ESC European Society of Cardiology

European Journal of Heart Failure (2019) **21**, 1270–1278
doi:10.1002/ejhf.1536

TRIAL DESIGN

Evaluation of the effect of sodium–glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial

Milton Packer[1,2]*, Javed Butler[3], Gerasimos S. Filippatos[4,5], Waheed Jamal[6], Afshin Salsali[7], Janet Schnee[7], Karen Kimura[8], Cordula Zeller[9], Jyothis George[6], Martina Brueckmann[6,10], Stefan D. Anker[11], and Faiez Zannad[12], on behalf of the EMPEROR-Reduced Trial Committees and Investigators

[1]Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, TX, USA; [2]Imperial College, London, UK; [3]University of Mississippi School of Medicine, Jackson, MI, USA; [4]Department of Cardiology, National and Kapodistrian University of Athens, Athens, Greece; [5]School of Medicine, Athens University Hospital Attikon, Athens, Greece; [6]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [7]Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA; [8]Boehringer Ingelheim Canada Ltd., Burlington, Canada; [9]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [10]Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Germany; [11]Department of Cardiology (CVK); and Berlin Institute of Health Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site, Berlin, Germany, Charité Universitätsmedizin Berlin, Berlin, Germany; and [12]Inserm INI-CRCT, CHRU, Université de Lorraine, Nancy, France

Received 17 April 2019; revised 20 May 2019; accepted 23 May 2019; online publish-ahead-of-print 16 July 2019

Drugs that inhibit the sodium–glucose co-transporter 2 (SGLT2) have been shown to reduce the risk of hospitalizations for heart failure in patients with type 2 diabetes. In populations that largely did not have heart failure at the time of enrolment, empagliflozin, canagliflozin and dapagliflozin decreased the risk of serious new-onset heart failure events by ≈30%. In addition, in the EMPA-REG OUTCOME trial, empagliflozin reduced the risk of both pump failure and sudden deaths, the two most common modes of death among patients with heart failure. In none of the three trials could the benefits of SGLT2 inhibitors on heart failure be explained by the actions of these drugs as diuretics or anti-hyperglycaemic agents. These observations raise the possibility that SGLT2 inhibitors could reduce morbidity and mortality in patients with established heart failure, including those without diabetes. The EMPEROR-Reduced trial is enrolling ≈3600 patients with heart failure and a reduced left ventricular ejection fraction (≤ 40%), half of whom are expected not to have diabetes. Patients are being randomized to placebo or empagliflozin 10 mg daily, which is added to all appropriate treatment with inhibitors of the renin–angiotensin system and neprilysin, beta-blockers and mineralocorticoid receptor antagonists. The primary endpoint is the time-to-first event analysis of the combined risk of cardiovascular death and hospitalization for heart failure, but the trial will also evaluate the effects of empagliflozin on renal function, cardiovascular death, all-cause mortality, and recurrent hospitalization events. By adjusting eligibility based on natriuretic peptide levels to the baseline ejection fraction, the trial will preferentially enrol high-risk patients. A large proportion of the participants is expected to have an ejection fraction < 30%, and the estimated annual event rate is expected to be at least 15%. The EMPEROR-Reduced trial is well-positioned to determine if the addition of empagliflozin can add meaningfully to current approaches that have established benefits in the treatment of chronic heart failure with left ventricular systolic dysfunction.

Keywords Heart failure • Diabetes • Reduced ejection fraction • SGLT2 inhibitors • Trial design

*Corresponding author. Baylor Heart and Vascular Institute, 621 N. Hall Street, Dallas, TX 75226, USA. Tel: +1 214 820-7500, Email: milton.packer@baylorhealth.edu
The copyright line for this article was changed on 21 October 2019 after original online publication.

In patients with type 2 diabetes, drugs that inhibit the sodium–glucose co-transporter 2 (SGLT2) have been shown to reduce the risk of hospitalizations for heart failure.[1–3] In populations that largely did not have heart failure at the time of enrolment, empagliflozin, canagliflozin and dapagliflozin reduced the risk of serious new-onset heart failure events by ≈30%.[3–7] In addition, in the EMPA-REG OUTCOME trial, empagliflozin reduced the risk of cardiovascular death, and this benefit was related to a reduced risk of pump failure and sudden deaths, the two most common modes of death among patients with heart failure.[1,2,4] In none of the three trials could the benefits of SGLT2 inhibitors on the development of heart failure be explained by the effects of these drugs on glycaemic control.[1–3]

These intriguing observations have raised important questions. SGLT2 inhibitors may prevent the onset of heart failure in high-risk patients, but can these drugs treat heart failure in those with an established diagnosis? If the benefits of SGLT2 inhibitors on heart failure are unrelated to their actions on blood glucose, could these drugs exert favourable effects in patients who have heart failure but who do not have diabetes? Would such benefits be seen in those who are already receiving appropriate drug treatments for heart failure? The answers to these questions have important implications for the treatment of the millions of people who have heart failure who remain at considerable risk of morbidity and mortality despite optimal treatment with angiotensin receptor–neprilysin inhibitors, beta-blockers and mineralocorticoid receptor antagonists.[8,9]

To address these questions, we are evaluating the effects of empagliflozin in two large-scale clinical trials, one focused on patients with a preserved ejection fraction (EMPEROR-Preserved, NCT03057951) and the other focused on patients with a reduced ejection fraction (EMPEROR-Reduced, NCT03057977). The two trials, taken together, constitute the EMPEROR Program. This paper describes the intent and design of the EMPEROR-Reduced study.

