ESC European Society of Cardiology

European Heart Journal (2022) **00**, 1–9
https://doi.org/10.1093/eurheartj/ehac144

CLINICAL RESEARCH
Heart failure and cardiomyopathies

Influence of atrial fibrillation on efficacy and safety of omecamtiv mecarbil in heart failure: the GALACTIC-HF trial

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Received 16 September 2021; revised 9 February 2022; accepted 7 March 2022

Abstract

Aims In GALACTIC-HF, the cardiac myosin activator omecamtiv mecarbil compared with placebo reduced the risk of heart failure events or cardiovascular death in patients with heart failure with reduced ejection fraction. We explored the influence of atrial fibrillation or flutter (AFF) on the effectiveness of omecamtiv mecarbil.

Methods and results GALACTIC-HF enrolled patients with New York Heart Association (NYHA) Class II–IV heart failure, left ventricular ejection fraction ≤35%, and elevated natriuretic peptides. We assessed whether the presence or absence of AFF, a pre-specified subgroup, modified the treatment effect for the primary and secondary outcomes, and additionally explored effect modification in patients who were or were not receiving digoxin. Patients with AFF ($n = 2245$, 27%) were older, more likely to be randomized as an inpatient, less likely to have a history of ischaemic aetiology or myocardial infarction, had a worse NYHA class, worse quality of life, lower estimated glomerular filtration rate, and higher N-terminal pro-B-type natriuretic peptide. The treatment effect of omecamtiv mecarbil was modified by baseline AFF (interaction $P = 0.012$), with patients without AFF at baseline deriving greater benefit. The worsening of the treatment effect by baseline AFF was significantly more pronounced in digoxin users than in non-users (interaction $P = 0.007$); there was minimal evidence of effect modification in those patients not using digoxin ($P = 0.47$) or in digoxin users not in AFF.

Conclusion Patients in AFF at baseline were less likely to benefit from omecamtiv mecarbil than patients without AFF, although the attenuation of the treatment effect was disproportionally concentrated in patients with AFF who were also receiving digoxin. Clinical Trial Registration: NCT02929329

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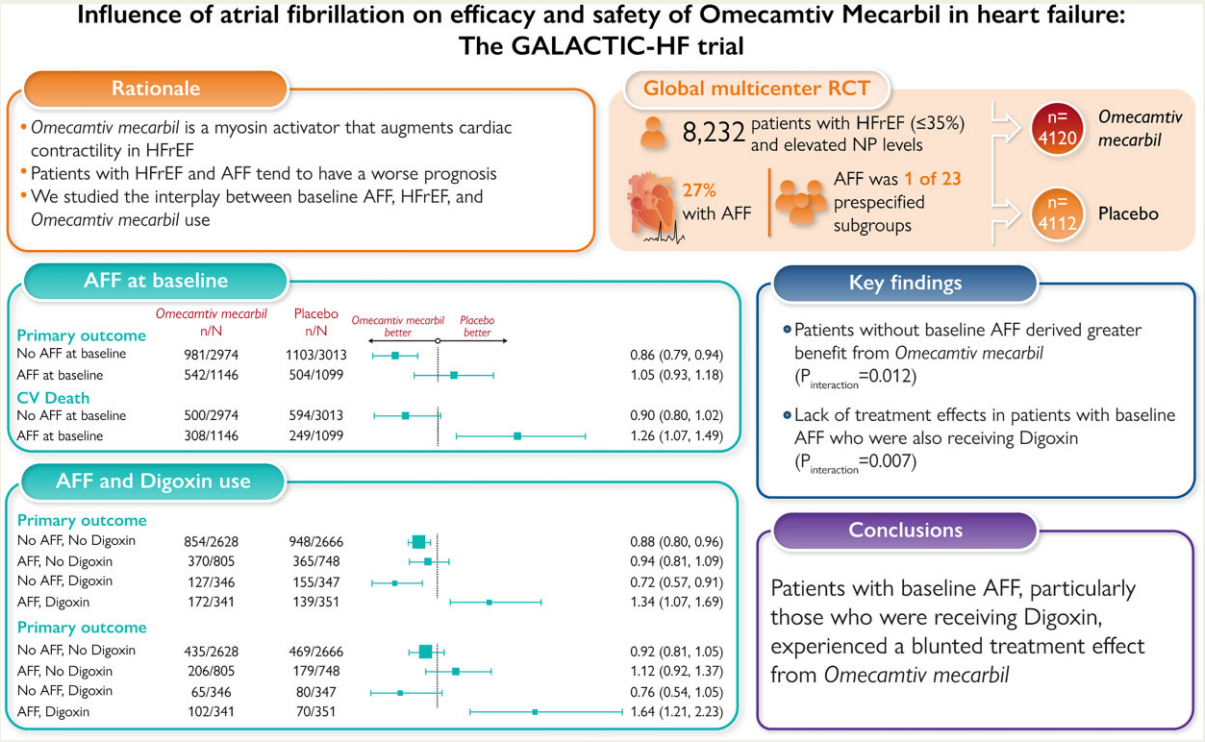

Structured Graphical Abstract In GALACTIC-HF, patients with atrial fibrillation or flutter (AFF) at baseline derived less benefit from Omecamtiv Mecarbil than patients not in AFF. This finding was primarily driven by those patients in AFF who were taking digoxin.

