Relationship between angina pectoris and outcomes in patients with heart failure and reduced ejection fraction: an analysis of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)

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Aim
Angina pectoris is common in patients with heart failure and reduced ejection fraction (HF-REF) but its relationship with outcomes has not been well defined. This relationship was investigated further in a retrospective analysis of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA).

Methods and results
Four thousand, eight hundred and seventy-eight patients were divided into three categories: no history of angina and no chest pain at baseline (Group A; n = 1240), past history of angina but no chest pain at baseline (Group B; n = 1353) and both a history of angina and chest pain at baseline (Group C; n = 2285). Outcomes were examined using Kaplan–Meier and Cox regression survival analysis. Compared with Group A, Group C had a higher risk of non-fatal myocardial infarction or unstable angina (HR: 2.36, 1.54–3.61; P < 0.001), this composite plus coronary revascularization (HR: 2.54, 1.76–3.68; P < 0.001), as well as HF hospitalization (HR: 1.35, 1.13–1.63; P = 0.001), over a median follow-up period of 33 months. There was no difference in cardiovascular or all-cause mortality. Group B had a smaller increase in risk of coronary events but not of heart failure hospitalization.

Conclusion
Patients with HF-REF and ongoing angina are at an increased risk of acute coronary syndrome and HF hospitalization. Whether these patients would benefit from more aggressive medical therapy or percutaneous revascularization is not known and merits further investigation.

Keywords
Angina pectoris • Heart failure • Reduced ejection fraction

Introduction
Although the cause of chronic heart failure (HF) with reduced ejection fraction (HF-REF) is attributed to coronary artery disease (CAD) in approximately two-thirds of patients in the developed world, little is known about symptomatic myocardial ischaemia in these individuals.1,2 While many trials have reported past history of myocardial infarction (MI), revascularization, and angina pectoris at
baseline, few described whether patients had current angina symptoms at the time of randomization. One exception was CHARM where 65% of patients with HF-REF had an investigator-reported ischaemic aetiology, 49% a past history of angina but only 21% current angina. In COMET, the overall prevalence of ischaemic heart disease was 53% and current angina was reported in 22% of patients.3,4 Similarly, previous reports on the relationship between CAD and prognosis in HF-REF have focused on ischaemic aetiology or history of ischaemic heart disease without distinguishing between patients with current symptoms and those without, with one exception.5 The presence of angina pectoris may indicate an area of viable myocardium susceptible to infarction thereby placing a patient with an already low left ventricular ejection fraction (LVEF) at risk of further reduction in systolic function, worsening HF and death from pump failure. Myocardial ischaemia without infarction might have similar adverse consequences. Likewise, infarction (and ischaemia) may lead to ventricular arrhythmias and the risk of sudden death in such vulnerable patients. Accordingly, in this post hoc analysis we have examined the relationship between current angina symptoms and outcomes in patients enrolled in CORONA, all of which had an ischaemic aetiology.6

Methods

Local ethics committees from participating sites approved the trial and all patients provided informed consent. A total of 5011 patients aged ≥ 60 years with symptomatic [New York Heart Association (NYHA) class II–IV], systolic (LVEF ≤40%, but ≤ 35% if NYHA class II) HF of ischaemic aetiology were enrolled. Patients were randomized to receive 10 mg of rosvastatin or matching placebo daily. The median follow-up was 32.8 months and rosvastatin did not reduce the risk of the primary composite outcome of death from cardiovascular (CV) causes, non-fatal MI, or non-fatal stroke.6,7 Investigators recorded a history of ‘past or current angina’ in the case report form at the time of enrolment using a checkbox system. Chest pain ‘during the past few days’ was also recorded and measured using a five-point exertion scale (0 no pain, 1 pain on heavy exertion, 2 on moderate exertion, 3 on slight exertion, and 4 on rest). While not specifically validated for this purpose, in our analysis, current chest pain was considered to reflect ongoing angina. Patients were classified into three mutually exclusive groups: those with no history of angina and no current chest pain at baseline (Group A), those with a past history of angina but no current chest pain at baseline (Group B) and those with a history of angina and current chest pain at baseline (Group C). Patients without a history of ‘past or current angina’ but who described chest pain at baseline, were excluded from this analysis (n = 133, 2.7%).

