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β-blockers, calcium antagonists, and mortality in stable coronary artery disease: an international cohort study

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Aims The effect of first-line antianginal agents, β-blockers, and calcium antagonists on clinical outcomes in stable coronary artery disease (CAD) remains uncertain.

Methods and results We analysed the use of β-blockers or calcium antagonists (baseline and annually) and outcomes in 22 006 stable CAD patients (enrolled 2009–2010) followed annually to 5 years, in the CLARIFY registry (45 countries). Primary outcome was all-cause death. Secondary outcomes were cardiovascular death and the composite of cardiovascular death/non-fatal myocardial infarction (MI). After multivariable adjustment, baseline β-blocker use was not associated with lower all-cause death [1345 (7.8%) in users vs. 407 (8.4%) in non-users; hazard ratio (HR) 0.94, 95% confidence interval (CI) 0.84–1.06; $P = 0.30$]; cardiovascular death [861 (5.0%) vs. 262 (5.4%); HR 0.91, 95% CI 0.79–1.05; $P = 0.20$]; or cardiovascular death/non-fatal MI [1272 (7.4%) vs. 340 (7.0%); HR 1.03, 95% CI 0.91–1.16; $P = 0.66$]. Sensitivity analyses according to β-blocker use over time and to prescribed dose produced similar results. Among prior MI patients, for those enrolled in the year following MI, baseline β-blocker use was associated with lower all-cause death [205 (7.0%) vs. 59 (10.3%); HR 0.68, 95% CI 0.50–0.91; $P = 0.01$]; cardiovascular death [132 (4.5%) vs. 49 (8.5%); HR 0.52, 95% CI 0.37–0.73; $P = 0.0001$]; and cardiovascular death/non-fatal MI [212 (7.2%) vs. 59 (10.3%); HR 0.69, 95% CI 0.52–0.93; $P = 0.01$]. Calcium antagonists were not associated with any difference in mortality.

Conclusion In this contemporary cohort of stable CAD, β-blocker use was associated with lower 5-year mortality only in patients enrolled in the year following MI. Use of calcium antagonists was not associated with superior mortality, regardless of history of MI.

Keywords Stable coronary artery disease • Beta-blockers • Calcium antagonists • Prognosis • Mortality

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Introduction

β-blockers and calcium antagonists are recommended for treatment of angina in patients with stable coronary disease (CAD).[1,2] They are widely used in stable CAD, including angina free patients[3] even though their role in improving outcomes remains uncertain. Large observational series have shown association of β-blocker use with improved outcomes in acute coronary syndromes.[4–6]

Randomized clinical trials (RCTs) established unequivocal benefits of β-blockers in chronic heart failure with left ventricular (LV) systolic dysfunction[7] and in relatively old trials in acute myocardial infarction (MI),[8] but no trials assessed their benefit compared with placebo in stable CAD.[9,10] Thus, the question was investigated in observational[11–14] and *post hoc* trial analyses.[15]

Regarding calcium antagonists, there are no data supporting a benefit on mortality and a few trials supporting a benefit on cardiovascular morbidity compared with placebo in stable CAD.[16,17] Trials comparing long-acting dihydropyridines[18] or non-dihydropyridines[19–21] with β-blockers in stable CAD found no difference in clinical outcomes.

In the absence of RCTs, we assessed the association between β-blocker or calcium antagonist use and clinical outcomes, focusing on mortality, in the prospective observational longitudinal registry of patients with stable CAD (CLARIFY; ISRCTN43070564) acknowledging that residual confounding factors from measured or unmeasured variables can persist even after adjustment.

Methods

Design, setting and participants

The present study is a *post hoc* analysis of the CLARIFY registry. The registry design has been previously described.[3] Briefly, 32 703 stable CAD outpatients were enrolled (November 2009–June 2010) in 45 countries and followed annually up to 5 years.

Patients were eligible for enrolment if they fulfilled ≥1 of the following criteria (not mutually exclusive): documented MI >3 months ago; coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) >3 months ago; chest pain with proven myocardial ischaemia; or previous coronary angiography showing ≥1 coronary stenosis >50%. Exclusion criteria were hospitalization for cardiovascular disease within the previous 3 months; planned revascularization; and conditions interfering with life expectancy including severe heart failure. Medical care was at the discretion of each physician. Each year 1% of the sites were randomly selected for on-site audits of 100% of data reporting.

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

Study outcomes

The primary outcome was all-cause mortality. Secondary outcomes were cardiovascular mortality and the composite of cardiovascular mortality/non-fatal MI. Exploratory analyses examined non-cardiovascular mortality, MI (fatal/non-fatal), and stroke (fatal/non-fatal).

