina patients, but the highest rate of BP  $< 140/90$  mmHg. Commonwealth countries were characterized by the oldest population, with the highest rate of family history of premature coronary disease, prior transient ischaemic attack, or CABG, and the lowest rate of use of single antiplatelet therapy and beta-blockers. Western/Central Europe had the highest proportion of males and the highest prevalence of lower extremity artery disease.

In the CLARIFY cohort, the 5-year crude rate of cardiovascular death or non-fatal MI was 8.0% (95% CI 7.7–8.3), the rate of cardiovascular death, non-fatal MI, or non-fatal stroke was 9.5% (95% CI 9.2–9.9), and the cardiovascular death rate was 5.5% (95% CI 5.3–5.8). Approximately 20% of cardiovascular deaths were due to MI and nearly 10% to stroke. All-cause death was 8.5% (95% CI 8.2–8.9) and non-cardiovascular death was 3.2% (95% CI 3.0–3.4). Approximately 15% of patients required coronary angiography during follow-up, of which half resulted in PCI and close to 10% in CABG ([Table 2](#)).

The primary event rate was 7.6% (95% CI 7.0–8.3) for female and 8.1% (95% CI 7.8–8.5) for male. Overall, 5-year event rates were similar regardless of the gender, but female were significantly less revascularized than male: 6.6% (95% CI 6.1–7.3) vs. 7.7% (95% CI 7.4–8.1), respectively for PCI ([Supplementary material online, Table S5](#)).

Patients with prior MI experienced worse outcomes than patients without prior MI. Rates of cardiovascular death or non-fatal MI were 9.1% (95% CI 8.7–9.5) and 6.4% (95% CI 6.0–6.9), respectively ( $P < 0.001$ ). They also had a significantly higher rate of cardiovascular death and of the triple composite endpoint. Compared with patients without angina, patients with angina had a higher rate of cardiovascular death or non-fatal MI with rates of 9.8% (95% CI 9.1–10.5) and 7.5% (95% CI 7.1–7.8), respectively ( $P < 0.001$ ). They also had higher rates of cardiovascular death and triple composite endpoint ([Table 2](#)).

There was an interaction between angina and history of MI regarding the primary endpoint ( $P = 0.0016$  with multivariable analysis), and the main secondary endpoints. This interaction was not time-dependent ([Supplementary material online, Table S6](#)). After stratification into four mutually exclusive subgroups according to the combined presence of angina at baseline and history of prior MI, angina was associated with a worse prognosis only in patients with a history of prior MI ([Take home figure](#)). In the subset of patients with prior MI, the 5-year rate of cardiovascular death or non-fatal MI was 11.8% (95% CI 10.9–12.9) for angina patients vs. 8.2% (95% CI 7.8–8.7) for non-angina patients ( $P < 0.001$ ). In the subset of patients without prior MI, this rate was 6.3% (95% CI 5.4–7.3) for angina patients vs.