Clinical outcomes

The outcomes analysed included the pre-defined secondary ‘coronary event’ endpoint in CORONA—the composite of sudden death, fatal or non-fatal MI, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), ventricular defibrillation by implantable cardioverter deﬁbrillator (ICD), resuscitation after cardiac arrest or hospitalization for unstable angina (UA). We also examined the more restricted composite of non-fatal MI, UA, PCI, or CABG so as to exclude sudden death and ventricular defibrillation by an ICD which may not, in many cases, reflect myocardial ischaemia or infarction. In addition, we analysed the composite of only non-fatal MI and UA as coronary revascularization may reflect physician preference and practice as much as disease activity. We also examined the composite of CV death or HF hospitalization, as the most commonly used measure of HF-related mortality and morbidity, and all-cause mortality.

Statistical analysis

Baseline characteristics for each group were presented as means and standard deviations for continuous variables (or medians for data not normally distributed) and percentages for categorical variables. One-way analysis of variance was used to compare continuous variables across groups and the χ2 test was used for categorical variables.

The relationship between history of ‘past or current angina’, with or without chest pain, at baseline and the endpoints described above was evaluated using Cox proportional-hazard models time-to-first event regression analyses, i.e. outcomes in Groups A and B were compared, as were those in Groups A and C. Both unadjusted analyses and adjusted analyses were carried out. The adjusted analyses used a previously published CORONA risk-model; the prognostically significant variables in that model were: age, sex, NYHA class, LVEF, body mass index (BMI), systolic blood pressure, heart rate, smoking, MI, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter (AF/F), stroke, intermittent claudication, pacemaker and ICD implantations, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, and log NT-proBNP.8 Data on these predictor variables were missing in 1% or less of patients except for history of CABG (9%) and NT proBNP (27%); patients with missing variables were omitted from analyses. Adjustment was also made for differences in baseline medications, namely loop or thiazide diuretics, aldosterone antagonists, ACE inhibitors, or angiotensin receptor blockers (ARBs), beta-blockers, digitalis glycoside, anti-arrhythmic therapy, antiplatelet or anticoagulant drugs, as well as for randomization to rosuvastatin or placebo. Linearity was assessed visually by plotting the data graphically and more formally by performing a Wald test. Proportionality assumptions were verified using the Schoenfeld residuals method. Kaplan–Meier cumulative event curves were presented by symptom category for fatal outcomes and composites with fatal and non-fatal components. The cumulative incidence function was used to analyse non-fatal outcomes to account for the competing risk of death. Finally, we examined the association between chest pain and outcomes with chest pain entered as a time-updated covariate in a Cox model. We adjusted for a history of angina and then all of the covariates noted above. A Bonferroni correction was used to correct for the multiple comparisons in relation to the coronary outcomes. A two-tailed P-value of <0.05 was considered statistically significant.

Results

There were 1240 patients (25.4%) in Group A (no history of angina and no chest pain at baseline), 1353 (27.7%) in Group B (history of angina but no chest pain), and 2285 (46.8%) in Group C (history of angina and chest pain at baseline). In Group C, 27% of patients described chest pain on heavy exertion, 49% on moderate exertion, 20% on slight exertion, and 4% at rest.

