Heart Failure Re-Hospitalizations and Subsequent Fatal Events in Coronary Artery Disease:

Insights from COMMANDER-HF, EPHESUS, and EXAMINE

Short title: Heart Failure in Coronary Artery Disease

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Abstract

Background: Patients with coronary artery disease (CAD) are at increased risk of developing and being hospitalised for heart failure (HFH). However, the risk of HFH versus ischemic events may vary among patients with CAD, depending on whether acute myocardial infarction (MI), left ventricular dysfunction or decompensated HF is present at baseline.

Aims: We aim to explore the risk of non-fatal events (HFH, MI, stroke) and subsequent death in three landmark trials, COMMANDER-HF, EPHESUS and EXAMINE that, together, included patients with CAD with and without reduced ejection fraction and acute MI.

Methods: Events, person-time metrics and time-updated Cox models.

Results: In COMMANDER-HF the event-rate for the composite of AMI, stroke or all-cause death was 13.5 (12.8-14.3) events/100py. Rates for AMI and stroke were much lower (2.2 [2.0-2.6] and 1.3 [1.1-1.6] events/100py, respectively) than the rate of HFH (16.9 [16.1-17.9] events/100py). In EPHESUS, the rates of MI and stroke were also lower than the rate of HFH: 7.2 (6.7-7.8), 1.9 (1.7-2.3), and 10.6 (9.9-11.3) events/100py, but this was not true for EXAMINE with 4.4 (4.0-4.9), 0.7 (0.6-0.9), and 2.4 (2.0-2.7) events/100py, respectively. In all three trials, a non-fatal event (HFH, MI or stroke) during follow-up doubled the risk of subsequent mortality. This most commonly followed a HFH.

Conclusions: A first or recurrent HFH is common in patients with CAD and AMI or HFrEF and indicates a poor prognosis. Preventing the development of heart failure after AMI and control of congestion in patients with CAD and HFrEF are key unmet needs and therapeutic targets.

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Key-words: even type; even-rates; heart failure; myocardial infarction; stroke.

Introduction

Strategies to prevent and treat coronary artery disease (CAD) have led to reductions in the incidence of myocardial infarction (MI) and subsequent mortality, driven by early restoration of myocardial blood flow and better secondary prevention by controlling cardiovascular risk factors and pharmacological interventions[1, 2]. In contrast, the incidence and prevalence of heart failure has increased, especially amongst older people, due (at least partially) to better survival after MI[3]. The development of heart failure often leads to substantial disability and impaired quality of life and is associated with high rates of hospitalizations and a poor prognosis[4]. Hospitalisations are often for worsening heart failure (HFH) that may be triggered by ischemia or many other factors[5, 6].

In the COMMANDER-HF trial, which included patients with a left ventricular ejection fraction (LVEF) <40%, heart failure with reduced ejection fraction (HFrEF) and coronary artery disease (CAD) in sinus rhythm plus a recent hospitalisation for worsening congestion, rivaroxaban 2.5mg bd added to background anti-platelet therapy did not reduce the rate of hospitalisation or death due to worsening heart failure but may have reduced vascular occlusive events[7-9]. These findings suggest that myocardial dysfunction rather than coronary events drive the progression of HFrEF with CAD[10]. Accordingly, we compared event-rates for HFH, MI and stroke as well as the risk of subsequent death after a non-fatal event (HFH, MI, and stroke) in COMMANDER-HF compared to EPHESUS (Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction)[11] and EXAMINE (Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes)[12].

Methods

Study populations

COMMANDER-HF was an international, double-blind, randomized trial comparing the factor-Xa inhibitor rivaroxaban (2.5 mg twice daily) vs. placebo. Key inclusion criteria included history of chronic HF for 3 or more months, left ventricular ejection fraction (LVEF) of 40% or less, history of coronary artery disease, absence of atrial fibrillation or other indication for chronic anticoagulation, and treatment for an episode of decompensated heart failure (i.e., the index event) within the previous 21 days. Decompensated HF was defined by symptoms of worsening dyspnea or fatigue, objective signs of congestion, and/or adjustment of HF medications requiring hospital admission or unscheduled parenteral diuretic[7, 13].

EPHESUS was an international, double-blind, randomized trial comparing eplerenone vs. placebo. Patients were eligible for enrolment if they had an acute MI, and a LVEF ≤40% plus HF or diabetes within 3 to 14 days before randomization[11].