Cardiovascular mortality was defined as death following MI or stroke, and other cardiovascular mortality (death ascribed to heart failure, cardiac or vascular procedure/surgery, ruptured aneurysm, pulmonary embolism). Unknown causes of death and death that could not be definitely ascribed to non-cardiovascular mortality were classed as cardiovascular for analyses. Outcomes were not adjudicated, but reported by investigators.

Statistical analyses

β-blocker and calcium antagonist use was assessed at baseline and yearly. Patients with a history of MI were categorized according to the delay since prior MI at the time of enrolment in three subgroups: ≤1 year, 1 to ≤3 years, and >3 years post-MI.

To account for the treatment status (β-blockers or calcium antagonists) of the patient prior to the event, sensitivity analyses were performed using as covariates the last available record of the use of β-blocker or calcium antagonist before an event. To assess the impact of β-blocker daily doses, sensitivity analyses based on ≤half dose, half to ≤full dose, or full target dose were performed. Full doses were defined according to usual clinical therapeutic dose for each β-blocker. For the five most frequently used β-blockers with an indication for post-MI secondary prevention, for LV systolic dysfunction, or for angina relief, full target daily doses were defined as 10 mg for bisoprolol,[22] 200 mg for metoprolol,[23] 100 mg for atenolol,[18] 50 mg for carvedilol,[24] and 10 mg for nebivolol.[25]

Hazard ratios (HRs) associated with β-blocker use vs. non-use and calcium antagonist use vs. non-use, and 95% confidence intervals (CIs) were calculated from Cox proportional hazards models. Hazard ratios were estimated after adjustment for cardiovascular risk factors, medical history of cardiovascular disease, treatments, geographical areas, and pulmonary comorbidities: systolic and diastolic blood pressure, LV ejection fraction, history of revascularization by PCI/CABG, asthma or chronic obstructive pulmonary disease (COPD), and the REACH cardiovascular event risk score.[26] The REACH score (detailed in Supplementary material online, *Table S1*) was used to adjust for sex, age, current smoking, diabetes, body mass index <20 kg/m^2, number of vascular beds involved (cerebrovascular, peripheral, and coronary artery disease), history of recent MI (≤1 year), heart failure or atrial fibrillation, statin or aspirin therapies, and geographical zones. Multivariable analyses were performed in patients who had a complete dataset for all the variables entered in the models, constituting the study cohort. In order to address missing data, especially regarding LV systolic function, a sensitivity analysis considered the same model with LV ejection fraction as a categorical variable (including a missing category).

The sensitivity analysis pertaining to the relation between β-blocker daily dose and outcomes, used an adjustment model based on the REACH risk score.

Data were managed and analysed by the Robertson Centre for Biostatistics (University of Glasgow, UK). All analyses were conducted using R and the survival package.[27]

Results

A total of 32 378 participants were available for analysis. At the end of 4 years 5111 (15.8%) and 5108 (15.8%) were censored respectively in the β-blocker analysis and the calcium antagonist analysis (details in Supplementary material online, *Tables S2* and *S3*). Overall a complete baseline dataset (with follow-up and no missing covariates) was available for 22 006 (68.0%) in the β-blocker use analysis, and for 22 004 (68.0%) for the calcium antagonist analysis. The sensitivity analysis including patients in whom LV ejection fraction was missing involved 31 987 patients (98.8% of the total study population).

Table 1 Baseline characteristics among patients analysed in the multivariable adjusted model according to β-blocker use (*n* = 22 006) or calcium antagonist use (*n* = 22 004)