Baseline characteristics

Baseline characteristics stratified by groups are presented in Table 1.
### Table 1  
Baseline characteristics of patients stratified by history of angina pectoris and current chest pain at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 4878)</td>
<td>No (n = 1240)</td>
<td>Yes (n = 1353)</td>
<td>Yes (n = 2285)</td>
<td>A vs. B</td>
</tr>
<tr>
<td>Age, years</td>
<td>72.7 ± 7.1</td>
<td>72.6 ± 7.1</td>
<td>73.1 ± 7.2</td>
<td>72.6 ± 7.0</td>
<td>0.061</td>
</tr>
<tr>
<td>Age ≥70 year (%)</td>
<td>3190 (65.4)</td>
<td>799 (44.4)</td>
<td>911 (67.3)</td>
<td>1480 (64.8)</td>
<td>0.120</td>
</tr>
<tr>
<td>Female (%)</td>
<td>1148 (23.5)</td>
<td>252 (20.3)</td>
<td>275 (20.3)</td>
<td>621 (27.2)</td>
<td>0.999</td>
</tr>
<tr>
<td>NYHA III/IV (%)</td>
<td>3069 (62.9)</td>
<td>666 (53.7)</td>
<td>784 (58.0)</td>
<td>1619 (70.9)</td>
<td>0.030</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>30.9 ± 6.5</td>
<td>30.1 ± 6.7</td>
<td>29.9 ± 6.5</td>
<td>31.8 ± 6.1</td>
<td>0.646</td>
</tr>
<tr>
<td>Systolic BP, mm/Hg</td>
<td>129.3 ± 16.5</td>
<td>128.9 ± 17.1</td>
<td>128.3 ± 17.0</td>
<td>130.1 ± 15.8</td>
<td>0.310</td>
</tr>
<tr>
<td>Heart rate, b.p.m.</td>
<td>71.7 ± 11.2</td>
<td>71.9 ± 11.5</td>
<td>71.5 ± 11.5</td>
<td>71.6 ± 10.9</td>
<td>0.382</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>27.2 ± 4.5</td>
<td>26.9 ± 4.6</td>
<td>27.0 ± 4.5</td>
<td>27.5 ± 4.5</td>
<td>0.578</td>
</tr>
<tr>
<td>BMI &gt;median (26.7 kg/m²) (%)</td>
<td>2467 (50.6)</td>
<td>584 (47.1)</td>
<td>673 (49.7)</td>
<td>1210 (53.0)</td>
<td>0.148</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>422 (8.7)</td>
<td>125 (10.1)</td>
<td>133 (9.8)</td>
<td>164 (7.2)</td>
<td>0.836</td>
</tr>
</tbody>
</table>

**Comparison of Groups A and B**

When patients with no history of angina or chest pain were compared with those with a history of angina and no chest pain, the main differences were in previous MI (Group A 49% vs. Group B 70%, respectively), CABG (8 vs. 32%) and PCI (9 vs. 17%). Other characteristics including age, sex, and LVEF were similar although more patients in Group A had a history of atrial fibrillation/flutter (28 vs. 22%).

**Comparison of Groups A and C**

More differences were noted when patients with no history of angina or chest pain were compared with those with a history of angina and chest pain. These included differences in proportion of women (Group A 20% vs. Group C 27%), proportion in NYHA class III/IV (54 vs. 71%), current smoking (10 vs. 7%); history of MI/CABG/PCI (49/8/9 vs. 60/17/10%), hypertension (57 vs. 71%), and baseline...
atrial fibrillation/flutter (28 vs. 22%). Patients in Group A also had a slightly but significantly lower LVEF (30 vs. 32%) and BMI (27 vs. 28 kg/m²) than those in Group C, as well as a higher serum creatinine (117 vs. 113 μmol/L) and baseline NT-proBNP (193 vs. 151 pmol/L).

Comparison of Groups B and C
The most notable differences between patients with a history of angina and no chest pain and those with a history of angina and chest pain were in proportion of women (20 vs. 27%), proportion in NYHA functional class III/IV (58 vs. 71%), LVEF (30 vs. 32%), history of MI/CABG/PCI (70/32/17 vs. 60/17/10%), hypertension (57 vs. 71%), serum creatinine (118 vs. 113 μmol/L), and NT-proBNP (187 vs. 151 pmol/L).

In addition to the above findings, patients in Group C had the lowest use of anti-arrhythmic and anti-coagulant drugs and the lowest rate of smoking; they had the highest prevalence of diabetes, the highest use of nitrates and highest systolic BP and LVEF.

Patients in Group A had the lowest use of beta-blockers and anti-platelet agents, highest prevalence of atrial fibrillation/flutter, highest use of digitalis glycosides, anti-arrhythmic drugs, and anti-coagulants, and highest NT-proBNP.

