Effects of Omecamtiv mecarbil in heart failure with reduced ejection fraction according to blood pressure: the GALACTIC-HF trial

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Short title: Omecamtiv mecarbil in HFrEF and low blood pressure.

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Abstract

Background

Patients with heart failure with reduced ejection fraction and low systolic blood pressure (SBP) have high mortality, hospitalizations, and poorly tolerate evidence-based medical treatment. Omecamtiv mecarbil may be particularly helpful in such patients. This study examined its efficacy and tolerability in patients with SBP ≤100 mmHg enrolled in GALACTIC-HF.

Methods

GALACTIC-HF enrolled patients with baseline SBP ≥85 mmHg with a primary outcome of time to cardiovascular death or first heart failure event. In this analysis, patients were divided according to their baseline SBP (≤100 mmHg versus >100 mmHg).

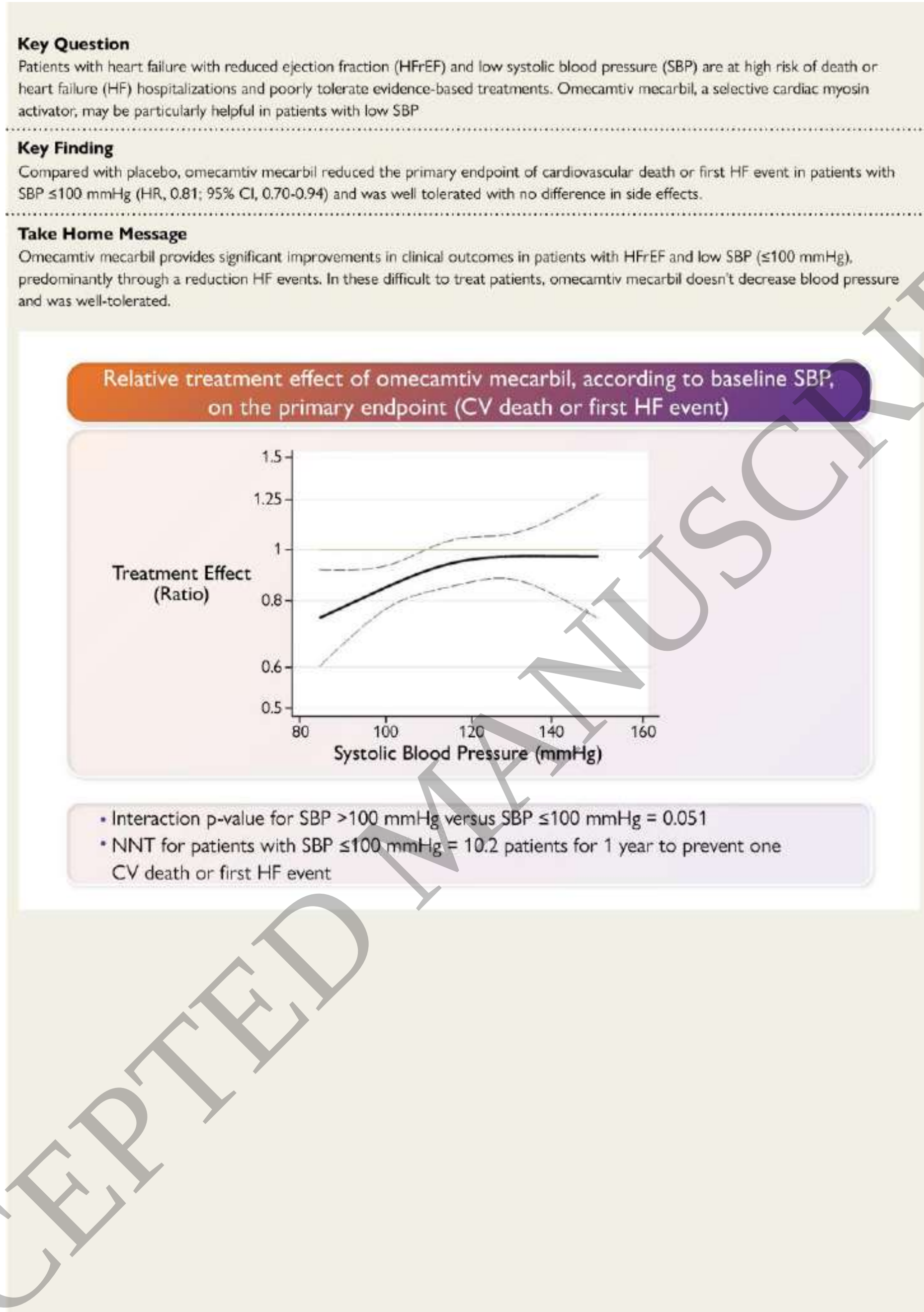
Results

Among the 8,232 analyzed patients, 1,473 (17.9%) had baseline SBP ≤100 mmHg and 6,759 (82.1%) had SBP >100 mmHg. The primary outcome occurred in 715 (48.5%) and 2,415 (35.7%) patients with SBP ≤100 mmHg and >100 mmHg, respectively. Patients with lower SBP were at higher risk of adverse outcomes. Omecamtiv mecarbil, compared with placebo, appeared to be more effective in reducing the primary composite endpoint in patients with SBP ≤100 mmHg (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.70-0.94) compared with those with SBP >100 mmHg (HR, 0.95; 95% CI, 0.88-1.03; p-value for interaction = 0.051). In both groups, omecamtiv mecarbil did not change SBP values over time and did not increase the risk of adverse events, as compared with placebo.

Conclusions

In GALACTIC-HF, risk reduction of heart failure outcomes with omecamtiv mecarbil compared with placebo was large and significant in patients with low SBP. Omecamtiv mecarbil did not affect SBP and was well tolerated independent of SBP values.

Keywords: heart failure; omecamtiv mecarbil; inotrope; myotrope; cardiovascular outcomes trial



Graphical Abstract

INTRODUCTION

Major advances have occurred in the treatment of heart failure (HF) with reduced ejection fraction (HFrEF). However, none of the drugs currently indicated to improve outcome directly affects impaired myocardial function, the primary abnormality leading to HF.[1-3] Traditional inotropic agents (calcitropes) have not improved outcomes in patients with HFrEF, and their untoward effects are related to the increase in intracellular free calcium concentrations.[4] Omecamtiv mecarbil is a myotrope and the first of a new class of direct cardiac myosin activators, improving cardiac function through an increase in actin-myosin interaction without affecting calcium transients.[4-7] Omecamtiv mecarbil increased left ventricular (LV) systolic function and decreased LV volumes, natriuretic peptide concentrations, and heart rate without meaningful changes in blood pressure in prior clinical studies.[8, 9] The Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) trial has demonstrated its beneficial effect on a composite of cardiovascular death or first HF event in 8,256 patients with symptomatic chronic HFrEF.[10]

Low systolic blood pressure (SBP) is reported in 10-20% of patients with HFrEF.[11] It can be a sign of severely impaired LV systolic function,[11] an independent predictor of outcome,[11-19] and a major cause of medication intolerance and lack of titration to target doses of evidence-based medical therapy in patients with HFrEF.[20-25] Treatment of patients with HFrEF and low SBP remains a major challenge for clinical practice. The unique mechanism of action of omecamtiv mecarbil, based on direct improvement of LV systolic function without direct effects on SBP, makes it potentially attractive for patients with low SBP.[26, 27] In GALACTIC-HF, a SBP of ≥85 mmHg and ≤140 mmHg was required for eligibility and SBP at baseline was lower compared with that of all other trials enrolling either outpatients or patients hospitalized with

HF.[28, 29] In addition, and unlike other HFrEF therapies, the beneficial effects of omecamtiv mecarbil tend to increase incrementally as LV ejection fraction (LVEF) decreases and with more severe HF.[10, 28, 30, 31] The aim of the present analysis was to evaluate the safety and efficacy of omecamtiv mecarbil in patients with HFrEF enrolled in the GALACTIC-HF trial (NCT02929329; EudraCT number 2016-002299-28) who had a low SBP at baseline.

