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RESEARCH ARTICLE

Concentration-dependent clinical and prognostic importance of high-sensitivity cardiac troponin T in heart failure and a reduced ejection fraction and the influence of empagliflozin: the EMPEROR-Reduced trial

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Aims Circulating troponin is an important measure of risk in patients with heart failure, but it has not been used to determine if disease severity influences the responses to drug treatments in randomized controlled trials.

Methods and results In the EMPEROR-Reduced trial, patients with class II–IV heart failure and a reduced ejection fraction were randomly assigned to placebo or empagliflozin 10 mg daily and followed for the occurrence of serious heart failure and renal events. High-sensitivity cardiac troponin T (hs-cTnT) was measured in 3636 patients (>97%) at baseline, and patients were divided into four groups based on the degree of troponin elevation. With increasing concentrations of hs-cTnT, patients were progressively more likely to have diabetes and atrial fibrillation, to have New York Heart Association class III–IV symptoms and been hospitalized for heart failure within the prior year, and to have elevated levels of natriuretic peptides and worse renal function (P-trend < 0.0001 for all comparisons), but importantly, the troponin groups did not differ with respect to ejection fraction. A linear relationship was observed between the logarithm of hs-cTnT and the combined risk of cardiovascular death or hospitalization for heart failure ($P = 0.0015$). When treated with placebo, patients with the highest levels of hs-cTnT had risks of cardiovascular death and hospitalization for heart failure that were 3–5 fold greater than those with values in the normal range. Patients with higher levels of hs-cTnT were also more likely to experience worsening of renal function and serious adverse renal events and showed the least improvement in health status (as measured by the Kansas City Cardiomyopathy Questionnaire). When compared with placebo, empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure, regardless of the baseline level of hs-cTnT, whether the effects of treatment were analysed as hazard ratios or absolute risk reductions.

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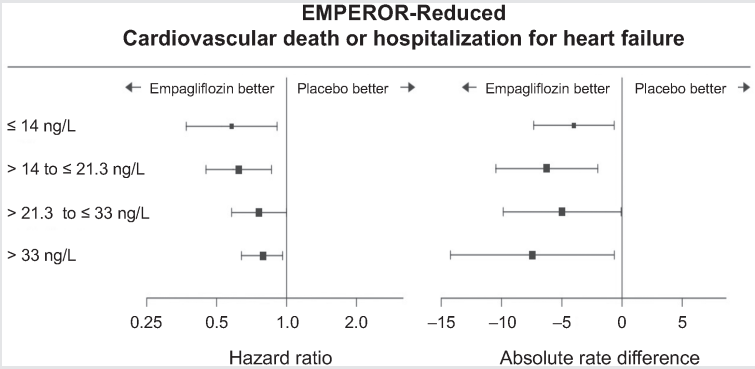
Conclusions Elevations in hs-cTnT reflect the clinical severity, stability and prognosis of patients with heart failure and a reduced ejection fraction, with biomarkers, comorbidities, clinical course and risks that are proportional to the magnitude of hs-cTnT elevation. Empagliflozin exerted favourable effects on heart failure and renal outcomes, regardless of the baseline concentration of hs-cTnT.

Graphical Abstract



EMPEROR-Reduced: cardiovascular death or hospitalization for heart failure. Forest plot of effect of empagliflozin on the combined risk of cardiovascular death or hospitalization for heart failure in each of the four troponin groups.

Keywords Troponin • Sodium–glucose co-transporter 2 inhibition • Empagliflozin

Introduction

Circulating concentrations of cardiac troponin (troponin I or troponin T) are increased in many patients with chronic heart failure with or without coronary artery disease, and these elevations identify patients with greater severity of disease and who are at increased risk of major clinical events.[1–3] Increases in troponin are particularly notable in those with worse ventricular function and in those in whom ejection fraction is more likely to decline and less likely to recover during long-term follow-up.[2,4–6] The level of cardiac troponin carries powerful prognostic information with respect to the risk of death or hospitalization, which is independent of ejection fraction or natriuretic peptides.[7–9] However, in most prior reports, comparisons have been carried out between patients with normal and abnormal troponins in a dichotomous manner,[3] and therefore, comparatively little is known as to whether the magnitude of elevation of cardiac troponin is important among those whose concentrations are already in the abnormally elevated range.

Because it is a powerful and objective biomarker of disease severity and risk, cardiac troponin may be particularly useful in determining if the severity of heart failure influences the efficacy of sodium–glucose co-transporter 2 (SGLT2) inhibitors. Both dapagliflozin and empagliflozin reduce the risk of cardiovascular death and hospitalization for heart failure in patients with heart failure and a reduced ejection fraction,[10,11] but a recent meta-analysis suggested that the benefits of these SGLT2 inhibitors may be attenuated in patients with the most advanced heart failure, as identified by the presence of New York Heart Association (NYHA) functional class III–IV symptoms.[12] However, these observations were difficult to interpret, since functional class is a subjective (often unstable) assessment, and measures of symptoms and exercise tolerance in patients with class II and III symptoms overlap considerably.[13,14] In contrast, cardiac troponin represents a stable objective measure of disease severity and prognosis, which adds incrementally to the information provided by ejection fraction and natriuretic peptides,[7–9] and it has been used to assess whether the severity of risk influences the efficacy of SGLT2 inhibitors in patients with type 2 diabetes (who largely did not have heart failure).[15] Accordingly, we evaluated the clinical and prognostic significance of cardiac troponin and its influence on the efficacy of empagliflozin in patients with heart failure and a reduced ejection fraction (with and without diabetes) who participated in the EMPEROR-Reduced trial.