Clinical outcomes

Coronary outcomes
The rate of all three coronary composite outcomes was higher in patients with a history of angina and chest pain at baseline (Group C), compared with patients with neither a history of angina nor chest pain (Group A), as shown in Table 2 and Figure 1. However, only the risk of the composites of MI or UA and MI, UA or coronary revascularization were increased significantly, with an approximate doubling of each in the unadjusted analyses for patients in Group C vs. A. This increase in risk persisted after adjustment for other prognostic variables. Patients in Group B had rates of these two outcomes intermediate between those in Group A and C, with a 50–90% increase in risk compared with Group A.

Heart failure outcomes
The risk of the composite of CV death or HF hospitalization was increased in Group C, but not in Group B, when compared with Group A (Table 2 and Figure 2). Examination of the components of this composite also showed no increase in risk of CV death in Groups B and C. However, patients with a history of angina and chest pain at baseline (Group C), had a modestly increased risk of HF hospitalization in the adjusted analyses [HR 1.35 (1.13–1.63); P = 0.001)], compared with patients with neither a history of angina or chest pain (Group A). A similar trend was seen when Group B was compared with Group A but the increase in risk was not statistically significant (Table 2 and Figure 2).

All-cause mortality
There was no difference in the risk of death between the three groups of patients (Table 2 and Figure 2).

Similar findings were also obtained when the relationship between current chest pain, irrespective of history of angina, and outcomes was analysed (Supplementary material online, appendix). Finally, analysis of the association between chest pain and outcomes with chest pain entered as a time-updated covariate in a Cox model also gave similar outcomes (Supplementary material online, appendix).

Discussion

In the ~5000 patients with HF-REF of ischaemic aetiology in CORONA, we found that 47% had current chest pain, presumed to be angina. This proportion is consistent with the few prior reports of ongoing angina in other studies, assuming that most or all of patients with angina (20–25% of patients overall) in those studies were among the patients with an ischaemic aetiology (50–70% of patients).

There were some notable differences between patients with chest pain at baseline and those without. In the former (Group C), 71% of patients were in NYHA functional class III or IV, compared with 58% of those in Group B (no current chest pain but history of angina) and 54% of patients in Group A (neither current chest pain nor history of angina). This worse functional status probably reflected myocardial ischaemia rather than severity of HF per se. Patients in Group C had the highest LVEF and blood pressure and lowest creatinine and NT-proBNP, in keeping with better overall haemodynamic status, despite their worse functional status. This finding highlights the potential of anti-ischaemic treatment to improve functional status in these patients.

Comparing the two groups of patients with a history of angina (Groups B and C), those without current chest pain (Group B) were more likely to have previously experienced an MI and much more likely to have undergone CABG (especially) or PCI. Lack of chest pain may therefore reflect the absence of viable ischaemic myocardium (because of infarction) or effective revascularization and suggests that this group was probably a heterogeneous mixture of patients.

Patients with current chest pain (Group C) were more than twice as likely to experience an acute coronary syndrome (ACS), or an ACS plus revascularization, as patients without a history of angina and without current chest pain (Group A). Patients with a history of angina but without current chest pain (Group B) were also more likely than those in Group A to experience an ACS but their risk was not as high as that of patients in Group C. This finding suggests that anti-ischaemic/anti-infarction treatment has the potential to reduce coronary events, as discussed below.

The risk of the expanded ‘coronary’ composite, including sudden-death, defibrillation by an ICD and resuscitated cardiac arrest was not increased as much as the risk of an ACS (or an acute ACS plus revascularization) in patients in Group C, compared with those in Group A (and not increased at all in Group B), suggesting that many or even most arrhythmic events in HF are not related to active ischaemia but rather to myocardial scars.