METHODS

Study design

The design, baseline characteristics and main results of the GALACTIC-HF trial have been previously reported.[10, 28, 29] In brief, this phase 3, global, double-blind, placebo-controlled randomized clinical trial compared omecamtiv mecarbil to placebo in 8,256 patients with symptomatic HFrEF (New York Heart Association [NYHA] functional class II to IV and LVEF ≤35%). Included patients were currently hospitalized for HF (inpatients) or had either an urgent visit to the emergency department for HF or a hospitalization for HF within 1 year (outpatients). All participants were on optimized background HF therapy and were required to have elevated natriuretic peptides (N-terminal pro-B-type natriuretic peptide [NT-proBNP] level ≥400 pg/ml [1,200 pg/ml for patients in atrial fibrillation] or B-type natriuretic peptide [BNP] ≥125 pg/ml [375 pg/ml for patients in atrial fibrillation]). Key exclusion criteria were hemodynamic or clinical instability requiring mechanical or intravenous therapy, SBP <85 mmHg or >140 mmHg, diastolic blood pressure >90 mmHg, estimated glomerular filtration rate (eGFR) <20 ml/min/1.73 m^2, a recent acute coronary syndrome or cardiovascular procedure (including planned procedures), and other conditions that would adversely affect participation in the trial. All participants provided informed consent and the study protocol was approved by the relevant local ethics committees.

Study outcomes

The pre-specified primary endpoint was a composite of the time-to-first HF event or cardiovascular death. Secondary outcomes of interest included first HF event, first HF hospitalization, cardiovascular death, and all-cause death. A HF event was defined as an urgent clinic visit, emergency department visit, or hospitalization for worsening HF leading to treatment intensification beyond change in oral diuretic therapy.[29] Additional exploratory outcomes and safety outcomes have also been published.[10, 29] All deaths, HF events, major cardiac ischemic events, and strokes were adjudicated by an independent external Clinical Events Committee (Duke Clinical Research Institute) using standardized definitions.[32]

Statistical analysis

In the present analysis, patients were divided into two baseline SBP categories: (i) low SBP, defined as SBP ≤100 mmHg, and (ii) SBP >100 mmHg. Continuous variables are reported as means and standard deviations or medians and interquartile ranges, as appropriate. Categorical variables are reported as number and percentages. Treatment effects on continuous outcomes were assessed via linear regression or quantile regression (for troponin) models adjusted for the corresponding baseline value of the parameter of interest. Survival analyses were conducted using Poisson regression models to estimate incidence rates, rate differences, and rate ratios and Cox proportional hazards models to estimate hazard ratios (HRs) adjusted for eGFR and stratified by region and inpatient status, as in the primary GALACTIC-HF analysis. Kaplan-Meier methods were used to construct cumulative incidence curves for time-to-event data. To allow for potentially non-linear associations between SBP and time-to-event outcomes, restricted cubic splines with 3 knots were applied to the Poisson regression models. Treatment effect modification was assessed via the introduction of interaction terms between randomized treatment assignment and baseline SBP categories. All analyses were performed using STATA version 16 (StataCorp, College Station, Texas, USA). All p-values <0.05 were considered statistically significant. All p-values were 2-sided.

RESULTS

Study population

Among the 8,232 patients analysed from the GALACTIC-HF trial, 1,473 (17.9%) had SBP ≤100 mmHg and 6,759 (82.1%) had SBP >100 mmHg. Mean baseline SBP values were 94.4 ± 5.1 mmHg and 121.3 ± 12.3 mmHg in each group, respectively. As shown in **Table 1**, patients with low SBP were younger and less likely to be from Eastern Europe and Russia. They were also more frequently randomized as inpatients and more likely to have atrial fibrillation/flutter, NYHA III-IV functional class, higher NT-proBNP values, and lower LVEF, Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score and eGFR values. Conversely, patients with SBP >100 mmHg were more likely to have history of hypertension, type 2 diabetes mellitus and ischemic aetiology of HF. Regarding HF therapy, patients with low SBP were less likely to be treated with a beta-blocker plus either an angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), or angiotensin receptor-neprilysin inhibitor (ARNI), though they had a higher use of ARNI alone. Patients with low SBP were also more likely to be treated with mineralocorticoid receptor antagonists, sodium-glucose co-transporter 2 (SGLT2) inhibitors, digitalis glycosides, cardiac resynchronization therapy and implantable cardioverter defibrillators, compared to the higher SBP group. Detailed baseline characteristic in patients with SBP ≤100 mmHg and SBP >100 mmHg, according to randomization status (omecamtiv mecarbil vs. placebo), are shown in **Supplementary Table 1**.

Impact of SBP on outcomes

During a median follow-up of 21.8 months (interquartile range, 15.4 to 28.6 months), the primary composite outcome of first HF event or cardiovascular death occurred in 2,415 (35.7%) patients with SBP >100 mmHg versus 715 (48.5%) patients with low SBP (HR, 0.70; 95% CI, 0.64 to 0.76; p<0.001). The incidence of the primary composite endpoint was 23.0 per 100 patient-years in the SBP >100 mmHg group versus 37.8 per 100 patient-years in the low SBP group. Patients with SBP >100 mmHg also had a lower risk of first HF event (HR, 0.70; 95% CI, 0.64 to 0.78; p<0.001), cardiovascular death (HR, 0.67; 95% CI, 0.59 to 0.75; p<0.001), all-cause death (HR, 0.72; 95% CI, 0.65 to 0.80; p<0.001), and first HF hospitalization (HR, 0.71; 95% CI, 0.65 to 0.79; p<0.001), as compared to those with low SBP.

As shown in **Figure 1A**, the incidence of the primary endpoint increased in both the omecamtiv mecarbil and placebo groups with decreasing SBP. A similar trend was observed for the incidence rate of first HF event (**Figure 1B**) and cardiovascular death (**Figure 1C**). The HR per each 5-mmHg decrease of SBP for the primary composite endpoint was of 1.07 (95% CI, 1.06 to 1.08; p<0.001). After adjustment for several covariates (age, female sex, race, region, inpatient setting, myocardial infarction, coronary artery bypass graft, percutaneous coronary revascularization, stroke, atrial fibrillation or flutter, diabetes mellitus, LVEF, NYHA class, ischemic HF aetiology, KCCQ, heart rate, NT-proBNP, troponin, eGFR), lower SBP remained independently associated with a higher risk of the primary composite endpoint (adjusted HR per each 5-mmHg decrease, 1.05; 95% CI, 1.03 to 1.06; p<0.001). Regarding secondary endpoints, in the overall population lower SBP was significantly associated with a higher risk of cardiovascular death (adjusted HR per each 5-mmHg decrease, 1.08; 95% CI, 1.06 to 1.09; p<0.001), all-cause death (adjusted HR per each 5-mmHg decrease, 1.06; 95% CI, 1.04 to 1.07;

p<0.001), first HF event (adjusted HR per each 5-mmHg decrease, 1.04; 95% CI, 1.03 to 1.06; p<0.001), and first HF hospitalization (adjusted HR per each 5-mmHg decrease, 1.04; 95% CI, 1.03 to 1.06; p<0.001).

Impact of SBP on the treatment effect of omecamtiv mecarbil

Omecamtiv mecarbil administration lead to an 8% reduction in the primary composite endpoint (HR, 0.92; 95% CI, 0.86 to 0.99; p=0.025) in the overall study group in GALACTIC-HF.[28] In a multivariable analysis of continuous covariate interactions of the pre-specified subgroups on the primary endpoint, SBP (per 10 mmHg) was not a significant modifier of the treatment effect of omecamtiv mecarbil (p=0.74). However, with respect to the univariate impact of SBP as a continuous variable, an inverse relationship was observed between the treatment effect of omecamtiv mecarbil for the primary endpoint and baseline SBP modelled as restricted cubic spline, with a larger treatment effect in patients with lower baseline SBP, particularly for SBP values below 100 mmHg (**Figure 2A**, p=0.098). A similar trend between the treatment effect of omecamtiv mecarbil and baseline SBP was observed for the secondary endpoint of first HF event alone, with a larger treatment effect in patients with SBP ≤100 mmHg (**Figure 2B**). Regarding cardiovascular death, an inverse relationship between the treatment effect of omecamtiv mecarbil and baseline SBP was observed, but the effect of omecamtiv mecarbil was not significant across the whole SBP spectrum, since the 95% CI of the treatment effect did not cross 1.00 for any SBP value (**Figure 2C**).

