Rationale and design of the EMPYREAN study

Hirohiko Motoki1, Izuru Masuda2, Shinji Yasuno3, Koji Oba4,5, Wataru Shoin1, Satoru Usami6, Yoshihiko Saito7, Masako Wak8, Mitsuhisa Komatsu9, Kenji Ueshima10, Yasuaki Nakagawa11, Cheol Son12,13, Shin Yonemitsu14, Shinya Hiramatsu15, Manako Konda16, Katsuya Onishi17 and Koichiro Kuwahara1*

1Department of Cardiovascular Medicine, Shinshu University School of Medicine, Matsumoto, Japan; 2Division of Diabetes, Endocrinology and Metabolism, Department of Internal Medicine, Shinshu University School of Medicine, Matsumoto, Japan; 3Division of Endocrinology and Metabolism, Department of Internal Medicine, Nara Medical University, Kashihara, Japan; 4Department of Biostatistics, School of Public Health, The University of Tokyo, Tokyo, Japan; 5Department of Biostatistics, The University of Tokyo, Tokyo, Japan; 6Department of Preventive Services, Kyoto University School of Public Health, Kyoto, Japan; 7Division of Cardiovascular Medicine, Nara Medical University, Kashihara, Japan; 8Department of Internal Medicine, Taigenkai Hospital, Ichinomiya, Japan; 9Department of Cardiovascular Medicine, Shinshu University School of Medicine, Matsumoto, Japan; 10Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan; 11Division of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan; 12Omics Research Center, National Cerebral and Cardiovascular Center, Suita, Japan; 13Department of Diabetes and Endocrinology, Osaka Red Cross Hospital, Osaka, Japan; 14Hiramitsu Heart Clinic, Nagoya, Japan; 15Department of Preventive Services, Kyoto University School of Public Health, Kyoto, Japan; 16Onishi Heart Clinic, Tsu, Japan

Abstract

Aims A sodium glucose cotransporter 2 (SGLT2) inhibitor was recently found to reduce heart failure hospitalization in the EMPA-REG OUTCOME trial. We have hypothesized that autonomic nerve activity may be modulated by SGLT2 inhibition. The current study aims to investigate the impact of empagliflozin on sympathetic and parasympathetic nerve activity in patients with type 2 diabetes mellitus.

Methods and results This ongoing study is a prospective, randomized, open-label, multicentre investigation of 134 patients with type 2 diabetes mellitus. The patients are randomly allocated to receive either empagliflozin or sitagliptin with the treatment goal of the Japan Diabetes Society guidelines. Ambulatory electrocardiographic monitoring is performed at the baseline and at 12 and 24 weeks of treatment. Analyses of heart rate variability are conducted using the MemCalc method, which is a combination of the maximum entropy method for spectral analysis and the non-linear least squares method for square analysis. The primary endpoint is the change in the low-frequency (0.04–0.15 Hz)/high-frequency (0.15–0.4 Hz) ratio from baseline to 24 weeks.

Conclusions This investigation on the effect of EMPagliflozin on cardiac sYmpathetic and parasympathetic neRve activity in Japanese pAtieNts with type 2 diabetes (EMPYREAN study) offers an important opportunity to understand the impact of SGLT2 inhibition on autonomic nerve activity in patients with type 2 diabetes.

Keywords Diabetes mellitus; SGLT2 inhibitors; Heart rate variability

Introduction

A resurgence of interest on the association between heart failure and type 2 diabetes mellitus (T2DM) has emerged with the increasing prevalence of patients concomitantly afflicted with both diseases. T2DM frequently coexists with cardiovascular disease to raise the risk of heart failure and heart failure-related complications, including death. The leading cause of death in T2DM is cardiovascular mortality, which is reportedly associated with diabetic cardiac autonomic neuropathy. Heart rate variability (HRV), which is measured by the variation between two consecutive beats, is the golden standard to evaluate cardiac autonomic function for various conditions, including myocardial infarction, cardiac transplantation, heart failure, and diabetic neuropathy. Impaired HRV is a marker of cardiovascular risk and is often used for early detection of cardiac autonomic neuropathy in T2DM patients. Low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.4 Hz) are components of the frequency domain parameters of HRV. LF is mediated by parasympathetic activity, and HF values are derived from both
sympathetic and parasympathetic activities on the heart, but with sympathetic predominance. LF/HF ratio represents sympathovagal balance, in which higher value indicates sympathetic predominance.22 Although the prognostic significance of impaired HRV in T2DM has been assessed in several studies,16–19 the impact of anti-diabetic drugs on cardiac autonomic function has not been well established.