Trial structure and oversight

The EMPEROR-Reduced trial is a phase III international, multicentre, randomized, double-blind, parallel-group, placebo-controlled trial that is evaluating the effects of empagliflozin on the morbidity and mortality of patients with established heart failure with a reduced ejection fraction (HFrEF), with or without type 2 diabetes. The trial is being conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The conduct of the study is approved by an institutional review board for each participating centre, and all participants provide written informed consent before study entry. The registration identifier on Clinicaltrials.gov is NCT03057977. The sponsors of the trial are Boehringer Ingelheim and Eli Lilly and Company.

The trial was designed by the Executive Committee, whose members include academic investigators as well as representatives of Boehringer Ingelheim. The Executive Committee was responsible for the development of the study protocol, and has scientific oversight on the development of the case report forms and the statistical plan. In addition, the Executive Committee is overseeing the pace of recruitment, the appropriateness of the patients being enrolled, and the quality and thoroughness of follow-up. The decisions and recommendations of the Executive Committee are reached through joint collaboration and by consensus. National leaders from key countries play a major regional role in encouraging recruitment and maintaining the commitment and dedication of investigators. An Endpoint Adjudication Committee is evaluating all reported and potential clinical events in a manner blinded to the treatment assignment, and these will be judged to have met (or not met) pre-specified criteria for a pre-specified endpoint or safety event. An independent Data Monitoring Committee is responsible for ongoing evaluation of the data that accrue during the course of the trial and are charged with making recommendations about continuation or termination of the trial. At a planned interim analysis, the Data Monitoring Committee may recommend to stop the trial for overwhelming efficacy, which will be guided by pre-specified stopping boundaries. The members of these Committees are listed in the *Appendix* .

Study patients

Participants in the EMPEROR-Reduced trial are men or women, aged ≥ 18 years who have had chronic heart failure (functional class II, III or IV) for at least 3 months and whose left ventricular ejection fraction is ≤ 40% at its most recent assessment prior to enrolment. Patients must be receiving all appropriate treatments for heart failure (as available and tolerated), including diuretics, inhibitors of the renin–angiotensin system and neprilysin, beta-blockers, mineralocorticoid receptor antagonists; the doses of these medications must be stable for at least 1 week prior to screening and remain constant during the screening period until randomization. When feasible, cardiac devices (e.g. a cardioverter-defibrillator or cardiac resynchronization therapy) are used in a manner consistent with local or international guidelines.

The intent of the trial is to enrol patients with heart failure whose expected event rate for the combined risk of cardiovascular death and hospitalization for heart failure will be at least 15% per year. To achieve this goal, the trial protocol requires that baseline levels of N-terminal prohormone B-type natriuretic peptide (NT-proBNP) will exceed pre-defined levels that will vary with the ejection fraction, i.e. the closer the ejection fraction is to the threshold value of 40%, the higher the qualifying value for circulating level of NT–proBNP:

- If the ejection fraction is ≤ 30%, the level of NT-proBNP will be ≥ 600 pg/mL in patients without atrial fibrillation and ≥ 1200 pg/mL in patients with atrial fibrillation.
- If the ejection fraction is 31–35%, the level of NT-proBNP will be ≥ 1000 pg/mL in patients without atrial fibrillation and ≥ 2000 pg/mL in patients with atrial fibrillation.
- If the ejection fraction is 36–40%, the level of NT-proBNP will be ≥ 2500 pg/mL in patients without atrial fibrillation and ≥ 5000 pg/mL in patients with atrial fibrillation.

- If the ejection fraction is > 40% but the patient has been hospitalized for heart failure within the 12 months prior to screening, the level of NT-proBNP will be ≥ 600 pg/mL in patients without atrial fibrillation and ≥ 1200 pg/mL in patients with atrial fibrillation.

The intent of these criteria is to minimize the recruitment of patients with chronic HFrEF who are at low risk of death or hospitalization.

Patients are excluded if (i) they have a cardiovascular disorder or are receiving treatments that increase the unpredictability of or may change the patients' clinical course, independent of heart failure; (ii) they have an untreated or undertreated cardiovascular condition that might influence the course of heart failure or tolerability of the study medications; (iii) they have a significant co-morbid condition that might influence the clinical course, independent of heart failure; or (iv) if they have any condition that might jeopardize patient safety, limit the patients' participation in the trial, or undermine the interpretation of trial data. All exclusion criteria are listed in *Table 1*.

Study visits and follow-up

Following a screening period lasting 4–28 days, patients who fulfil all eligibility criteria will be randomized double-blind (in a 1:1 manner) to receive placebo or empagliflozin 10 mg daily, in addition to their usual therapy for heart failure (*Figure 1*). The dose of empagliflozin for this trial was selected based on the observed reduction in the risk of cardiovascular death produced by 10 mg daily in a large-scale trial in patients with type 2 diabetes.[1]

Randomization is performed by using a permuted block design with a computer pseudo-random number generator and is stratified by (i) geographical region (North America, Latin America, Europe, Asia, other); (ii) diabetes status at screening; and (iii) estimated glomerular filtration rate [eGFR by the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation] at screening < 60 or ≥ 60 mL/min/1.73 m^2). It is expected that approximately half of the patients will not have diabetes at the time of their enrolment. Following randomization, all appropriate treatments for heart failure or other medical conditions may be initiated, adjusted or altered at the clinical discretion of each patient's physician or healthcare provider according to each patient's needs.

Patients will be evaluated periodically at pre-specified study visits. This assessment will include a description of each patient's New York Heart Association functional class as well as reporting of adverse events. Quality of life related to heart failure will be evaluated using the Kansas City Cardiomyopathy Questionnaire at randomization, after 3, 8 and 12 months of double-blind treatment, and at the end of double-blind treatment. Various biomarkers and end-organ functional assessments will include (but not be restricted to) the periodic measurement of glycated haemoglobin, NT-proBNP, renal function (including eGFR and urinary albumin-to-creatinine ratio) and liver function tests; blood samples are banked for future biomarker analyses.