EXAMINE was an international, double-blind, randomized trial comparing the DPP-IV inhibitor alogliptin vs. placebo. Patients were eligible for enrolment if they had type-2 diabetes mellitus and had experienced an acute coronary syndrome within 15 to 90 days before randomization[12, 14].

The three trials were conducted in accordance with the Declaration of Helsinki and approved by the site ethics committees. All participants gave written informed consent to participate in the studies.

Study outcomes

The primary efficacy outcome in COMMANDER-HF was the composite of death from any cause, MI, or stroke. In EPHESUS the primary efficacy outcomes were a composite of death from cardiovascular causes or hospitalization for cardiovascular causes (including heart failure, acute myocardial infarction, stroke, or ventricular arrhythmia), and death from any cause. In EXAMINE the primary endpoint was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. HFH was a main secondary end-point of both the COMMANDER-HF and EXAMINE trials.

Statistical analysis

Similar methods were applied across the studied trials. Number and proportion of events, person-time exposures and time-to-first event-rates (per 100 person-years) were computed. A "smoothed" hazard function was plotted for each time-to-first event to assess the event pattern throughout the follow-up. To make the comparisons easier to interpret we plotted all-cause death, HFH, MI, and stroke over time using the same x-scale and y-scale for all trials. Cumulative incidence rates were computed using the Nelson-Aalen method in the placebo arm of the respective trials to ease the between-trail comparison without the effect of treatments. To assess the risk of death after the first non-fatal events; time-updated Cox models were performed in the placebo groups of the respective trials adjusting for potential baseline confounders, as described in previous analysis[15]. In COMMANDER-HF the adjustment was performed on age, sex, race, diabetes, prior MI, prior stroke, history of percutaneous coronary intervention or coronary artery bypass grafting (PCI/CABG), NYHA class, body mass index, systolic blood pressure, anemia, estimated glomerular filtration rate (eGFR), dual anti-platelet therapy, rivaroxaban or placebo allocation, and geographical region stratification. The treatment effect of rivaroxaban vs. placebo was tested by the

intention-to-treat principle at different follow-up times with stratification by region and "right censored" times (6 months, 12 months, and/or last censor). The proportional hazards assumption was tested by plotting the Schoenfeld residuals over time; the residuals were independent of time and no evidence of proportional hazards violation was found. A 2-sided p value of <0.05 was considered significant. Stata® version 16 (StataCorp. 2019. College Station, TX: StataCorp LLC) was used for the analyses.

Results

Baseline characteristics

In COMMANDER-HF a total of 5022 patients were included with a median follow-up duration of 21.1 months (percentile$_{25\text{-}75}$, 12.9-32.8), the mean age was 66±10 years, 77% were male, 82% white, and 41% had diabetes. In EPHESUS a total of 6632 patients were included with a median follow-up duration of 15.6 months (percentile$_{25\text{-}75}$, 11.9-20.6), the mean age was 64±11 years, 71% were male, 90% white, and 32% had diabetes. In EXAMINE a total of 5380 patients were included with a median follow-up duration of 19.2 months (percentile$_{25\text{-}75}$, 12.0-26.4), the mean age was 61±10 years, 68% were male, 73% white, and all patients had diabetes (by inclusion criteria). The characteristics of the patients enrolled in the respective trials are described in the ***Supplemental Table 1***.

Event rates

In COMMANDER-HF the primary outcome (a composite of MI, stroke or all-cause death) overall event rate was 13.5 (12.8-14.3) events per 100 person-years; the event rate was higher in the first 6 months and decreased thereafter: 16.8 (15.2-18.5) in the first 6 months vs. 11.9 (11.0-12.9) events per 100 person-years beyond the 12th month of follow-up. Similar findings were observed for the composite of MI, stroke or cardiovascular death. The

major contributor for the observed event rate was all-cause death with an overall event rate of 11.2 (10.6-11.9) with similar findings observed for cardiovascular death. ***Table 1***. The overall rate of MI was low: 2.2 (2.0-2.6) events per 100 person-years, but slightly higher within the first 6 months of follow-up: 3.2 (2.6-4.0) in the first 6 months vs. 1.6 (1.3-2.0) events per 100 person-years beyond the 12th month of follow-up. The rate of stroke was even lower and more homogeneous over time with an overall event rate of 1.3 (1.1-1.6) events per 100 person-years. ***Table 1***. The rate of HFH was the highest among all outcomes with an overall rate of 16.9 (16.1-17.9) events per 100 person-years that was much higher in the first 6 months: 29.3 (27.1-31.6) vs. 9.3 (8.4-10.3) after 12 months of follow-up. ***Table 1, Figure 1 & Figure 2***. Bleeding rates were overall low: $\leq$2 events per 100 person-years. ***Supplemental Table 2***. Details on multiple other events (e.g., sudden death, "pump failure" death, non-HFH) are also presented in the ***Supplemental Table 2***. No major variations of the treatment effect (rivaroxaban vs. placebo) over time were found. ***Supplemental Table 3***.

