ESC European Society of Cardiology

European Journal of Heart Failure (2022) **24**, 1883–1891
doi:10.1002/ejhf.2677

RESEARCH ARTICLE

Heart failure outcomes according to heart rate and effects of empagliflozin in patients of the EMPEROR-Preserved trial

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Received 16 August 2022; accepted 27 August 2022; online publish-ahead-of-print 4 October 2022

Aims Empagliflozin reduces cardiovascular death (CVD) or heart failure hospitalization (HHF) in patients with heart failure and preserved ejection fraction (HFpEF). Treatment effects and safety in relation to resting heart rate (RHR) have not been studied.

Methods and results The interplay of RHR and empagliflozin effects in EMPEROR-Preserved was evaluated. We grouped patients ($n = 5988$) according to their baseline RHR (<70 bpm [$n = 2650$], 70–75 bpm [$n = 967$], >75 bpm [$n = 1736$]) and explored the influence of RHR on CVD or HHF (primary outcome) and its components in sinus rhythm or atrial fibrillation/flutter (AF) and adverse events. We studied the efficacy of empagliflozin across the RHR spectrum. Compared to placebo, empagliflozin did not change heart rate over time. The primary outcome (p for trend = 0.0004) and its components CVD (p trend = 0.0002), first HHF (p for trend = 0.0099) and all-cause death ($p < 0.0001$) increased with RHR only in sinus rhythm but not AF. The risk increase with RHR was similar in patients with heart failure and mildly reduced ejection fraction (left ventricular ejection fraction [LVEF] 40–49%) and HFpEF (LVEF ≥50%). Baseline RHR had no influence on the effect of empagliflozin on the primary outcomes (p for trend = 0.20), first HHF (p for trend = 0.49). There were no clinically relevant differences in adverse events between empagliflozin and placebo across the RHR groups.

Conclusion Resting heart rate associates with outcomes only in sinus rhythm but not in AF. Empagliflozin reduced outcomes over the entire RHR spectrum without increase of adverse events.

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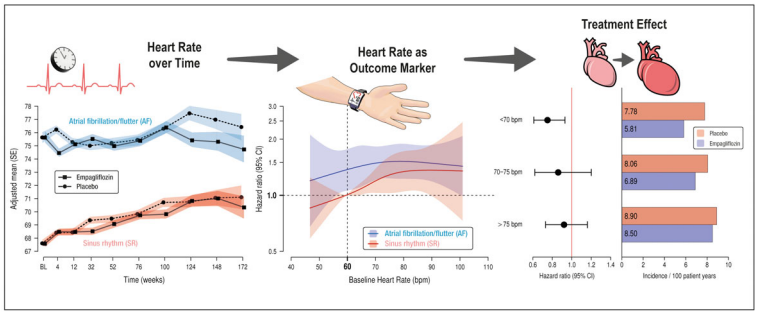
Graphical Abstract

Key question(s)	Key finding(s)	Take-home message
Does resting heart rate in sinus rhythm or atrial fibrillation associate with outcomes in atrial fibrillation or sinus rhythm and modifies the treatment effect of empagliflozin.	Empagliflozin did not change heart rate over time.The primary outcome increased with resting heart rate only in sinus rhythm but not in atrial fibrillation. Baseline resting heart rate had no influence on the treatment effect of empagliflozin.	Resting heart rate associates with outcomes only in sinus rhythm but not in atrial fibrillation. Empagliflozin reduced outcomes over the entire resting heart rate spectrum without increase of adverse events.



Effect of resting heart rate on outcomes and effect of empagliflozin across the resting heart rate spectrum. CI, confidence interval; SE, standard error.

Keywords Empagliflozin • Heart failure • Cardiovascular outcomes • Resting heart rate • Atrial fibrillation

Introduction

Sodium–glucose cotransporter 2 (SGLT-2) inhibitors are recommended in recent guidelines with a class IA evidence for treatment of heart failure with reduced ejection fraction (HFrEF)[1,2] as they reduced cardiovascular death (CVD) and hospitalization for heart failure (HHF) in patients with HFrEF.[3,4] Resting heart rate (RHR) associates with increased HHF and CVD from a RHR rate of 70 bpm upwards,[5] and selective RHR reduction with ivabradine results in reduction of CVD and HHF in HFrEF.[6] Also beta-blockers might meaningfully mediate their effects in HFrEF in part by reducing RHR.[7] In patients with heart failure with preserved ejection fraction (HFpEF), empagliflozin reduced the composite of CVD and HHF[8] but the interplay of these effects with RHR is unknown. Data on the RHR risk association in HFpEF are limited and coming from the CHARM trial[9] and the I-Preserve trial[10] showing a risk to RHR association in sinus rhythm but not in atrial fibrillation/flutter (AF).[9,10] As the data on interplay of HR with outcomes in AF are sparse and the interaction with the treatment effects of empagliflozin in HFpEF are unknown, we have conducted a post-hoc analysis on RHR–risk relationship, effects of empagliflozin on RHR and the treatment effect of empagliflozin according to RHR in patients with sinus rhythm or AF from EMPEROR-Preserved.

Methods

Study design

The design, baseline characteristics[11] and results[8] of the EMPEROR-Preserved trial have been published previously. The ethics committees of each of the 622 participating institutions in 23 countries approved the protocol and all patients gave written informed consent. The registration identifier at ClinicalTrials.gov is NCT03057951.