Keywords Heart failure • Atrial fibrillation • Myosin activator • Digoxin

Introduction

Atrial fibrillation is common in patients with heart failure and contributes to morbidity and mortality. The prevalence of atrial fibrillation or flutter (AFF) in heart failure with reduced ejection fraction (HFrEF) has varied in contemporary clinical trials; in the CHARM program, 17% of patients with left ventricular ejection fraction (LVEF) ≤40% had atrial fibrillation which was associated with an ∼30% increased risk of cardiovascular death or hospitalization for heart failure.[1] The proportion of patients with atrial fibrillation was higher in EMPHASIS-HF (34%), with a slightly lower risk of heart failure hospitalization.[2] Nevertheless, the presence of atrial fibrillation at baseline did not modify the treatment effect of either candesartan or eplerenone in these trials. In contrast, the presence of atrial fibrillation did appear to attenuate the treatment effect of beta blockers in clinical trials of those agents.[3]

The myosin activator omecamtiv mecarbil augments cardiac sarcomeric function by facilitating the actin–myosin interaction resulting in an increase in contractile force.[4] In the GALACTIC-HF trial, omecamtiv mecarbil reduced the risk of a composite of cardiovascular death or heart failure event in patients with HFrEF.[5] The presence of AFF at baseline was one of two pre-specified subgroups that modified the effectiveness of omecamtiv mecarbil after multivariable analyses, with omecamtiv mecarbil appearing less effective in patients with AFF at baseline. In this analysis, we assessed whether baseline AFF modified the effectiveness of omecamtiv mecarbil with respect to additional endpoints and explore additional potential factors that may have influenced this effect modification.

Methods

Study design and patient eligibility

GALACTIC-HF was a multicenter international randomized placebo-controlled trial comparing omecamtiv mecarbil to placebo in 8232 patients with HFrEF. The details of the study design and primary results have been previously published.[6] Eligible patients were required to have symptomatic heart failure [New York Heart Association (NYHA) Class II–IV], LVEF ≤35% within 12 months of screening, elevation of N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥400 pg/mL (or 1200 pg/mL for patients in atrial fibrillation at screening) or elevation in B-type natriuretic peptide (BNP) ≥125 pg/mL (or 375 pg/mL for patients in atrial fibrillation at screening), and were required to have either been hospitalized for heart failure at enrolment or hospitalized or treated urgently in an emergency department for heart failure within a year prior to screening. Patients were required to be on optimized medical therapy prior to enrolment. Details of the inclusion and exclusion criteria have been published.[6] The study protocol was approved by each participating institution and all patients signed written informed consent.

Exposure and outcomes

The presence of AFF was identified at the screening by investigators on electrocardiography and recorded on case report forms. Atrial fibrillation or flutter at baseline was one of 23 pre-specified subgroups. The primary study outcome was time to first heart failure event (defined as either a hospitalization for heart failure or an urgent non-hospitalized heart failure visit) or cardiovascular death.

Statistical analyses

Baseline characteristics were summarized using means and standard deviations for normally distributed continuous outcomes, using medians and interquartile ranges for non-normal continuous variables, and using counts and percentages for categorical variables. Groups of patients with and without AFF at baseline were compared using two-sample *t*-tests, Wilcoxon rank-sum tests, and Pearson's χ^2 tests, respectively. Time-to-event outcomes were summarized using Kaplan–Meier cumulative incidence curves and analysed using Cox proportional hazards models. The primary endpoint in this analysis was the same primary endpoint as in the original analysis of the GALACTIC-HF trial, a composite of time-to-first heart failure event or cardiovascular death. The risk of the primary endpoint in those with AFF was assessed adjusting for baseline variables chosen from the following baseline covariates: age, sex, race, region, inpatient status, diabetes, stroke, ischaemic aetiology, history of myocardial infarction, history of bypass surgery, LVEF, NYHA class, baseline Kansas City Cardiomyopathy Questionnaire clinical summary score, systolic blood pressure, body mass index, heart rate, NT-proBNP, troponin I, estimated glomerular filtration rate (eGFR), angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor–neprilysin inhibitor use, beta blocker use, mineralocorticoid receptor antagonist use, sodium–glucose cotransporter 2 inhibitor use, cardiac resynchronization (CRT), and implantable cardioverter defibrillator (ICD) use.