Methods

The design of the EMPEROR-Reduced trial has been described previously.[11] Ethics approval was obtained at each study site, and all patients provided informed consent; the registration identifier at ClinicalTrials.gov is NCT03057977.

Participants had NYHA class II–IV heart failure and an ejection fraction ≤40%, and were receiving all appropriate treatments for heart failure. We preferentially enrolled patients with an ejection fraction of ≤30% by requiring those with higher ejection fractions to have been hospitalized for heart failure within 12 months or to have more significantly increased levels of N-terminal prohormone B-type natriuretic peptide (NT-proBNP). High-sensitivity cardiac troponin T (hs-cTnT, Roche Diagnostics, Risch-Rotkreuz, Switzerland) was measured at the baseline visit, and assays were performed at a central laboratory. Patients were randomized double-blind (in a 1:1 ratio) to receive placebo or empagliflozin 10 mg daily, in addition to their usual therapy for heart failure. Following randomization, patients were periodically assessed for major outcomes and health status related to heart failure and the need for intensification of diuretic therapy.

The primary endpoint was the composite of cardiovascular death or hospitalization for heart failure, analyzed as time-to-first event. The first secondary endpoint was the occurrence of all (first and recurrent) hospitalizations for heart failure. The second secondary endpoint was the slope of the change in estimated glomerular filtration rate (eGFR) during double-blind treatment. Serious adverse renal outcomes included chronic dialysis, renal transplant, a sustained eGFR reduction of ≥40%, or a sustained eGFR <15 mL/min/1.73 m^2 (if baseline eGFR ≥30) or sustained eGFR <10 mL/min/1.73 m^2 (if baseline eGFR <30). Additional analyses included (i) the two components of the primary endpoint; (ii) time to reported outpatient intensification of diuretics; and (iii) changes in the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score at 52 weeks. The protocol did not specify the measurement of hs-cTnT at post-randomization follow-up visits, and banked blood samples have not yet been analysed for hs-cTnT.

Outcome measures and statistical analysis

Values for hs-cTnT were used to define four subgroups of patients. First, those with a normal reference value (≤14 ng/L) were identified, and those with elevated values were then divided into tertiles of equal size, which were designated as having mildly increased, moderately increased and markedly increased hs-cTnT.

For time-to-first event analyses, between-group differences were assessed using a Cox proportional hazards model, with pre-specified covariates of age, gender, region, diabetes, ejection fraction, and eGFR at baseline. For the analysis of total events, between-group differences were assessed using a joint frailty model, with cardiovascular death as a competing risk, using the same covariates as the time-to-first event analyses. The eGFR slope analysis was based on on-treatment data using a random coefficient model with age and baseline eGFR as linear covariates and sex, region, ejection fraction, diabetes, and baseline eGFR-by-time, treatment-by-hs-cTnT, and treatment-by-time-by-hs-cTnT interaction terms. For the comparison of absolute risk reduction, between-group event rate differences were assessed using the Poisson regression model for time-to-first event analyses and using the negative binomial model for the analysis of total events, using the same covariates as the time-to-first event analyses. Additionally, the influence of the logarithm of hs-cTnT on the incidence of cardiovascular death or hospitalization for heart failure was evaluated by a linear regression analysis, weighted by the number of patients in each group; because of exceptional skewness, the 1% of patients with extreme values for cTnT (i.e. $>\log_e 5.0$) were excluded from this analysis.

Since the four troponin groups were ordered, *P*-trend tests were used to evaluate the influence of baseline values for hs-cTnT on (i) baseline characteristics; (ii) the rates and risks of major heart failure and renal outcomes in the placebo group; and (iii) the effects of empagliflozin on heart failure and renal outcomes, using the covariate adjustments described above.

All analyses of troponin were exploratory and were not described in the original study protocol.

Results

Of the 3636 randomized patients who had a baseline measurement of hs-cTnT, 803 (22%) patients had a hs-cTNT below the 99th percentile for a normal population (≤14 ng/L). Among those with an increased hs-cTnT, tertiles were defined as >14–21.3 ng/L, >21.3–33 ng/L and >33 ng/L, with each tertile comprised of approximately 26% of the patients. The distribution of values of hs-cTnT was markedly skewed, with 1% of the patients having values >150 ng/L.