Variables	β-blockers (*n* = 17 135)	No β-blockers (*n* = 4871)	*P*-value	Calcium antagonists (*n* = 5885)	No calcium antagonists (*n* = 16 119)	*P*-value
REACH cardiovascular event risk score	11.00 (9.00–13.00)	11.00 (9.00–13.00)		11.00 (9.00–13.00)	11.00 (9.00–13.00)	
	11.2 ± 3.1	11.1 ± 3.2	0.49	11.5 ± 3.1	11.0 ± 3.2	
CV risk factors						
Gender male	78.3%	78.0%	0.70	74.0%	79.8%	<0.0001
Age (years)	63.3 ± 10.5	65.5 ± 10.7	<0.0001	65.7 ± 10.0	63.1 ± 10.7	<0.0001
Smoking						
Current	12.3%	11.9%		10.2%	13.0%	
Former	46.5%	46.8%		45.3%	47.0%	
Never	41.2%	41.3%	0.74	44.6%	40.1%	<0.0001
Family history of premature CAD	29.1%	28.3%	0.33	29.2%	28.8%	0.55
Treated hypertension	74.0%	66.1%	<0.0001	87.4%	66.7%	<0.0001
Diabetes	30.4%	26.6%	<0.0001	35.8%	27.3%	<0.0001
Dyslipidaemia	79.0%	78.0%	0.12	82.9%	77.3%	<0.0001
Past medical history						
Myocardial infarction	64.8%	52.5%	<0.0001	52.5%	65.6%	<0.0001
Percutaneous coronary intervention	58.9%	56.8%	0.01	55.6%	59.5%	<0.0001
Peripheral arterial disease	10.3%	13.1%	<0.0001	14.1%	9.8%	<0.0001
Carotid disease	8.9%	9.0%	0.82	12.0%	7.8%	<0.0001
Stroke	3.8%	4.4%	0.06	5.4%	3.4%	<0.0001
Hospitalization for CHF	5.9%	4.6%	0.0006	5.1%	5.8%	0.07
Atrial fibrillation/flutter	7.8%	7.5%	0.53	8.3%	7.5%	0.04
Asthma/COPD	5.0%	5.8%	<0.0001	10.0%	6.4%	<0.0001
Clinical examination						
Systolic blood pressure (mmHg)	131.0 ± 16.8	131.1 ± 15.8	0.61	135.3 ± 16.7	129.5 ± 16.2	<0.0001
Diastolic blood pressure (mmHg)	77.7 ± 10.0	77.2 ± 9.6	0.001	78.4 ± 10.2	77.3 ± 9.8	<0.0001
Resting heart rate (b.p.m.)	67.4 ± 10.3	69.7 ± 11.3	<0.0001	68.4 ± 10.6	67.7 ± 10.6	<0.0001
Current angina	25.0%	21.4%	<0.0001	28.1%	22.8%	<0.0001
Current heart failure symptoms	20.1%	13.0%	<0.0001	18.9%	18.4%	0.43
LVEF measurements						
Mean LVEF %	55.6 ± 11.1	58.0 ± 10.4	<0.0001	57.9 ± 10.1	55.5 ± 11.2	<0.0001
LVEF ≤45%	18.7%	12.8%	<0.0001	12.3%	19.3%	<0.0001
Medications						
Aspirin	89.1%	83.8%	<0.0001	86.7%	88.3%	0.002
Thienopyridine	28.5%	29.5%	0.16	28.6%	28.7%	0.81
Dual antiplatelet therapy	28.9%	27.0%	0.009	26.8%	28.3%	0.03
Statins	85.6%	79.8%	<0.0001	84.1%	84.4%	0.49
Angiotensin-converting enzyme inhibitors	57.2%	42.7%	<0.0001	48.8%	55.9%	<0.0001
Angiotensin II receptor blockers	25.5%	31.5%	<0.0001	35.6%	23.6%	<0.0001
β-blockers	NA	NA	NA	69.6%	80.9%	<0.0001
Calcium antagonists	23.9%	36.7%	<0.0001	NA	NA	NA

Data are % for categorical data, and mean ± standard deviation or median (interquartile range) for continuous data depending on the distribution.
CAD, coronary artery disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; NA, not available.

β-blocker analyses

At baseline, β-blockers were used in 17 135 (77.9%) patients. Among 4871 non-users, 1931 had a prior history of intolerance or contraindication to β-blockers, mainly due to asthma/COPD (*n* = 558), bradycardia (*n* = 555), fatigue (*n* = 551), erectile dysfunction (*n* = 270), and hypotension (*n* = 269). For patients in whom dose was available, 45.1% received less than half of the target dose, 41.6% half to less than full dose, and 13.3% the full target dose. The five most frequently used β-blockers were bisoprolol (35.6%), metoprolol (27.2%), carvedilol (12.6%), atenolol (12.3%), and nebivolol (6.5%).

Table 2 Multivariable adjusted associations according to β-blocker use and calcium antagonist use at baseline

5-Year outcomes	β-blockers (n = 17 135)	No β-blockers (n = 4871)	HR (95% CI)	P-value	Calcium antagonists (n = 5885)	No calcium antagonists (n = 16 119)	HR (95% CI)	P-value
Primary outcome								
All-cause mortality	1345 (7.8%)	407 (8.4%)	0.94 (0.84–1.06)	0.30	493 (8.4%)	1259 (7.8%)	1.02 (0.91–1.13)	0.76
Secondary outcomes								
Cardiovascular mortality	861 (5.0%)	262 (5.4%)	0.91 (0.79–1.05)	0.20	311 (5.3%)	812 (5.0%)	1.01 (0.88–1.16)	0.87
Cardiovascular mortality/non-fatal MI	1272 (7.4%)	340 (7.0%)	1.03 (0.91–1.16)	0.66	457 (7.8%)	1155 (7.2%)	1.05 (0.94–1.17)	0.39
Exploratory analyses								
Non-cardiovascular mortality	484 (2.8%)	145 (3.0%)	1.00 (0.83–1.21)	0.99	182 (3.1%)	447 (2.8%)	1.03 (0.86–1.22)	0.77
MI	587 (3.4%)	140 (2.9%)	1.14 (0.94–1.37)	0.18	214 (3.6%)	513 (3.2%)	1.12 (0.95–1.32)	0.17
Stroke	375 (2.2%)	92 (1.9%)	1.13 (0.89–1.42)	0.32	150 (2.5%)	317 (2.0%)	1.18 (0.96–1.43)	0.11