Similarly, the treatment effect of omecamtiv mecarbil was assessed by Cox proportional hazards models incorporating treatment and AFF status as an interaction term, and adjusted for randomization strata and eGFR as was performed in the primary analysis. In *post hoc* exploratory analyses, we further assessed the influence of baseline digoxin use on this effect modification, as well as differences in 6 week levels of troponin I and omecamtiv mecarbil pharmacokinetic levels, which were assessed by immunoassay. Tests of Schoenfeld residuals were used to assess the proportional hazards assumptions of all Cox models used to report treatment effect estimates and treatment–covariate interactions. All reported *P*-values are two-sided, and *P*-values < 0.05 were considered statistically significant. All analyses were conducted using STATA (Version 16, College Station, TX, USA).

Results

Overall baseline characteristics of patients in GALACTIC-HF have been previously reported.[7] A total of 2245 (27%) patients were in AFF at baseline. Compared with those who were not in AFF at baseline, these patients were older, less likely to be female, more likely to be white, and were more likely to be randomized in the inpatient setting (*Table 1*). Additionally, they were less likely to have a history of hypertension, stroke, ischaemic heart failure aetiology, or myocardial infarction. They had slightly higher LVEF and were more likely to be in a higher NYHA class. Natriuretic peptides were higher in patients with AFF by study design. With respect to background heart failure medications, both patients with and without AFF were receiving an excellent standard of care medical therapy, with the notable exception that patients with baseline AFF were substantially more likely to be treated with digoxin.

In both treatment groups crude event rates for the primary outcome, for the first hospitalization for heart failure, for cardiovascular death, and for all-cause death were higher in patients with AFF at baseline compared with those not in AFF (*Table 2*). In adjusted analyses of patients in the placebo group, the risk for all primary outcomes was greater in patients with AFF compared with those without AFF at baseline [hazard ratio (HR) 1.13, 95% confidence interval (CI) 1.01, 1.28]. The treatment effect for the primary outcome comparing omecamtiv mecarbil to placebo was greater in patients who were not in AFF at baseline (*P*-interaction = 0.012). This interaction remained significant after multivariate adjustment incorporating all pre-specified subgroup interactions. Similar findings were observed for the endpoints of cardiovascular death (*P*-interaction = 0.002), heart failure hospitalizations (*P*-interaction = 0.013), and all-cause mortality (*P*-interaction < 0.001) (*Table 2*, *Figure 1* and Supplementary material online, *Figure S1*). When comparing patients with and without AFF at baseline, there were no significant differences in treatment-related changes in NT-proBNP (baseline AFF: HR 0.89, 95% CI 0.84, 0.94; baseline no AFF: HR 0.90, 95% CI 0.83, 0.97), or troponin I (baseline AFF: HR 1.23, 95% CI 1.18, 1.28; baseline no AFF: HR 1.30, 95% CI 1.22, 1.38). The percentage of patients who died of cardiovascular causes was similar in these four groups (see Supplementary material online, *Table S1*). There was a smaller proportion of sudden cardiac deaths and a higher proportion of heart failure deaths in those patients in atrial fibrillation receiving omecamtiv mecarbil (see Supplementary material online, *Table S2*). Thirty-four percentage of patients were implanted with either a CRT or ICD device (or both). The results were similar regardless of CRT/ICD implantation. No statistically significant violations of proportional hazards assumptions were detected (all $P > 0.05$).

Because of notable differences in pharmacologic background therapy in patients with AFF compared with those without AFF at baseline, we explored in *post hoc* analyses additional potential interactions that could influence the effect modification between AFF and treatment with respect to outcomes. We found that the treatment effect attenuation for the primary outcome in patients with AFF was significantly more pronounced in digoxin users, comprising 31% of all AFF patients, than in non-users (*P*-interaction = 0.007). There was strong evidence of effect modification in digoxin users (*P*-interaction $<$ 0.001) and minimal evidence of effect modification in non-users (*P*-interaction = 0.47), suggesting harm in AFF patients also using digoxin, but treatment benefits in all other patients. Similar patterns were also observed for the outcomes of heart failure hospitalization, cardiovascular death, and all-cause death (*Figure 2*).

In patients with AFF at baseline taking omecamtiv mecarbil, there was less troponin I increase (*P* = 0.026) at 6 weeks in those taking digoxin (+29%, +21% to +38%) compared with those not taking digoxin (+45%, +38% to 53%), while 6-week omecamtiv mecarbil plasma concentrations were similar (median 286 vs. 280 ng/mL, *P* = 0.78). In patients in whom digoxin doses were known, they were similar in both treatment arms (0.12 vs. 0.12 mg, *P* = 0.85) and similar in patients with and without AFF at baseline (0.12 vs. 0.12 mg, *P* = 0.44). The deleterious observed effect of omecamtiv mecarbil on the primary composite outcome within the digoxin/AFF subgroup did not appear to be modified by baseline eGFR or heart

Table 1 Baseline characteristics in patients with and without atrial fibrillation or flutter at baseline