Studied patients and procedures

Patients with heart failure and an ejection fraction of >40% were screened and those fulfilling eligibility criteria were randomized double-blind in a 1:1 fashion to receive placebo or empagliflozin 10 mg daily in addition to their usual therapy. EMPEROR-Preserved randomized 5988 patients with New York Heart Association class II–IV heart failure. Patients were required to have elevated N-terminal pro-hormone B-type natriuretic peptide (NT-proBNP) levels (>900 pg/ml or > 300 pg/ml in patients with or without AF, respectively) and have evidence of structural heart disease (left ventricular hypertrophy or left atrial enlargement) or a documented HHF within the 12 months prior to enrolment. Patients with or without diabetes were enrolled. During follow-up, all accompanying treatments could be altered or initiated according to the

changes in the clinical status of the patients at the discretion of the investigator.

All randomized individuals were followed up for the occurrence of pre-specified outcomes for the entire duration of the trial regardless of whether the study participants had taken the study medication or were adherent with the study procedures according to the intention-to-treat principle. RHR and blood pressure were taken after resting for 3 min in a sitting position in the presence of the study nurse or investigator. Pulse rate was taken electronically or by palpation for 1 min to reduce variability, in particular in the care of AF. Only patients with complete data on RHR and blood pressure entered the analysis. Patients with paced rhythms or unknown baseline rhythm were excluded from this analysis.

Outcome analyses

Patients were grouped according to RHR at baseline (<70 bpm, 70–75 bpm, >75 bpm) and the groups were studied further by subdividing them into groups with sinus rhythm or AF and HFpEF (ejection fraction ≥50%) or heart failure with mildly reduced ejection fraction (HFmrEF; ejection fraction 40–49%). The cut-offs for RHR were chosen according to previous literature in patients with HFrEF.[5,6,9,10,12] RHR >70 bpm is the cut-off from where risk for HHF is increased,[5,9,10] while the risk is increased for CVD at >75 bpm.[5,12] Consistently, the treatment effect for HHF after RHR reduction with ivabradine is positive at >70 bpm,[5,6] while the death endpoints become significantly reduced by heart rate reduction with ivabradine at >75 bpm. While these interventional data are obtained in patients with HFrEF, similar findings were observed in HFpEF.[9,10] Therefore, the cut-offs <70 bpm (no increase of risk), 70–75 bpm (increase of HHF with positive effects of heart rate reduction) and >75 bpm (positive association with CVD with treatment effects on death endpoints) were chosen.

We evaluated the risk of HF events, CVD and all-cause death treated with placebo and empagliflozin according to RHR. Finally, we compared the effects of empagliflozin versus placebo on the primary composite outcome and its components and all-cause mortality in the overall population and in patients separated by HFmrEF (ejection fraction 40–49%) or HFpEF (ejection fraction ≥50%). In order to understand the influence of post-randomization changes of RHR on empagliflozin's effects, we studied the treatment effects of empagliflozin using RHR at baseline, week 4 and time-updated RHR as covariates (landmark analysis), only considering events after week 4 as the change in RHR from baseline to week 4 was incorporated in the model. Finally, we explored adverse events according to RHR.

Clinical outcomes

The primary endpoint of the composite of adjudicated CVD or HHF was analysed as time-to-first event. The first secondary endpoint was the occurrence of all adjudicated HHF.

Statistical analyses

The effect of empagliflozin compared with placebo on the time-to-first event analyses was examined across the RHR groups using Cox proportional hazard regression models with pre-specified covariates of sex, geographical region, diabetes status at baseline, left ventricular ejection fraction, age and estimated glomerular filtration rate at baseline. The interaction between the RHR subgroups and treatment group on the occurrence of the pre-specified outcomes was tested using a treatment-by-RHR interaction trend test. The first secondary outcome of total (first and recurrent) HHF was evaluated with the use of the joint frailty model that accounted for informative censoring because of CVD. Changes in heart rate over time were analysed in a mixed model with repeated measures. The frequencies of the pre-specified safety outcomes were investigated in a logistic regression model adjusted with the same covariates as the Cox model.

The association between hazard and RHR as continuous variable was analysed non-parametrically using restricted cubic splines allowing for non-linear relationships. Four knots (5th, 35th, 65th, and 95th percentile of baseline RHR) were chosen for the analysis. Hazard ratios (HR) and 95% confidence bands depending on RHR are evaluated using 60 bpm as reference (HR = 1).

All analyses were performed by the sponsor, after agreeing on a statistical analysis plan with the executive committee of EMPEROR-Preserved using SAS version 9.4 (SAS Institute, Cary, NC, USA). All *p*-values reported are 2-sided and $p < 0.05$ was considered as statistically significant in all cases. No adjustments for multiple testing were made due to the exploratory nature of the study.