Univariate subgroup analysis showed a 19% relative risk reduction in the primary composite endpoint among patients with SBP ≤100 mmHg randomized to omecamtiv mecarbil, as compared to placebo (HR, 0.81; 95% CI, 0.70 to 0.94), with an absolute risk reduction of 9.8 events per 100 patient-years in this subgroup (**Table 2, Figure 3**). Among patients with SBP

>100 mmHg, no significant difference in the primary outcome was observed between those randomized to omecamtiv mecarbil vs. placebo (HR, 0.95; 95% CI, 0.88 to 1.03; interaction p-value for SBP >100 mmHg versus SBP ≤100 mmHg = 0.051).

The beneficial effect of treatment with omecamtiv mecarbil in patients with SBP ≤100 mmHg was driven predominantly by a reduction in first HF event (**Figure 2B**). Although there was not a significant interaction between SBP as two-categories covariate (≤100 mmHg vs. >100 mmHg) and treatment with omecamtiv mecarbil for first HF event (interaction p-value = 0.08), a larger reduction in first HF event was observed with omecamtiv mecarbil in patients with SBP ≤100 mmHg (HR, 0.81; 95% CI, 0.69 to 0.96) than in those with SBP >100 mmHg (HR, 0.95; 95% CI, 0.87 to 1.04) (**Table 2**). No significant impact of omecamtiv mecarbil, as compared to placebo, was observed for the secondary endpoints of first HF hospitalization, cardiovascular death and all-cause death, considered alone, across the two SBP categories (**Table 2**).

Trend of SBP over time, other outcomes, and safety of omecamtiv mecarbil by SBP

The trend of SBP over time in patients randomized to omecamtiv mecarbil or placebo is depicted in **Figure 4**, showing a similar increase in SBP among patients in both groups (p<0.001 in all groups). From baseline to week 24 (**Table 3**), there was no significant effect of omecamtiv mecarbil on SBP as compared to placebo across both SBP categories (interaction p-value = 0.06). Reduction in NT-proBNP by omecamtiv mecarbil was observed in both SBP categories (interaction p-value = 0.06), with a 18% (95% CI, 10% to 26%) reduction in patients with SBP ≤100 mmHg (p <0.001) and a 9% (95% CI, 5% to 13%) reduction in patients with SBP >100 mmHg (p=0.004) (**Table 3**). Furthermore, a small reduction in heart rate and a small increase in troponin I were observed with omecamtiv mecarbil, which did not differ across SBP categories (interaction p-value = 0.18 for heart rate, interaction p-value = 0.89 for troponin I).

No significant differences were observed in adverse events between omecamtiv mecarbil and placebo groups across the two SBP categories, except for the incidence of any treatment-emergent serious adverse events and of adjudicated first stroke, which were significantly lower among patients with SBP ≤100 mmHg treated with omecamtiv mecarbil (**Table 4**).

DISCUSSION

Our results show that omecamtiv mecarbil, compared with placebo in GALACTIC-HF, had a greater effect on the primary outcome of cardiovascular death or first HF event in patients with a baseline SBP ≤100 mmHg, with a 19% relative risk reduction and a 9.8 events per 100 patient-years absolute risk reduction in these patients (**Structured Graphical Abstract**). A numerically larger reduction in NT-proBNP values was also observed in these patients with a 18% reduction of NT-proBNP at week 24. In addition, omecamtiv mecarbil had no significant effect on SBP and was well tolerated in all patients, independent of baseline SBP values.

SBP is related to stroke volume and peripheral hypoperfusion and is a powerful independent prognostic marker in patients with HF.[11, 33, 34] The lack of decrease in SBP with omecamtiv mecarbil, compared with placebo, and the benefit and tolerance of this drug in patients with the lowest SBP are consistent with its unique mechanism of action based on a direct improvement in cardiac systolic function with no direct effect on neuro-hormonal mechanisms and peripheral resistance.[4, 9] These results are consistent with other recent analyses of GALACTIC-HF demonstrating a greater benefit of omecamtiv mecarbil in patients with lower baseline LVEF[30] and in those with evidence of more severe HF.[31]

GALACTIC-HF enrolled the largest proportion of patients with SBP ≤100 mmHg out of any HFrEF studies to date, and we therefore used this cut-off to define our patient groups. Recent randomized trials investigating ARNI in patients with HFrEF did not include patients with SBP

<95 or 100 mmHg at screening or randomization, respectively.[35-37] Similarly, previous trials with beta-blockers, with the notable exception of Carvedilol prospective randomized cumulative survival (COPERNICUS) trial, and recent trials with SGLT2 inhibitors or vericiguat also excluded patients with SBP <95-100 mmHg.[38-43] In contrast, GALACTIC-HF included patients with SBP ≥85 mmHg, thus providing data on 1,473 enrolled patients with SBP ≤100 mmHg. In our study, patients with low SBP at baseline were less likely to receive evidence-based medical therapy, including ACEi, ARBs and beta-blockers, and had baseline characteristics consistent with more severe HF, as shown by their higher NYHA classes, lower LVEF, worse KCCQ total symptom score, and higher NT-proBNP levels. However, omecamtiv mecarbil showed progressively greater reduction in the incidence of the primary composite outcome as baseline SBP decreased, consistent with its direct effect on myocardial function and the critical role of impaired LV systolic function in the patients with more severe HF.[7-10, 28-31] A lowest value of SBP of 85 mmHg for study enrolment was used also in COPERNICUS trial. The absolute benefit from treatment with carvedilol, versus placebo, was the greatest in patients with the lowest SBP, consistently with the long-term improvement in cardiac function with this agent.[40, 44]

The beneficial effects of omecamtiv mecarbil in patients with low SBP are particularly relevant when considering that these patients are less likely to tolerate evidence-based medical therapy of HFrEF.[11, 15, 16, 20-25] Interestingly, among the 2,079 patients with HFrEF who did not complete the pre-randomization run-in period in the recent Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With an Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, hypotension was one of the most frequent reasons for study drug discontinuation (29.4% and 22.5% of patients who discontinued the study for adverse events during enalapril and sacubitril-valsartan run-in period, respectively).[23] Moreover, although very effective in patients who were able to tolerate it, sacubitril-valsartan was associated with a higher risk of symptomatic hypotension as compared to enalapril among the 8,442 patients with HFrEF who completed the run-in period and were randomized in the PARADIGM-HF trial (14.0% with sacubitril-valsartan vs. 9.2% with enalapril, p<0.001).[37] Thus, SBP reduction is not an untoward event by itself but it may rather reduce tolerability of neurohormonal modulators when it becomes symptomatic. Also in COPERNICUS, although the absolute benefit of treatment with carvedilol was the greatest in the patients with the lowest SBP at baseline, the patients with lower initial SBP were more likely to have an adverse event, be intolerant to high doses of the study drug or require its permanent withdrawal (p < 0.001 for all).[44] SGLT2 inhibitors seem to be less likely to cause hypotension than neurohormonal modulators.[26, 45, 46] The effects of omecamtiv mecarbil in patients with low SBP in GALACTIC-HF are therefore of major value, since they indicate that omecamtiv mecarbil is both well tolerated and has increasing treatment effect at lower SBP with beneficial effects on outcome in patients who often cannot tolerate a neuro-hormonal modulator. Of note, SBP increased from baseline in both treatment groups, though with a numerically larger extent with omecamtiv mecarbil. However, survivor bias might have impacted these results since omecamtiv mecarbil numerically decreased risk of poor outcomes in patients with low SBP, so that there were more patients with low SBP in this group.

Study limitations

The present study has some limitations. First, it represents a *post-hoc* analysis of the GALACTIC-HF randomized trial since no subgroup analysis was pre-specified according to the reported SBP categories (≤100 mmHg vs. >100 mmHg). The SBP categories chosen in our study were arbitrary, although they are clinically meaningful and appear to be useful in clinical practice. Furthermore, subgroup analyses may have limited statistical power because of limited sample size and number of events. However, the analyses of SBP as a continuous variable were performed on the entire GALACTIC-HF population (n=8,232 patients). Another potential limitation is that baseline SBP was investigator-reported. Finally, other patients' characteristics may influence the treatment effect of omecamtiv mecarbil in patients with HFrEF.

CONCLUSIONS

Treatment of patients with HFrEF and low SBP is a major challenge as they do not often tolerate evidence-based treatment. Among patients with symptomatic, chronic HFrEF, enrolled in GALACTIC-HF, treatment with omecamtiv mecarbil compared with placebo was associated with a large and significant reduction in the risk of the composite endpoint of cardiovascular death or first HF event in patients with low baseline SBP (≤100 mmHg). Omecamtiv mecarbil was safe and well-tolerated across different baseline SBP values and did not significantly affect SBP over time.