The recent EMPA-REG OUTCOME trial on T2DM patients clarified the prognostic impact of the antihyperglycaemic agent empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as reducing mortality and heart failure hospitalization risk.23 Although SGLT2 inhibitors may have potential applications beyond T2DM, such as for heart failure, the mechanisms underlying the cardioprotective effects of SGLT2 inhibitors remain incompletely understood. A significant reduction in arterial blood pressure was observed in the absence of increased heart rate in patients treated with empagliflozin in the EMPA-REG trial.23 Moreover, incidence of sudden death was less in pooled empagliflozin group than placebo (1.1% vs. 1.6%).23 Thus, the present investigation on the effect of EMPagliflozin on cardiac sympathetic and parasympathetic nerve activity in Japanese pAtieNts with type 2 diabetes (EMPERY study; UMIN Clinical Trials Registry identifier UMIN000029194. Registered 19 September 2017, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?reptno=R000033375) has been designed to investigate our hypothesis that empagliflozin modulates cardiac autonomic function of patients with T2DM.

Table 1 Inclusion and exclusion criteria

| Inclusion criteria |
|--------------------|
| All of the following criteria must be met: |
| • Subjects with T2DM on a diet and exercise regimen who have HbA1c ≥6.5% and ≤10.0% at screening and during run-in phase |
| • SGLT2/DPP4-naive (no anti-diabetic therapy with SGLT2 inhibitors or DPP4 inhibitors for ≥12 weeks prior to randomization) |
| • Age ≥20 and <75 years |
| • Body mass index ≥18.5 and ≤40 kg/m² at screening |
| • Signed and dated written informed consent prior to screening |

| Exclusion criteria |
|--------------------|
| • Treatment with insulin or glucagon-like peptide-1 receptor agonist |
| • Neuropathy evidenced by orthostatic hypotension, diabetic neuropathy, or autonomic disturbance |
| • Proliferative retinopathy |
| • Estimated glomerular filtration rate <45 mL/min/1.73 m² (a) or creatinine clearance <50 mL/min (b) at screening or during run-in phase |
| • Treatment with prohibited medications in this study protocol |
| • SGLT2 inhibitors other than empagliflozin, DPP4 inhibitors other than sitagliptin, insulin, GLP-1 receptor antagonists, alpha-blockers, beta-blockers, verapamil, diltiazem, digitalis, or antiarrhythmic drugs |
| • Chronic obstructive lung disease under treatment |
| • Sleep apnoea syndrome |
| • Indication of liver disease defined by serum levels of alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase above three times the upper limit of normal during screening or run-in phase |
| • Acute coronary syndrome or stroke within 12 weeks prior to informed consent |
| • Planned cardiac surgery or angioplasty within 12 weeks prior to informed consent |
| • Surgical intervention for obesity within 2 years prior to informed consent |
| • Any uncontrolled endocrine disorder apart from T2DM |
| • Alcohol or drug abuse within 12 weeks of informed consent that would interfere with trial participation or any ongoing condition leading to decreased compliance with study procedures or study drug intake |
| • Treatment with anti-obesity drugs |
| • Arrhythmia or atrial flutter |
| • Implanted permanent pacemaker |
| • Frequent premature atrial/ventricular contraction (according to the Minnesota Code Classification System for electrocardiographic findings) |
| • Bundle branch block |
| • Sick sinus syndrome or atrio-ventricular block more than the second degree |
| • Pre-menopausal women who were nursing, pregnant, or requesting maternity |
| • Medical history of cancer and/or treatment for cancer within the last 5 years |
| • Contraindications to background therapy according to the local label |
| • Treatment with systemic steroids, hyperthyroidism, or hypothyroidism under treatment |
| • Intake of an investigational drug in another trial within 30 days prior to informed consent of this trial or participating in another trial involving an investigational drug and/or follow-up |
| • Any clinical condition that would jeopardize patient safety while participating in this clinical trial |

(a) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, and Hishida A, on behalf of the collaborators developing the Japanese equation for estimating GFR. Revised equations for estimating glomerular filtration rate from serum creatinine in Japan. Am J Kidney Dis. 2009; 53:982–992. (b) Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31–41. DPP4, dipeptidyl peptidase 4; GLP-1, G-protein-coupled receptor 1; HbA1c, haemoglobin A1c; SGLT2, sodium glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

ESC Heart Failure 2020; 7: 3134–3141
DOI: 10.1002/ehf2.12825
Study design

The EMPYREAN study is an ongoing multicentre, randomized, open-label (empagliflozin vs. sitagliptin), assessor-blinded, active controlled using sitagliptin, parallel-group clinical trial planned to test the hypothesis that empagliflozin improves autonomic disturbance in patients with T2DM during 24 weeks of treatment. Before patient enrolment, the study protocol was approved by the certified review board of Shinshu University School of Medicine. This study is being conducted in accordance with the Declaration of Helsinki. Written informed consent is obtained from each patient before enrolment. Personal information about potential and enrolled participants is kept confidential, and subject data are de-identified using participant numbers.