Investigators are expected to meticulously document all relevant clinical events that occur from the time of randomization until the trial completion. All randomized patients will be followed for the occurrence of pre-specified primary and secondary outcome events for the entire duration of the trial, regardless of whether the study participants are taking their study medications or are fully compliant with study procedures.

Primary and secondary endpoints

The primary endpoint of the EMPEROR-Reduced trial is the time-to-first-event analysis of the combined risk of adjudicated cardiovascular death or adjudicated hospitalization for heart failure. The primary analysis will be based on the intention-to-treat principle and include all randomized patients — from day of randomization until the end of the planned treatment period — whether or not they are continuing to receive the study medications. During the trial close-out period, patients will return for an end-of-treatment visit and will be followed for an additional 30 days off treatment. Primary events occurring during this follow-up period will not be included in the primary analysis of efficacy, but will be included in a separate analysis.

Differences between the placebo and empagliflozin groups for the primary endpoint will be assessed for statistical significance using a Cox proportional hazards model, with pre-specified covariates of age, gender, geographical region, diabetes status at baseline, left ventricular ejection fraction, and eGFR at baseline. Age, ejection fraction and eGFR will be included in the model as continuous variables.

Secondary endpoints will be analysed in a stepwise hierarchical manner so as to preserve the overall type one error rate at a study-wide level of 0.05 (two-sided). The first-listed secondary endpoint is the occurrence of adjudicated hospitalizations for heart failure (including first and recurrent events), which will be evaluated using a joint frailty model that includes the consideration of cardiovascular death as a potential source of informative censoring. If this endpoint is successfully achieved, the analysis will proceed to the second-listed secondary endpoint, i.e. the analysis of the slope of the change in eGFR (CKD-EPI) from baseline, which will be evaluated by a random coefficient model allowing for random intercept and random slope per patient. If the trial is not stopped at interim, an alpha of 0.001 is assigned to this analysis, and the remaining alpha is applied to a patient-level meta-analysis, which will be prospectively carried out to evaluate the effects of empagliflozin (as compared with placebo) in the EMPEROR-Reduced and EMPEROR-Preserved trials combined. The endpoints for this meta-analysis include a composite renal endpoint, cardiovascular death, time to new onset of diabetes in patients without diabetes, and all-cause mortality; these are also designated as secondary endpoints in the individual trials. If the null hypothesis is not rejected at any step in the process of sequential analysis, subsequent hypothesis testing will be considered to be exploratory, and *P*-values will be considered to be nominal. All safety analyses will be based on the treated set, which consists of all patients who received at least one dose of the trial medication.

Table 1 Exclusion criteria

Cardiovascular diseases or treatments that increase the unpredictability of or change the patients' clinical course, independent of heart failure
Myocardial infarction (increase in cardiac enzymes in combination with symptoms of ischaemia or new ischemic ECG changes), coronary artery bypass graft surgery, or other major cardiovascular surgery, stroke or transient ischaemic attack in past 90 days
Heart transplant recipient, or listed for heart transplant. Currently implanted left ventricular assist device
Cardiomyopathy based on infiltrative diseases (e.g. amyloidosis), accumulation diseases (e.g. haemochromatosis, Fabry disease), muscular dystrophies, cardiomyopathy with reversible causes (e.g. stress cardiomyopathy), hypertrophic obstructive cardiomyopathy, or known pericardial constriction
Diagnosis of peripartum cardiomyopathy or cardiomyopathy induced by chemotherapy within 12 months
Any severe (obstructive or regurgitant) valvular heart disease expected to lead to surgery during the trial period
Acute decompensated heart failure requiring intravenous diuretics, vasodilators, inotropic agents or mechanical support within 1 week of screening and during the screening period prior to randomization
ICD or cardiac resynchronization therapy within 3 months prior to screening or if there is an intent to implant either device for 3 months following screening
Untreated or undertreated cardiovascular conditions that might influence the course of heart failure or tolerability of the study medications
Atrial fibrillation or atrial flutter with a resting heart rate > 110 b.p.m. documented by ECG at screening
Untreated ventricular arrhythmia with syncope in a patient without an ICD within 3 months prior to screening
Symptomatic bradycardia or second or third degree heart block without a pacemaker after adjustment of beta-blocker therapy, if appropriate
Systolic blood pressure ≥ 180 mmHg at randomization. If systolic blood pressure is 151–179 mmHg, the patient should be receiving ≥3 anti-hypertensive drugs
Symptomatic hypotension and/or a systolic blood pressure < 100 mmHg at screening or at randomization
Significant co-morbid conditions that might influence the clinical course, independent of heart failure
Chronic pulmonary disease requiring home oxygen, oral corticosteroid therapy or hospitalization for exacerbation within 12 months; significant chronic pulmonary disease; or primary pulmonary arterial hypertension
Acute or chronic liver disease, defined by serum levels of transaminases or alkaline phosphatase more than three times the upper limit of normal at screening
Impaired renal function, defined as eGFR < 20 mL/min/1.73 m^2 (CKD-EPI) or requiring dialysis at the time of screening
Haemoglobin < 9 g/dL at screening
Major surgery (major according to the investigator's assessment) performed within 90 days prior to screening, or major scheduled elective surgery (e.g. hip replacement) within 90 days after screening
Gastrointestinal surgery or gastrointestinal disorder that could interfere with trial medication absorption
Any documented active or suspected malignancy or history of malignancy within 2 years prior to screening, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix, or low risk prostate cancer (patients with pre-treatment PSA < 10 ng/mL, and biopsy Gleason score of ≤ 6 and clinical stage T1c or T2a)
Presence of any other disease than heart failure with a life expectancy of < 1 year (in the opinion of the investigator)
Any condition that might jeopardize patient safety, limit the patients' participation in the trial, or undermine the interpretation of trial data
Current use or prior use of a SGLT2 inhibitor or combined inhibitor of SGLT1 and SGLT2 within 12 weeks prior to screening or randomization. Discontinuation of a SGLT2 inhibitor or combined inhibitor of SGLT1 and SGLT2 inhibitor for the purposes of study enrolment is not permitted
Known allergy or hypersensitivity to any SGLT2 inhibitors
History of ketoacidosis
Patients who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial
Currently enrolled in another investigational device or drug study or are less than 30 days since the completion of a trial of another investigational device or drug study. Any patient receiving any investigational treatment other than the study medications for this trial
Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, will make the patient unlikely to fulfil the trial requirements or complete the trial
Women who are pregnant or are nursing or who plan to become pregnant while in the trial
Any other clinical condition that would jeopardize patient safety while participating in this trial or may prevent the subject from adhering to the trial protocol

CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; PSA, prostate-specific antigen; SGLT, sodium–glucose co-transporter.

Sample size calculations and study conduct

The trial will be carried out as an event-driven study and will continue until 841 adjudicated primary endpoint events have occurred, unless the trial is stopped early following a recommendation of the Data Monitoring Committee. This number of events is expected to provide the ability to detect a 20% difference in relative risk of a primary endpoint event (two-sided alpha = 0.05), with 90% power. Based on the assumption of a ≈15% event rate per year

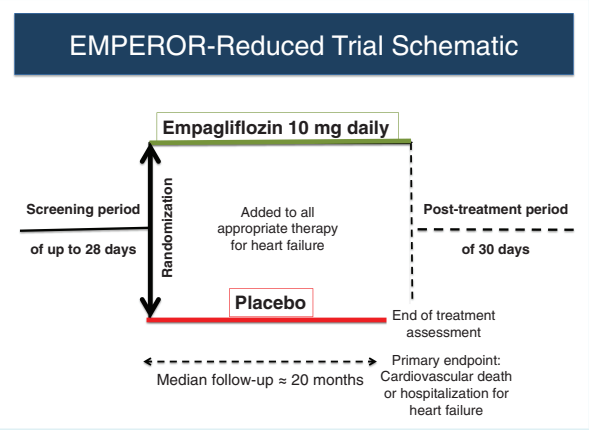

Figure 1 Design for the EMPEROR-Reduced trial.

in the placebo arm and a recruitment period of 18 months and a follow-up period of 20 months, the protocol specified an original target of 2850 patients, with the option of increasing the number of randomized patients up to 4000 patients, if the accumulation of primary endpoint events over calendar time is slower than expected. Based on ongoing monitoring of event accrual and the presentation of the phenotype results from the DECLARE–TIMI 58 trial,[10] it was decided to set the number of randomized patients at approximately 3600 (1800 patients per treatment group). The target number of patients was determined without any knowledge of any unblinded trial data and prior to the planned formal interim analysis of efficacy by the Data Monitoring Committee. Each patient will be followed for a minimum of 6 months following randomization.

Following the accrual of at least 500 primary endpoint events, the Data Monitoring Committee will carry out one pre-specified interim efficacy analysis, and based on this analysis, it may recommend early termination of the study if a critical *P*-value for a benefit on empagliflozin is achieved for both the primary endpoint and for the analysis of cardiovascular death alone. The critical *P*-value is determined by a Hwang–Shih–De Cani alpha-spending function with parameter gamma of −8, which at approximately 500 events (60% of the total number of expected events) yields a one-sided alpha level of 0.001.[11]

Discussion

The ongoing EMPEROR-Reduced trial is evaluating the effect of SGLT2 inhibition with empagliflozin on the risk of cardiovascular death or hospitalization for heart failure in patients with established symptoms of heart failure that are accompanied by evidence of systolic dysfunction (i.e. a left ventricular ejection fraction ≤40% and meaningfully increased levels of natriuretic peptides). In contrast to previous completed trials with SGLT2 inhibitors,[1–3] the EMPEROR-Reduced trial will fully characterize the phenotypic characteristics of patients and will ensure that the efficacy of empagliflozin is evaluated in patients already receiving all other appropriate treatments for heart failure. Importantly, because the reported benefits of SGLT2 inhibitors on heart failure do not appear to be related to their effects on glycaemic control,[1,2] the trial is enrolling patients with or without diabetes. It is expected that the diabetic and non-diabetic subgroups will each be large enough to explore the presence of a treatment-by-diabetic status interaction if one exists. However, since the benefits of SGLT2 inhibitors in heart failure are not related to glucose-lowering and have been observed in non-diabetic models of HFrEF,[12] such an interaction is not anticipated.

An important feature of the EMPEROR-Reduced trial is its focus on the recruitment of patients who have moderate-to-severe heart failure who are at particularly high risk of cardiovascular death and a hospitalization for worsening heart failure. To achieve this goal, we have specified eligibility thresholds for entry levels of NT-proBNP that are more stringent than any other prior or ongoing heart failure trial. Each patient who is enrolled in the EMPEROR-Reduced study is expected to be at particularly high risk, because they exhibit marked decreases in ejection fraction and/or marked increases in circulating levels of natriuretic peptides and/or have had a recent hospitalization for heart failure; most patients are expected to fulfil more than one of these enrichment criteria. As a result, the trial is expected to recruit patients with a greater severity of heart failure than those who are being enrolled in another large-scale heart failure outcomes trials with the SGLT2 inhibitor, dapagliflozin (DAPA-HF).[13] The enrolment of lower-risk patients with milder degrees of heart failure likely explains why the DAPA-HF trial is designed to be larger in size (approximately 4700 patients) and why an urgent visit for worsening heart failure (but without the need for hospitalization) is included as a component of the primary endpoint in that study. As a result of the implementation of our enrichment criteria, these additional design features of DAPA-HF were unnecessary in the design of the EMPEROR-Reduced trial.