HRs, CIs, and P-values are derived from comparing β-blocker users/non-users and calcium antagonist users/non-users at baseline in a survival analysis using Cox proportional hazards models with multivariable adjustment for the REACH cardiovascular event score,[26] systolic/diastolic blood pressure, left ventricular ejection fraction, history of percutaneous coronary artery, coronary artery bypass graft, peripheral artery disease, and asthma/chronic obstructive pulmonary disease.
CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

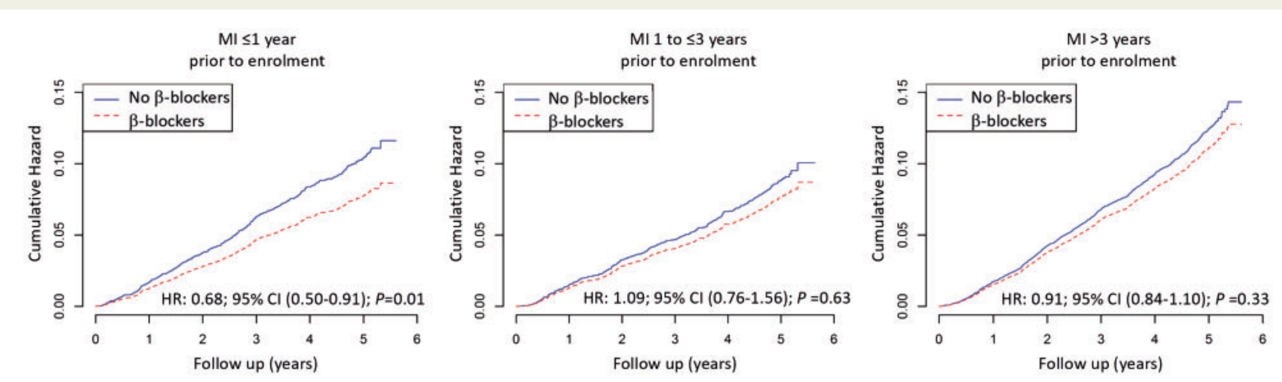


Figure 1 Cumulative hazard of all-cause mortality according to ß-blocker use at baseline, categorized by the time elapsed since the index myocardial infarction prior to enrolment. P-values, hazard ratios, and confidence intervals are derived from comparing β-blocker users to non-users at baseline in a survival analysis from Cox proportional hazards models with multivariable adjustment for the REACH cardiovascular event risk score,[26] systolic/blood pressure, left ventricular ejection fraction, history of coronary revascularization, peripheral artery disease, and asthma/chronic obstructive pulmonary disease. CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

Three quarters of patients were male. Compared with non-users, users were younger, had higher prevalence of cardiovascular risk factors, more frequent history of previous MI or hospitalization for heart failure, and less frequent asthma/COPD. Users had lower resting heart rate, similar blood pressure, and higher prevalence of current heart failure symptoms. Twenty-five percent of users had current angina despite β-blocker therapy. They had lower LV systolic function and received more frequently evidence-based preventive treatments. Despite these differences in baseline characteristics, the REACH cardiovascular risk score was similar between groups (*Table 1*). Baseline characteristics of all enrolled patients with data pertaining to β-blocker use gave similar results (Supplementary material online, *Table S4*).

Overall, the rate of death was 1.80 per 100 patient years. Event rates are detailed in Supplementary material online,*Table S5*. For the primary and secondary outcomes, multivariable adjusted HRs showed no association between β-blocker use at baseline and outcomes. The HR for all-cause mortality was 0.94 (95% CI 0.84–1.06) (*Take home figure*, *Table 2*). Hazard ratios for cardiovascular mortality and the composite of cardiovascular mortality/non-fatal MI were 0.91 (95% CI 0.79–1.05) and 1.03 (95% CI 0.91–1.16), respectively. Regarding exploratory analyses, there were no associations between β-blockers and outcomes (*Table 2*).

Among patients with MI ≤1 year prior to enrolment, β-blocker use was associated with a lower risk of all-cause mortality [205 (7.0%) for users vs. 59 (10.3%) for non-users, HR 0.68, 95% CI 0.50–0.91; $P = 0.01$], lower cardiovascular mortality [132 (4.5%) for users vs. 49 (8.5%) for non-users, HR 0.52, 95% CI 0.37–0.73; $P = 0.0001$], and lower cardiovascular mortality/non-fatal MI [212 (7.2%) for users vs. 59 (10.3%) for non-users, HR 0.69, 95% CI 0.52–0.93; $P = 0.01$].