Similarly, the risk of death from any cause (and CV causes) was not increased in patients with chest pain (or in those with a history of angina but no chest pain), compared with patients with neither of these. This observation appears puzzling as it implies that the increased risk of ACS in patients in Group C did not lead to an increased risk of death due to pump failure or arrhythmia, as might be expected. However, even in patients with ischaemic HF and ongoing chest pain, MI and UA are relatively infrequent events. In our study, a first event of this type occurred in only ~10% of patients,
Table 2  Association between history of angina, recent chest pain and clinical outcomes

<table>
<thead>
<tr>
<th>Angina/chest pain</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Unadjusted</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Unadjusted</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of angina</td>
<td>History of angina</td>
<td>History of angina</td>
<td>History of angina</td>
<td>History of angina</td>
<td>History of angina</td>
<td>History of angina</td>
<td>History of angina</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>(n = 1240)</td>
<td>(n = 1353)</td>
<td>(n = 2285)</td>
<td>n (%)</td>
<td>HR (95% CI)</td>
<td>P-value</td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Current chest pain</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Unadjusted</td>
<td>Adjusted&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>(n = 1240)</td>
<td>(n = 1353)</td>
<td>(n = 2285)</td>
<td>n (%)</td>
<td>HR (95% CI)</td>
<td>P-value</td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.10 (0.92, 1.30)</td>
<td>1.13 (0.90, 1.43)</td>
<td>1.32 (1.14, 1.54)</td>
<td>0.287</td>
<td>0.920</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>1.48 (1.20, 1.81)</td>
<td>2.04 (0.82, 1.15)</td>
<td>0.713</td>
<td></td>
</tr>
</tbody>
</table>

Coronary outcomes

- Any coronary event composite<sup>b</sup>
  - Group A: 241 (19.4)
  - Group B: 289 (21.4)
  - Group C: 580 (25.4)
  - HR (95% CI): 1.10 (0.92, 1.30)
  - P-value: 0.287
  - Adjusted<sup>a</sup> HR (95% CI): 1.32 (1.14, 1.54)
  - P-value: 0.001

- Non-fatal MI, UA, PCI or CABG
  - Group A: 72 (5.8)
  - Group B: 115 (8.5)
  - Group C: 292 (12.8)
  - HR (95% CI): 1.46 (1.09, 1.96)
  - P-value: 0.011
  - Adjusted<sup>a</sup> HR (95% CI): 2.23 (1.72, 2.89)
  - P-value: < 0.001

Heart failure outcomes

- CV death or HF hospitalization
  - Group A: 468 (37.7)
  - Group B: 529 (39.1)
  - Group C: 902 (39.5)
  - HR (95% CI): 1.02 (0.90, 1.16)
  - P-value: 0.703
  - Adjusted<sup>a</sup> HR (95% CI): 1.04 (0.93, 1.17)
  - P-value: 0.458

- CV death
  - Group A: 295 (23.8)
  - Group B: 332 (24.5)
  - Group C: 514 (22.5)
  - HR (95% CI): 1.02 (0.87, 1.19)
  - P-value: 0.839
  - Adjusted<sup>a</sup> HR (95% CI): 0.92 (0.80, 1.06)
  - P-value: 0.269

- HF hospitalization
  - Group A: 293 (23.6)
  - Group B: 341 (25.2)
  - Group C: 621 (27.2)
  - HR (95% CI): 1.06 (0.90, 1.24)
  - P-value: 0.482
  - Adjusted<sup>a</sup> HR (95% CI): 1.15 (1.00, 1.32)
  - P-value: 0.050

All-cause death

- Group A: 379 (30.6)
  - Group B: 435 (33.2)
  - Group C: 634 (27.8)
  - HR (95% CI): 1.04 (0.90, 1.19)
  - P-value: 0.661
  - Adjusted<sup>a</sup> HR (95% CI): 0.88 (0.78, 1.01)
  - P-value: 0.060

HRs based upon Kaplan–Meier analysis for mortality outcomes and mortality/morbidity composite outcomes and the cumulative incidence function for non-fatal outcomes.

<sup>a</sup>See text of Methods for variables adjusted for: CV, cardiovascular; HF, heart failure.