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Conflicts of interest: Dr. Metra has received funding to his institution from Amgen and Cytokinetics as participant to the Executive Committee during the trial and for patients' enrolment; has received consulting fees for participation to advisory boards from AstraZeneca, Bayer, and Boehringer Ingelheim; has received personal fees as member of Executive or Data Monitoring Committees of sponsored clinical trials from LivaNova and Vifor Pharma; has received speaker fees from Abbott Vascular and Edwards Therapeutics for speeches at sponsored meetings; and has participated on Data Safety Monitoring boards for Actelion. Dr. Claggett has received consulting fees from Amgen, Cardurion, Corvia, Myokardia, and Novartis. Dr. Diaz has received research grants and other payment or honoraria from Amgen. Dr. Felker has received grant funding to his institution from American Heart Association, Amgen, Bayer, Bristol Myers Squibb, CSL-Behring, Cytokinetics, Merck, Myokardia, and National Institutes of Health; has received consulting fees from Abbott, American Regent, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cardionomic, Cytokinetics, Medtronic, Myovant, Novartis, Reprieve, Sequana, Windtree Therapuetics, and Whiteswell; and has participated on Data Safety Monitoring boards or advisory boards for EBR Systems, LivaNova, Medtronic, Siemens, Rocket Pharma, and V-Wave. Dr. McMurray has received funding to his institution from Amgen and Cytokinetics for his participation in the Steering Committee for the ATOMIC-HF, COSMIC-HF and GALACTIC-HF trials and meetings and other activities related to these trials; has received personal fees from Abbott, Alkem Metabolics, Eris Lifesciences, Hikma, Lupin, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Servier, Sun Pharmaceuticals, and The Corpus; and has received funding paid to his institution for activities related to trials or other activities from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardurion, DalCor, GlaxoSmithKline, Ionis Pharmaceuticals, KBP Biosciences, Novartis, and Theracos. Dr. Solomon has received grant funding to his institution from Actelion, Alnylam, Amgen, AstraZeneca, Bayer, Bellerophon, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis Pharmaceuticals, Lilly, Mesoblast, MyoKardia, National Institutes of Health/National Heart, Lung, and Blood Institute, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI; and has received consulting fees from Abbott, Action, Akros, Alnylam, American Regent, Amgen, Anacardio, Arena, AstraZeneca, Bayer, Boeringer-Ingelheim, Bristol Myers Squibb, Cardiac Dimensions, Cardior, Cardurion, CellProThera, Corvia, Cytokinetics, Daiichi-Sankyo, Dinaqor, GlaxoSmithKline, Janssen, Lexicon, Lilly, Merck, Moderna, Myokardia, Novartis, Puretech Health, Quantum Genomics, Roche, Sanofi Pasteur, Sarepta, Tenaya, Theracos, and Tremeau. Dr. Bonderman has received research grants from Abbott, Bayer, Boehringer Ingelheim, Novartis, Pfizer, SOBI, and Zoll; has received consulting fees from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Ionis Pharmaceuticals, Novartis, Novo Nordisk, Pfizer, SOBI, and Zoll; has received speaker fees or honoraria and support for attending meetings and/or travels from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Ionis Pharmaceuticals, MSD, Novartis, Pfizer, SOBI, and Zoll; and is in the European Society of Cardiology Working Group on Pulmonary Circulation & Right Ventricular Function. Dr. Fang has served on the Board of Directors for the Heart Failure Society of America. Dr. Fonseca has received personal fees for consulting from AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Servier, and Vifor

Pharma; has received honoraria for lectures and educational events from AstraZeneca, Bayer, Boehringer Ingelheim, Servier, and Vifor Pharma; has received honoraria for lectures from Novartis; has received support for attending meetings and/or travel from Bayer, Servier, and Vifor Pharma; has participated on advisory boards for Bayer, Boehringer Ingelheilm, Novartis, and Vifor Pharma; and has received grants for medical writing from Merck Serono and Roche. Dr. Goncalvesova has received consulting fees from AOP Orphan Pharmaceuticals, Bayer, Boehringer Ingelheim, Novartis, and Servier; has received personal fees from Bayer, Boehringer Ingelheim, Janssen Pharmaceuticals, Novartis, Pfizer, and Servier; and is the President of the Slovak Society of Cardiology. Dr. Howlett has received grants and consulting fees from Amgen, AstraZeneca, Boehringer Ingelheim, Novartis, Novo Nordisk, and Pfizer; has received personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, Novo Nordisk, and Pfizer; and is Co-Chair of the Heart Failure Pathway Group of the Province of Alberta, Heart Failure lead at University of Calgary, and in the Canadian Cardiovascular Society Guidelines and Development Committees. Dr. Li has received research agreements from Amgen during the conduct of the study through the National Center for Cardiovascular Diseases. Dr. O'Meara has received support to her institution (Montreal Heart Institute) for being local Principal Investigator and member of the Steering Committee of the GALACTIC-HF trial from Amgen and Cytokinetics; has received grant funding to her institution (Montreal Heart Institute) for clinical trials from AstraZeneca, American Regent, Cardurion, and Canadian Institutes of Health Research (CIHR); has received consulting fees from AstraZeneca, Bayer, Cytokinetics, Boehringer Ingelheim, Eli Lilly, and Janssen; has received speaker fees or other honoraria from AstraZeneca, Bayer, and Boehringer Ingelheim; and has participated on Data Safety Monitoring boards or advisory boards for Bayer, Boehringer Ingelheim, and the independent COLpEF trial. Dr. Abbasi is an employee and shareholder of Amgen. Drs. Heitner, Kupfer, and Malik are employees and shareholders of Cytokinetics. Dr. Teerlink has received personal fees as Chairperson of the GALACTIC-HF Executive Committee from Amgen and Cytokinetics; has received personal fees for research contracts and/or consulting fees from 3ive Labs, Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardurion, Medtronic, Merck, Novartis, Verily, ViCardia, and Windtree Therapeutics; has served as Secretary and Treasurer of Heart Failure Society of America; and is currently President-Elect of the Heart Failure Society of America. The other authors have no conflicts of interest to disclose.

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FIGURE LEGENDS

Structured Graphical Abstract

In GALACTIC-HF, treatment with omecamtiv mecarbil compared with placebo was associated with a large and significant reduction in the risk of the composite endpoint of cardiovascular death or first HF event in patients with low baseline SBP (≤100 mmHg).

CI = confidence interval; CV = cardiovascular; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; NNT = number needed to treat; SBP = systolic blood pressure.

Figure 1: Incidence rate of clinical outcomes according to baseline SBP.

The figure shows the incidence rate of the primary composite endpoint (panel A), first HF event (panel B), and cardiovascular death (panel C) according to baseline SBP in patients treated with omecamtiv mecarbil (blue lines) or placebo (dark lines).

CV = cardiovascular; HF = heart failure; SBP = systolic blood pressure.

Figure 2: Relative treatment effect of omecamtiv mecarbil, according to baseline SBP, on clinical outcomes.

The figure shows the relative treatment effect of omecamtiv mecarbil vs. placebo, according to baseline SBP, on the primary composite endpoint (panel A), first HF event (panel B), and cardiovascular death (panel C).

CV = cardiovascular; HF = heart failure; SBP = systolic blood pressure.

Figure 3: Kaplan-Meier curves for the primary endpoint by SBP categories.

The figure shows Kaplan-Meier curves for the primary composite endpoint according to treatment with omecamtiv mecarbil or placebo in patients with baseline SBP ≤100 mmHg (panel A) and in those with baseline SBP >100 mmHg (panel B). Hazard ratios and 95% confidence intervals are also reported.

HR = hazard ratio; OM = omecamtiv mecarbil; SBP = systolic blood pressure.

Figure 4: Trend of systolic blood pressure over time.

The figure shows the trend of SBP over time according to treatment with omecamtiv mecarbil or placebo in patients with baseline SBP ≤100 mmHg (panel A) and in those with baseline SBP >100 mmHg (panel B).

OM = omecamtiv mecarbil; SBP = systolic blood pressure.

TABLES

Table 1: Baseline Characteristics of GALACTIC-HF Patients across SBP Subgroups.