Table 3 **Multivariable adjusted associations according to β-blocker use at baseline categorized by the time elapsed since the index MI prior to enrolment**

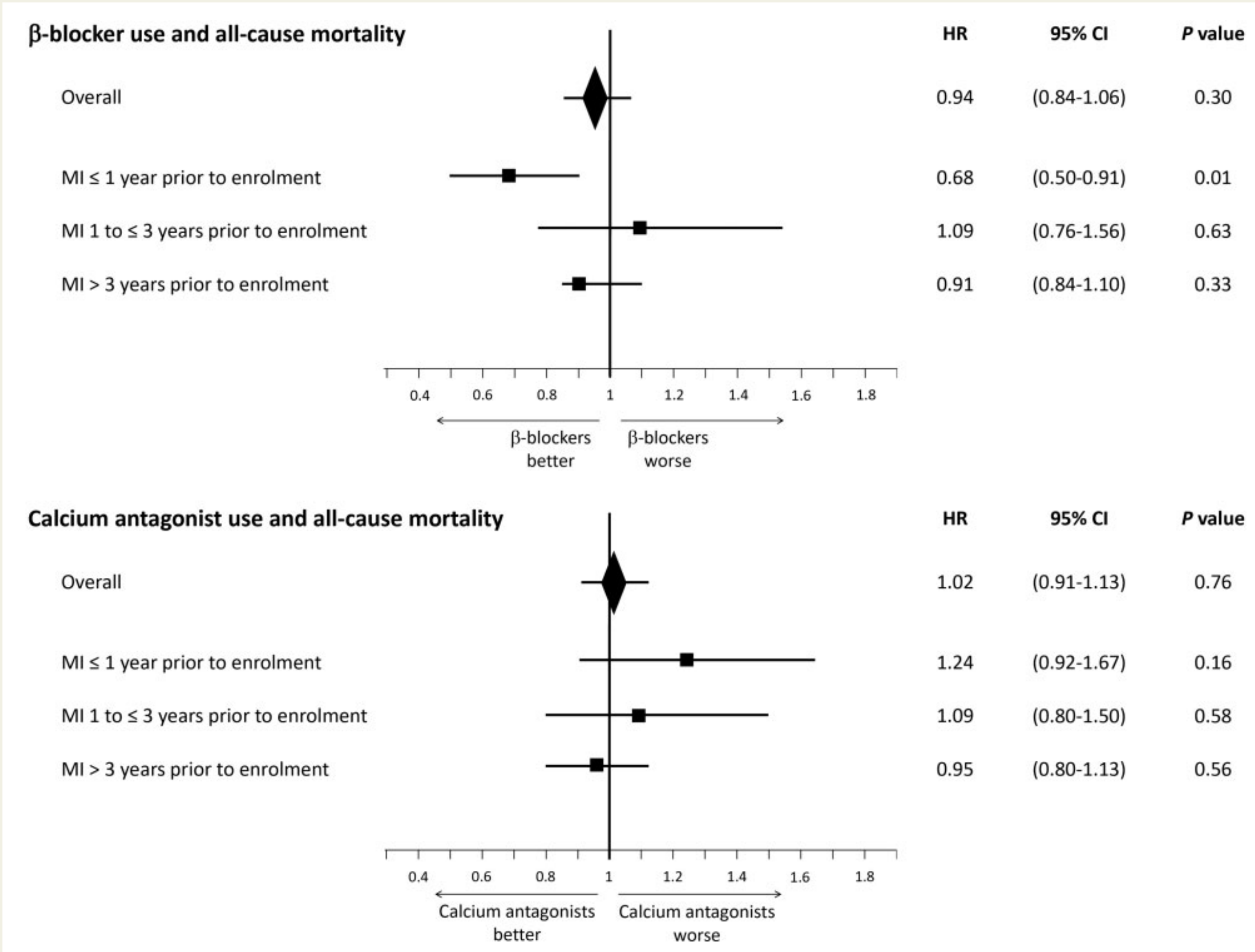
5-Year outcomes	MI ≤1 year (n = 3506)				1 year < MI ≤ 3 years (n = 2932)				MI >3 years (n = 7222)			
	β-blockers (n = 2931)	No β-blockers (n = 575)	HR (95% CI)	P-value	β-blockers (n = 2426)	No β-blockers (n = 506)	HR (95% CI)	P-value	β-blockers (n = 5746)	No β-blockers (n = 1476)	HR (95% CI)	P-value
Primary outcome												
All-cause mortality	205 (7.0%)	59 (10.3%)	0.68 (0.50–0.91)	0.01	177 (7.3%)	40 (7.9%)	1.09 (0.76–1.56)	0.63	551 (9.6%)	158 (10.7%)	0.91 (0.84–1.10)	0.33
Secondary outcomes												
Cardiovascular mortality	132 (4.5%)	49 (8.5%)	0.52 (0.37–0.73)	0.0001	111 (4.6%)	28 (5.5%)	0.99 (0.64–1.53)	0.96	366 (6.4%)	104 (7.0%)	0.90 (0.72–1.13)	0.37
Cardiovascular mortality/non-fatal MI	212 (7.2%)	59 (10.3%)	0.69 (0.52–0.93)	0.01	173 (7.1%)	37 (7.3%)	1.05 (0.73–1.52)	0.78	513 (8.9%)	132 (8.9%)	1.00 (0.82–1.21)	0.97
Exploratory analyses												
Non-CV mortality	73 (2.5%)	10 (1.7%)	1.42 (0.73–2.77)	0.31	66 (2.7%)	12 (2.4%)	1.32 (0.70–2.51)	0.39	185 (3.2%)	54 (3.7%)	0.94 (0.69–1.28)	0.69
MI	122 (4.2%)	27 (4.7%)	0.85 (0.56–1.31)	0.47	88 (3.6%)	15 (3.0%)	1.25 (0.71–2.18)	0.44	222 (3.9%)	51 (3.5%)	1.10 (0.81–1.50)	0.54
Stroke	60 (2.0%)	8 (1.4%)	1.45 (0.69–3.06)	0.33	49 (2.0%)	11 (2.2%)	1.04 (0.52–2.06)	0.91	150 (2.6%)	40 (2.7%)	0.98 (0.69–1.40)	0.92