In addition to the primary endpoint, the EMPEROR-Reduced trial is designed to evaluate another important potential benefit of SGLT2 inhibition, i.e. an effect of these drugs to slow the rate of worsening of renal function.[2,7] In patients with diabetes, the action of SGLT2 inhibitors to promote sodium delivery to the macula densa results (through tubuloglomerular feedback) in afferent arteriolar vasoconstriction and, thereby, an amelioration of glomerular hyperfiltration with lessening of the attendant risk of renal parenchymal injury.[14,15] Presumably as a result of the activation of this mechanism, SGLT2 inhibitors have been shown to slow the rate of progression of renal disease in patients with type 2 diabetes, even after only 1–2 years of treatment;[4] such benefits are greater in magnitude and occur more rapidly with SGLT2 inhibitors than with anti-diabetic drugs that have greater anti-hyperglycaemic effects (e.g. glucagon-like peptide-1 receptor agonists).[14] However, the role of glomerular hyperfiltration in the progression of renal dysfunction in patients with chronic heart failure who do not have diabetes is not clear; the current trial may provide important insights into this question.[14,16,17]

In addition to the trial's primary and secondary endpoints, the current programme is designed to determine if the favourable effect of empagliflozin on cardiovascular death seen in a large-scale trial in patients with type 2 diabetes[1] will be replicated in patients with chronic heart failure. Unless the magnitude of the

mortality benefit is striking, neither the EMPEROR-Reduced nor the EMPEROR-Preserved trials (when each is considered alone) are likely to be sufficiently large to adequately evaluate the possibility that empagliflozin might reduce the risk of cardiovascular death. However, in the current programme, a hierarchical testing procedure has been pre-specified that will combine the occurrence of cardiovascular deaths across the two heart failure trials (EMPEROR-Reduced and EMPEROR-Preserved) on an individual patient-level basis. If (as expected) the drug's effect to reduce the risk of heart failure hospitalization is confirmed, the combined analysis of fatal events across the two trials should have sufficient power to allow an unbiased assessment of the effect of empagliflozin on cardiovascular mortality across the full spectrum of patients with chronic heart failure, with or without left ventricular systolic dysfunction. This approach is predicated on the expectation that any drug-related reduction in mortality risk is not meaningfully influenced by ejection fraction, and thus, heterogeneity across the trials will not affect the ability of the mortality data to be pooled.

In a post hoc analysis of the DECLARE–TIMI 58 trial, the investigators collected information on ejection fraction measured before randomization in a subset of patients, in order to determine which phenotype of heart failure [i.e. HFrEF or heart failure with a preserved ejection fraction (HFpEF)] was more likely to experience a reduction in heart failure events with dapagliflozin.[10] The investigators found that the magnitude of the reduction in the risk of heart failure hospitalizations appeared to be greater in patients with HFrEF than in HFpEF, and cardiovascular death was reduced only in patients with HFrEF. The most striking benefit was observed in patients with the lowest baseline left ventricular ejection fraction (i.e. $<30\%$). Intriguingly, the EMPEROR-Reduced trial was originally designed to be enriched for these patients, long before the phenotype results of DECLARE–TIMI 58 were known. However, the findings with dapagliflozin must be interpreted cautiously since these post hoc analyses are based on incomplete data that were collected only in patients with type 2 diabetes.

If the EMPEROR-Reduced trial confirms a favourable effect on empagliflozin on the study's pre-specified primary and secondary endpoints, the trial will not necessarily be able to discern the relative contribution of diverse mechanisms to explain the observed benefits. In patients with type 2 diabetes, treatment with SGLT2 inhibitors causes a natriuresis and weight loss, and the haemoconcentration produced by these drugs in earlier trials suggests a meaningful contraction of plasma volume and interstitial fluid which might be beneficial in patients with chronic heart failure.[1,18] However, such a mechanism is not likely to contribute to benefits of the drug in chronic heart failure if our patients are adequately treated with diuretics and if the dose of diuretics is appropriately adjusted to the clinical needs of the patients during the course of the trial. More importantly, intensification of diuretic therapy has not led to a dramatic decrease in cardiovascular mortality or sudden death in patients with heart failure.[19]

What mechanism(s) might then be responsible for such a striking cardioprotective effect of SGLT2 inhibitors in HFrEF? SGLT2 inhibitors increase fasting levels of ketone bodies, and thus, they have been hypothesized to enhance the utilization of this efficient metabolic fuel in the failing heart.[20–22] However, the findings of experimental studies have provided inconsistent support for this hypothesis.[23–25] Instead, it has been proposed that SGLT2 inhibitors may slow the course of cardiomyocyte injury and loss by inhibiting the sodium–hydrogen exchanger-1 (NHE-1) in the myocardium, whose overactivity may lead to increases in intracellular sodium and calcium, which can impair cardiomyocyte function and viability.[26–31] Interestingly, empagliflozin has also been shown to inhibit the activation of Ca++/calmodulin-dependent kinase II, which contributes to the activation of NHE-1 in the heart.[32–34] The actions of empagliflozin to prevent calcium overload may explain why the drug prevents the time-dependent decline in systolic cardiac function seen in experimental pressure overload-induced heart failure.[35,36]

Regardless of the mechanisms that might be in play, the EMPEROR-Reduced trial is well-positioned to determine if the addition of SGLT2 inhibitors could add meaningfully to current approaches that have established benefits in the treatment of chronic heart failure. The findings of the trial are likely to advance both our understanding of the disease as well as our treatment options.