	SBP ≤100 mmHg (N=1473)	**SBP >100 mmHg (N=6759)**	**p-value**
Demographics			
Age (years), mean (SD)	63.4 ± 11.9	64.8 ± 11.2	**<0.001**
Sex, female, n (%)	314 (21.3)	1435 (21.2)	0.94
Race, n (%)			**<0.001**
Asian	202 (13.7)	508 (7.5)	
Black or African American	89 (6.0)	473 (7.0)	
Other*	103 (7.0)	460 (6.8)	
White	1079 (73.3)	5318 (78.7)	
Geographic Region, n (%)			**<0.001**
Asia	190 (12.9)	480 (7.1)	
Eastern Europe / Russia	244 (16.6)	2437 (36.1)	
Latin and South America	302 (20.5)	1272 (18.8)	
US and Canada	278 (18.9)	1108 (16.4)	
Western Europe / South Africa / Australasia	459 (31.2)	1462 (21.6)	
Randomization Setting: In-patient	449 (30.5)	1635 (24.2)	**<0.001**
Clinical Characteristics			
Medical Conditions, n (%)			
History of Myocardial Infarction	599 (40.7)	2836 (42.0)	0.36
History of Coronary Artery Bypass Surgery	251 (17.0)	1066 (15.8)	0.23
History of Percutaneous Coronary Revascularization	433 (29.4)	2005 (29.7)	0.84
Stroke	147 (10.0)	607 (9.0)	0.23

	SBP ≤100 mmHg (N=1473)	SBP >100 mmHg (N=6759)	p-value
Atrial fibrillation or flutter at Screening	438 (29.7)	1807 (26.7)	**0.019**
Hypertension	753 (51.1)	5031 (74.4)	**<0.001**
Type 2 diabetes mellitus	533 (36.2)	2776 (41.1)	**<0.001**
Heart Failure History			
LVEF (%), mean (SD)	24.3 ± 6.3	27.0 ± 6.2	**<0.001**
NYHA classification, n (%)			**<0.001**
Class II	728 (49.4)	3640 (53.9)	
Class III	678 (46.0)	2938 (43.5)	
Class IV	67 (4.5)	181 (2.7)	
Ischemic heart failure etiology	709 (48.1)	3706 (54.8)	**<0.001**
KCCQ Total Symptom Score, median [Q1, Q3]	66.7 [45.8, 87.5]	69.8 [50.0, 87.5]	**0.002**
Outpatient	72.9 [55.2, 89.6]	75.0 [55.2, 91.7]	0.09
Inpatient	51.0 [30.2, 71.9]	54.2 [33.3, 70.8]	0.34
Vitals and Laboratory Parameters			
SBP (mmHg), mean (SD)	94.4 ± 5.1	121.3 ± 12.3	**<0.001**
Heart rate (bpm), mean (SD)	72.4 ± 12.3	72.4 ± 12.1	1.00
NT-proBNP (pg/mL), median [Q1, Q3]	2829 [1432, 5592]	1856 [924, 3770]	**<0.001**
Cardiac Troponin I (ng/L), median [Q1, Q3]	29 [14, 55]	26 [14, 50]	**0.035**
eGFR (mL/min/1.73m^2), median [Q1, Q3]	55.3 [40.7, 71.6]	59.4 [44.9, 74.4]	**<0.001**
Medications and Cardiac Devices, n (%)			
ACEi, ARB or ARNi	1249 (84.8)	5910 (87.4)	**0.006**
ARNi	416 (28.2)	1185 (17.5)	**<0.001**
BB	1357 (92.1)	6406 (94.8)	**<0.001**

	SBP ≤100 mmHg (N=1473)	SBP >100 mmHg (N=6759)	p-value
MRA	1192 (80.9)	5205 (77.0)	**0.001**
SGLT2 Inhibitors	52 (3.5)	166 (2.5)	**0.020**
Ivabradine	109 (7.4)	424 (6.3)	0.11
Digitalis Glycosides	287 (19.5)	1098 (16.2)	**0.003**
Cardiac Resynchronization Therapy	322 (21.9)	836 (12.4)	**<0.001**
Implantable Cardioverter Defibrillator	632 (42.9)	1982 (29.3)	**<0.001**

*Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or multiple self-identified races.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; eGFR, estimated glomerular filtration rate; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT2, sodium-glucose co-transporter 2.

1 **Table 2: Clinical Outcomes**

Outcome by SBP	Omecamtiv mecarbil		Placebo			
	n/N (%)	Rate (per 100 pt-yrs)	n/N (%)	Rate (per 100 pt-yrs)	HR (95% CI); p-value	ARR (per 100 pt-yrs)
Primary Outcome					Interaction p = 0.051	
SBP ≤100 mmHg	350/781 (45%)	33.4	365/692 (53%)	43.2	0.81 (0.70, 0.94); p=0.005	9.8
SBP >100 mmHg	1173/3339 (35%)	22.4	1242/3420 (36%)	23.6	0.95 (0.88, 1.03); p=0.19	1.2
First HF Event					Interaction p = 0.08	
SBP ≤100 mmHg	273/781 (35%)	26.1	284/692 (41%)	33.6	0.81 (0.69, 0.96); p=0.013	7.5
SBP >100 mmHg	904/3339 (27%)	17.3	952/3420 (28%)	18.1	0.95 (0.87, 1.04); p=0.30	0.9
First HF Hospitalization					Interaction p = 0.16	
SBP ≤100 mmHg	264/781 (34%)	24.9	267/692 (39%)	30.6	0.85 (0.71, 1.00); p=0.06	5.6
SBP >100 mmHg	878/3339 (26%)	16.6	912/3420 (27%)	17.2	0.97 (0.88, 1.06); p=0.49	0.6
CV Death					Interaction p = 0.27	
SBP ≤100 mmHg	195/781 (25%)	15.0	192/692 (28%)	17.0	0.91 (0.75, 1.12); p=0.38	1.9
SBP >100 mmHg	613/3339 (18%)	10.0	606/3420 (18%)	9.7	1.03 (0.92, 1.15); p=0.59	-0.3
All-cause Death					Interaction p = 0.28	
SBP ≤100 mmHg	245/781 (31%)	18.9	241/692 (35%)	21.3	0.91 (0.76, 1.09); p=0.31	2.4
SBP >100 mmHg	822/3339 (25%)	13.4	824/3420 (24%)	13.2	1.02 (0.92, 1.12); p=0.75	-0.3

2 Data are reported as n/N (%), rate (per 100 patient-years), HR with 95% CI and ARR.

3 ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; SBP, systolic blood pressure.

Table 3: Treatment Effects of Omecamtiv Mecarbil versus Placebo on Selected Vital Signs and Laboratory Values from Baseline to Week 24.

Variable Difference (95% CI) p-value	**SBP ≤100 mmHg (N=1473)**	**SBP >100 mmHg (N=6759)**	**p-value**
SBP (mmHg)	+1.1 (-0.5, +2.7) 0.17	-0.6 (-1.4, +0.1) 0.09	0.06
Heart rate (bpm)	-2.3 (-3.5, -1.1) <0.001	-1.4 (-1.9, -0.9) <0.001	0.18
Potassium (mmol/L)	-0.02 (-0.08, 0.04) 0.43	+0.01 (-0.02, +0.03) 0.69	0.36
Creatinine (mg/dL)	-0.02 (-0.06, +0.02) 0.36	0.01 (-0.00, +0.03) 0.15	0.13
NT-proBNP (pg/mL; Ratio)	0.82 (0.74, 0.90) <0.001	0.91 (0.87, 0.95) <0.001	0.06
Troponin I (ng/L)	+5 (+3, +7) <0.001	+4 (+3, +5) <0.001	0.89

Values represent treatment effects as evaluated by between-group differences of change from baseline to Week 24.

CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.