In EPHESUS the overall event rate of the composite outcome of MI, stroke or cardiovascular death was 16.2 (15.4-17.1) events per 100 person-years; the event rate was higher in the first 6 months and decreased thereafter: 28.6 (26.7-30.6) in the first 6 months vs. 7.8 (6.8-9) events per 100 person-years beyond the 12th month of follow-up. In EPHESUS, the MI rates were more than 3-fold higher than in COMMANDER-HF, with an overall event rate of 7.2 (6.7-7.8) events per 100 person-years, also highest in the first 6 months. The rate of stroke was similar to that found in COMMANDER-HF with an overall value of 1.9 (1.7-2.3) events per 100 person-years. ***Table 1***. The HFH rates were lower than those found in COMMANDER-HF. The overall rate was 10.6 (9.9-11.3) events per 100 person-years, but also highest early in the follow-up. ***Table 1, Figure 1 & Figure 2***.

In EXAMINE the overall event rate of the composite outcome of MI, stroke or cardiovascular death was 7.7 (7.1-8.4) events per 100 person-years; the event rate was higher in the first 6 months and decreased thereafter. In EXAMINE, the MI rates were 2-fold higher than in COMMANDER-HF, with an overall event rate of 4.4 (4.0-4.9) events per 100 person-years, also highest in the first 6 months. The rate of stroke was lower than in COMMANDER-HF with an overall value of 0.7 (0.6-0.9) events per 100 person-years. ***Table 1***. The HFH rates were much lower than those found in COMMANDER-HF and EPHESUS. The overall rate was 2.4 (2.0-2.7) events per 100 person-years, but also highest early in the follow-up. ***Table 1, Figure 1 & Figure 2***.

Deaths after a non-fatal event

In COMMANDER-HF, having a non-fatal event during the follow-up increased the risk of subsequent death by ≈2-fold. The risk was similar for all non-fatal events, but slightly higher after an MI: MI adjusted HR (95%CI) =2.31 (1.73-2.61), p<0.001; HFH adjusted HR (95%CI) =1.81 (1.59-2.05), p<0.001; stroke adjusted HR (95%CI) =1.75 (1.31-2.33), p<0.001. The absolute numbers and proportion of HFH events preceding death was much higher than the proportion of MI or stroke: HFH 517 (46.9%), MI 106 (9.6%), Stroke 53 (4.8%). ***Table 2, Figure 3 & Figure 4***.

In EPHESUS, having a non-fatal event during the follow-up increased the risk of subsequent death by 2 to 3-fold. The risk was higher after an MI or stroke, than after a HFH: MI adjusted HR (95%CI) =3.16 (2.72-3.67), p<0.001; stroke adjusted HR (95%CI) =3.01 (2.38-3.81), p<0.001; HFH adjusted HR (95%CI) =2.23 (1.94-2.58), p<0.001. The absolute numbers and proportion of HFH events preceding death was also higher than the proportion of MI or stroke: HFH 316 (30.6%), MI 261 (25.3%), Stroke 82 (8.0%). ***Table 2, Figure 3 & Figure 4***.

In EXAMINE, having a non-fatal event during the follow-up increased the risk of subsequent death by 1.5 to 2.5-fold. In EXAMINE the risk was higher after a HFH than after a MI or stroke: HFH adjusted HR (95%CI) =2.50 (1.80-3.48), p<0.001; MI adjusted HR (95%CI) =1.59 (1.15-2.19), p=0.005); stroke adjusted HR (95%CI) =1.49 (0.70-3.18), p=0.30. The absolute numbers and proportion of HFH events preceding death were similar to MI and higher than stroke: HFH 48 (14.7%), MI 46 (14.1%), Stroke 7 (2.2%). ***Table 2, Figure 3 & Figure 4***.