	No atrial fibrillation/flutter ($n = 5987$)	Atrial fibrillation/flutter ($n = 2245$)	*P*-value
Demographics			
Age, years	63 ± 12	68 ± 10	< 0.001
Female sex	1340 (22.4%)	409 (18.2%)	< 0.001
Race			< 0.001
Asian	556 (9.3%)	154 (6.9%)	
Black	487 (8.1%)	75 (3.3%)	
Other	433 (7.2%)	130 (5.8%)	
White	4511 (75.3%)	1886 (84.0%)	
Geographic region			< 0.001
Asia	522 (8.7%)	148 (6.6%)	
Eastern Europe/Russia	1790 (29.9%)	891 (39.7%)	
Latin America	1226 (20.5%)	348 (15.5%)	
USA and Canada	1138 (19.0%)	248 (11.0%)	
Western Europe/South Africa/Australasia	1311 (21.9%)	610 (27.2%)	
Randomization setting: inpatient	1361 (22.7%)	723 (32.2%)	< 0.001
Clinical characteristics			
Hypertension	4136 (69.1%)	1648 (73.4%)	< 0.001
Type 2 diabetes mellitus	2431 (40.6%)	878 (39.1%)	0.22
History of stroke	497 (8.3%)	257 (11.4%)	< 0.001
Ischaemic heart failure aetiology	3341 (55.8%)	1074 (47.8%)	< 0.001
History of myocardial infarction	2683 (44.8%)	752 (33.5%)	< 0.001
History of coronary artery bypass surgery	950 (15.9%)	367 (16.3%)	0.60
History of percutaneous coronary revascularization	1900 (31.7%)	538 (24.0%)	< 0.001
LVEF, %	26 ± 6	27 ± 6	< 0.001
NYHA class			< 0.001
II	3353 (56.0%)	1015 (45.2%)	
III	2473 (41.3%)	1143 (50.9%)	
IV	161 (2.7%)	87 (3.9%)	
KCCQ total symptom score	71 [51, 90]	64 [44, 83]	< 0.001
Outpatient	76 [56, 92]	70 [52, 88]	< 0.001
Inpatient	55 [35, 73]	48 [29, 68]	<0.001
SBP, mmHg	117 ± 16	115 ± 15	< 0.001
Heart rate, b.p.m.	71 ± 12	75 ± 13	< 0.001
NT-proBNP, pg/mL	1675 [812, 3579]	2873 [1699, 5294]	< 0.001
Cardiac troponin I, ng/L	25 [13, 48]	31 [16, 59]	< 0.001
eGFR, mL/min/1.73 m^2	61 [46, 76]	53 [40, 68]	< 0.001
Heart failure therapies			
ACEi, ARB, or ARNi	5246 (87.6%)	1913 (85.2%)	0.004

Continued

Table 1 *Continued*

	No atrial fibrillation/flutter ($n = 5987$)	Atrial fibrillation/flutter ($n = 2245$)	*P*-value
ARNi	1172 (19.6%)	429 (19.1%)	0.63
Beta blockers	5650 (94.4%)	2113 (94.1%)	0.66
MRA	4627 (77.3%)	1770 (78.8%)	0.13
SGLT2 inhibitors	164 (2.7%)	54 (2.4%)	0.40
Ivabradine	510 (8.5%)	23 (1.0%)	< 0.001
Digoxin	693 (11.6%)	692 (30.8%)	< 0.001
Cardiac resynchronization therapy	815 (13.6%)	343 (15.3%)	0.05
Implantable cardioverter defibrillator	1913 (32.0%)	701 (31.2%)	0.53

rate (see Supplementary material online, *Table S3*). In addition, the mean concentration among patients randomized to omecamtiv mecarbil did not significantly differ according to digoxin/AFF status ($P = 0.87$; see Supplementary material online, *Table S4*). The rate of incident atrial fibrillation based on adverse event reporting for patients who were not in AFF at baseline was 3.1 (95% CI 2.7, 3.6) per 100 patient-years in the omecamtiv group compared with 3.7 (95% CI 3.2, 4.3) per 100 patient-years in the placebo group ($P = 0.11$).

Discussion

We found that AFF, present in 27% of patients enrolled in GALACTIC-HF at baseline, was associated with an increased risk of adverse outcomes. Atrial fibrillation or flutter at baseline attenuated the treatment effect of omecamtiv mecarbil, even after multivariable adjustment, although this attenuation was disproportionally concentrated in patients who were also receiving digoxin. Importantly, patients without baseline AFF, but who were receiving digoxin, as well as patients with baseline AFF who were not receiving digoxin, did not demonstrate an increase in adverse outcomes (*Structured Graphical Abstract*). These findings may have important implications for the use of omecamtiv mecarbil.