Results

Patient characteristics

A total of 5988 patients were randomly assigned to receive either empagliflozin ($n = 2997$, 10 mg once daily) or placebo ($n = 2991$). The flow is summarized in online supplementary *Figure S1*. Online supplementary *Table S1* shows the baseline characteristics of patients according to baseline RHR. Patients with a high RHR tended to be more frequently female and have higher NT-pro-BNP levels. There was no difference in the treatment intensity of beta-blockers. A total of 498 patients had paced rhythm and were excluded from the analysis (online supplementary *Figure S1*). Patients in sinus rhythm tended to have a lower RHR than patients in AF (online supplementary *Figure S2*). RHR over time was not different between placebo and empagliflozin treated patients but was higher in AF compared to sinus rhythm (online supplementary *Figure S3*). RHR tended to increase over time from baseline to week 172 in patients with RHR in sinus rhythm and AF (online supplementary *Figure S3*).

Association of resting heart rate with outcomes

The relationship of RHR with outcomes was studied by calculating the incidence rates for major endpoints in the overall population as there was no significant difference in RHR between the empagliflozin and placebo groups at baseline and over time in AF or sinus rhythm (online supplementary *Figure S2*). The cumulative incidence function of the primary endpoint (CVD or HHF), first HHF, CVD and all-cause death according to RHR is shown in *Figure 1*. The incidence rate of the primary outcome was 6.78 at RHR <70 bpm, 7.47 (70–75 bpm) and 8.70 events/100

patient-years (>75 bpm) (p for trend = 0.0004). Increased event rates were also observed for time to first adjudicated HHF (p for trend = 0.0099), first and recurrent HHF (p for trend = 0.012), CVD (p for trend = 0.0002) and all-cause death ($p < 0.0001$). Forest plots (*Figure 2*) summarize these data.

The population was separated by HFmrEF (ejection fraction 40–49%) (primary outcome: p for trend across RHR = 0.01) and HFpEF (ejection fraction ≥50%) (p for trend = 0.01) (*Figure 3A*). The data for the primary outcome were similar in HFmrEF and HFpEF. The data are summarized in *Figure 3*. Interestingly, there was no association of RHR with outcomes in AF (primary outcome: p for trend = 0.55) but for patients in sinus rhythm (p for trend = 0.005). Similar findings were observed for first HHF (*Figure 3B*), CVD (*Figure 3C*) and all-cause death (*Figure 3D*). To account for the non-linear relationship of the RHR–risk association, the HRs for patients in sinus rhythm and AF are given in *Figure 4*. For the primary outcome and first HHF, the reference was taken at 60 bpm as it was shown that the optimal RHR for patients in sinus rhythm on treatment occurred between 50–60 bpm.[3] The cubic spline regression showed an increase of risk up to approximately at >75 bpm in sinus rhythm, while the risk in AF was elevated over the whole spectrum of RHR compared to the nadir in sinus rhythm without meaningful differences across the spectrum of RHR. Similar results were observed for CVD and all-cause death (online supplementary *Figure S4*).

Effect of empagliflozin on efficacy outcomes

The relative risk reduction of the primary outcome by empagliflozin was similar over the entire RHR spectrum (primary endpoint: p for trend = 0.20). Similar results were observed for first HHF (p for trend = 0.49) as well as for CVD (p for trend = 0.64) and all-cause death (p for trend = 0.18). There was no overall effect of empagliflozin on mortality across all RHR groups (*Figure 5C,D*). Furthermore, we evaluated in a landmark analysis the treatment effect of empagliflozin on the primary endpoint analysing events occurring after week 4 by including baseline RHR, baseline RHR plus RHR at week 4, plus time-updated mean RHR with and without treatment interaction to the factors of the standard model. With all models, the HR was between 0.84 and 0.85 for the primary outcome (online supplementary *Figure S5*). Finally, the treatment effect of empagliflozin was not different between AF and sinus rhythm at each level of RHR (primary outcome, <70 bpm:

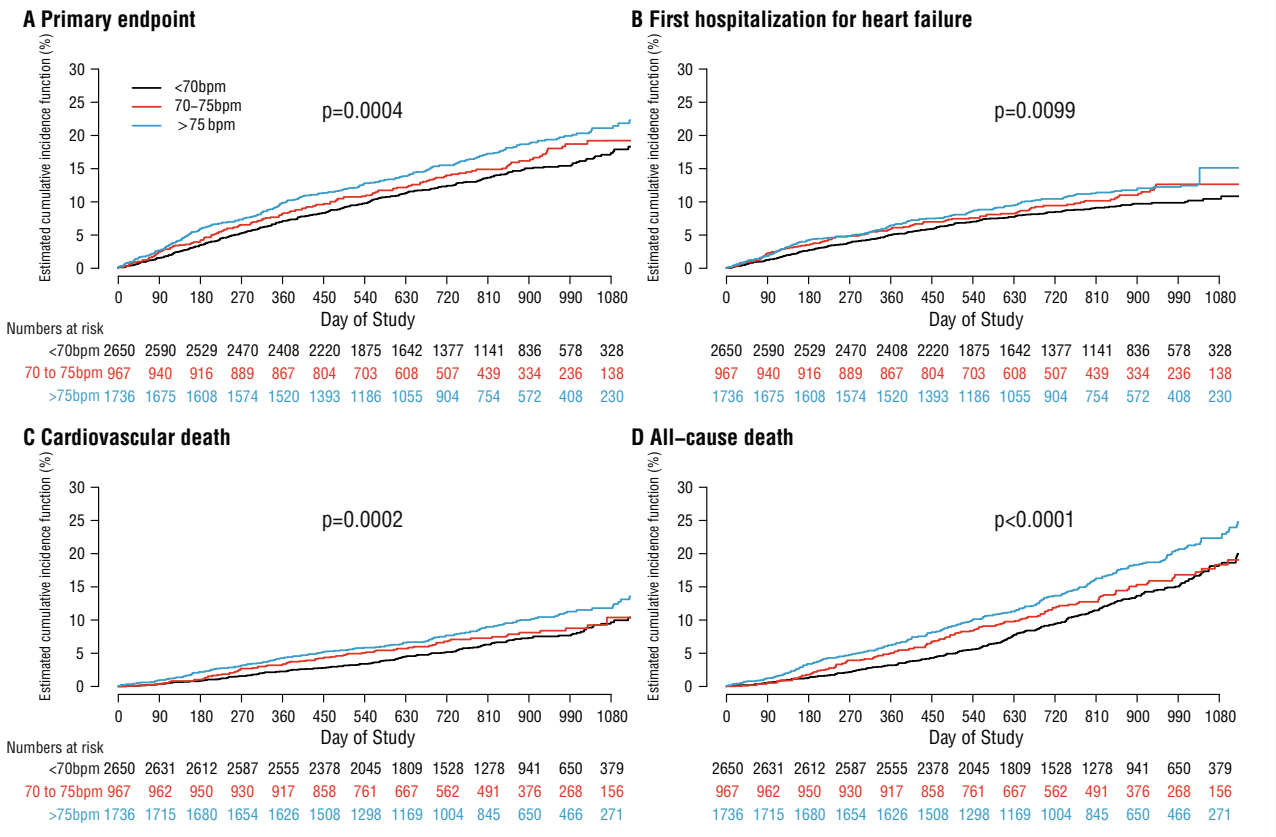


Figure 1 Incidence of heart failure outcomes by resting heart rate. Cumulative incidence function of the primary outcome (composite of first heart failure hospitalization or cardiovascular death) (*A*), first hospitalization for heart failure (*B*), cardiovascular death (*C*) and all-cause death (*D*) according to resting heart rate. Data were adjusted for competing risk by death types, which were not part of the endpoint under investigation (e.g. all-cause death for heart failure hospitalization).