1 **Table 4: Safety Outcomes.**

Safety outcomes OM: n (%) Placebo: n (%) RR (95% CI) p-value	**SBP ≤100 mmHg (N=1473)**	**SBP >100 mmHg (N=6759)**
Any Treatment-Emergent Serious Adverse Events	OM: 495 (63.5) P: 496 (72.0) RR: 0.88 (0.82, 0.95) p <0.001	OM: 1878 (56.4) P: 1939 (56.8) RR: 0.99 (0.95, 1.03) p = 0.72
Adverse Event: Ventricular Tachyarrhythmia	OM: 70 (9.8) P: 75 (11.5) RR: 0.85 (0.63, 1.16) p = 0.32	OM: 220 (7.5) P: 229 (7.6) RR: 0.99 (0.83, 1.18) p = 0.88
Serious Adverse Event: Ventricular Arrhythmia Requiring Treatment	OM: 28 (3.6) P: 32 (4.6) RR: 0.77 (0.47, 1.27) p = 0.31	OM: 91 (2.7) P: 95 (2.8) RR: 0.98 (0.74, 1.30) p = 0.90
Adjudicated First Major Cardiac Ischemic Events	OM: 28 (3.6) P: 26 (3.8) RR: 0.95 (0.56, 1.61) p = 0.85	OM: 172 (5.2) P: 162 (4.7) RR: 1.09 (0.88, 1.34) p = 0.43
Positively Adjudicated Myocardial Infarction	OM: 18 (2.3) P: 17 (2.5) RR: 0.94 (0.49, 1.80) p = 0.84	OM: 104 (3.1) P: 101 (3.0) RR: 1.06 (0.81, 1.38) p = 0.70
Adjudicated First Stroke	OM: 6 (0.8) P: 17 (2.5) RR: 0.31 (0.12, 0.79) p = 0.009	OM: 70 (2.1) P: 95 (2.8) RR: 0.75 (0.56, 1.02) p = 0.07

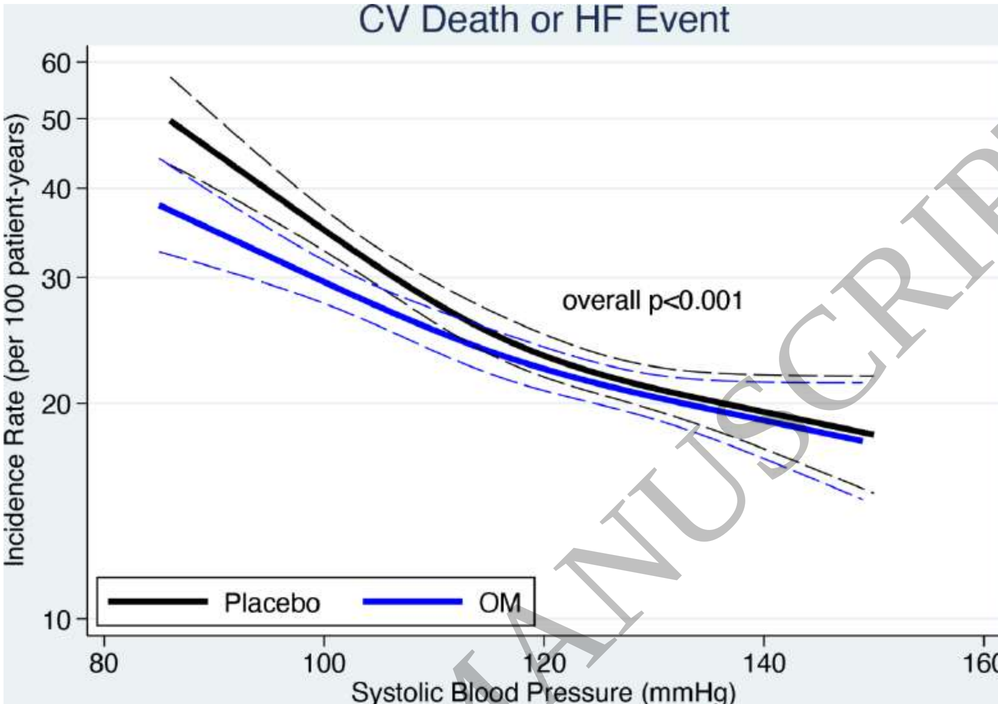
2

3 Values are presented as n (%) and RR with 95% CI.

4 CI, confidence interval; OM, omecamtiv mecarbil; P, placebo; RR, relative risk; SBP, systolic blood pressure.

FIGURES

Figure 1



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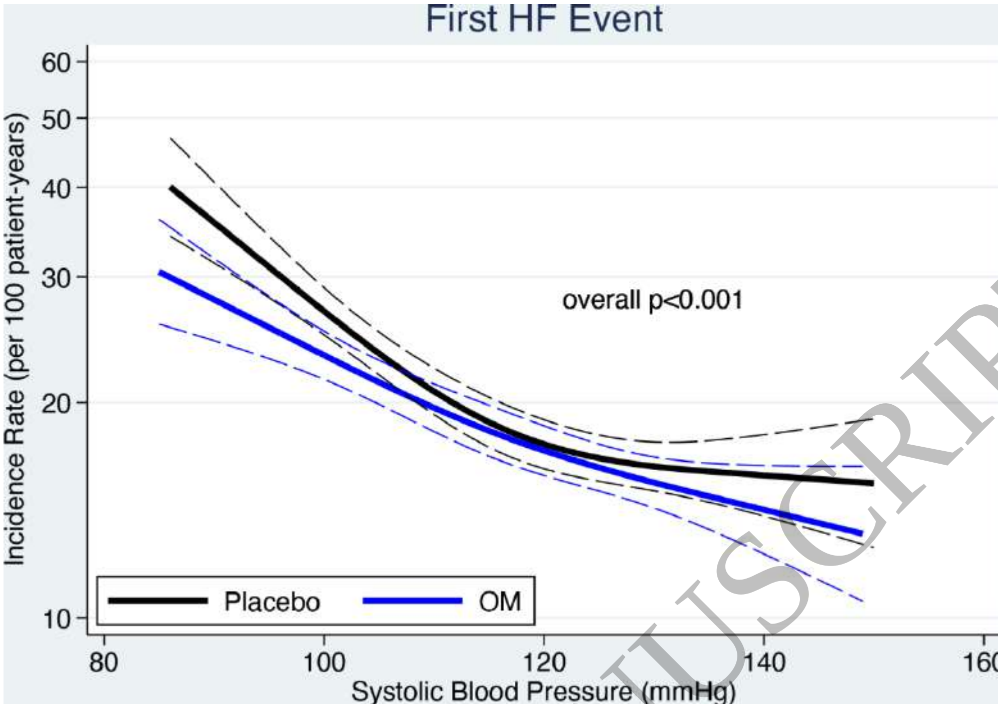

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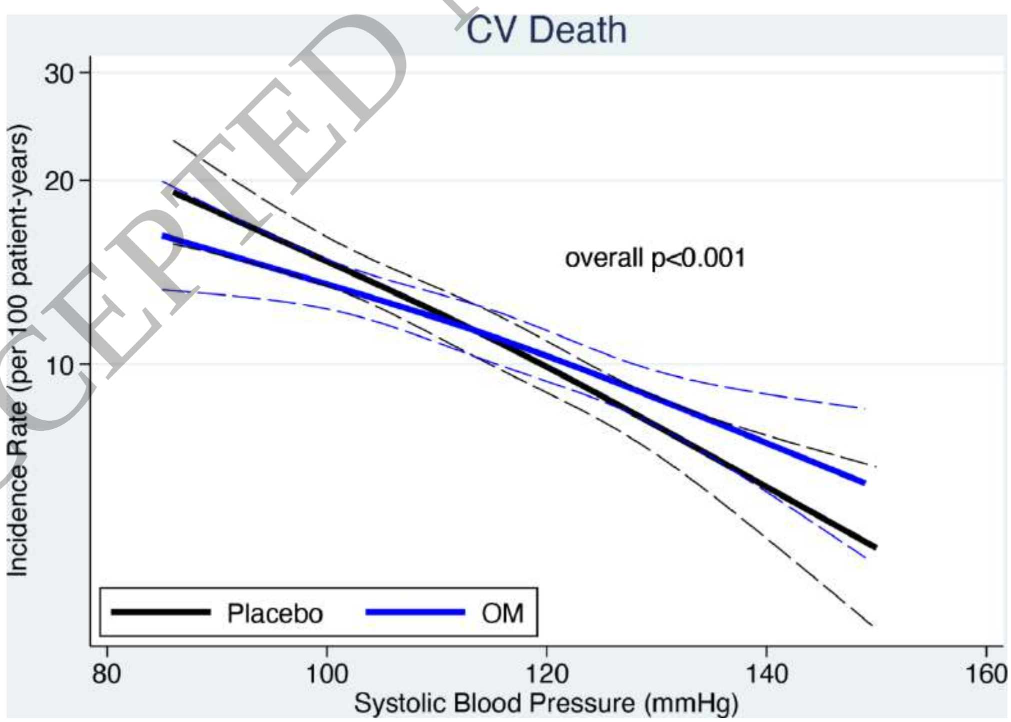