Relation of troponin and baseline characteristics

At baseline, we observed a stepwise relationship between increases in circulating hs-cTnT and clinical measures of heart failure severity and instability (*Table 1*). With increasing concentrations of hs-cTnT, patients were more likely to have NYHA functional class III–IV symptoms and lower KCCQ scores at baseline, and they were more likely to have experienced worsening of NYHA class within 3 months or to have been hospitalized for heart failure within the prior year (*P*-trend < 0.0001 for all comparisons). As hs-cTnT progressively increased, there was a parallel stepwise increase in circulating levels of NT-proBNP and uric acid and a stepwise decrease in eGFR; in addition, the prevalence of diabetes and atrial fibrillation increased as hs-cTnT levels rose (*P*-trend < 0.0001 for all comparisons). Yet, left ventricular ejection fraction did not differ across the troponin subgroups, and systolic blood pressure did not decrease as levels of hs-cTnT increased. Interestingly, as levels of hs-cTnT progressively increased, there was a stepwise increase in the use of digitalis glycosides and high doses of loop diuretics, whereas the utilization of neurohormonal antagonists (beta-blockers, mineralocorticoid receptor antagonists and neprilysin inhibitors) progressively decreased (*P*-trend ≤ 0.02 to <0.0001 for all comparisons).

Relation of troponin and clinical course

When treated with placebo and followed for a median of 16 months, there was a stepwise relationship between the baseline concentration of hs-cTnT and the clinical course of heart failure. The combined risk of cardiovascular death or hospitalization for heart failure was 10.0, 17.1, 21.4 and 37.2 events per 100 patient-years of follow-up in patients with ≤14 ng/L, >14–21.3 ng/L, >21.3–33 ng/L and >33 ng/L, respectively (*P*-trend < 0.0001; *Table 2*). Cumulative incidence plots of the risk of a primary endpoint in the four troponin subgroups are shown in *Figure 1A*. When troponin was considered as a

Table 1 Baseline characteristics of patients according to baseline troponin

	cTnT ≤ 14 (*n* = 803)	cTnT > 14–21.3 (*n* = 938)	cTnT > 21.3–33 (*n* = 949)	cTnT > 33 (*n* = 946)	*P*-trend
Age (years)	62.0 ± 11.5	67.1 ± 10.1	68.1 ± 10.8	69.4 ± 10.7	<0.0001
Women, *n* (%)	302 (37.6)	245 (26.1)	180 (19.0)	142 (15.0)	<0.0001
Race, *n* (%)					
White	519 (64.6)	682 (72.7)	682 (71.9)	682 (72.1)	0.008
Black	72 (9.0)	53 (5.7)	54 (5.7)	68 (7.2)	
Asian	166 (20.7)	160 (17.1)	179 (18.9)	157 (16.6)	
Region, *n* (%)					
North America	82 (10.2)	104 (11.1)	106 (11.2)	122 (12.9)	0.056
Latin America	307 (38.2)	328 (35.0)	289 (30.5)	334 (35.3)	
Europe	250 (31.1)	344 (36.7)	378 (39.8)	337 (35.6)	
Asia	99 (12.3)	127 (13.5)	138 (14.5)	122 (12.9)	
Clinical course of HF					
Duration of HF (years), median (IQR)	3.2 (1.2, 7.7)	4.0 (1.2, 8.8)	4.7 (1.8, 9.7)	4.4 (1.7, 9.1)	<0.0001
NYHA functional class III–IV, *n* (%)	146 (18.2)	210 (22.4)	254 (26.7)	292 (30.8)	<0.0001
Worsening NYHA class within 3 months, *n* (%)	32 (4.0)	56 (6.0)	62 (6.5)	77 (8.1)	0.0003
Hospitalization for HF within 12 months, *n* (%)	196 (24.4)	293 (31.2)	295 (31.1)	340 (35.9)	<0.0001
Body mass index (kg/m^2)	27.8 ± 5.4	27.7 ± 5.4	27.9 ± 5.3	28.1 ± 5.5	0.26
LV ejection fraction (%)	27.5 ± 5.5	27.3 ± 6.0	27.5 ± 6.2	27.5 ± 6.3	0.91
KCCQ clinical summary score	73.4 ± 20.5	72.0 ± 21.5	71.0 ± 21.6	65.7 ± 22.6	<0.0001
Systolic blood pressure (mmHg)	120.6 ± 15.1	122.2 ± 15.7	121.8 ± 15.7	123.2 ± 16.1	0.002
Heart rate (bpm)	70.6 ± 11.6	71.4 ± 11.9	71.3 ± 11.8	71.8 ± 11.7	0.06
NT-proBNP (pg/mL), median (IQR)	1252 (783, 2043)	1678 (1024, 2763)	2168 (1342, 3747)	2847 (1602, 5527)	<0.0001
eGFR (mL/min/1.73 m^2)	74.0 ± 19.9	64.3 ± 19.9	58.6 ± 19.9	52.9 ± 21.3	<0.0001
Serum uric acid (mg/dL)	6.4 ± 1.8	6.9 ± 1.9	7.3 ± 2.1	7.7 ± 2.2	<0.0001
Cardiovascular history, *n* (%)					
Hypertension	523 (65.1)	668 (71.2)	707 (74.5)	731 (77.3)	< 0.0001
Prior myocardial infarction	325 (40.5)	400 (42.6)	438 (46.2)	422 (44.6)	0.038
Atrial fibrillation or atrial flutter	225 (28.0)	352 (37.5)	398 (41.9)	426 (45.0)	<0.0001
Diabetes mellitus	309 (38.5)	448 (47.8)	481 (50.7)	574 (60.7)	<0.0001
Treatment of HF, *n* (%)					
High doses of loop diuretics	118 (14.7)	162 (17.3)	225 (23.7)	293 (31.0)	0.021
Beta-blocker	765 (95.3)	895 (95.4)	904 (95.3)	877 (92.7)	0.013
Mineralocorticoid receptor antagonist	600 (74.7)	683 (72.8)	677 (71.3)	638 (67.4)	0.0005
Sacubitril/valsartan	178 (22.2)	183 (19.5)	193 (20.3)	151 (16.0)	0.003
Cardiac glycosides	90 (11.2)	145 (15.5)	166 (17.5)	177 (18.7)	<0.0001
Implantable cardioverter-defibrillator[a]	217 (27.0)	292 (31.3)	335 (35.3)	291 (30.8)	0.043
Cardiac resynchronization therapy[b]	46 (5.7)	113 (12.0)	132 (13.9)	142 (15.0)	<0.0001