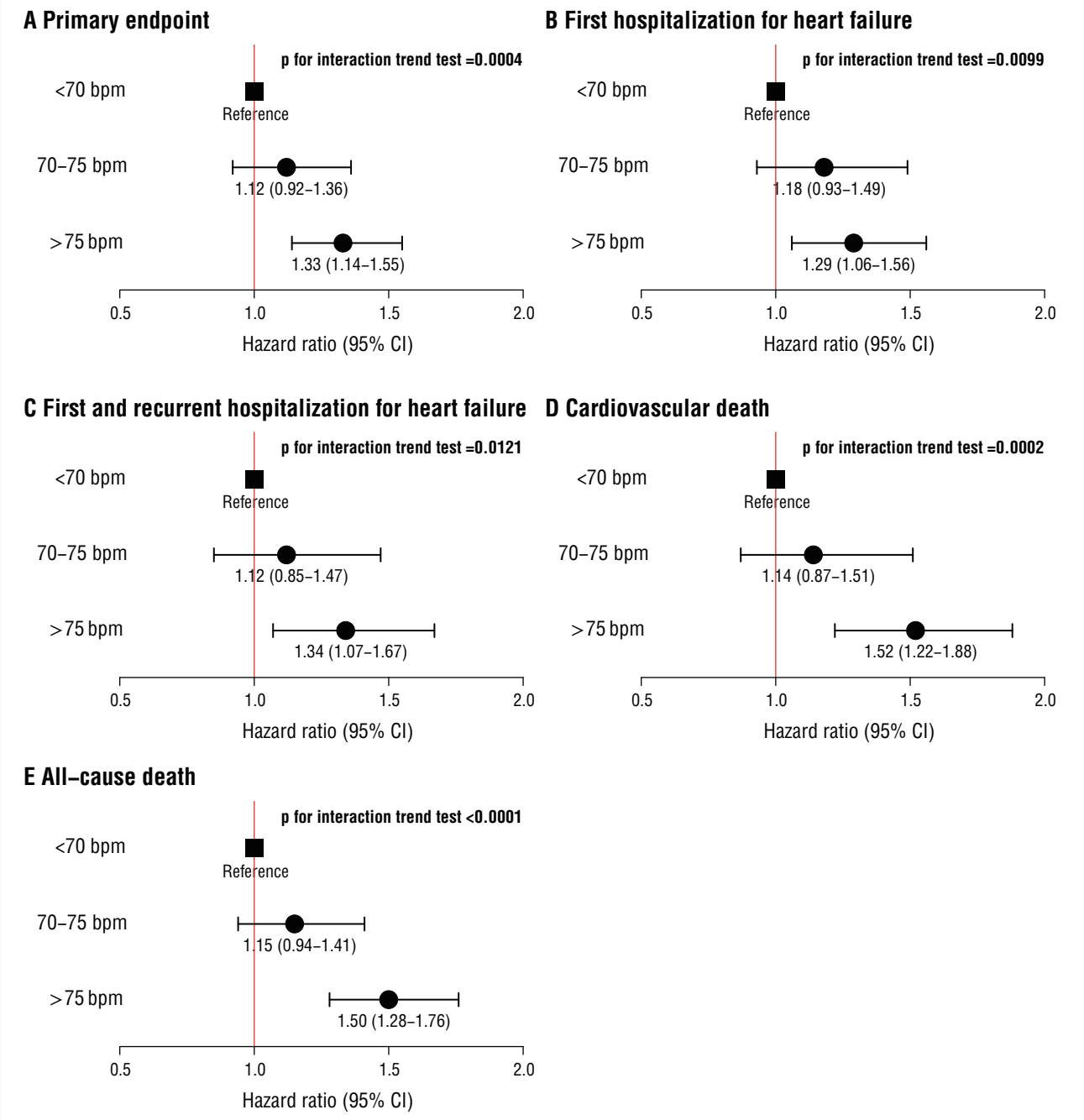


Figure 2 Outcomes according to resting heart rate. Hazard ratio for the primary endpoint (*A*), first hospitalization for heart failure (*B*), first and recurrent hospitalization for heart failure (*C*), cardiovascular death (*D*) and all-cause death (*E*) according to resting heart rate. <70 bpm is given as a reference. CI, confidence interval.

interaction $p = 0.87$, 70–75 bpm: interaction $p = 0.57$, >75 bpm: interaction $p = 0.96$).

Safety assessments

The number of patients with any adverse events leading to discontinuation of study medication was not different between RHR groups and was not meaningfully different between empagliflozin and placebo across RHR. Specifically, there was no difference between acute renal failure, hypotension, urinary tract infection and hypoglycaemic events (online supplementary *Table S2*).

Discussion

Resting heart rate significantly associates with the primary composite outcome of CVD and HHF, its components as well as all-cause

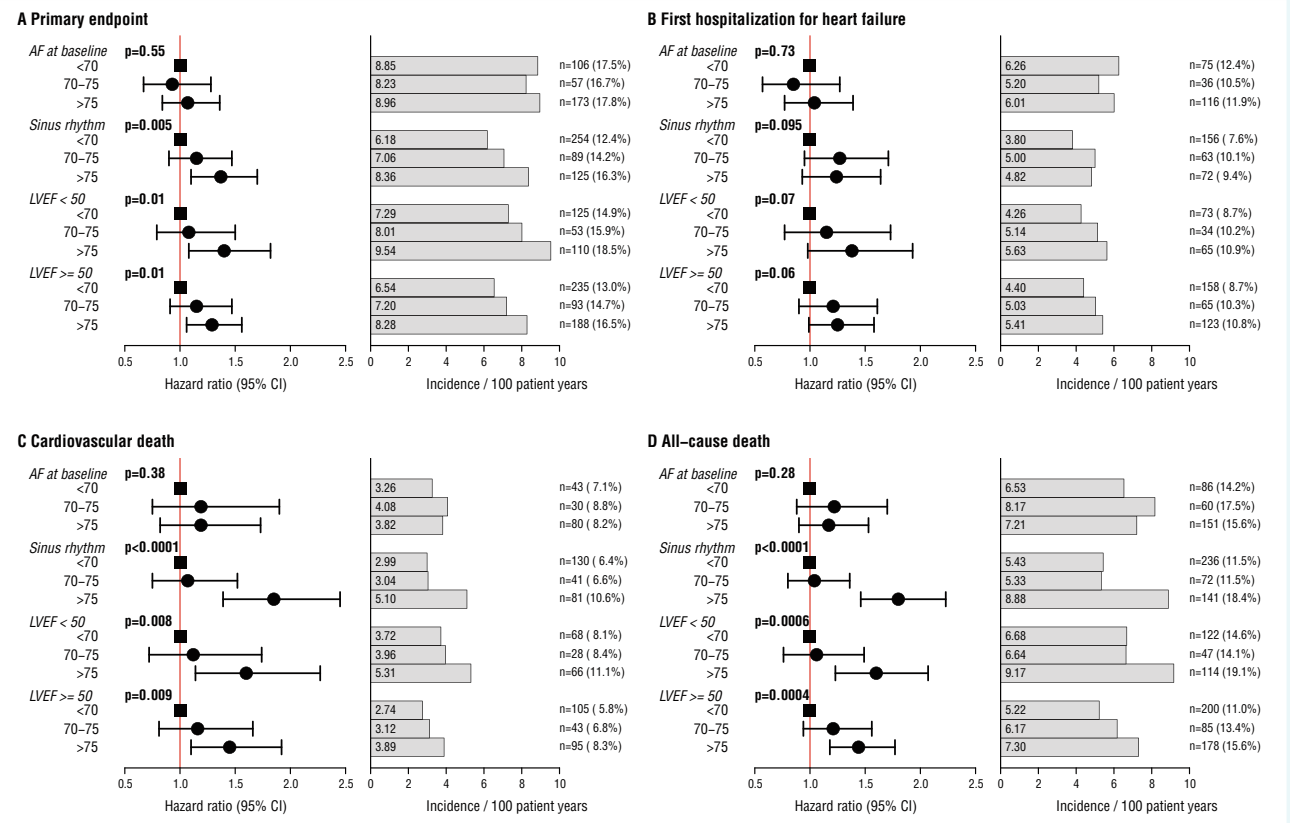


Figure 3 Outcomes according to ejection fraction, rhythm and heart rate. Hazard ratio and incidence per 100 patient-years for the primary endpoint (*A*), first hospitalization for heart failure (*B*), cardiovascular death (*C*) and all-cause death (*D*) in patients with atrial fibrillation/flutter (AF), sinus rhythm, left ventricular ejection fraction (LVEF) 40–49% and LVEF ≥50%. <70 bpm is given as reference. CI, confidence interval.