Discussion

Our study shows that HFHs are frequent and associated with poor outcomes in patients with CAD. However, depending on the population studied the type of events and their rate may vary widely. Patients with decompensated HF but without an acute MI (as in COMMANDER-HF), present a high rate of HF re-hospitalizations frontloaded early within the follow-up; the HFH rates are much superior (8-fold or even higher) to those of MI or stroke (despite the presence of underlying CAD) and greatly increase the risk for subsequent death (≈2-fold higher). In EPHESUS, with high-risk acute MI patients, HF re-hospitalizations were more frequent than recurrent MI and also independently associated with a poor prognosis. In EXAMINE the recurrent MI rates were higher than HFH, but HFH was also frequent and associated with a poorer prognosis than MI. Together, these data show that a large window of opportunity to reduce events still exists and that targeting HF is key in this endeavour.

COMMANDER-HF was designed with the hypothesis that thrombin would play a central role in the HF progression of patients with CAD[13]. Inhibiting the factor Xa with rivaroxaban could lead to the reduction of thrombin and related pathways associated with myocyte injury, inflammation, endothelial dysfunction and microvascular thrombosis, which

could then result in a reduction of ischemic/thrombotic events and also HF hospitalizations and mortality via thrombin-related pathways[16, 17]. The inclusion of patients early (within 21 days) of a decompensated HF episode would enrich the trial for outcome events. This was indeed what happened, with the vast majority of these events being HFH on which rivaroxaban had no effect[8, 18]. By computing the risk of death after the non-fatal events, one may observe that the risk of dying after a HFH was similar to the risk of dying after a stroke or MI. However, HFH were a much more frequent event than MI or stroke, making HF re-hospitalizations as a main target for improvement. Even in patients who had an acute MI (as in EPHESUS and EXAMINE), HF re-hospitalizations represent a major burden with deleterious consequences. Similarly, in a post-hoc analysis of the ALTITUDE trial (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints) that included patients with type 2 diabetes plus chronic kidney disease, cardiovascular disease or both, the proportion of patients experiencing a HFH was higher than that of MI or stroke, and the greatest number of deaths occurred in the group who had a HFH first[19].

Up-to-date HFrEF treatment including an angiotensin-receptor neprilysin inhibitor (ARNI), a sodium glucose co-transporter inhibitor (SGLT2i), and a mineralocorticoid receptor antagonist (MRA) may lead to a 50% event reduction compared with treatment with angiotensin converting enzyme/angiotensin receptor blocker (ACEi/ARB) and a beta-blocker[20]; however, it should be noted that the implementation of HF-modifying therapies remains an issue even in developed countries[21-25]. Notwithstanding, while the therapeutic armamentarium for chronic HFrEF may sharply reduce events rates, if implemented; post worsening HF remains an unmet need with high recurrent HFH and mortality, and offers an opportunity to test and implement novel strategies. Such opportunity was tested in the PIONEER-HF (Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure) trial,

where initiation of sacubitril/valsartan upon stabilization of a decompensated HF episode led to a greater reduction in the NT-pro BNP than enalapril without increasing adverse events[26]. In VICTORIA-HF (Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction) patients had to have evidence of worsening HF and most patients (67%) had been hospitalized for HF in the previous 3 months which resulted in a high rate of HFH and death in this trial, slightly reduced with vericiguat treatment[23]. In COMPASS (Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease) patients with a HF history also had a higher rate of all the studied events, including HFH[27, 28].

These examples show that the opportunity for improvement in populations that had a recent HF hospitalization, MI or both is considerable and optimizing the use of therapies that have been shown to improving outcomes is key to achieve this goal [29].

Limitations

The findings here depicted may only be generalized to patients with similar characteristics of those included in these trials, due to the relatively young, white and male populations included, our findings may not be applicable to patients with different characteristics. Furthermore, the inclusion/exclusion criteria and level of monitoring performed in a trial context may further limit the generalization of these results to patients in the community, but allows a detailed assessment of adjudicated cause-specific events. The timing of enrollment after the acute event was similar in COMMANDER-HF and EPHESUS (less than 21 and 3 to 14 days, respectively), but more widespread in EXAMINE (15 to 90 days) which might have contributed to the lower overall event rate in EXAMINE. The follow-up times were slightly different between trials (median in months of 21 in COMMANDER-HF, 16 in EPHESUS, and 19 in EXAMINE), which might have influenced the event rates and the assessment of fatal events after non-fatal ones. EPHESUS was published almost 20 years

ago; the MI therapeutics have improved much since and the observed high death risk after MI could be lower in a contemporary cohort.

Conclusions

The burden of HF re-hospitalizations is enormous in patients with CAD and is associated with a high risk of subsequent death. Reducing HF in CAD represents an unmet need that should be addressed in future studies.