<sup>b</sup>Events included sudden death, fatal or non-fatal MI, PCI, CABG, ventricular defibrillation by ICD, resuscitation after cardiac arrest, hospitalization for UA.
compared with death in nearly 30%, meaning that ACS are likely to have only a small effect on mortality. This does not preclude the possibility of a modest mortality benefit from revascularization, a conclusion consistent with the Surgical Treatment for Ischaemic Heart Failure trial (STICH), which showed that CABG did not reduce all-cause mortality in patients with HF-REF, although there was a borderline-significant reduction in CV death.9

In contrast, patients in Group C had a modestly increased risk of HF hospitalization compared with those in Group A; there was a numerically smaller and non-significant trend in the same direction when Group B was compared with Group A. This finding is of interest given that patients in Group C had a better overall HF risk-profile and is consistent with the view that myocardial ischaemia may precipitate some HF hospitalizations and the results of STICH.10 Although the STICH investigators did not report HF hospitalization as an individual outcome, CABG did reduce the composite of all-cause death or HF hospitalization [HR: 0.84 (0.71–0.98); P = 0.03].9

The potential to reduce morbidity appears greatest in patients with chest pain (presumed angina), as patients in Group C had the highest rate of coronary and HF events. However, we cannot preclude benefit in patients without ongoing chest pain as patients in our Group B, as discussed above, were heterogeneous (and more than half had undergone coronary revascularization) and we did not have a non-ischaemic comparator group for Group A (patients with neither a history of angina or current chest pain but all of ischaemic aetiology). We know that patients with an ischaemic aetiology have worse outcomes than those with non-ischaemic HF and coronary revascularization might still improve outcomes in the former.11,12

We know of only two other studies to examine the relationship between angina and outcomes in HF-REF. Mentz et al. examined outcomes in 2376 patients with CAD and a LVEF <40%, either with (n = 1412) or without (n = 964) angina over a median follow-up of 4.5 years. In an adjusted analysis, patients with angina were less likely to experience the composite of death, MI or revascularization than those without angina (5-year risk 85 vs. 87%; P = 0.01) but not death from any cause (41% in both groups), the latter finding consistent with the present study.5 This US cohort had a very high revascularization rate compared with CORONA where only 3.3% of patients underwent PCI and 1.2% CABG, i.e. CORONA better reflects the unaltered ‘natural history’ of CAD in HF-REF.

Of the 3029 patients in COMET, 53% of patients had an ischaemic aetiology and 22% had current angina at baseline. Angina was not associated with worse clinical outcomes in adjusted analyses, possibly because of lack of power. COMET included fewer patients with an ischaemic aetiology (~1600 vs. 5011 in CORONA), angina (~670 vs. 2285) and did not examine coronary events, which were the
outcomes which showed the clearest increase in patients with chest pain in CORONA.\textsuperscript{3,13}

The most obvious implication of our study is the potential for therapeutic benefit from relief of myocardial ischaemia and prevention of coronary events, which might include improvement in functional capacity and reduction in hospitalization for ACS and, importantly, HF. While this has been demonstrated to some extent with CABG, the possible benefit of PCI is unknown but is under investigation.\textsuperscript{14}

Pharmacological interventions should also be considered, including anti-ischaemic therapy (e.g. nicorandil which has been shown to reduce hospitalization for angina) and anti-thrombotic therapy.\textsuperscript{15}

Our study has a number of limitations. We assumed chest pain at baseline represented angina pectoris which may not always be correct; conversely myocardial ischaemia may be present in HF even in the absence of epicardial CAD.\textsuperscript{16} The subgroups examined in our analysis were not pre-specified and our findings have the inherent limitations of all post hoc analyses. We did not have the results of coronary angiography and the severity of CAD may be independently related to prognosis.\textsuperscript{11} Our results cannot be generalized to all patients with HF, particularly those with preserved LVEF.

In summary, angina is a common symptom in patients with HF-REF and is associated with worse functional status, increased risk of acute coronary events, and HF hospitalization. These findings highlight the potential for anti-ischaemic and anti-infarction strategies to improve symptoms and outcomes in HF, but these need to be tested in randomized controlled-trials.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

**Conflict of interest:** J.G.F.C. received grants and personal fees from ASTRA-ZENECA during the conduct of the CORONA study; H.W. received personal fees from ASTRA-ZENECA during the conduct of the CORONA study.

**References**