In the pre-specified subgroup analyses of GALACTIC-HF, we found evidence of significant treatment heterogeneity for two pre-specified subgroups that withstood multivariable adjustment: LVEF above or at or below the median, and the presence or absence of AFF at baseline. Both patients with LVEF at or below the median and patients not in AFF demonstrated the greatest treatment effect. In contrast, in the COSMIC-HF trial which served as the pilot for GALACTIC-HF, we found no direct evidence of heterogeneity by atrial fibrillation on any of the outcomes.[8]

The heterogeneity associated with AFF at baseline appeared to be driven by digoxin use, yet this interaction appeared limited only to patients with AFF, and patients taking digoxin who were not in AFF appeared to respond well to omecamtiv mecarbil. Similarly, there was no evidence of heterogeneity in the treatment response to omecamtiv mecarbil in AFF patients not taking digoxin. There are a number of potential explanations for these findings. First,

Table 2 Outcomes in patients without and with atrial fibrillation/flutter at baseline

Outcome	No atrial fibrillation/flutter				HR (95% CI); *P*-value	Atrial fibrillation/flutter				HR (95% CI); *P*-value	Interaction *P*-value
	OM		Placebo			OM		Placebo			
	n/N	Rate[a]	n/N	Rate[a]		n/N	Rate[a]	n/N	Rate[a]		
Primary outcome	981/2974 (33%)	20.7	1103/3013 (37%)	24.2	0.86 (0.79, 0.94); $P < 0.001$	542/1146 (47%)	34.8	504/1099 (46%)	32.7	1.05 (0.93, 1.18); $P = 0.47$	0.012
CV death	500/2974 (17%)	9.2	549/3013 (18%)	10.2	0.90 (0.80, 1.02); $P = 0.09$	308/1146 (27%)	15.7	249/1099 (23%)	12.5	1.26 (1.07, 1.49); $P = 0.007$	0.002
Heart failure hospitalization	715/2974 (24%)	15.0	796/3013 (26%)	17.3	0.87 (0.79, 0.97); $P = 0.009$	427/1146 (37%)	27.1	383/1099 (35%)	24.4	1.09 (0.95, 1.25); $P = 0.23$	0.013
All-cause death	672/2974 (23%)	12.3	739/3013 (25%)	13.7	0.90 (0.81, 0.99); $P = 0.039$	395/1146 (34%)	20.1	326/1099 (30%)	16.4	1.25 (1.08, 1.45); $P = 0.003$	< 0.001

OM, omecamtiv mecarbil.
[a]Rate per 100 patient-years.