death. This association was present in patients with sinus rhythm and not observed in AF. There was no difference between patients with an ejection fraction of 40–49% (HFmrEF) or ≥50% (HFpEF). The treatment effects of empagliflozin were not modified by RHR. Serious adverse events were not related to RHR and not different between placebo and empagliflozin (*Graphical Abstract*).

Resting heart rate is a significant predictor for poor outcomes in chronic heart failure with HFrEF with sinus rhythm >70 bpm.[5,12] In patients after myocardial infarction, stroke or proven vascular disease, RHR predicts incident HHF[13,14] and is associated with outcomes in patients with specific cardiac conditions like Takotsubo syndrome[15] and peripartum cardiomyopathy.[16] In turn, specific RHR reduction with ivabradine in HFrEF reduced CVD and HHF.[6] High RHR is also associated with increased vascular stiffness and left ventricular systolic and diastolic function in a mouse model with HFpEF.[17] As stiffness and impaired relaxation[18,19] are clinically important features of HFpEF and RHR reduction improves arterial–ventricular coupling,[20] RHR reduction was tested in patients with HFpEF without effects on ventricular stiffness and relaxation as well as quality of life and 6-min walking distance.[21] In patients from EMPEROR-Preserved, we observed an association of RHR with the primary composite of CVD and HHF as well as first and recurrent HHF, CVD and all-cause death. These data are consistent with secondary analyses from CHARM[9] and I-Preserve.[10] The lowest risk was observed at a RHR between 50–60 bpm in sinus rhythm, which is in line with the on-treatment optimal achieved RHR in patients with HFrEF.[5] Mechanistically, a high RHR shortens the length of diastole[22] and worsens vascular elastance and ventricular loading.[23,24] On exercise, high heart rate increases energy expenditure without contributing to cardiovascular output and associated was the poorer contractility.[24–26] Nevertheless, it has not been proven that length of diastole is related to symptoms or outcomes in HFpEF, as an outcome study on selective RHR reduction in HFpEF has never been performed.

Interestingly, no association between RHR and outcomes was observed in patients with AF. In a small number of patients, this was also seen in CHARM-Preserved[9] and in I-Preserve.[10] The irregularity of the heartbeat has recently shown to importantly affect ventricular remodelling in human myocardium.[27] In ventricular myocytes from patients with AF, Ca^{2+} transients were reduced, which was reproduced in irregularly paced stem cell-derived cardiomyocytes.[27] Furthermore, irregularly paced cardiomyocytes secreted factors propagating myocardial fibrosis, among them transforming growth factor-β and connective tissue growth factor.[28] Therefore, one might suggest that the irregularity of the