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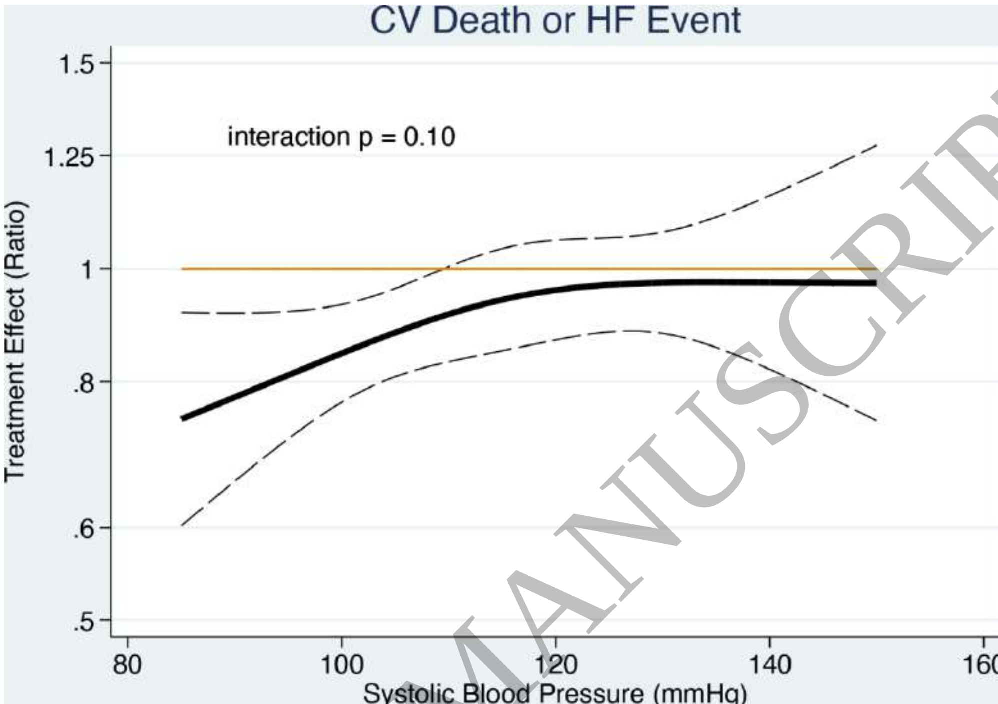
Figure 2



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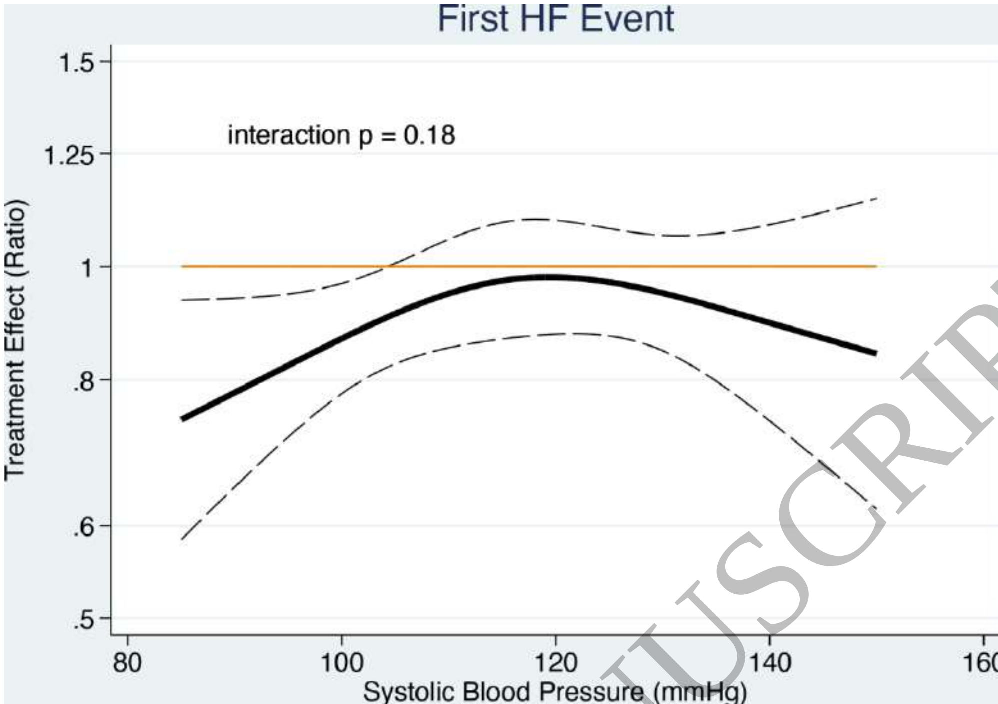

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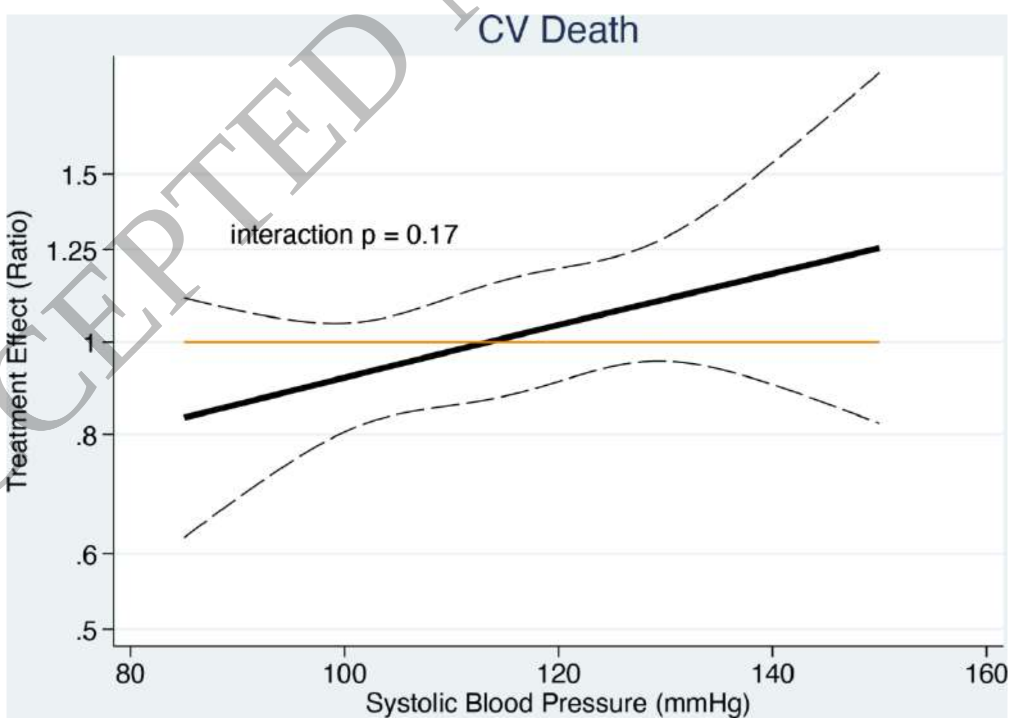