**Table 1** Baseline characteristics according to history of MI status or according to current angina status

	Prior MI (N = 19 595)	No prior MI (N = 13 100)	P-value	Angina at baseline (N = 7212)	No angina at baseline (N = 25 479)	P-value
<b>Risk factors and lifestyle</b>						
Age (years)	63.1 ± 10.7 (19 587)	65.8 ± 9.4 (13 093)	<0.001	63.04 ± 10.2 (7208)	64.5 ± 10.5 (25 468)	<0.001
Male	80.8% (15 825/19 589)	72.8% (9534/13 096)	<0.001	71.5% (5154/7210)	79.3% (20 203/25 471)	<0.001
Treated hypertension	69.1% (13 538/19 591)	73.8% (9669/13 099)	<0.001	78.5% (5658/7212)	68.9% (17 549/25 477)	<0.001
Diabetes	28.6% (5601/19 589)	29.7% (3895/13 099)	0.026	28.6% (2062/7212)	29.2% (7433/25 474)	0.332
Dyslipidaemia	75.9% (14 877/19 591)	73.5% (9622/13 099)	<0.001	78.8% (5683/7212)	73.9% (18 815/25 476)	<0.001
<b>Smoking status</b>						
Current	14.3% (2805/19 594)	9.7% (1272/13 099)	<0.001	15.0% (1078/7212)	11.8% (2999/25 479)	<0.001
Former	49.2% (9641/19 594)	41.7% (5463/13 099)		41.4% (2982/7212)	47.6% (12 121/25 479)	
Never	36.5% (7148/19 594)	48.6% (6364/13 099)		43.7% (3152/7212)	40.7% (10 359/25 479)	
Family history of premature coronary disease	29.1% (5704/19 590)	27.7% (3622/13 098)	0.004	35.4% (2552/7212)	26.6% (6773/25 476)	<0.001
No physical activity	15.5% (3040/19 588)	17.2% (2246/13 095)	<0.001	14.6% (1056/7211)	16.6% (4230/25 472)	<0.001
<b>Medical history</b>						
Myocardial infarction	100.0% (19 595/19 595)	0.0% (0/13 100)	NA	62.5% (4507/7211)	59.2% (15 084/25 478)	<0.001
PCI	60.3% (11 812/19 594)	56.1% (7348/13 099)	<0.001	41.9% (3018/7211)	63.4% (16 140/25 477)	<0.001
CABG	21.5% (4217/19 592)	26.6% (3484/13 099)	<0.001	19.3% (1392/7210)	24.8% (6308/25 476)	<0.001
<b>Cerebrovascular disease</b>						
Stroke	4.1% (801/19 593)	3.9% (513/13 100)	0.437	5.3% (383/7211)	3.7% (931/25 477)	<0.001
Transient ischemic attack	2.8% (541/19 592)	3.5% (460/13 100)	<0.001	4.8% (345/7211)	2.6% (656/25 476)	<0.001
Carotid disease	6.7% (1312/19 594)	8.9% (1162/13 100)	<0.001	9.6% (694/7211)	7.0% (1779/25 478)	<0.001
<b>Peripheral arterial disease</b>						
Lower extremity artery disease	9.7% (1900/19 590)	10.2% (1338/13 099)	0.126	13.0% (938/7212)	9.0% (2301/25 475)	<0.001
Aortic abdominal aneurysm	1.6% (311/19 592)	1.5% (193/13 099)	0.412	1.2% (89/7211)	1.6% (415/25 475)	0.016
Hospitalization for HF	5.5% (1085/19 593)	3.4% (445/13 100)	<0.001	7.5% (537/7211)	3.9% (993/25 477)	<0.001
Atrial fibrillation/flutter	6.4% (1255/19 593)	8.1% (1057/13 100)	<0.001	7.4% (531/7211)	7.0% (1781/25 477)	0.275
Asthma/COPD	7.3% (1437/19 593)	7.5% (982/13 100)	0.584	9.1% (654/7211)	6.9% (1765/25 477)	<0.001
<b>Clinical examination</b>						
Angina symptoms	23.0% (4507/19 591)	20.6% (2704/13 098)	<0.001	100.0% (7212/7212)	0.0% (0/25 479)	NA
HF symptoms	18.5% (3628/19 590)	10.0% (1296/13 098)	<0.001	40.4% (2912/7211)	7.9% (2013/25 478)	<0.001
Systolic BP (mmHg)	130.1 ± 16.6 (19 576)	132.5 ± 16.6 (13 094)	<0.001	133.5 ± 17.5 (7211)	130.3 ± 16.4 (25 455)	<0.001
Diastolic BP (mmHg)	77.3 ± 10.1 (19 576)	77.3 ± 9.8 (13 094)	0.940	79.5 ± 10.7 (7211)	76.6 ± 9.7 (25 455)	<0.001
Pulse (b.p.m.)	68.3 ± 10.5 (19 577)	68.1 ± 10.7 (13 091)	0.074	69.8 ± 10.9 (7212)	67.8 ± 10.5 (25 452)	<0.001
Body mass index (kg/m <sup>2</sup> )	28.1 ± 4.7 (19 573)	27.6 ± 4.5 (13 081)	<0.001	28.6 ± 4.8 (7202)	27.7 ± 4.5 (25 448)	<0.001
<b>Paraclinical parameters</b>						
LVEF (%)	53.7 ± 11.2 (13 963)	60.0 ± 9.6 (8554)	<0.001	55.3 ± 10.4 (5422)	56.3 ± 11.3 (17 091)	<0.001
<b>Coronary arteries involved<sup>a</sup></b>						
Left main	7.9% (1555/19 585)	9.9% (1293/13 097)	<0.001	8.7% (624/7210)	8.7% (2224/25 469)	0.837
LAD	55.9% (10 947/19 585)	62.0% (8113/13 097)	<0.001	44.5% (3211/7210)	62.2% (15 848/25 469)	<0.001
Cx	34.9% (6834/19 585)	37.9% (4959/13 097)	<0.001	29.5% (2128/7210)	37.9% (9663/25 469)	<0.001
RCA	44.5% (8711/19 585)	42.2% (5520/13 097)	<0.001	36.8% (2655/7210)	45.4% (11 574/25 469)	<0.001
Bypass graft	7.7% (1510/19 585)	8.6% (1120/13 097)	0.006	7.5% (543/7210)	8.2% (2087/25 469)	0.068
No significant stenosis	3.1% (608/19 585)	3.4% (449/13 097)	0.105	3.9% (284/7210)	3.0% (773/25 469)	<0.001
Angiography not done <12 months	16.5% (3223/19 585)	11.8% (1540/13 097)	<0.001	31.7% (2282/7210)	9.7% (2481/25 469)	<0.001
<b>Baseline medications</b>						
Aspirin	89.1% (17 446/19 587)	85.8% (11 236/13 097)	<0.001	89.1% (6423/7212)	87.4% (22 258/25 471)	<0.001
Any antiplatelet therapy	95.8% (18 761/19 590)	94.2% (12 342/13 097)	<0.001	95.0% (6854/7212)	95.2% (24 248/25 474)	0.598
Dual antiplatelet therapy	28.8% (5647/19 590)	26.7% (3496/13 097)	<0.001	23.8% (1717/7212)	29.2% (7425/25 474)	<0.001
Oral anticoagulants	8.1% (1590/19 573)	8.2% (1078/13 089)	0.716	7.9% (569/7208)	8.3% (2101/25 453)	0.324
Lipid lowering agents	93.6% (18 333/19 590)	90.5% (11 853/13 097)	<0.001	91.3% (6584/7212)	92.7% (23 601/25 474)	<0.001