Disclosures

Dr Ferreira is a consultant for Boehringer-Ingelheim. Dr Zannad reports steering committee personal fees from Applied Therapeutics, Amgen, Bayer, Boehringer, Novartis, Janssen, Cellprothera and CVRx, advisory board personal fees from, AstraZeneca, Vifor Fresenius, Cardior, Cereno pharmaceutical, Corvidia, Merck, Myokardia, NovoNordisk and Owkin, stock options at Cereno and G3Pharmaceutical, and being the founder of the Global Cardiovascular Clinical Trialist Forum. Dr Lam has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the Advisory Board/ Steering Committee/ Executive Committee for Abbott Diagnostics, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Biofourmis, Boehringer Ingelheim, Boston Scientific, Corvia Medical, Cytokinetics, Darma Inc., Us2.ai, JanaCare, Janssen Research & Development LLC, Medtronic, Menarini Group, Merck, MyoKardia, Novartis, Novo Nordisk, Radcliffe Group Ltd., Roche Diagnostics, Sanofi, Stealth BioTherapeutics, The Corpus, Vifor Pharma and WebMD Global LLC; and serves as co-founder & non-executive director of Us2.ai. Dr Greenberg reports consulting fees from Amgen, Cytokinetics, EBR Systems, Impulse Dynamics, Ionis, Jaan, Janssen, Merck,

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Table 1. Event rates per 100 person-years by intervals of follow-up time

Time (months)	Person-years	Events	Rate (per100py)
COMMANDER-HF (n =5022)			
MI, stroke, ACM			
0 to 6	2403	404	16.8 (15.2-18.5)
6 to 12	2151	290	13.5 (12-15.1)
Beyond 12	4946	590	11.9 (11-12.9)
Total	9500	1284	13.5 (12.8-14.3)
MI, stroke, CVD			
0 to 6	2403	367	15.3 (13.8-16.9)
6 to 12	2151	263	12.2 (10.8-13.8)
Beyond 12	4946	491	9.9 (9.1-10.8)
Total	9500	1121	11.8 (11.1-12.5)
MI			
0 to 6	2412	78	3.2 (2.6-4)
6 to 12	2169	59	2.7 (2.1-3.5)
Beyond 12	5048	79	1.6 (1.3-2)
Total	9629	216	2.2 (2-2.6)
Stroke			
0 to 6	2420	41	1.7 (1.2-2.3)
6 to 12	2183	30	1.4 (1-2)
Beyond 12	5075	56	1.1 (0.8-1.4)
Total	9679	127	1.3 (1.1-1.6)
ACM			
0 to 6	2429	320	13.2 (11.8-14.7)
6 to 12	2202	239	10.9 (9.6-12.3)
Beyond 12	5180	543	10.5 (9.6-11.4)
Total	9810	1102	11.2 (10.6-11.9)
CVD			
0 to 6	2429	282	11.6 (10.3-13)
6 to 12	2202	212	9.6 (8.4-11)
Beyond 12	5180	435	8.4 (7.6-9.2)
Total	9810	929	9.5 (8.9-10.1)
HFH			
0 to 6	2265	663	29.3 (27.1-31.6)
6 to 12	1872	344	18.4 (16.5-20.4)
Beyond 12	4009	373	9.3 (8.4-10.3)
Total	8146	1380	16.9 (16.1-17.9)
EPHESUS (n =6632)			
MI, stroke, CVD			
0 to 6	2998	857	28.6 (26.7-30.6)
6 to 12	2676	280	10.5 (9.3-11.8)