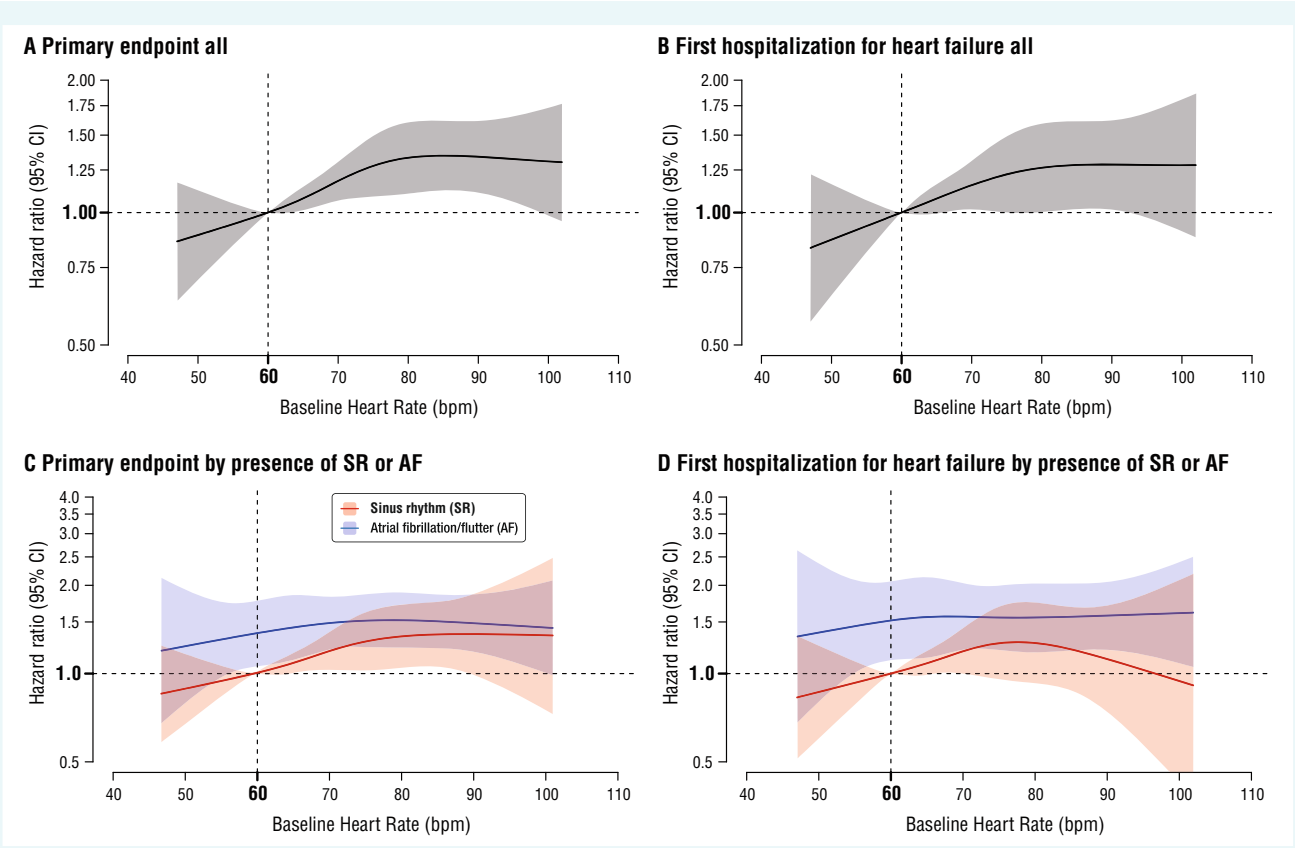


Figure 4 Outcomes according to resting heart rate as a continuous variable. Hazard ratio for the primary endpoint (*A*), first hospitalization for heart failure (*B*) in all patients and the primary endpoint (*C*) and first hospitalization for heart failure (*D*), by presence of sinus rhythm or atrial fibrillation/flutter according to resting heart rate as a continuous variable. CI, confidence interval.

heartbeat could overcome the RHR–risk association since irregularity as such appears to be involved in myocytic[27] and interstitial[28] remodelling. In patients with AF and HFrEF, also the beneficial effects of beta-blockers were not detected[29] and the RHR–risk association disappeared.[30] Finally, strict versus lenient rate control did not change outcomes in patients with AF and HF.[31] Therefore, AF appears to be a condition where the RHR–risk association, but also the efficacy of interventions primarily acting through heart rate reduction, such as beta-blockers,[7] are abolished.[29,30]

Empagliflozin reduced the composite of CVD and HHF as well as first and recurrent HHF.[8] Among the patients included in the EMPEROR-Preserved trial were patients with HFmrEF (ejection fraction 40–49%) and HFpEF (ejection fraction ≥50%).[7,10] In these two groups, there was no different RHR–risk association. In agreement with previous studies, modification of RHR with beta-blockers produced similar effects on outcomes in HFrEF and HFmrEF.[32] Furthermore, no different treatment effects of empagliflozin were observed across the RHR spectrum. The empagliflozin effects were maintained and were not different compared to the overall population across the RHR groups. Therefore, RHR is not an effect modifier of empagliflozin's treatment effects and indicates that even in patients at high risk with higher RHR, the risk–RHR association does not overplay the treatment effects of empagliflozin. Accordingly, there were no safety issues at high or low RHR with adverse events of empagliflozin compared to placebo, indicating that a particular RHR is not a reason to withhold empagliflozin treatment from HFpEF patients.

Limitations

Treatment was not randomized to RHR groups and may be subject to invisible confounding. Furthermore, separating this population by sinus rhythm or AF and HFmrEF or HFpEF rendered numbers lower with the consequence of a limited power to detect changes. However, this is the largest population in HFpEF patients to study the RHR–risk association and treatment effects of empagliflozin in HFpEF patients in sinus rhythm.

Conclusion

Empagliflozin reduces the risk of HF events across all RHR groups. The risk indicator RHR does not limit empagliflozin effects and tolerability, but might serve as a risk marker also for HFpEF in sinus rhythm.