HRs, CIs, and *P*-values are derived from comparing β-blocker users to non-users at baseline, with categorization by the time elapsed since MI prior to enrolment, in a survival analysis using Cox proportional hazards models with multivariable adjustment for the REACH cardiovascular event score,[26] systolic/diastolic blood pressure, left ventricular ejection fraction, history of percutaneous coronary artery, coronary artery bypass graft, peripheral artery disease, and asthma/chronic obstructive pulmonary disease.
CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

Table 4 Multivariable adjusted associations according to calcium antagonists use at baseline categorized by the time elapsed since the index MI prior to enrolment

5-Year outcomes	MI ≤1 year ($n = 3506$)				1 year < MI ≤ 3 years ($n = 2931$)				MI >3 years ($n = 7222$)			
	Calcium antagonists ($n = 594$)	No calcium antagonists ($n = 2912$)	HR (95% CI)	*P*-value	Calcium antagonists ($n = 617$)	No calcium antagonists ($n = 2314$)	HR (95% CI)	*P*-value	Calcium antagonists ($n = 1880$)	No calcium antagonists ($n = 5342$)	HR (95% CI)	*P*-value
Primary outcome												
All-cause mortality	58 (9.8%)	206 (7.1%)	1.24 (0.92–1.67)	0.16	53 (8.6%)	164 (7.1%)	1.09 (0.80–1.50)	0.58	183 (9.7%)	526 (9.8%)	0.95 (0.80–1.13)	0.56
Secondary outcomes												
Cardiovascular mortality	36 (6.1%)	145 (5.0%)	1.12 (0.77–1.63)	0.55	34 (5.5%)	105 (4.5%)	1.09 (0.73–1.62)	0.68	121 (6.4%)	349 (6.5%)	0.97 (0.78–1.19)	0.74
Cardiovascular mortality/non-fatal MI	52 (8.8%)	219 (7.5%)	1.05 (0.77–1.44)	0.74	50 (8.1%)	160 (6.9%)	1.05 (0.76–1.45)	0.77	176 (9.4%)	469 (8.8%)	1.05 (0.88–1.26)	0.58
Exploratory analyses												
Non-cardiovascular mortality	22 (3.7%)	61 (2.1%)	1.46 (0.88–2.40)	0.14	19 (3.1%)	59 (2.5%)	1.10 (0.65–1.87)	0.72	62 (3.3%)	177 (3.3%)	0.93 (0.69–1.25)	0.58
MI	27 (4.5%)	122 (4.2%)	0.97 (0.63–1.49)	0.89	23 (3.7%)	80 (3.5%)	0.95 (0.59–1.53)	0.84	83 (4.4%)	190 (3.6%)	1.24 (0.96–1.62)	0.10
Stroke	16 (2.7%)	52 (1.8%)	1.38 (0.78–2.45)	0.27	16 (2.6%)	44 (1.9%)	1.19 (0.66–2.13)	0.57	55 (2.9%)	135 (2.5%)	1.00 (0.73–1.38)	0.98

HRs, CIs, and *P*-values are derived from comparing calcium antagonist users to non-users at baseline, with categorization by the time elapsed since MI prior to enrolment in a survival analysis using Cox proportional hazards models with multivariable adjustment for the REACH cardiovascular event score,[26] systolic/diastolic blood pressure, left ventricular ejection fraction, history of percutaneous coronary artery, coronary artery bypass graft, peripheral artery disease, and asthma/chronic obstructive pulmonary disease.
CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.