Beyond 12	2586	202	7.8 (6.8-9)
Total	8259	1339	16.2 (15.4-17.1)
MI			
0 to 6	3016	427	14.2 (12.9-15.6)
6 to 12	2703	106	3.9 (3.2-4.7)
Beyond 12	2632	71	2.7 (2.1-3.4)
Total	8351	604	7.2 (6.7-7.8)
Stroke			
0 to 6	3091	86	2.8 (2.3-3.4)
6 to 12	2822	44	1.6 (1.2-2.1)
Beyond 12	2758	38	1.4 (1-1.9)
Total	8671	168	1.9 (1.7-2.3)
ACM			
0 to 6	3111	590	19 (17.5-20.6)
6 to 12	2851	243	8.5 (7.5-9.7)
Beyond 12	2808	199	7.1 (6.2-8.1)
Total	8769	1032	11.8 (11.1-12.5)
CVD			
0 to 6	3111	534	17.2 (15.8-18.7)
6 to 12	2851	196	6.9 (6-7.9)
Beyond 12	2808	160	5.7 (4.9-6.7)
Total	8769	890	10.1 (9.5-10.8)
HFH			
0 to 6	2952	594	20.1 (18.6-21.8)
6 to 12	2610	160	6.1 (5.2-7.2)
Beyond 12	2536	101	4 (3.3-4.8)
Total	8098	855	10.6 (9.9-11.3)
EXAMINE (n =5380)			
MI, stroke, CVD			
0 to 6	2504	283	11.3 (10.1-12.7)
6 to 12	2100	160	7.6 (6.5-8.9)
Beyond 12	3429	178	5.2 (4.5-6)
Total	8033	621	7.7 (7.1-8.4)
MI			
0 to 6	2511	168	6.7 (5.8-7.8)
6 to 12	2114	95	4.5 (3.7-5.5)
Beyond 12	3470	97	2.8 (2.3-3.4)
Total	8094	360	4.4 (4-4.9)
Stroke			
0 to 6	2551	23	0.9 (0.6-1.4)
6 to 12	2190	15	0.7 (0.4-1.1)
Beyond 12	3667	23	0.6 (0.4-0.9)
Total	8409	61	0.7 (0.6-0.9)

ACM			
0 to 6	2558	119	4.7 (3.9-5.6)
6 to 12	2204	81	3.7 (3-4.6)
Beyond 12	3708	126	3.4 (2.9-4)
Total	8470	326	3.8 (3.5-4.3)
CVD			
0 to 6	2558	97	3.8 (3.1-4.6)
6 to 12	2204	61	2.8 (2.2-3.6)
Beyond 12	3708	84	2.3 (1.8-2.8)
Total	8470	242	2.9 (2.5-3.2)
HFH			
0 to 6	2531	105	4.1 (3.4-5)
6 to 12	2156	42	1.9 (1.4-2.6)
Beyond 12	3587	48	1.3 (1-1.8)
Total	8273	195	2.4 (2-2.7)

Legend: MI, myocardial infarction; CVD, cardiovascular death; ACM, all-cause mortality;

HFH, heart failure re-hospitalization.

Table 2. Death after a non-fatal event

Events	Event and death	Event and survival	Adj. HR (95%CI)	P
COMMANDER-HF				
HFH				
N=1380	517 (46.9%)	863 (22.0%)	1.81 (1.59-2.05)	<0.001
MI				
N=216	106 (9.6%)	110 (2.8%)	2.13 (1.73-2.64)	<0.001
Stroke				
N=127	53 (4.8%)	74 (1.9%)	1.75 (1.31-2.33)	<0.001
Total	1102	3920		
EPHESUS				
HFH				
N=855	316 (30.6%)	539 (9.6%)	2.23 (1.94-2.58)	<0.001
MI				
N=604	261 (25.3%)	343 (6.1%)	3.16 (2.72-3.67)	<0.001
Stroke				
N=168	82 (8.0%)	86 (1.5%)	3.01 (2.38-3.81)	<0.001
Total	5600	1032		
EXAMINE				
HFH				
N=195	48 (14.7%)	147 (2.9%)	2.50 (1.80-3.48)	<0.001
MI				
N=360	46 (14.1%)	314 (6.2%)	1.59 (1.15-2.19)	0.005
Stroke				
N=61	7 (2.2%)	54 (1.1%)	1.49 (0.70-3.18)	0.30
Total	5054	326		

Legend: MI, myocardial infarction; HFH, heart failure re-hospitalization.

Figure 1. Smoothed hazard function over time

A) COMMANDER-HF

B) EPHESUS

C) EXAMINE

Caption: the cumulative hazard function is on the y axis and the follow-up time in years is displayed in the x axis.

Figure 2. Cumulative incidence of events in the placebo groups of the respective trials

Caption: the individual events are displayed on the y axis and the follow-up time in years is displayed in the x axis.

Figure 3. Proportion of deaths following a non-fatal event in each trial

Legend: HFH, heart failure hospitalization; MI, myocardial infarction. Y-scale, percentage (%).

Caption: the figure represents the proportion of all deaths that occurred after a non-fatal event in each trial. For example, in COMMANDER-HF 47% of all deaths occurred after a HFH.

Figure 4. Cumulative incidence of death after a non-fatal event

A) COMMANDER-HF

B) EPHESUS

C) EXAMINE

Legend: HFH, heart failure hospitalization; MI, myocardial infarction.