Continued

**Table 1 Continued**

	<b>Prior MI (N = 19 595)</b>	<b>No prior MI (N = 13 100)</b>	<b>P-value</b>	<b>Angina at baseline (N = 7212)</b>	<b>No angina at baseline (N = 25 479)</b>	<b>P-value</b>
Statins	84.7% (16 583/19 590)	80.3% (10 512/13 097)	<0.001	82.9% (5978/7212)	82.9% (21 115/25 474)	0.998
Beta-blockers	79.0% (15 471/19 591)	69.8% (9136/13 096)	<0.001	78.8% (5681/7212)	74.3% (18 924/25 474)	<0.001
Calcium antagonists	23.0% (4504/19 588)	33.6% (4405/13 095)	<0.001	31.8% (2296/7212)	26.0% (6613/25 470)	<0.001
Ivabradine	10.3% (2015/19 588)	9.2% (1203/13 097)	0.001	21.3% (1533/7211)	6.6% (1685/25 473)	<0.001
Nitrates or other antianginal drugs <sup>b</sup>	30.6% (5990/19 581)	30.0% (3930/13 096)	0.262	55.9% (4030/7209)	23.1% (5887/25 467)	<0.001
ACE-inhibitors or ARB	79.6% (15 588/19 584)	71.3% (9333/13 095)	<0.001	80.3% (5794/7212)	75.1% (19 127/25 473)	<0.001
Diuretics	30.5% (5962/19 585)	27.6% (3621/13 097)	<0.001	36.2% (2609/7212)	27.4% (6975/25 469)	<0.001
NSAID	4.8% (929/19 581)	5.2% (684/13 097)	0.051	6.4% (459/7211)	4.5% (1155/25 465)	<0.001
Amiodarone/dronedaron	3.2% (623/19 581)	2.6% (338/13 096)	0.002	3.7% (265/7211)	2.7% (697/25 465)	<0.001
Insulin in diabetics	21.6% (1209/5599)	21.5% (838/3894)	0.932	23.3% (481/2062)	21.1% (1566/7432)	0.932
Oral diabetic drugs in diabetics	68.4% (3834/5599)	70.4% (2742/3894)	0.044	68.1% (1404/2062)	69.6% (5174/7432)	<0.001

Groups according to history of prior MI or angina are non-mutually exclusive.

Data are expressed in mean ± standard deviation for continuous variables or % for categorical variables. For categorical data, the number of concerned patients/number of available data are indicated in brackets. For continuous data, the number of available data are indicated in brackets.