Conflict of interest: M.P. has consulted for Abbott, Actavis, Akcea, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Gilead, Johnson & Johnson, NovoNordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics and Theravance. J.B. has received research support from the National Institutes of Health, Patient Centered Outcomes Research and the European Union, and he has served as a consultant for Abbott, Adrenomed, Amgen, Array, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CVRx, G3 Pharmaceutical, Innolife, Janssen, LinaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, V-Wave Limited, and Vifor. G.S.F. has received fees and/or research grants from Novartis, Bayer, Cardiorentis, Vifor, Servier, Alere, and Abbott. W.J., A.S., J.S., K.K., C.Z., J.G., and M.B. are employess of Boehringer Ingelheim. S.D.A. has recently received fees for steering committtee activity, advisory board work and/or speaking from AstraZeneca, Bayer, Boehringer, Brahms, Novartis, Respicardia, Servier, and Vifor, and he has received grants for the execution of investigator initiated trials from Abbott Vascular and Vifor. F.Z. has recently received steering committte or advisory board fees from Amgen, AstraZeneca, Bayer, Boehringer, Boston Scientific, Cardior, CVRx, Janssen, Livanova, Merck, Mundipharma, Novartis, NovoNordisk and Vifor Fresenius.

Appendix

Committees for the EMPEROR-Reduced trial

Executive Committee

Milton Packer (Chair), Baylor University Medical Center, Dallas, TX, USA.

Stefan D. Anker (Vice-Chair), Berlin Institute of Health Center for Regenerative Therapies (BCRT); Berlin, Germany.

Javed Butler, University of Mississippi, Jackson, MI, USA.

Gerasimos Filippatos, National and Kapodistrian University of Athens School of Medicine, Athens, Greece.
Faiez Zannad, Université de Lorraine, Inserm INI-CRCT, CHRU, Nancy, France.
Jyothis George, Boehringer-Ingelheim International, Ingelheim, Germany.
Martina Brueckmann, Boehringer-Ingelheim International, Ingelheim, Germany.

National Coordinators

Argentina:	Sergio Perrone, FLENI Foundation, Departamento de Cardiologia, Buenos Aires.
Australia:	Stephen Nicholls, Monash University, Clayton, Victoria.
Belgium:	Stefan Janssens, Universitair Ziekenhuis Leuven, Leuven.
Brazil:	Edmar Bocchi, São Paulo University Medical School, São Paulo, Brazil.
Canada:	Nadia Giannetti, Centre Universitaire de Sante McGill, Montreal, Quebec.
Canada:	Subodh Verma, St. Michael's Hospital, University of Toronto, Ontario.
China:	Zhang Jian, Fuwai Hospital Chinese Academic of Medical Science, Beijing.
Czech Republic:	Jindrich Spinar, University Hospital, Masaryk University Hospital, Brno.
France:	Marie-France Seronde, Centre Hospitalier Régional et Universitaire de Besançon, Besançon.
Germany:	Michael Böhm, Universitätsklinikum des Saarlandes und Medizinische Fakultät der Universität des Saarlandes, Homberg.
Hungary:	Bela Merkely, Semmelweis University, Budapest.
India:	Vijay Chopra, Medanta, The Medicity, Gurugram.
Italy:	Michele Senni, ASST Papa Giovanni XXIII, Bergamo.
Italy:	Stefano Taddei, Azienda Ospedaliero Universitaria Pisana, Pisa.
Japan:	Hiroyuki Tsutsui, Kyushu University, Fukuoka City.
Republic of Korea:	Dong-Ju Choi, Seoul National University Bundang Hospital, Seoul.
Mexico:	Eduardo Chuquiure, Instituto Nacional de Cardiologia Dr Ignacio Chavez Riera, Cuidad de Mexico.
Netherlands:	Hans Pieter Brunner La Rocca, Maastricht University Medical Center, Maastricht.
Poland:	Piotr Ponikowski, Wrocław Medical University, Wroclaw.
Spain:	Jose Ramon Gonzalez Juanatey, Complejo Hospitalario Universitario de Santiago, A Coruña.
United Kingdom:	Iain Squire, Glenfield Hospital, Leicester.
United States:	Javed Butler, University of Mississippi, Jackson.
United States:	James Januzzi, Harvard Medical School, Massachusetts General Hospital, Boston.
United States:	Ileana Pina, DMC Specialty Center-Heart Hospital, Detroit.

Consulting Statistician

Stuart J. Pocock, London School of Hygiene and Tropical Medicine, London, UK.

Clinical Events Committee

Peter Carson (Chair), Veterans Affairs Medical Center in Washington, Washington, USA.
Wolfram Doehner, Charité Universitätsmedizin Berlin, Berlin, Germany.
Alan Miller, University of Florida Health, Jacksonville, FL, USA.
Markus Haas, Theresienkrankenhaus, Mannheim, Germany.
Steen Pehrson, University Hospital Rigshospitalet, Copenhagen, Denmark.
Michel Komajda, Institut de Cardiologie, Boulevard de l'Hôpital, Paris, France.
Inder Anand, University of Minnesota Medical School and VA Medical Center La Jolla, CA, USA.
John Teerlink, University of California, San Francisco, CA, USA.
Alejandro Rabinstein, Mayo Clinic College of Medicine, Rochester, MN, USA.
Thorsten Steiner, Klinikum Frankfurt Höchst, Frankfurt, Germany.
Hooman Kamel, Presbyterian Hospital/Weill Cornell Medical Center, New York, NY, USA.
Georgios Tsivgoulis, University of Tennessee Health Science Center, Memphis, TN, USA.
James Lewis, Georgetown University Hospital, Potomac, MD, USA.
James Freston, University of Connecticut Medical Center, Farmington, CT, USA.
Neil Kaplowitz, University of Southern California, Los Angeles, CA, USA.
Johannes Mann, KfH Nierenzentrum München-Schwabing, Munich, Germany.
Mark Petrie, University of Glasgow, Glasgow, UK.