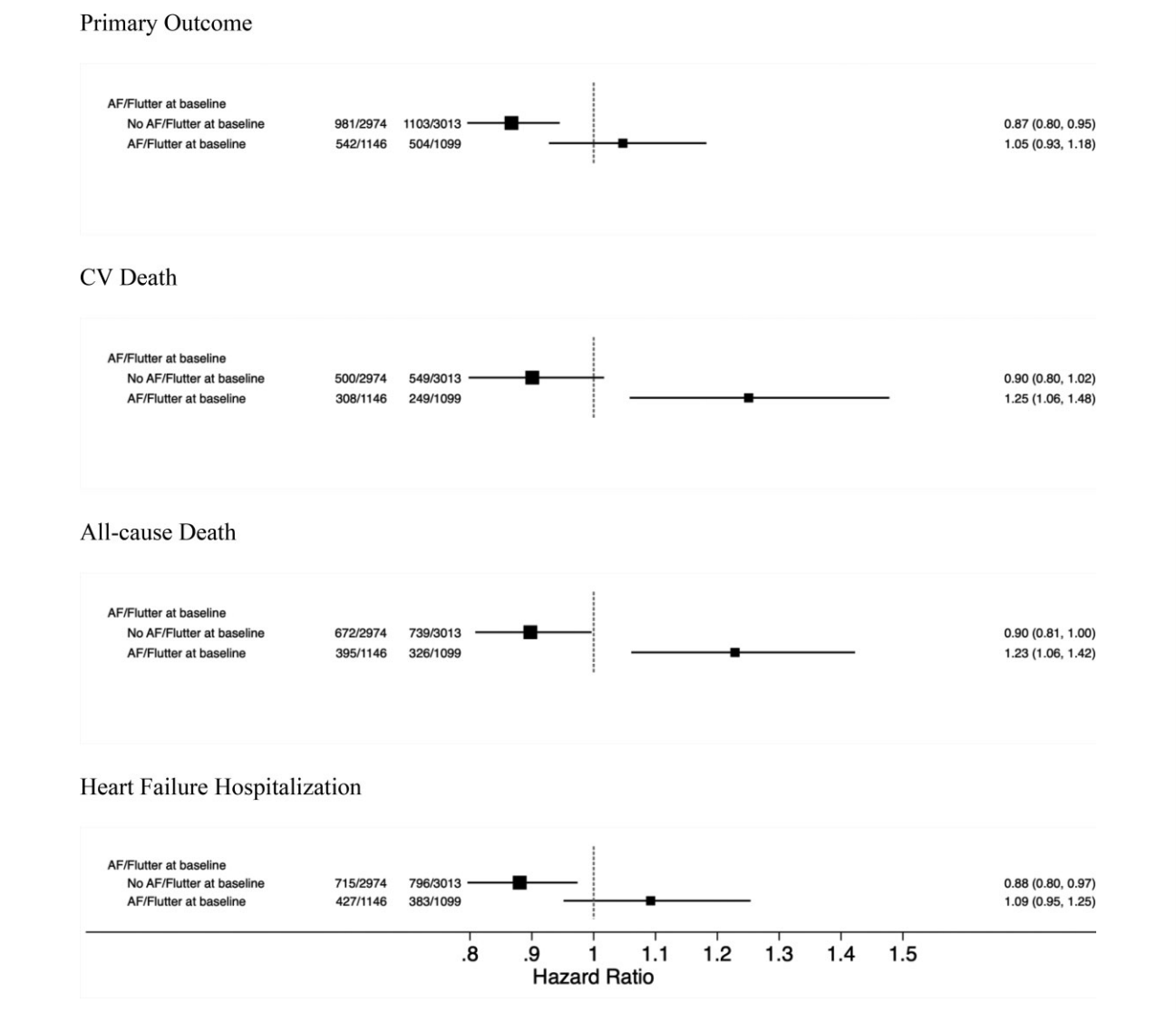

Figure 1 Outcomes by atrial fibrillation/flutter status at baseline. AF, atrial fibrillation; CV, cardiovascular.

the rationale for digoxin use is likely different in patients in AFF, where digoxin is primarily used for rate control, while in patients without AFF, digoxin is mainly used as an adjunct to standard of care heart failure therapy due to its inotropic properties. Patients who were not in AFF but were prescribed digoxin had lower ejection fraction, a group that in prior analyses appears to derive greater benefit from omecamtiv mecarbil.[9]

Another possible explanation for these findings is a pharmacokinetic interaction between the two drugs. This is less likely given the finding that plasma drug concentration levels for omecamtiv mecarbil were similar both in patients with AFF at baseline who were or were not taking digoxin and in digoxin patients who were or were not in AFF. It is also important to note, in the setting of the pharmacokinetic-based dose titration algorithm embedded within GALACTIC-HF, the dosing of omecamtiv mecarbil was similar in the patients with baseline AFF receiving digoxin compared with those patients with AFF not receiving digoxin, and in the patients on digoxin who were or were not in AFF. Alternatively, it is also conceivable that omecamtiv mecarbil may have resulted in altered digoxin concentrations. However, a Phase 1 study evaluating drug–drug interactions between omecamtiv mecarbil and digoxin revealed <8% change in digoxin exposure with coadministration of omecamtiv mecarbil, and urinary elimination of digoxin was comparable between digoxin administered alone and digoxin in conjunction with omecamtiv mecarbil.[10]

Another possibility is the presence of a pharmacodynamic interaction between omecamtiv mecarbil and digoxin, although the mechanistic basis of these findings remains unclear. The finding that there is a differential impact of digoxin that is dependent on whether the patients were in AFF or not highlights the complexity of this hypothesis. Several other studies have suggested increased risk in atrial fibrillation patients taking digoxin. The AnTicoagulation and Risk factors In Atrial fibrillation-Cardiovascular Research Network (ATRIA-CVRN) study examined the association between newly initiated digoxin and the risks of death and hospitalization in patients with incident atrial fibrillation and without heart failure, and showed