Categorical and continuous variables were compared across groups by  $\chi^2$  and Student's *t*-test, respectively. Continuous variables are presented by mean or median according to the distribution.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; BP, blood pressure; CABG, coronary artery bypass graft; COPD, chronic obstructive coronary disease; HF, heart failure; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable; NSAID, non-steroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention; RCA, right coronary artery; SD, standard deviation.

<sup>a</sup>With stenosis >50% at coronary angiography or having required revascularization in the past.

<sup>b</sup>Other antianginal drugs: molsidomine, nicorandil, ranolazine, or trimetazidine.

**Table 2 Five-year event rates (95% CI) in the entire cohort and according to history of prior MI or the presence of anginal symptoms at baseline**

	<b>All CLARIFY (N = 32 703)</b>	<b>Prior MI (N = 19 595)</b>	<b>No prior MI (N = 13 100)</b>	<b>P-value</b>	<b>Angina (N = 7212)</b>	<b>No angina (N = 25 479)</b>	<b>P-value</b>
Primary outcome							
CV death or Non-fatal MI	8.0 (7.7–8.3)	9.1 (8.7–9.5)	6.4 (6.0–6.9)	<0.001	9.8 (9.1–10.5)	7.5 (7.1–7.8)	<0.001
Secondary outcomes							
CV death	5.5 (5.3–5.8)	6.3 (5.9–6.6)	4.4 (4.0–4.8)	<0.001	6.3 (5.7–6.9)	5.3 (5.0–5.6)	0.001
Non-CV death	3.2 (3.0–3.4)	3.3 (3.1–3.6)	3.0 (2.7–3.3)	0.096	3.0 (2.6–3.5)	3.3 (3.0–3.5)	0.295
All-cause death	8.5 (8.2–8.9)	9.4 (9.0–9.8)	7.3 (6.8–7.8)	<0.001	9.1 (8.4–9.8)	8.4 (8.0–8.8)	0.050
CV death non-fatal MI or non-fatal stroke	9.5 (9.2–9.9)	10.7 (10.3–11.2)	7.7 (7.2–8.2)	<0.001	11.6 (10.8–12.4)	8.9 (8.5–9.3)	<0.001
Fatal MI	1.1 (1.0–1.2)	1.4 (1.3–1.6)	0.7 (0.5–0.8)	<0.001	1.5 (1.2–1.8)	1.0 (0.9–1.2)	0.001
Fatal stroke	0.6 (0.5–0.7)	0.7 (0.6–0.8)	0.5 (0.4–0.6)	0.034	0.9 (0.7–1.2)	0.5 (0.4–0.6)	<0.001
Non-fatal MI	2.8 (2.6–3.0)	3.2 (2.9–3.5)	2.2 (1.9–2.5)	<0.001	3.9 (3.5–4.4)	2.5 (2.3–2.7)	<0.001
Non-fatal stroke	1.9 (1.7–2.0)	2.0 (1.8–2.3)	1.6 (1.4–1.9)	0.006	2.3 (1.9–2.7)	1.7 (1.6–1.9)	0.006
Hospitalization for heart failure	5.4 (5.2–5.7)	6.4 (6.1–6.8)	3.9 (3.6–4.3)	<0.001	10.7 (10.0–11.5)	3.9 (3.6–4.1)	<0.001
Coronary angiography	15.0 (14.6–15.4)	14.2 (13.7–14.8)	16.1 (15.4–16.8)	<0.001	19.7 (18.7–20.7)	13.6 (13.2–14.1)	<0.001
PCI	7.5 (7.2–7.8)	7.1 (6.8–7.5)	7.9 (7.5–8.5)	0.006	9.6 (8.9–10.3)	6.8 (6.5–7.2)	<0.001
CABG	1.5 (1.4–1.7)	1.6 (1.4–1.8)	1.4 (1.2–1.7)	0.345	2.5 (2.2–2.9)	1.2 (1.1–1.4)	<0.001

Groups according to history of prior MI or angina are non-mutually exclusive.

All risks are described as Kaplan–Meier estimates with their 95% CI. *P*-values for group comparisons were estimated by log-ranks tests.

CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; PCI, percutaneous coronary intervention.