Take home figure Multivariable adjusted associations with all-cause mortality according to β-blocker use and calcium antagonist use at baseline, overall and after categorization by time since myocardial infarction prior to enrolment. *P*-values, hazard ratios, and confidence intervals are derived from comparing β-blocker users to non-users and calcium antagonist users to non-users at baseline in a survival analysis from Cox proportional hazards models with multivariable adjustment for the REACH cardiovascular event risk score,[26] systolic/blood pressure, left ventricular ejection fraction, history of coronary revascularization, peripheral artery disease, and asthma/chronic obstructive pulmonary disease. CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

In patients with prior MI >1 year, there was no difference in outcomes between groups (*Figure 1*, *Take home figure*, and *Table 3*).

In patients with no history of PCI, β-blocker use at baseline was associated with lower cardiovascular death [427 (6.1%) for users vs. 155 (7.4%) for non-users and HR 0.81, 95% CI 0.67–0.98; $P = 0.03$] (Supplementary material online, *Table S6*). There was no association between β-blocker use and mortality after categorization by presence of angina (Supplementary material online, *Table S7*). Sensitivity analyses according to the last assessment of β-blocker use prior to an event showed consistent results with no difference in risk for all outcomes except for an association with stroke (HR 1.39, 95% CI 1.10–1.74; $P = 0.005$) (Supplementary material online, *Table S8*).

Sensitivity analyses pertaining to β-blocker doses showed consistent results (Supplementary material online,*Table S9*).

When considering LV ejection fraction as a categorical variable and including a missing category, analyses performed among 31 987 patients showed consistent results. β-blocker use ($n = 24$ 119) compared with non-use ($n = 7868$) was not associated with lower all-cause death [1856 (7.7%) and 666 (8.5%), respectively with a HR 0.96, 95% CI 0.87–1.05; $P = 0.33$] or lower cardiovascular death [1184 (4.9%) and 419 (5.3%), respectively with HR 0.95, 95% CI 0.85–1.07; $P = 0.43$] (Supplementary material online, *Table S10*).

Calcium antagonist analyses

At baseline, calcium antagonists were used in 5885 (26.7%) patients. Among users, 4697 (79.8%) were receiving long-acting dihydropyridines, 864 (14.7%) diltiazem and 286 (4.9%) verapamil.

Users included more females, were older, with higher prevalence of cardiovascular risk factors, more frequent history of peripheral artery disease, carotid disease, stroke or asthma/COPD, and less frequent history of prior MI or hospitalization for heart failure. Users had higher resting heart rate and blood pressure. They had higher prevalence of current anginal symptoms, despite calcium antagonist therapy, and higher LV ejection fraction. Users had less antiplatelet therapy, more angiotensin II receptor blockers. Despite these differences, the REACH cardiovascular risk score was similar between groups (*Table 1*). Baseline characteristics of all enrolled patients with data pertaining to calcium antagonist use found similar results (Supplementary material online, *Table S4*).

Overall the rate of death was 1.80 per 100 patient years. Event rates are detailed in Supplementary material online, *Table S11*. Multivariable adjusted HRs for the primary and secondary outcomes, as well as exploratory analyses showed no association between calcium antagonist use at baseline and any outcome (*Take home figure*, *Table 2*).

There was no association between calcium antagonist use and mortality, regardless of the history of PCI or presence of angina (Supplementary material online, *Tables S12 and S13*). In patients with MI in the year preceding enrolment, there was no association between calcium antagonist use and mortality (*Take home figure*, *Table 4*).

Sensitivity analyses considering the last assessment of calcium antagonist use prior to an event gave consistent results (Supplementary material online, *Table S8*).

When considering LV ejection fraction as a categorical variable and including a missing category, analyses performed among 31 984 patients showed consistent results. Calcium antagonist use ($n = 8735$) compared with non-use ($n = 23\,249$) was not associated with lower all-cause death [722 (8.3%) and 1800 (7.7%), respectively with HR 0.97, 95% CI 0.89–1.06; $P = 0.56$] or lower cardiovascular death [456 (5.2%) and 1147 (4.9%), respectively with HR 0.98, 95% CI 0.87–1.09; $P = 0.67$] (Supplementary material online, *Table S10*).

Discussion

In this large international study of contemporary stable CAD with a high rate use of evidence-based secondary prevention therapies, β-blocker use at baseline was associated with lower 5-year all-cause mortality only in patients enrolled in the year following MI.

Results were consistent when considering change of β-blocker use before an event and doses of β-blockers. The use of calcium antagonists was not associated with any differences in outcome. β-blocker use appeared associated with lower cardiovascular mortality in patients with no history of PCI.