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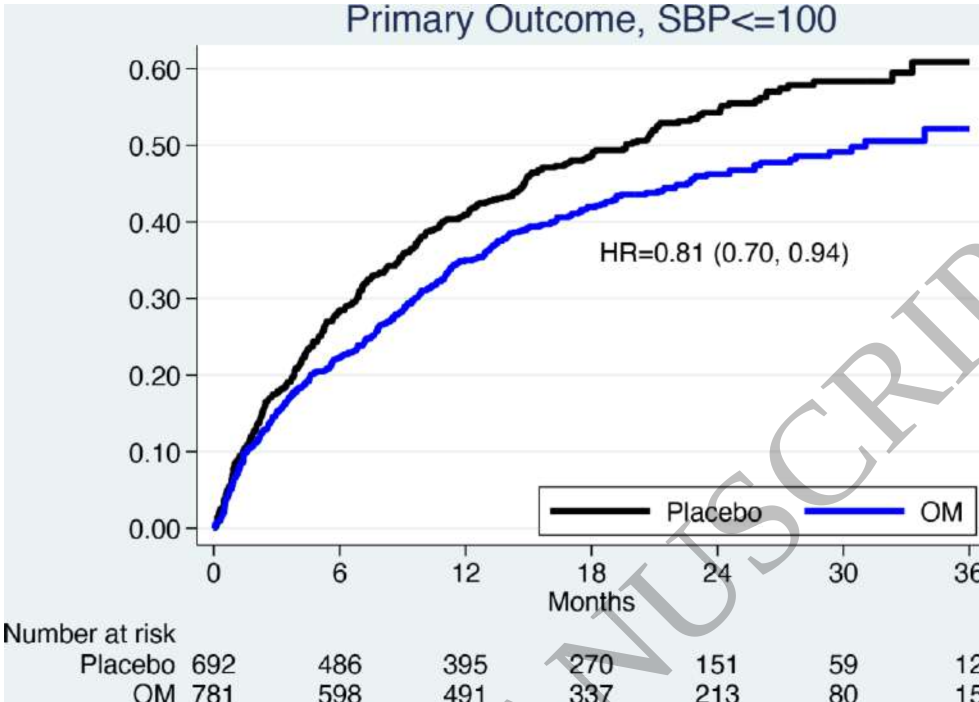
Figure 3



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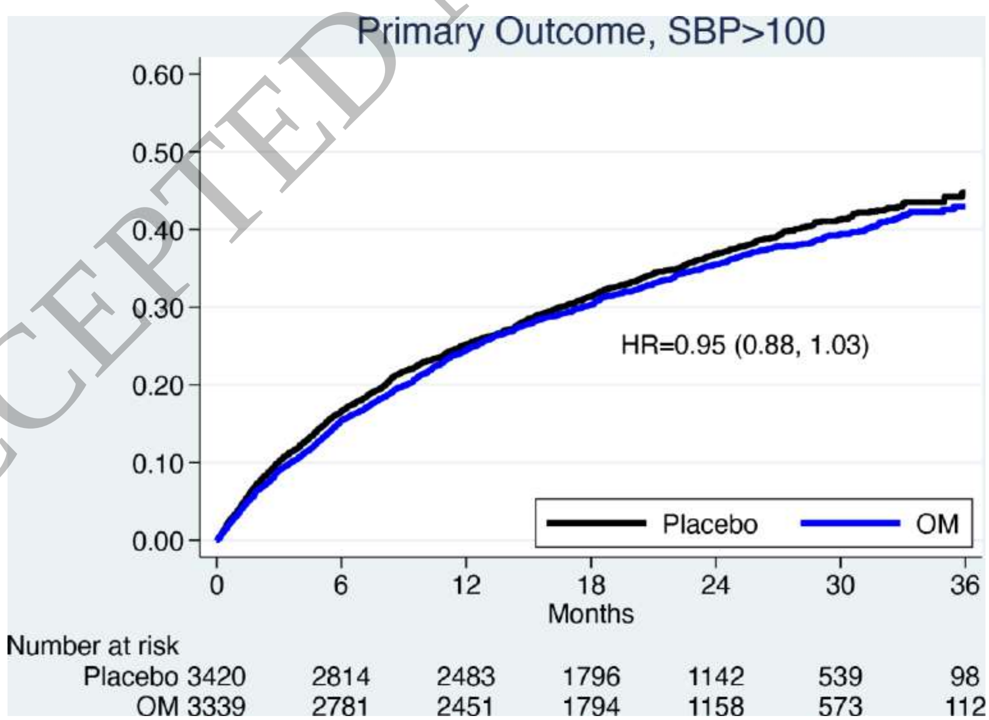

Figure 3B
183x259 mm (5.9 x DPI)

Figure 4

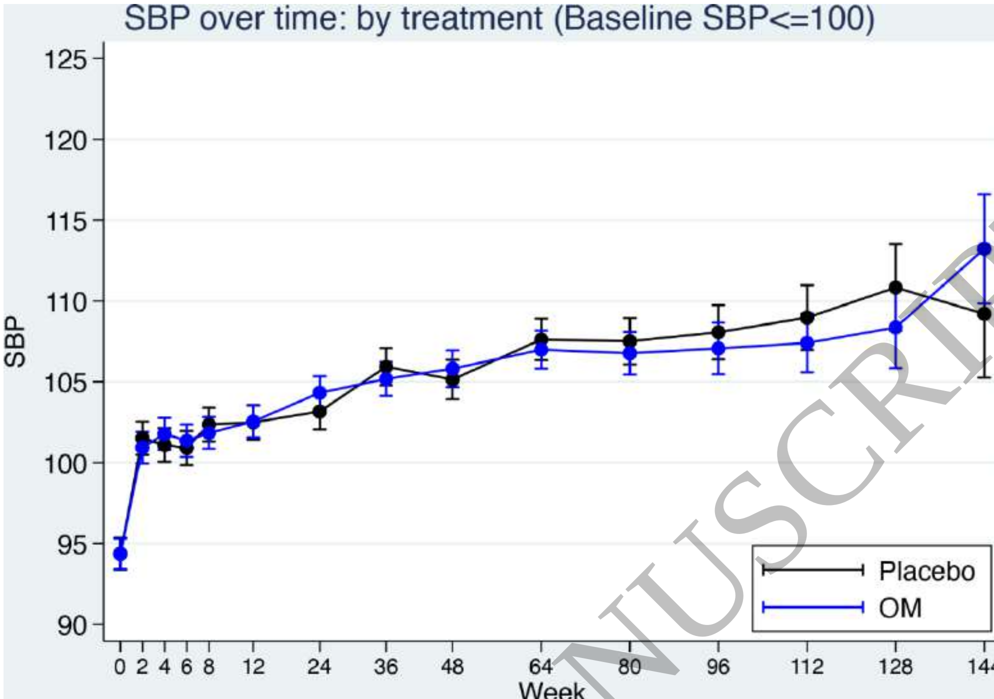

Figure 4A
183x259 mm (5.9 x DPI)

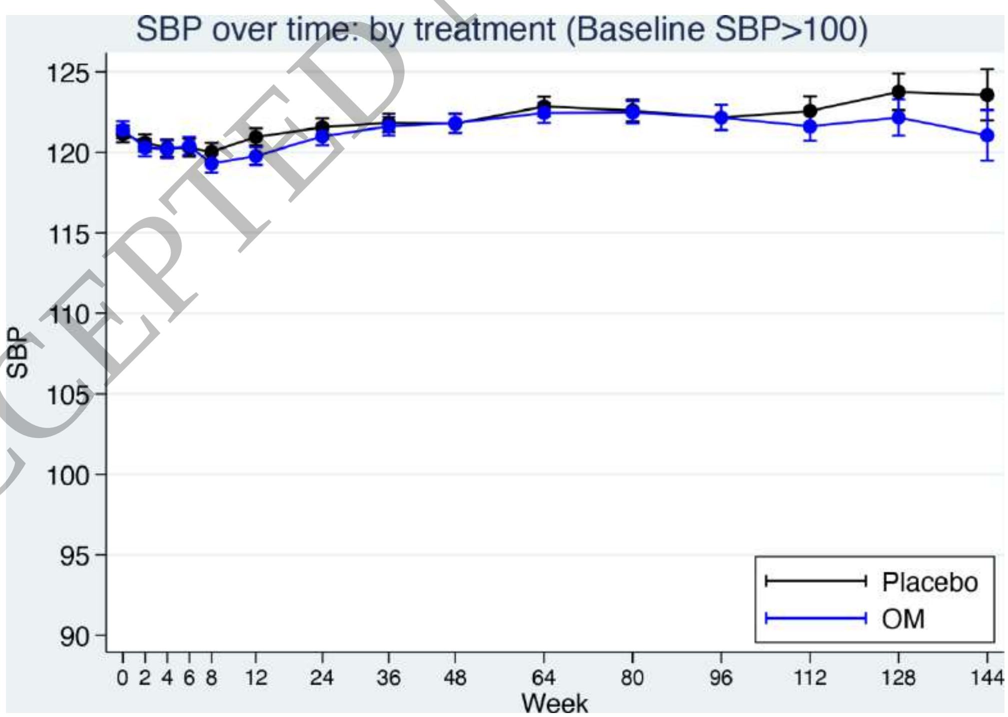

Figure 4B
183x259 mm (5.9 x DPI)