**Table 3** Five-year outcomes according to combined history of prior MI and angina status

	Prior MI <sup>a</sup> (N = 19 595)		P-value	No prior MI <sup>b</sup> (N = 13 100)		P-value
	Angina (N = 4507) 5-year event rate % (95% CI)	No angina (N = 15 084) 5-year event rate % (95% CI)		Angina (N = 2704) 5-year event rate % (95% CI)	No angina (N = 10 394) 5-year event rate % (95% CI)	
Primary outcome						
CV death or non-fatal MI	11.8 (10.9–12.9)	8.2 (7.8–8.7)	<0.001	6.3 (5.4–7.3)	6.4 (5.9–7.0)	>0.99
Secondary outcomes						
Cardiovascular death	7.7 (7.0–8.6)	5.8 (5.4–6.2)	<0.001	3.7 (3.1–4.6)	4.6 (4.2–5.1)	0.111
Non-CV death	3.3 (2.8–3.9)	3.3 (3.0–3.7)	>0.99	2.5 (1.9–3.2)	3.1 (2.8–3.5)	0.069
All-cause death	10.8 (9.9–11.8)	8.9 (8.5–9.5)	<0.001	6.1 (5.2–7.1)	7.6 (7.1–8.2)	0.017
CV death non-fatal MI or non-fatal stroke	13.7 (12.7–14.8)	9.8 (9.3–10.3)	<0.001	8.0 (7.0–9.1)	7.6 (7.1–8.2)	0.448
Fatal MI	2.0 (1.6–2.5)	1.2 (1.1–1.5)	<0.001	0.6 (0.4–1.0)	0.7 (0.5–0.9)	0.939
Fatal stroke	1.2 (0.9–1.6)	0.5 (0.4–0.7)	<0.001	0.5 (0.3–0.8)	0.5 (0.4–0.7)	0.860
Non-fatal MI	4.6 (4.0–5.3)	2.7 (2.5–3.0)	<0.001	2.8 (2.2–3.5)	2.0 (1.8–2.4)	0.034
Non-fatal stroke	2.5 (2.0–3.0)	1.9 (1.7–2.1)	0.019	1.9 (1.4–2.5)	1.5 (1.3–1.8)	0.189
Hospitalization for heart failure	13.0 (12.0–14.1)	4.4 (4.0–4.7)	<0.001	6.8 (5.9–7.9)	3.1 (2.8–3.5)	<0.001
Coronary angiography	19.0 (17.8–20.3)	12.8 (12.2–13.4)	<0.001	20.7 (19.2–22.4)	14.9 (14.2–15.7)	<0.001
PCI	9.2 (8.3–10.1)	6.5 (6.1–7.0)	<0.001	10.2 (9.1–11.5)	7.3 (6.8–7.9)	<0.001
CABG	2.5 (2.1–3.1)	1.3 (1.1–1.5)	<0.001	2.5 (1.9–3.2)	1.2 (0.9–1.4)	<0.001

Groups according to history of prior MI or angina are mutually exclusive.

<sup>a</sup>Among the subset with prior MI angina status was missing for four patients.

<sup>b</sup>Among the subset without prior MI angina status was missing for two patients.

All risks are described as Kaplan–Meier estimates with their 95% CI. P-values for group comparisons were estimated by log-rank tests.

CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; PCI, percutaneous coronary intervention.

6.4% (95% CI 5.9–7.0) for patients without angina ( $P > 0.99$ ). Similar results were found for most secondary outcomes (Table 3).

There were substantial variations in crude event rates across geographical zones. Asia had the lowest rate of primary outcome and the lowest mortality (all-cause, cardiovascular, and non-cardiovascular). Conversely, Central/South America had the highest rate of primary outcome and the highest mortality, driven by the highest cardiovascular death (Supplementary material online, Table S7).