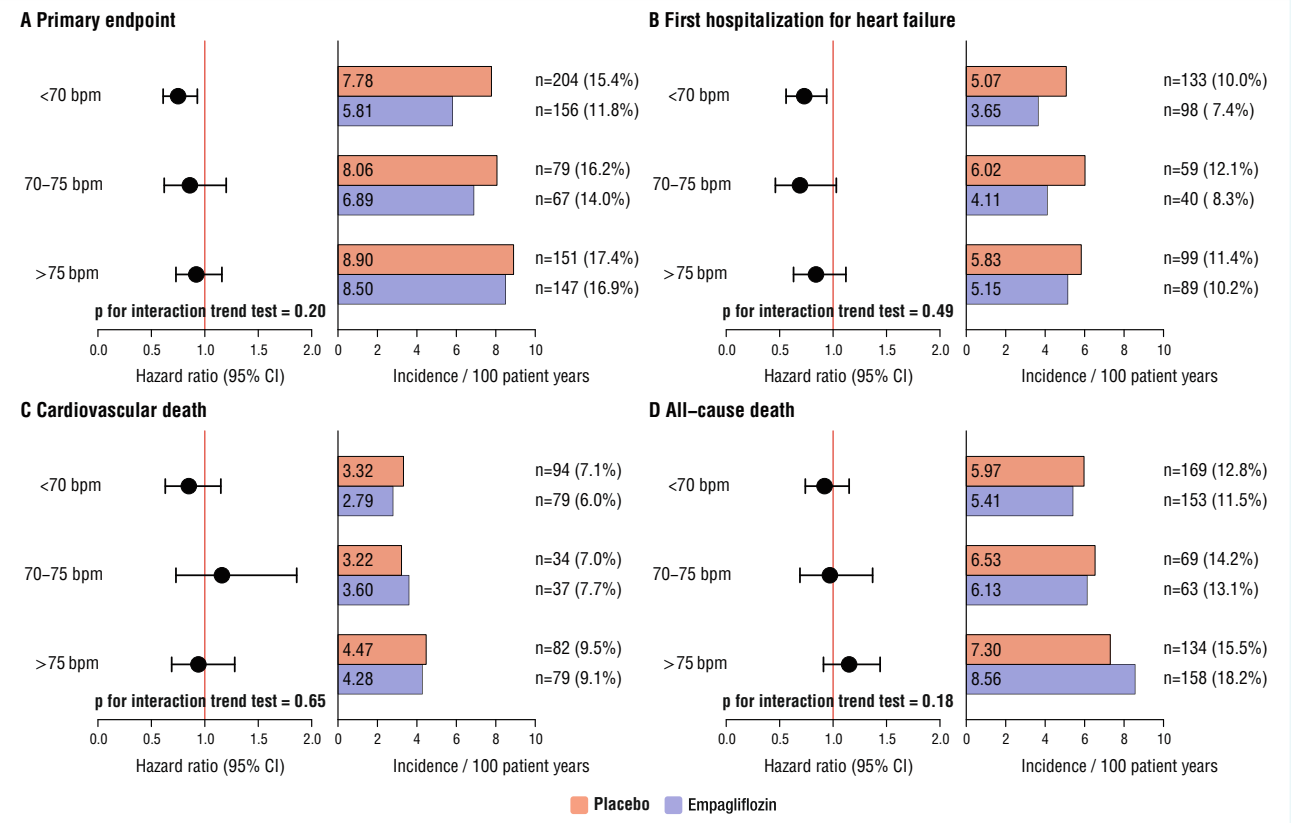


Figure 5 Empagliflozin effects across resting heart rate. Hazard ratio (*left*) and incidence rate per 100 patient-years (*right*) for empagliflozin compared to placebo according to resting heart rate for the primary endpoint (*A*), first hospitalization for heart failure (*B*), cardiovascular death (*C*) and all-cause death (*D*). CI, confidence interval.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgement

We are grateful to Armin Schweitzer for technical and editorial help as well as artwork.

Funding

All authors were involved in the EMPEROR-Preserved trial, which was funded by Boehringer Ingelheim Germany and Eli Lilly and company.

Conflict of interest: M.B. is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project number 322900939) and reports personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Medtronic, Novartis, Servier and Vifor during the conduct of the study. J.B. reports consulting fees from Boehringer Ingelheim, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, Sequana Medical, V-Wave Ltd., and Vifor; personal fees from Boehringer Ingelheim during the conduct of the study. F.M. reports grants and personal fees from Medtronic, personal fees from Recor, Boehringer Ingelheim and Berlin Chemie; he is supported by Deutsche Gesellschaft für Kardiologie (DGK), Deutsche Forschungsgemeinschaft (SFB TRR219) and Deutsche Herzstiftung and has received scientific support and/or speaker honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Medtronic Merck and ReCor Medical. G.F. reports Committee Member contributions in trials; personal fees from Boehringer Ingelheim during the conduct of the study. J.P.F. reports consulting fees from Boehringer Ingelheim during the conduct of the study. S.P. reports personal fees from Boehringer Ingelheim during the conduct of the study. Jonathan Slawik reports no conflicts. M.B. is an employee of Boehringer Ingelheim. B.L. is an employee of Eli Lilly and Company. E.S. is an employee of mainanalytics, contracted by Boehringer Ingelheim. C.W. reports personal fees from Boehringer Ingelheim during the conduct of the study; personal fees from Akebia, AstraZeneca, Bayer, Eli Lilly, GSK, GILEAD, MSD, Mundipharma, Sanofi-Genzyme and Vifor Fresenius outside the submitted work. F.Z. has received steering committee or advisory board fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cardior, CVRx, Janssen, Livanova, Merck, Mundipharma, Novartis, Novo Nordisk,

and Vifor Fresenius; personal fees from Boehringer Ingelheim during the conduct of the study. M.P. reports consulting fees from Boehringer Ingelheim, during the conduct of the study; consulting fees from Abbvie, Actavis, Altimmune, Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, Caladrius, Casana, CSL Behring, Cytokinetics, Imara, Lilly, Moderna, Novartis, Reata, Relypsa, Salamandra. S.D.A. reports grants and personal fees from Vifor Int. and Abbott Vascular, and personal fees from AstraZeneca, Bayer, Brahms, Boehringer Ingelheim, Cardiac Dimensions, Novartis, Occlutech, Servier, and Vifor Int; personal fees from Boehringer Ingelheim during the conduct of the study.

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