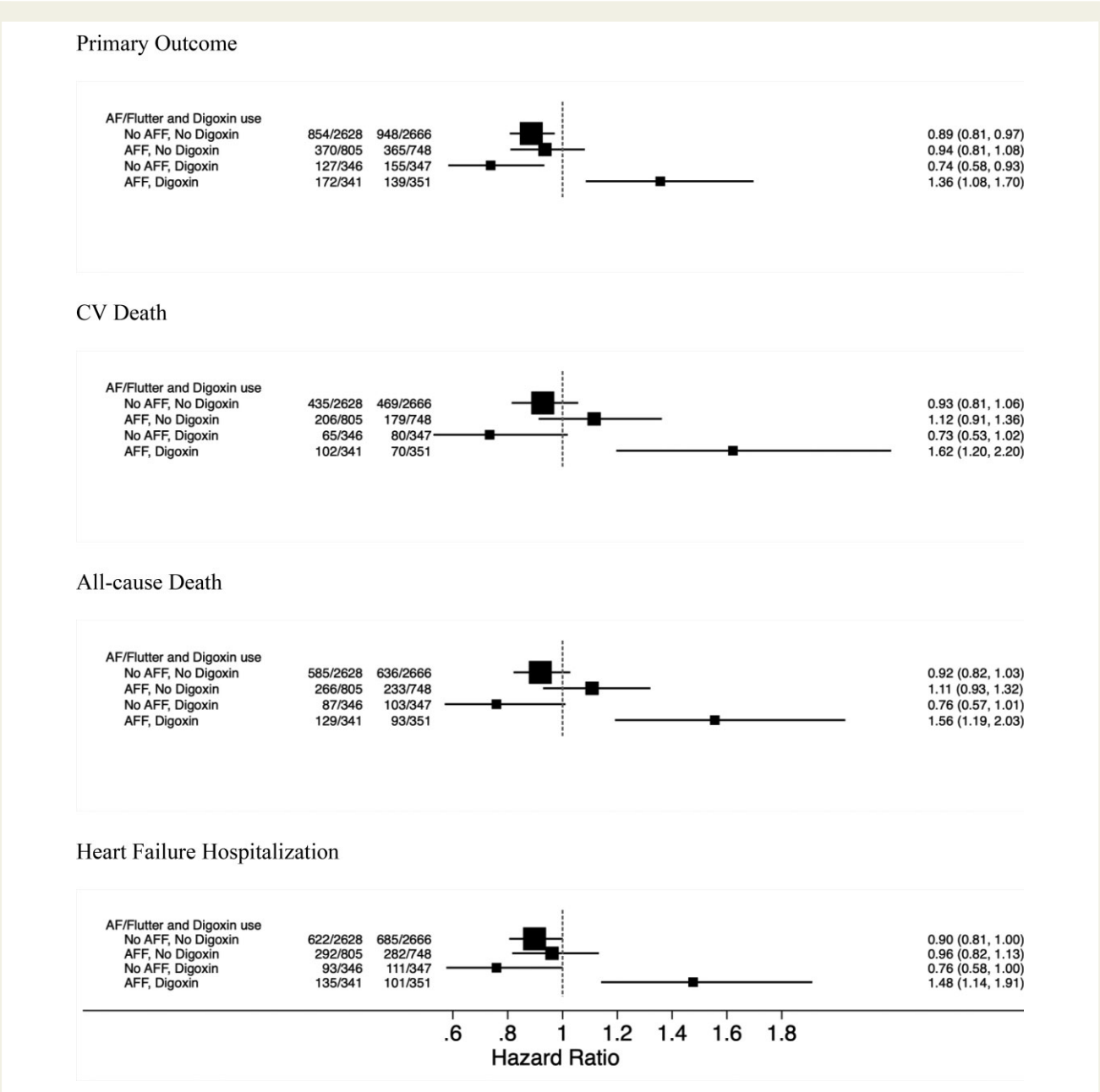

Figure 2 Outcomes by atrial fibrillation/flutter (AFF) status and digoxin use at baseline. AF, atrial fibrillation.

that digoxin use was independently associated with a 71% higher risk of death (HR 1.71, 95% CI 1.52, 1.93) and a 63% higher risk of hospitalization (HR 1.63, 95% CI 1.56, 1.71).[11] Similarly, while the ARISTOTLE study found no overall increase in the risk of death in patients with atrial fibrillation treated with digoxin, those with a serum digoxin concentration ≥1.2 ng/mL had a 56% increased hazard of mortality (adjusted HR 1.56; 95% CI 1.20, 2.04) compared with those not on digoxin, results that were similar for patients with and without heart failure.[12] While we did not see evidence of increased digoxin dose at baseline in patients in AFF compared with those not in AFF, digoxin is typically titrated to higher doses in patients for whom it is being prescribed for rate control compared with doses utilized for inotropy, and post-randomization digoxin concentrations may have been higher in these patients. Finally, while it is possible that omecamtiv mecarbil might potentiate the adverse effects of digoxin in patients in AFF, this does not appear to be mediated by a differential elevation in serum troponin in AFF patients taking digoxin. Nevertheless, the lower 95% CI for all outcomes in AFF patients taking digoxin were >1.0 raises concern that the use of omecamtiv mecarbil in patients with AFF taking digoxin might be associated with increased harm.

A number of limitations of this analysis should be noted. While AFF at baseline was a pre-specified subgroup in GALACTIC-HF, the use of digoxin was not, and the influence of digoxin use on the noted AFF effect modification should be considered exploratory and hypothesis-generating, especially given the very small number

of patients in this subgroup. Nevertheless, the potential that the combination use of omecamtiv mecarbil and digoxin in patients with AFF might be associated with harm should give these findings more credence. We were unable to directly assess the effects of omecamtiv mecarbil on digoxin levels and cannot determine if increased digoxin levels in AFF patients taking omecamtiv mecarbil might have mediated the increased risk in these patients.

In summary, we found that AFF at baseline was associated with lower effectiveness of omecamtiv mecarbil at reducing cardiovascular death or heart failure events in patients with HFrEF, but that in *post hoc* analyses this attenuation was disproportionally concentrated in patients who were also receiving digoxin. While these results suggest that patients in AFF not taking digoxin may benefit similarly from omecamtiv mecarbil as those not in AFF, they also raise the concern that combination use of omecamtiv mecarbil and digoxin in those with AFF may be harmful.