Scientific Excellence Committee

Richard Bernstein, Feinberg School of Medicine of Northwestern University, Chicago, IL, USA.
Alfred Cheung, University of Utah, Salt Lake City, UT, USA.
Jennifer Green, Duke University Hospital, Durham, NC, USA.
James Januzzi, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA.
Sanjay Kaul, Cedars-Sinai Medical Center, Los Angeles, CA, USA.

Carolyn Lam Su Ping, Yong Loo Lin School of Medicine, Singapore.
Gregory Lip, University of Birmingham, Birmingham, UK.
Nikolaus Marx, Universitätsklinikum Aachen, Aachen, Germany.
Peter McCullough, Baylor University Medical Center; Dallas, TX, USA.
Cyrus Mehta, Harvard T.H Chan, School of Public Health, Cambridge, MA, USA.
Piotr Ponikowski, Wrocław Medical University, Wroclaw, Poland.
Julio Rosenstock, Dallas Diabetes and Endocrine Center, University of Texas Southwestern Medical Center, Dallas, TX, USA.
Naveed Sattar, University of Glasgow, Glasgow, UK.
Benjamin Scirica, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA.
Hiroyuki Tsutsui, Kyushu University, Fukuoka City, Japan.
Subodh Verma, St. Michael's Hospital, Toronto, Canada.
Christoph Wanner, University Clinic, Würzburg, Germany.

Data Monitoring Committee

Francine K. Welty (Chair), Harvard Medical School, Boston, MA, USA.
Klaus G. Parhofer, University of Munich, Munich, Germany.
Tim Clayton, London School of Hygiene and Tropical Medicine, London, UK.
Terje R. Pedersen, Oslo University Hospital, Oslo, Norway.
Kennedy R. Lees, University Department of Medicine & Therapeutics, Western Infirmary, Glasgow, UK.
Marvin A. Konstam, Tufts University School of Medicine, Boston, MA, USA.
Barry Greenberg, UC San Diego Medical Center, La Jolla, CA, USA.
Mike Palmer, N Zero 1 Ltd, Wilmslow, Cheshire, UK.

References

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–2128.
2. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–657.
3. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JP, Ruff CT, Gause-Nilsson IA, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347–357.
4. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenn BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;**380**:2295–2306.
5. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Trial Investigators. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. *Eur Heart J* 2016;**37**:1526–1534.
6. Fitchett D, Butler J, van de Borne P, Zinman B, Lachin JM, Wanner C, Woerle HJ, Hantel S, George JT, Johansen OE, Inzucchi SE; EMPA-REG OUTCOME Trial Investigators. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME trial. *Eur Heart J* 2018;**39**:363–370.
7. Rådholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, Fulcher G, Barrett TD, Shaw W, Desai M, Matthews DR, Neal B. Canagliflozin and heart failure in type 2 diabetes mellitus. *Circulation* 2018;**138**:458–468.
8. Packer M. How have millions of people with heart failure benefited from our research over the last 10-15 years? The sounds of dead silence. *Eur J Heart Fail* 2017;**19**:1353–1354.
9. Packer M. Who should deliver medical therapy for patients with chronic heart failure? An immediate call for action to implement a community-based collaborative solution. *Circ Heart Fail* 2017;**10**:e004332.
10. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RH, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JP, Bonaca MP, Ruff CT, Desai AS, Goto S, Johansson PA, Gause-Nilsson I, Johanson P, Langkilde AM, Raz I, Sabatine MS, Wiviott SD; DECLARE–TIMI 58 Investigators. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation* 2019;**139**:2528–2536.
11. Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. *Stat Med* 1990;**9**:1439–1445.
12. Yurista SR, Silljé HH, Oberdorf-Maass SU, Schouten EM, Pavez Giani MG, Hillebrands JL, van Goor H, van Veldhuisen DJ, de Boer RA, Westenbrink BD. Sodium-glucose co-transporter 2 inhibition with empagliflozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction. *Eur J Heart Fail* 2019;**21**:862–873.
13. McMurray JJ, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD; DAPA-HF Committees and Investigators. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail* 2019;**21**:665–675.
14. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, Fagan NM, Woerle HJ, Johansen OE, Broedl UC, von Eynatten M. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014;**129**:587–597.
15. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;**375**:323–334.
16. Hallow KM, Gebremichael Y, Helmlinger G, Vallon V. Primary proximal tubule hyperreabsorption and impaired tubular transport counterregulation determine glomerular hyperfiltration in diabetes: a modeling analysis. *Am J Physiol Renal Physiol* 2017;**312**:F819–F835.
17. Packer M, Claggett B, Lefkowitz MP, McMurray JJ, Rouleau JL, Solomon SD, Zile MR. Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial. *Lancet Diabetes Endocrinol* 2018;**6**:547–554.
18. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJ, Boulton DW. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. *Diabetes Obes Metab* 2018;**20**:479–487.
19. Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE, Cropp AB, Frid DJ, Nye RG, Pressler ML, Wertheimer JH, Packer M; PRAISE Investigators. Prospective Randomized Amlodipine Survival Evaluation. Diuretic resistance predicts mortality in patients with advanced heart failure. *Am Heart J* 2002;**144**:31–38.
20. Butler J, Hamo CE, Filippatos G, Pocock SJ, Bernstein RA, Brueckmann M, Cheung AK, George JT, Green JB, Januzzi JL, Kaul S, Lam CS, Lip GYH, Marx N, McCullough PA, Mehta CR, Ponikowski P, Rosenstock J, Sattar N, Salsali A, Scirica BM, Shah SJ, Tsutsui H, Verma S, Wanner C, Woerle HJ, Zannad F, Anker SD; Trials Program EMPEROR. The potential role and rationale for treatment of heart failure with sodium-glucose co-transporter 2 inhibitors. *Eur J Heart Fail* 2017;**19**:1390–1400.
21. Ferrannini E, Mark M, Mayoux E. CV protection in the EMPA-REG OUTCOME trial: a "thrifty substrate" hypothesis. *Diabetes Care* 2016;**39**:1108–1114.
22. Mudaliar S, Alloju S, Henry RR. Can a shift in fuel energetics explain the beneficial cardiorenal outcomes in the EMPA-REG OUTCOME study? A unifying hypothesis. *Diabetes Care* 2016;**39**:1115–1122.
23. Verma S, Rawat S, Ho KL, Wagg CS, Zhang L, Teoh H, Dyck JE, Uddin GM, Oudit GY, Mayoux E, Lehrke M, Marx N, Lopaschuk GD. Empagliflozin increases cardiac energy production in diabetes: novel translational insights into the heart failure benefits of SGLT2 inhibitors. *JACC Basic Transl Sci* 2018;**3**:575–587.
24. Abdurrachim D, Teo XQ, Woo CC, Chan WX, Lalic J, Lam CS, Lee PT. Empagliflozin reduces myocardial ketone utilization while preserving glucose utilization in diabetic hypertensive heart disease: a hyperpolarized ^{13}C magnetic resonance spectroscopy study. *Diabetes Obes Metab* 2019;**21**:357–365.

25. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, Ishikawa K, Watanabe S, Picatoste B, Flores E, Garcia-Ropero A, Sanz J, Hajjar RJ, Fuster V, Badimon JJ. Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. *J Am Coll Cardiol* 2019;**73**:1931–1944.
26. Baartscheer A, Hardziyenka M, Schumacher CA, Belterman CN, van Borren MM, Verkerk AO, Coronel R, Fiolet JW. Chronic inhibition of the Na^+/H^+-exchanger causes regression of hypertrophy, heart failure, and ionic and electrophysiological remodelling. *Br J Pharmacol* 2008;**154**:1266–1275.
27. Baartscheer A, Schumacher CA, Wüst RC, Fiolet JW, Stienen GJ, Coronel R, Zuurbier CJ. Empagliflozin decreases myocardial cytoplasmic Na^+ through inhibition of the cardiac Na^+/H^+ exchanger in rats and rabbits. *Diabetologia* 2017;**60**:568–573.
28. Uthman L, Baartscheer A, Bleijlevens B, Schumacher CA, Fiolet JW, Koeman A, Jancev M, Hollmann MW, Weber NC, Coronel R, Zuurbier CJ. Class effects of SGLT2 inhibitors in mouse cardiomyocytes and hearts: inhibition of Na^+/H^+ exchanger, lowering of cytosolic Na^+ and vasodilation. *Diabetologia* 2018;**61**:722–726.
29. Packer M, Anker SD, Butler J, Filippatos G, Zannad F. Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure: proposal of a novel mechanism of action. *JAMA Cardiol* 2017;**2**:1025–1029.
30. Packer M. Activation and inhibition of sodium-hydrogen exchanger is a mechanism that links the pathophysiology and treatment of diabetes mellitus with that of heart failure. *Circulation* 2017;**136**:1548–1559.
31. Packer M. Reconceptualization of the molecular mechanism by which SGLT2 inhibitors reduce the risk of heart failure events. *Circulation* 2019, in press.
32. Vila-Petroff M, Mundiña-Weilenmann C, Lezcano N, Snabaitis AK, Huergo MA, Valverde CA, Avkiran M, Mattiazzi A. Ca^{2+}/calmodulin-dependent protein kinase II contributes to intracellular pH recovery from acidosis via Na^+/H^+ exchanger activation. *J Mol Cell Cardiol* 2010;**49**:106–112.
33. Mustroph J, Wagemann O, Lücht CM, Trum M, Hammer KP, Sag CM, Lebek S, Tarnowski D, Reinders J, Perbellini F, Terracciano C, Schmid C, Schopka S, Hilker M, Zausig Y, Pabel S, Sossalla ST, Schweda F, Maier LS, Wagner S. Empagliflozin reduces Ca/calmodulin-dependent kinase II activity in isolated ventricular cardiomyocytes. *ESC Heart Fail* 2018;**5**:642–648.
34. Anker SD, Butler J. Empagliflozin, calcium, and SGLT1/2 receptor affinity: another piece of the puzzle. *ESC Heart Fail* 2018;**5**:549–551.
35. Byrne NJ, Parajuli N, Levasseur JL, Boisvenue J, Beker DL, Masson G, Fedak PW, Verma S, Dyck JR. Empagliflozin prevents worsening of cardiac function in an experimental model of pressure overload-induced heart failure. *JACC Basic Transl Sci* 2017;**2**:347–354.
36. Lee HC, Shiou YL, Jhuo SJ, Chang CY, Liu PL, Jhuang WJ, Dai ZK, Chen WY, Chen YF, Lee AS. The sodium-glucose co-transporter 2 inhibitor empagliflozin attenuates cardiac fibrosis and improves ventricular hemodynamics in hypertensive heart failure rats. *Cardiovasc Diabetol* 2019;**18**:45.