Plus-minus values are means ± standard deviation.
cTnT, high-sensitivity cardiac troponin T (ng/L); eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; NYHA, New York Heart Association.
The median values for hs-cTnT for the four groups are 10.3, 17.5, 25.9 and 47.4, respectively.
P-values refer to the trend test for the relationship between troponin and a specific baseline variable. Patients who self-identified with ≥1 race or with no race are classified as 'other'; data for 'other' or missing for both race and region are not shown.
[a]Implantable cardioverter-defibrillator with or without cardiac resynchronization therapy.
[b]Cardiac resynchronization therapy with or without a defibrillator.

continuous variable, a linear relationship was observed between the logarithm of hs-cTnT and the combined risk of cardiovascular death or hospitalization for heart failure (*Figure 1B*) during double-blind therapy ($P = 0.0015$).

Additionally, we observed a stepwise relationship between the circulating level of hs-cTnT and the rate of total hospitalizations for heart failure, the need for outpatient intensification of diuretics, and the risks of cardiovascular death and all-cause mortality, with rates/risks of an event in the highest troponin group being 3–5 times greater than in the normal troponin group (*Table 2*). The magnitude of improvement in KCCQ at 52 weeks in the placebo group was progressively attenuated as hs-cTnT increased. In parallel, as the baseline values of hs-cTnT increased, there was a stepwise acceleration in the decline in eGFR over time and a stepwise increase in the risk of a serious adverse renal outcome.

Table 2 Rates of heart failure and renal events in the placebo group according to baseline troponin

	cTnT ≤ 14 (*n* = 406)	cTnT > 14–21.3 (*n* = 488)	cTnT > 21.3–33 (*n* = 475)	cTnT > 33 (*n* = 452)	*P*-trend
Cardiovascular death or hospitalization for heart failure, *n* with event (rate per 100 pt-yr)	53 (10.0)	99 (17.1)	122 (21.4)	175 (37.2)	<0.0001
Hazard ratio (95% CI), compared with cTnT ≤ 14	–	1.71 (1.22, 2.41)	2.20 (1.58, 3.08)	3.68 (2.64, 5.12)	
Total (first and recurrent) hospitalizations for heart failure, *n* of events	47	117	165	212	<0.0001
Hazard ratio (95% CI), compared with cTnT ≤ 14	–	2.29 (1.49, 3.52)	3.25 (2.10, 5.01)	5.51 (3.53, 8.58)	
Time to first hospitalization for heart failure, *n* with event (rate per 100 pt-yr)	36 (6.8)	76 (13.1)	97 (17.0)	125 (26.6)	<0.0001
Hazard ratio (95% CI), compared with cTnT ≤ 14	–	1.91 (1.27, 2.86)	2.55 (1.72, 3.80)	3.80 (2.56, 5.66)	
Cardiovascular death, *n* with event (rate per 100 pt-yr)	23 (4.1)	37 (5.8)	41 (6.3)	93 (16.3)	<0.0001
Hazard ratio (95% CI), compared with cTnT ≤ 14	–	1.43 (0.84, 2.43)	1.58 (0.93, 2.68)	4.02 (2.44, 6.61)	
All-cause mortality, *n* with event (rate per 100 pt-yr)	29 (5.2)	53 (8.2)	54 (8.3)	120 (21.0)	<0.0001
Hazard ratio (95% CI), compared with cTnT ≤ 14	–	1.51 (0.95, 2.40)	1.52 (0.95, 2.43)	3.71 (2.39, 5.77)	
Intensification of diuretics, *n* with event (rate per 100 pt-yr)	57 (11.2)	87 (15.0)	123 (22.6)	139 (30.4)	<0.0001
Hazard ratio (95% CI), compared with cTnT ≤ *14*	–	1.25 (0.89, 1.76)	1.81 (1.31, 2.51)	2.43 (1.74, 3.39)	
Change in KCCQ at 52 weeks (adjusted mean, 95% CI)	+5.3 (3.4, 7.2)	+4.3 (2.6, 6.1)	+3.6 (1.8, 5.4)	+2.2 (0.3, 4.2)	0.025
Slope of decline in eGFR (mL/min/1.73 m^2/year) (adjusted mean, 95% CI)	−1.4 (−2.4, −0.3)	−2.2 (−3.1, −1.2)	−2.3 (−3.2, −1.3)	−3.5 (−4.5, −2.4)	0.25
Composite of serious adverse renal outcomes, *n* with event (rate per 100 pt-y)	8 (1.8)	14 (2.9)	13 (2.6)	23 (5.3)	0.028
Hazard ratio (95% CI), compared with cTnT ≤ 14	–	1.53 (0.63, 3.73)	1.51 (0.60, 3.78)	2.67 (1.10, 6.48)	