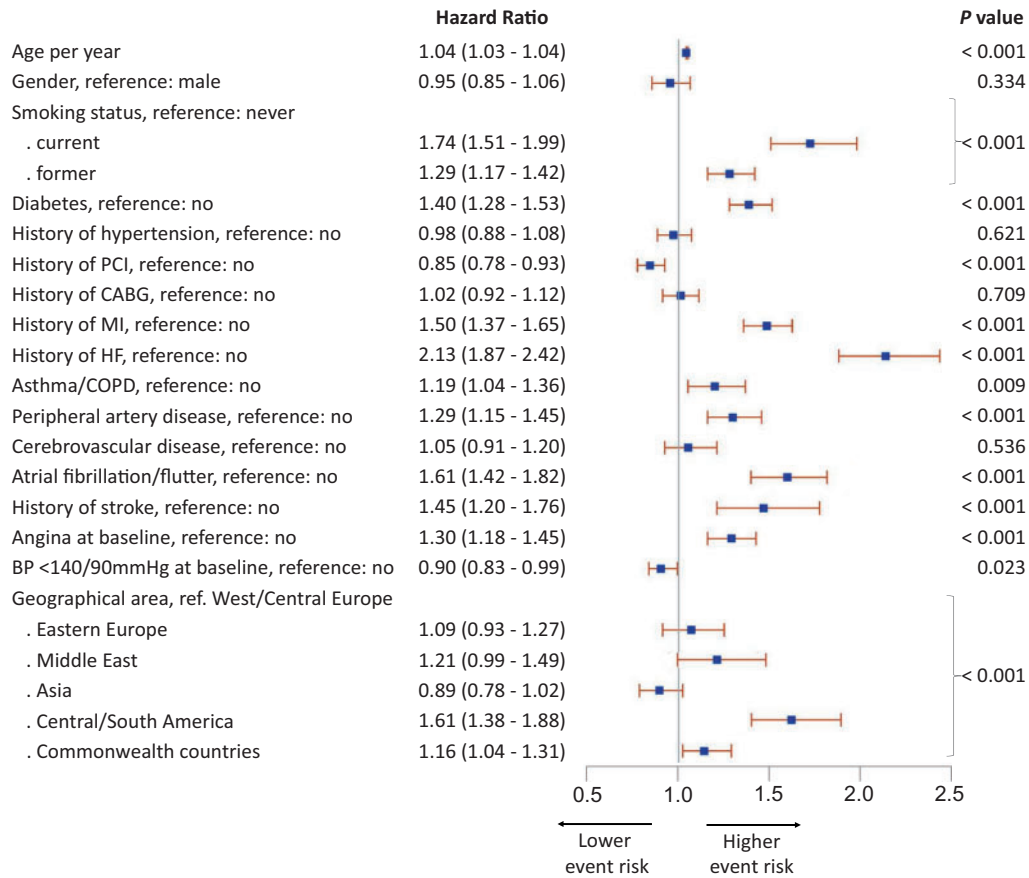
Multivariable analysis identified the main independent predictors of the primary composite outcome of cardiovascular death or non-fatal MI (Figure 1) as history of hospitalization for HF (HR = 2.13; 95% CI 1.87–2.42), current smoking (HR = 1.74; 95% CI 1.51–1.99), atrial fibrillation/flutter (HR = 1.61; 95% CI 1.42–1.82), living in Central/South America (HR = 1.61; 95% CI 1.38–1.88), prior MI (HR = 1.50; 95% CI 1.37–1.65), prior stroke (HR = 1.45; 95% CI 1.20–1.76), diabetes (HR = 1.40; 95% CI 1.28–1.53), current angina (HR = 1.30; 95% CI 1.18–1.45), PAD (HR = 1.29; 95% CI 1.15–1.45), and former smoker (HR = 1.29; 95% CI 1.17–1.42). Age was also an independent predictor (HR = 1.04; 95% CI 1.03–1.04 for each 1-year increase). A lower risk of cardiovascular death or non-fatal MI was independently predicted by prior PCI (HR = 0.85; 95% CI 0.78–0.93) and BP <140/90 mmHg (HR = 0.90; 95% CI 0.83–0.99). Gender was not an independent predictor of cardiovascular death or non-fatal MI (HR = 0.95; 95% CI 0.85–1.06, for female) as illustrated in Figure 1. Univariate/multivariable analyses are reported in Supplementary material online, Table S8. After adjustment with interaction between

prior MI and angina, the effect of these predictors was similar (Supplementary material online, Figure S2).

## Discussion

This large, international, observational, cohort of chronic coronary syndrome patients provides several important observations with direct clinical implications.

First, since prior registries, such as Euro Heart Survey on stable angina<sup>12</sup> and REACH<sup>17,18</sup> were started, the clinical characteristics of patients with chronic coronary syndrome have changed. Compared with the Euro Heart Survey on stable angina (enrolment 2002), and with the REACH registry (enrolment 2003–2004), more patients in CLARIFY were well treated in terms of exposure to secondary prevention therapies, regardless of the clinical profile or geographical area of enrolment. Moreover, patients in CLARIFY had more diverse clinical profiles than in the Euro Heart Survey, which was focused exclusively on patients with angina and without revascularization, and than in the REACH registry, which enrolled patients at risk for or with established atherothrombosis, including chronic coronary syndrome but which did not encompass the full spectrum of this syndrome. For example, REACH did not enroll patients with documented coronary disease but without prior MI or PCI. This observation highlights the changing picture of chronic coronary artery disease, a population which used to be defined largely via its angina



**Figure 1** Forest plot for multivariable analysis to determine the main predictors of cardiovascular death or myocardial infarction in the entire CLARIFY population. BP, blood pressure; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.

symptoms, but which now covers a broad spectrum of clinical presentations, and prior medical history.