Supplementary material

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

Funding

This work was supported by a grant from Amgen, Cytokinetics, and Servier.

Conflicts of interest: S.D.S. reports funding to his institution from Amgen and Cytokinetics during the conduct of the study; grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, and Us2.al outside the submitted work; consulting fees from Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, MyoKardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, and Sarepta outside the submitted work; and participation on a Data Safety Monitoring Board or Advisory Board for Janssen outside the submitted work. B.L.C. reports consulting fees from Amgen, Boehringer-Ingelheim, Cardurion, Corvia, MyoKardia, and Novartis outside the submitted work. R.D. reports grants from Amgen outside the submitted work and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Amgen outside the submitted work. G.M.F. reports research grants and consultancy funding to his institution from Amgen and Cytokinetics during the conduct of the study; grants from the National Institutes of Health, the American Heart Association, Novartis, Bayer, Bristol Myers Squibb, and Merck outside the submitted work; consulting fees from Novartis, Bristol Myers Squibb, Medtronic, AstraZeneca, Abbott, Reprieve, and Sequana outside the submitted work; participation on a Data Safety Monitoring Board or Advisory Board for Amgen, Merck, Medtronic, EBR Systems, V-Wave, Liva Nova, Siemens, and Rocket Pharma outside the submitted work. J.J.V.M. reports funding to his institution from Amgen and Cytokinetics during the conduct of the study; personal lecture fees from Abbott, Alkem Metabolics, Eris Lifesciences, Hikma, Lupin, Sun Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Servier, and the Corpus outside the submitted work; and consultancy fees paid to his institution from KBP Biosciences, Bayer, AstraZeneca, Theracos, Ionis, DalCor Pharmaceuticals, Novartis, GSK, Bristol Myers Squibb, Boehringer Ingelheim, Cardurion, and Alnylam outside the submitted work. M.M. reports personal fees for presentations from AstraZeneca, Abbott vascular, Amgen, and Edwards Therapeutics outside the submitted work; personal fees as member of Trials' Committees or speaker fees at sponsored meetings from Actelion, Amgen, Servier, Livanova, Vifor pharma, and WindTree Therapeutics. G.F. reports grants or contracts from the European Commission outside the submitted work; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Bayer and Boehringer Ingelheim outside the submitted work; participation on a Data Safety Monitoring Board or Advisory Board for Bayer and Boehringer Ingelheim outside the submitted work; and other financial or non-financial interests as a Committee Member for Medtronic, Vifor, Amgen, Servier, and Novartis outside the submitted work. A.R.G. reports consulting fees for clinical trials from Amgen, Novartis, KOWA, and Bayer outside the submitted work; personal payments or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Boehringer Ingelheim, AstraZeneca, and Novo Nordisk outside the submitted work; support for attending meetings and/or travel from Pfizer, AstraZeneca, and Boehringer Ingelheim outside the submitted work; leadership or fiduciary role as President, Bulgarian Society of Cardiology 2020-22 outside the submitted work. M.B.Y. reports funding to his institution from Amgen, Bayer, Novartis, and Dalcor Pharmaceuticals outside the submitted work. F.Z. reports consulting fees from Cardior, Cereno pharmaceutical, Cellprothera, Owkin, Novo Nordisk, Vifor, and Fresenius outside the submitted work; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Boehringer and Bayer outside the submitted work; payment for expert testimony from Cardiorentis outside the submitted work; stock or stock options in Cereno pharmaceutical outside the submitted work; and steering committee personal fees from Applied Therapeutics, Amgen, Bayer, Boehringer, CVRx, Novartis, and Merck outside the submitted work. J.R.T. reports research contracts and consulting fees as a chairperson from Amgen and Cytokinetics during the conduct of the study; research funding from Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Medtronic, Novartis, and Windtree Therapeutics outside the submitted work; consulting fees from Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Medtronic, Novartis, Verily, and Windtree Therapeutics outside the submitted work; leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid for Heart Failure Society of America as a Secretary, Treasurer and President-Elect. S.K., S.B.H., and F.I.M. report employment by Cytokinetics Incorporated and stock or stock options in Cytokinetics Incorporated outside the submitted work. Z.M.M., R.C., V.M., P.S., and T.S declare no conflict of interest.

Data availability

Qualified researchers may submit a request containing the research objectives, endpoints/outcomes of interest, a statistical analysis plan, data requirements, a publication plan, and qualifications of the researcher(s). Requests are reviewed by a committee of internal and external advisors. If approved, information necessary to address the research question will be provided under the terms of a data sharing agreement. Data sharing requests will be considered after applications for marketing authorization in the US and Europe have been reviewed and final decisions rendered. There is no end date for eligibility to submit a data sharing request for this study. Requests may be submitted to medicalaffairs@cytokinetics.com.

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