All analyses except for total hospitalizations for heart failure, change in KCCQ and slope of decline in eGFR are time-to-first event.
CI, confidence interval; cTnT, high-sensitivity cardiac troponin T (ng/L); eGFR, estimated glomerular filtration rate; KCCQ, Kansas City Cardiomyopathy Questionnaire; pt-yr, patient-years.

Influence of troponin on effect of empagliflozin on clinical outcomes

When compared with placebo, empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart mfailure, regardless of the baseline level of hs-cTnT (*Table 3*). When considered as a hazard ratio, the magnitude of the effect of empagliflozin was somewhat larger in patients with hs-cTnT in the normal range (*P*-trend = 0.12), but when considered as absolute risk reduction, the magnitude of the benefit of SGLT2 inhibition was somewhat larger in patients with the highest hs-cTnT (*Graphical Abstract*). When considered as a continuous variable, the treatment by $\log_e$ hs-cTnT interaction was nominally significant ($P = 0.043$) with a greater effect of empagliflozin on the combined risk of cardiovascular death or hospitalization for heart failure in patients with lower levels of hs-cTnT when displayed as a hazard ratio, but not when displayed as absolute risk reduction (*Figure 2*).

In addition to the effect on the primary endpoint, empagliflozin reduced the risk of total hospitalizations for heart failure, first hospitalizations for heart failure and first intensification of diuretics and was accompanied by an improvement in KCCQ score at 52 weeks. In addition, empagliflozin slowed the rate of decline in eGFR and decreased the risk of a serious adverse renal outcome. Because of the relatively small size of the troponin subgroups and the sparseness of certain events, many of these estimates were imprecise. Nevertheless, there was no consistent influence of baseline hs-cTnT on the effects of empagliflozin on these endpoints (*Table 3*).

Discussion

In the patients with a reduced ejection fraction who participated in the EMPEROR-Reduced trial, more than 75% had circulating levels