Second, in this cohort without severe HF, major cardiovascular event rates were overall relatively low compared with previous registries,<sup>12,18</sup> but encompassed substantial variation across geographic zones. This may be related to secular trends in cardiovascular disease but also to different selection criteria resulting in enrolment of a lower risk population. In the CORONOR registry (enrolment 2010–2011), which recruited an older population (mean age 66.9 ± 11.6 years), half of deaths were non-cardiovascular and the rate of cardiovascular death was slightly higher (1.3 per 100 patient-years) than in the present study.<sup>19</sup> Compared with contemporary randomized clinical trials (RCTs), CLARIFY patients were overall at lower risk than those from COMPASS<sup>20</sup> (who required coronary artery disease enrichment criteria to be enrolled), from FOURIER<sup>21</sup> (with a higher prevalence of prior MI) or from CANTOS<sup>22</sup> (where all patients had a prior MI).

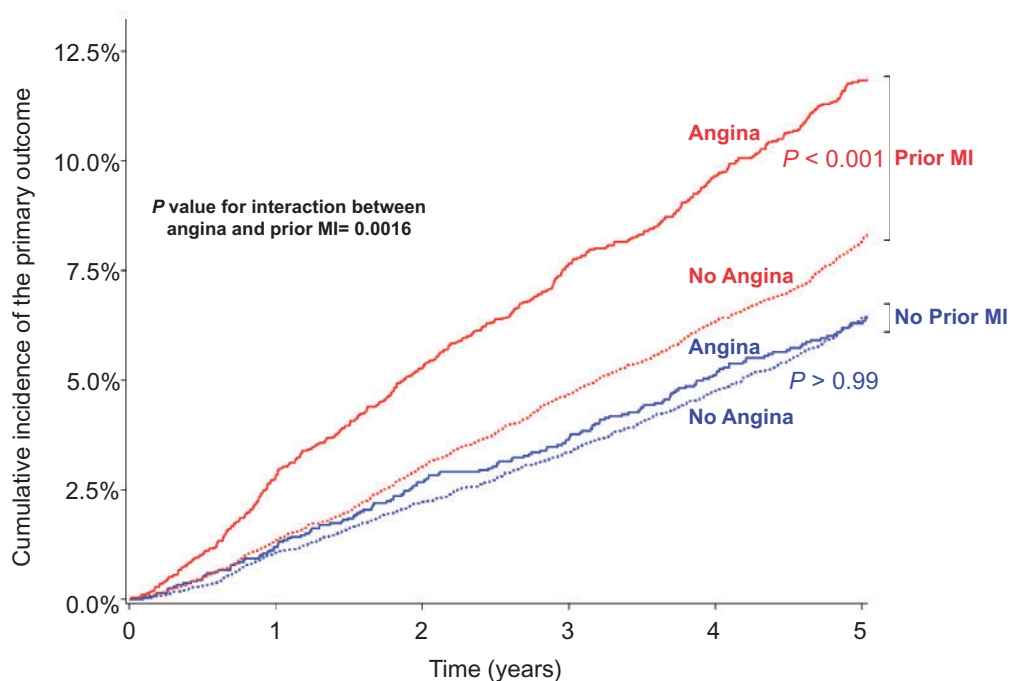
Third, major predictors of cardiovascular death or non-fatal MI were a history of hospitalization for HF and other comorbidities, such as atrial fibrillation or PAD, suggesting that these comorbidities must not be considered as incidental in chronic coronary syndrome patients and need to be more carefully targeted and treated. Conventional cardiovascular risk factors were also predictors of

poor outcomes, highlighting that prevention and treatment of these factors remains a major goal.

Fourth, the profile of women and men with chronic coronary syndrome differ substantially<sup>15</sup> with a higher rate of HF with preserved LVEF for women. However, gender was not an independent predictor of the primary outcome and 5-year event rates were overall similar regardless of the gender, other than a lower incidence of revascularization in women. These results highlight the need of further analyses to better understand gender determinants of outcome.