No RCT has shown a benefit of β-blockers compared with placebo on hard clinical outcomes in stable CAD without LV systolic dysfunction. Evidence of these agents improving outcome is derived from old trials in acute MI, mostly performed before the advent of secondary prevention and reperfusion therapies; the benefit of β-blockers was mainly driven by their use in the acute phase of MI.[10]

Observational studies and *post hoc* RCT analyses have questioned the benefit from β-blockers on mortality, notwithstanding limitations in these studies relating to sample size, geographical scope, or selected patient profile. FAST-MI[12] found no association between β-blocker cessation 1 year after MI and all-cause mortality. A French reimbursement database study[14] showed no impact on mortality of stopping β-blockers beyond 1 year after MI without heart failure. The Kaiser Permanente study[13] showed evidence of lower risk of death with β-blocker use in patients enrolled in the acute phase after MI. The REACH[11] registry found no association between β-blocker use and mortality in stable CAD outpatients but suggested benefit in patients with recent prior MI (<1 year); however, LV function and β-blocker type or dose were unknown. The present results are consistent with a *post hoc* analysis of the CHARISMA trial[15] showing no association between β-blocker use and lower mortality in a selected trial population of stable patients with or without prior MI. However, outcomes may differ between the selected patient populations enrolled in clinical trials and patients enrolled using similar criteria in population based observational studies.[28,29]

In the assessment of calcium antagonists in stable CAD (Supplementary material online, *Table S14*), the ACTION[16] trial failed to demonstrate improved mortality compared with placebo. TIBET[18] and APSIS[19] trials did not show any improvement in mortality when compared with β-blockers. Other RCTs performed in hypertensive CAD patients failed to demonstrate an improvement in mortality with calcium antagonists compared with placebo[17] or compared with β-blocker.[20] A meta-analysis[21] did not find lower mortality. There are no robust observational studies from which we can draw conclusions.

While RCTs are the gold standard to test the efficacy of medical therapies,[30] observational studies may be useful when evaluating the impact of long-term use of drugs in broad patient populations.[28]

There are several strengths to the current analyses. CLARIFY was a large international study encompassing various profiles within stable CAD (e.g. with or without prior MI or prior revascularization and with or without angina or ischaemia) and capturing LV function, uses of treatments over time, doses of β-blockers, and also detailed information regarding contraindications or intolerance to β-blockers. Multivariable adjustment used the REACH risk score as it correlates well with outcomes.[26] Finally, the most robust outcome, all-cause mortality, was the main outcome of the present analysis, and the results were consistent when accounting for β-blocker or calcium antagonist status over time, dose, after categorization by presence of angina or history of PCI or when including patients with missing LV ejection fraction in the adjustment model.

These findings about β-blockers as well as those from previous studies are contrary to the preconceived notion that they are beneficial for all CAD patients. β-blockers demonstrated their benefit in term of clinical outcomes in settings where there was sympathetic neuro-hormonal activation (LV systolic dysfunction, congestive heart failure, and acute MI). The absence of benefit in stable CAD without LV dysfunction or stabilized CAD remote from MI may be explained by the lack of sympathetic activation. Regarding calcium antagonists and mortality in a contemporary cohort, our findings are consistent with the results from available RCTs.[16]

Limitations

There are several limitations to this analysis. Analyses were not formally prespecified before data collection and the methods of analysis were not prospectively defined. Patients with severe heart failure or life-threatening arrhythmias as a complication to recent MI and in whom the benefit of β-blockers is clear were excluded. Outcomes were not adjudicated. However, the results were consistent for non-adjudicated outcomes and for all-cause mortality. Observational studies have inherent limitations: residual confounding from measured or unmeasured variables cannot be excluded (related to both contraindication and indication bias) and could contribute to the observed differences in mortality between groups. In addition, enrolment and follow-up did not start at the time of treatment initiation or at the time of diagnosis, which can cause bias. A third of patients without β-blocker at baseline were nor treated because of prior symptoms of intolerance or contraindication, which may reflect imbalance in baseline risk between groups related in particular to comorbidities such as asthma or COPD. It is noteworthy, however, that the REACH score at baseline was nearly identical between β-blocker users and non-users.

Conclusions

In this large contemporary cohort of stable CAD after multivariable adjustment including LV ejection fraction, β-blockers were not associated with lower all-cause mortality or improved outcomes, except in patients enrolled in the year following an MI. The use of calcium antagonists was not associated with superior outcomes, regardless of a prior history of MI.

Considering previous studies and this present analysis, β-blockers should be preferentially used in the first year following MI. Beyond 1 year following MI or in stable CAD patients without prior MI, both β-blockers and calcium antagonists may be used for symptom relief but a mortality benefit should not be assumed. A large adequately powered RCT would be required to settle the issue of whether first line anti-ischaemic agents impact prognosis and outcomes in patients with stable CAD. However, it is uncertain whether it would be feasible to mobilize the resources and patient numbers to adequately address this question.

Supplementary material

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

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