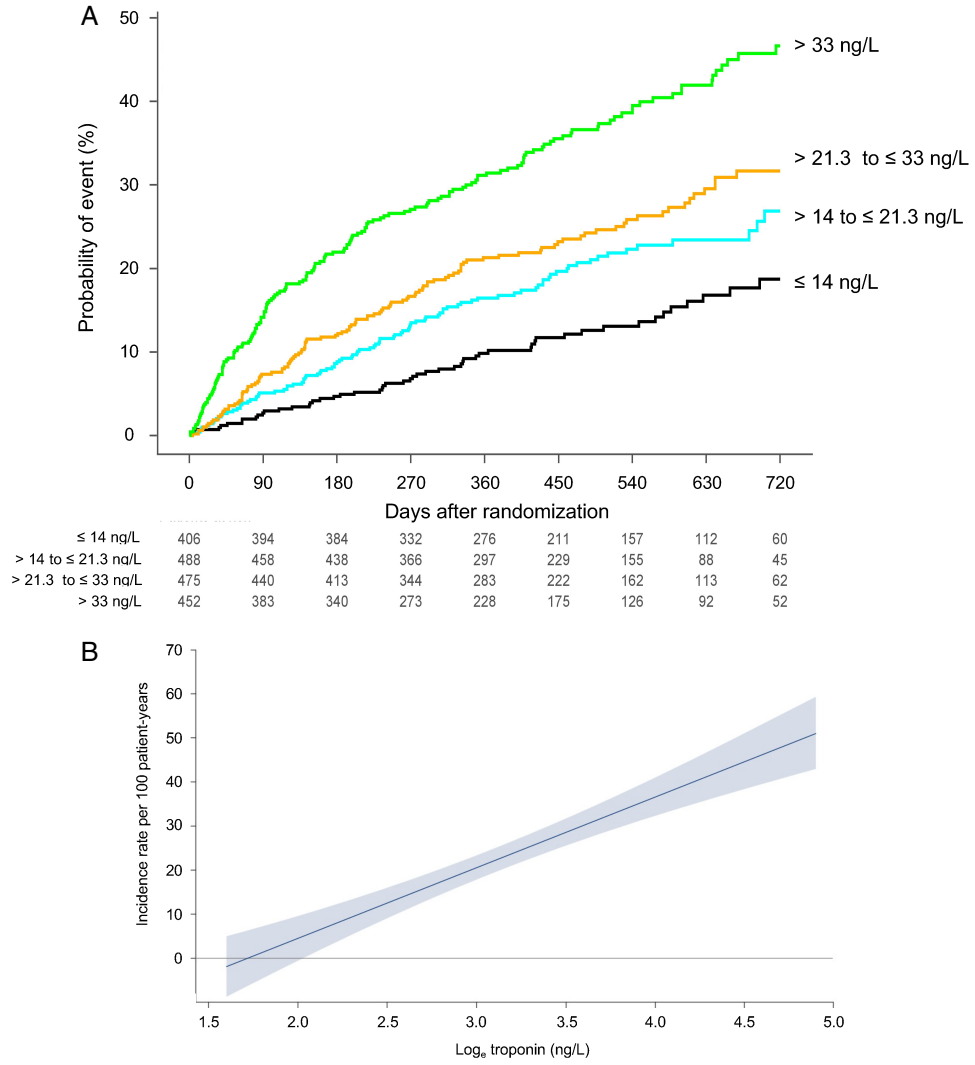


Figure 1 (*A*) Cumulative incidence plots for cardiovascular death or hospitalization for heart failure in placebo-treated patients in four troponin groups. (*B*) Weighted regression for the relation of log$_e$ troponin and incidence of cardiovascular death or hospitalization for heart failure in the placebo group. Area in blue depicts 95% confidence intervals. Because of exceptional skewness, the 1% of patients with extreme values for baseline troponin (i.e. > log$_e$ > 5.0) were excluded from this analysis.

of hs-cTnT higher than the normal range for a healthy population, and we observed a stepwise relationship between the circulating concentration of hs-cTnT and the severity and instability of heart failure. Increasing levels of hs-cTnT were associated with progressively lower KCCQ scores and more advanced NYHA functional class and an increasing likelihood of a recent history of worsening NYHA class or hospitalization for heart failure. Progressive increases in hs-cTnT from the normal range to markedly increased levels were paralleled by a stepwise increase in circulating levels of NT-proBNP (a marker of cardiac wall stress) and uric acid (a marker of oxidative stress[16]) and a stepwise decline in renal function, and these were accompanied by increasing prevalence of diabetes and atrial fibrillation. Previous studies have reported many (but not all) of these associations with troponin,[7–9,16–21] but most earlier reports evaluated fewer than 1000 patients,[8] and none distinguished the clinical features among patients with increasingly abnormal concentrations of hs-cTnT. In contrast, our novel finding of statistically compelling concentration-dependent associations with severity and comorbidities (*P*-trend < 0.0001) in a large cohort suggests that our clinical characterization of patients with a troponin elevation represents replicable findings, despite the multiplicity of comparisons performed in the current study.

Importantly, a single measurement of hs-cTnT at baseline was a powerful predictor of both worsening heart failure and renal function in patients with heart failure and a reduced ejection fraction. We observed a linear relationship between the natural logarithm of hs-cTnT and the combined risk of cardiovascular death or hospitalization for heart failure, and as the concentration of hs-cTnT

Table 3 Effects of empagliflozin on major heart failure and renal outcomes, according to baseline troponin (hazard ratios and absolute risk reductions)

	cTnT ≤ 14 (*n* = 803)	cTnT > 14–21.3 (*n* = 938)	cTnT > 21.3–33 (*n* = 949)	cTnT > 33 (*n* = 946)	*P*-trend
Cardiovascular death or hospitalization for heart failure (time-to-first event)					
Hazard ratio (95% CI)	0.58 (0.37, 0.91)	0.62 (0.45, 0.86)	0.76 (0.58, 1.00)	0.79 (0.64, 0.98)	0.12
Absolute risk reduction (95% CI)	4.1 (0.7, 7.5)	6.6 (2.3, 10.9)	4.9 (−0.1, 9.9)	8.3 (1.2, 15.4)	0.38
Total (first and recurrent) hospitalizations for heart failure					
Hazard ratio (95% CI)	0.82 (0.49, 1.37)	0.37 (0.23, 0.57)	0.71 (0.50, 1.01)	0.78 (0.56, 1.07)	0.18
Absolute risk reduction (95% CI)	1.6 (−2.5, 5.7)	12.4 (7.1, 17.7)	8.2 (0.2, 16.2)	9.1 (−2.9, 21.2)	0.36
First hospitalization for heart failure (time-to-event)					
Hazard ratio (95% CI)	0.63 (0.37, 1.07)	0.45 (0.30, 0.68)	0.68 (0.50, 0.92)	0.79 (0.62, 1.02)	0.07
Absolute risk reduction (95% CI)	2.5 (−0.4, 5.3)	7.3 (3.8, 10.9)	5.3 (0.9, 9.7)	6.0 (0.0, 12.0)	0.42
Cardiovascular death (time-to-event)					
Hazard ratio (95% CI)	0.62 (0.33, 1.23)	1.15 (0.73, 1.81)	1.16 (0.76, 1.77)	0.77 (0.57, 1.03)	0.63
Absolute risk reduction (95% CI)	1.5 (−0.7, 3.6)	−0.8 (−3.5, 2.0)	−1.1 (−3.9, 1.8)	3.9 (−0.4, 8.1)	0.37
Intensification of diuretics (time-to-event)					
Hazard ratio (95% CI)	0.87 (0.59, 1.27)	0.67 (0.48, 0.93)	0.58 (0.44, 0.77)	0.62 (0.48, 0.80)	0.20
Absolute risk reduction (95% CI)	1.3 (−2.7, 5.3)	4.9 (0.8, 9.0)	9.1 (4.2, 14.1)	11.4 (5.2, 17.6)	0.003
Change in KCCQ at 52 weeks (adjusted mean, 95% CI)	+1.7 (−0.9, 4.3)	+2.2 (−0.2, 4.6)	+1.7 (−0.8, 4.1)	+1.4 (−1.1, 3.9)	0.76
Slope of decline in eGFR (mL/min/1.73 m^2/year) (adjusted mean, 95% CI)	+1.3 (−0.1, 2.6)	+2.5 (1.3, 3.8)	+2.1 (0.8, 3.3)	+1.4 (0.1, 2.7)	0.87
Composite of serious adverse renal events (time-to-event)					
Hazard ratio (95% CI)	0.65 (0.21, 2.00)	0.23 (0.07, 0.80)	0.37 (0.13, 1.03)	0.63 (0.34, 1.19)	0.49
Absolute risk reduction (95% CI)	0.6 (−1.0, 2.3)	2.2 (0.6, 3.9)	1.6 (−0.1, 3.3)	2.0 (−0.8, 4.7)	0.51