Fifth, history of prior MI and angina symptoms were both major determinants of adverse cardiovascular outcomes, with a significant statistical interaction. These results complement the previous findings where angina was shown to be prognostically important, while silent ischaemia without angina was not associated with a worse prognosis at 1 year.<sup>14</sup>

While a history of prior MI was a determinant of poor prognosis regardless of angina symptoms, angina had different implications depending on the patient profile. Although angina was associated with a poor prognosis, this was only true in patients with prior MI but not in patients without prior MI. Patients with angina usually have relatively infrequent episodes of ischaemia often occurring in response to exercise or emotional stress, and in the absence of a suitable substrate



**Take home figure** Kaplan–Meier estimate curves for cardiovascular death or myocardial infarction according to angina status and history of prior myocardial infarction. *P*-value for interaction between angina and prior MI= 0.0016. CV, cardiovascular; MI, myocardial infarction.

unlikely to cause harm. A previous MI is a circumstance where such a normally benign episode of ischaemia may lead to a devastating outcome with a much higher risk to develop serious ventricular arrhythmias or acute HF.

Moreover, the state of coronary arteries is an important determinant of outcome in patients with angina. Given the expected higher prevalence of vulnerable plaques in patients with previous MI, it is expected that the latter will fare worst irrespective of the severity or even extent of atherosclerotic disease. The implications of this finding are clear: patients with prior MI and angina symptoms represent 14% of the chronic coronary syndrome population and are at highest risk. They deserve more intensive monitoring and management and particular attention should be devoted to implementing secondary prevention strategies and ensuring targets are met.<sup>23–26</sup> A clearer understanding of which patient profiles have the worst outcomes is necessary to focus follow-up efforts and appropriately target new therapies that are either expensive or can have carry risks and side effect (e.g. rivaroxaban,<sup>20</sup> PCSK9 inhibitors<sup>21</sup>, or canakinumab<sup>22</sup>). In contrast, patients with angina but no prior MI may not deserve aggressive non-invasive testing.

When attempting to improve patient care, RCTs and registries are both useful. While RCTs are the gold-standard to evaluate new therapies, they are often restricted to highly selected populations and may not reflect daily practice.<sup>27</sup> In contrast, registries are poorly suited to determine treatment efficacy or safety but provide important data on large number of patients from routine clinical practice in

terms of describing patient characteristics, management and outcomes and identifying gaps between evidence and practice. Guidelines on secondary prevention of chronic patients are available, but largely rely on relatively old data pertaining to trials done in MI survivors.<sup>28,29</sup> Large observational studies in patients with chronic coronary syndrome are scarce, or are often focused on patients with angina,<sup>30</sup> or restricted to a single geographic area.<sup>31–33</sup>

Despite the size, scope, and quality of the CLARIFY registry, this analysis has several limitations, some of which are inherent to observational studies. Outcomes were not adjudicated and, given the difficulty in ascribing death to a specific cause in long-term outpatient studies, the incidence of cardiovascular mortality, in contrast to total mortality, should be taken with caution. Monitoring was limited each year to a random selection of 1% of the centres. These results refer only to enrolled patients and reflect the CLARIFY inclusion criteria. They do not necessarily apply to all chronic coronary syndrome patients encountered in daily practice. This study may not be extrapolated to patients managed in the USA, as there were no patients enrolled in this country due to lack of local sponsor. Despite a broad geographic scope encompassing 45 countries, CLARIFY only reflects countries and regions with high- or middle-income. The results cannot be extrapolated to important and large areas, such as most of Africa and regions in Asia where access to expensive medical care is limited. Causes of two-thirds of cardiovascular death (non-related to an MI or a stroke) were classified as other cardiovascular death and consequently were assumed rather than proven



cardiovascular death, as is often the case in long-term outpatient studies where many deaths can occur out of hospital and where documentation is often limited or absent.

In conclusion, this international study provides helpful information to characterize the spectrum of patients with chronic coronary syndrome and inform patient management and future studies in this population, across various geographic regions. In this broad population with chronic coronary syndrome, rates of major cardiovascular events were lower than those observed in historical datasets, which may reflect improved global medical care particularly the high rates of use of evidence-based therapies. Although angina was associated with a poor prognosis, this was only true in patients with prior MI. Patients with both angina and prior MI are an easily identifiable high-risk group which may deserve more intensive treatment.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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