Shown are the hazard ratios of the effects of empagliflozin with placebo. Absolute risk reductions are displayed as risk in the placebo group minus the risk in the empagliflozin group in events per 100 patient-years of follow-up.
CI, confidence interval; cTnT, high-sensitivity cardiac troponin T (ng/L); eGFR, estimated glomerular filtration rate; KCCQ, Kansas City Cardiomyopathy Questionnaire.

progressively increased, there was a stepwise increase in the subsequent risk of cardiovascular death, total hospitalizations for heart failure and outpatient intensification of diuretics, and there was a stepwise acceleration in the decline in eGFR over time and a stepwise increase in the risk of a serious adverse renal outcome. Remarkably, patients in the highest hs-cTnT group had risks that were 3−5 fold greater than those with values in the normal range. The prognostic importance of hs-cTnT has been well-documented in numerous reports of patients with heart failure,[7−9,19,22,23] but most earlier studies simply dichotomized patients into groups with 'normal' and 'abnormal' values (without distinguishing among patients with elevated hs-cTnT), and only one study reported the ability of troponin to predict worsening renal function (although not in patients with heart failure).[24] A few studies[8,9,23,25] have noted a stepwise relationship between hs-cTnT and mortality in patients with heart failure, but in these reports, nearly 50% of the patients had values in the normal range; most patients were not receiving modern-day neurohormonal antagonists; and none examined the relationship of hs-cTnT to non-fatal heart failure events. Interestingly, hs-cTnT had powerful prognostic importance even though patients with elevated hs-cTnT concentrations in the current study did not have lower left ventricular ejection fractions or lower systolic blood pressures, in contrast to most previous reports.[9,19−21]

It seems likely that the prognostic importance of hs-cTnT is related to the ability of the biomarker to reflect the severity and clinical instability of heart failure as well as its ability to reflect the existence of critical comorbidities (diabetes, atrial fibrillation and chronic kidney disease) that are known to be accompanied by an accelerated rate of progression of heart muscle dysfunction, although these were not reflected by the measurement of ejection fraction or systolic blood pressure in the current analysis. However, it is noteworthy that, as levels of hs-cTnT progressively increased, there was increased utilization of drugs that have been associated with an increased mortality (i.e. digitalis glycosides and high doses of loop diuretics[26,27]) and decreased utilization of neurohormonal antagonists that have favourable effects on survival (i.e. beta-blockers, mineralocorticoid receptor antagonists and neprilysin inhibitors). Similar associations with background therapy have been reported by others.[8,18−20] The finding that the effect of neprilysin inhibition to slow the progression of heart failure is accompanied by an early decrease in troponin[28] suggests that the effect of drugs on troponin may parallel their effects on the risk of death. Changes in the concentration of troponin have prognostic significance that adds to the information provided by the baseline value.[20]

The ability of hs-cTnT to objectively assess the clinical severity of heart failure allowed us to determine if patients with advanced heart failure respond as favourably to SGLT2 inhibition as do patients with mild-to-moderate disease. Recent evidence suggests that disease severity may influence the magnitude of the benefits

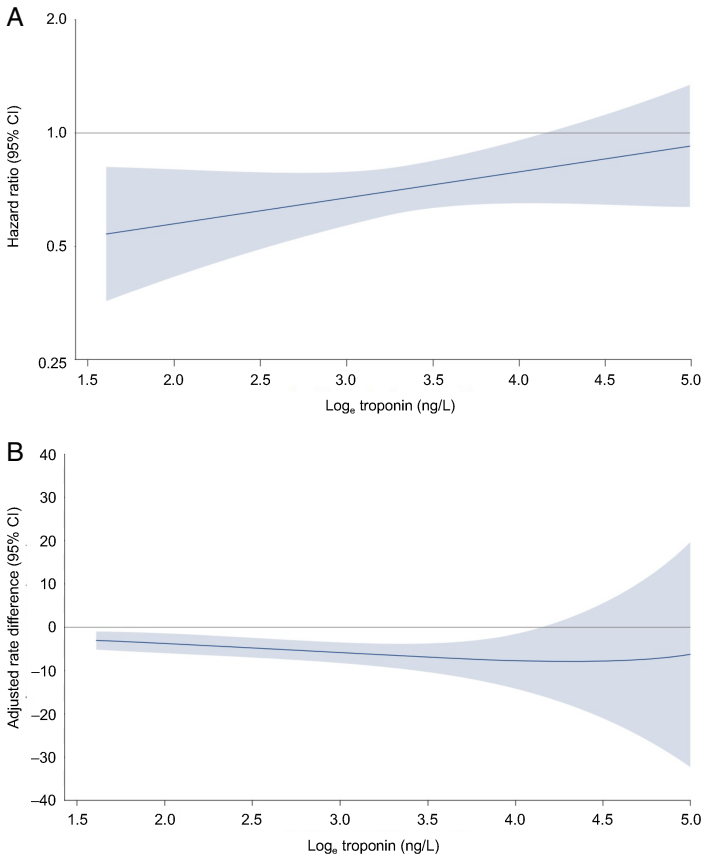


Figure 2 Relation of baseline troponin and the effect of empagliflozin on cardiovascular death or hospitalization for heart failure, displayed as a hazard ratio (*A*) and as absolute risk reduction (*B*). Area in blue depicts 95% confidence intervals (CI). Because of exceptional skewness, the 1% of patients with extreme values for baseline troponin (i.e. > $\log_e$ > 5.0) were excluded from this analysis.

of certain drugs for heart failure; e.g. the response to vericiguat appears to be attenuated in patients with markedly increased levels of natriuretic peptides[29] and the response to omecamtiv mecarbil appears to be enhanced in patients with very low ejection fractions.[30] We could not rely on these two biomarkers of disease severity in the EMPEROR-Reduced trial, since we designed the study to enrich our patient population for low values for ejection fraction and high values for natriuretic peptides. Consequently, we elected to use hs-cTnT as a primary measure of heart failure severity (in accordance with the findings of others[23]), and we noted that empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure, regardless of the baseline level of hs-cTnT. When considered as a hazard ratio, the magnitude of the effect of empagliflozin was somewhat larger in patients with hs-cTnT concentrations in the normal range, but when considered as absolute risk reduction, the magnitude of the benefit of SGLT2 inhibition was somewhat larger in patients with the highest hs-cTnT. Taken collectively, these observations alleviate concerns raised by a recent meta-analysis that suggested that the benefits of SGLT2 inhibitors may be attenuated in patients with NYHA functional class III–IV symptoms.[12] However, unlike hs-cTnT, NYHA functional class is a subjective assessment that is prone to rapid changes,[13,14] and thus, it is not poised to reliably distinguish responders and non-responders to treatment. For example, concerns that sacubitril/valsartan may be less effective in class III–IV patients based on subgroup analysis of one large-scale trial[31] were not confirmed in a later study that demonstrated the efficacy of neprilysin inhibition in severely limited patients.[32]

The findings of the present study should be interpreted in the context of its strengths and limitations. The current analysis represents one of the largest and most detailed examinations of the clinical features and prognostic implications of hs-cTnT, and it is the first trial to evaluate the influence of troponin on the response to drug treatment in heart failure. However, the EMPEROR-Reduced trial was designed to focus on higher-risk patients, thus explaining why only one-fifth of our patients had values for hs-cTnT in the normal range, a proportion that was lower than earlier reports.[8,9,19,20] Nevertheless, the large number of patients with abnormally increased hs-cTnT allowed us to examine stepwise relationships among those with elevated values, which previous studies were unable to do. Importantly, in the current analysis, we measured hs-cTnT only at baseline, and thus, we have not evaluated the effects of empagliflozin on troponin or the meaningfulness of drug-induced changes in troponin on the

clinical status and prognosis of patients. These assessments are currently planned, since hs-cTnT is one of several key biomarkers that we will be measuring on blood samples that were prospectively collected and banked during the trial.

In conclusion, our findings demonstrate that elevations in hs-cTnT reflect the clinical severity, stability and prognosis of patients with heart failure and a reduced ejection fraction, with biomarkers, comorbidities and risks that are proportional to the magnitude of hs-cTnT elevation. Patients with the highest hs-cTnT had risks that were generally >3-fold greater than those with values in the normal range. Empagliflozin exerted favourable effects on heart failure and renal outcomes, regardless of the baseline concentration of hs-cTnT.

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