Inclusion and exclusion criteria

We aim to recruit a total of 134 participants across approximately 20 sites in Japan. Recruitment for the trial began in December 2017 and will end in April 2020. Eligible participants for the trial are patients with T2DM aged 20 to 74 years who meet the enrolment criteria detailed in Table 1. Briefly, eligible patients include those with a diagnosis of T2DM, haemoglobin A1c (HbA1c) ranging from 6.5% to 10.0% (7.0% to 10.0% for patients treated with sulfonylurea or glinide), no anti-diabetic therapy with SGLT2 inhibitors or dipeptidyl peptidase 4 inhibitor (DPP4-I) agents for ≥12 weeks prior to randomization, and body mass index ≥18.5 and ≤40 kg/m² at screening.

Details of the exclusion criteria are listed in Table 1. Briefly, patients with any of the following are excluded: treatment with insulin or glucagon-like peptide-1 receptor agonist, neuropathy evidenced by orthostatic hypotension, estimated glomerular filtration rate <45 mL/min/1.73 m², prohibited medications in this study protocol, atrial fibrillation or atrial flutter, implanted permanent pacemaker, sick sinus syndrome or atrio-ventricular block of more than second degree, treatment with systemic steroids, hyperthyroidism, or hypothyroidism under treatment.

Trial design and follow-up

Eligible patients undergo a 4 week screening period (Figure 1), during which time background glucose-lowering therapy is continued unchanged. The purpose of the screening period is to evaluate participants’ willingness and ability to adhere to the treatment and follow-up planned in the trial and evaluate baseline clinical characteristics. Background therapy for hypertension, dyslipidaemia, and diabetes mellitus is screened as summarized in Table 2. Blood/urine sampling (on-site and central measurement), electrocardiogram (ECG) recording, the Schellong test, and 24 h Holter ECG are also performed. For the Schellong test, blood pressure is measured with an automated oscillometric device using a standard protocol. Blood pressure in the supine position is measured after 15 min of rest, followed next by measurement in a standing position after 3 min of standing. While standing, participants are asked whether they feel any dizziness, or light-headedness, and the examiner notes whether it is transient or nontransient. The procedure is aborted for safety reasons if necessary. Orthostatic hypotension is defined as a drop in systolic blood pressure of ≥20 mmHg or a drop in diastolic blood pressure of ≥10 mmHg from the supine to the standing position at treatment with insulin or glucagon-like peptide-1 receptor agonist, neuropathy evidenced by orthostatic hypotension, estimated glomerular filtration rate <45 mL/min/1.73 m², prohibited medications in this study protocol, atrial fibrillation or atrial flutter, implanted permanent pacemaker, sick sinus syndrome or atrio-ventricular block of more than second degree, treatment with systemic steroids, hyperthyroidism, or hypothyroidism under treatment.

Figure 1 EMPYREAN study protocol. Eligible patients undergo a 4 week screening period to evaluate baseline clinical characteristics. Blood/urine sampling, ECG recording, the Schellong test, and 24 h Holter ECG are performed. Following the screening period, patients still meeting the inclusion/exclusion criteria are randomized (1:1) to receive either empagliflozin (EMPA) 10 mg or sitagliptin (SITA) 50 mg once daily in addition to their background therapy. Twenty-four hours of Holter ECG is performed at 12 and 24 weeks of treatment. Heart rate variability is analysed in the time-frequency domain as shown in Table 5. ECG, electrocardiogram.
Table 2 Background therapy

| Indication              | Class                                                                 |
|-------------------------|----------------------------------------------------------------------|
| Hypertension            | Calcium channel blockers, Angiotensin-converting enzyme inhibitors, Angiotensin II receptor blockers, Diuretics, Mineral corticoid receptor antagonists, Others |
| Dyslipidaemia           | Statins, Omega-3 fatty acids, Intestinal cholesterol absorption inhibitors, PCSK9 inhibitors, Others |
| Diabetes mellitus       | Sulfonylureas, Thiazolidines, Biguanides, Alpha-glucosidase inhibitors, Glinides, Others |
| Others                  | PCSK9, proprotein convertase subtilisin/kexin type 9.                  |

Table 3 Details of blood/urine sampling

| Blood test (on-site)          | Complete bloodWBC, RBC, Hb, Hct, Ptt count |
|-------------------------------|------------------------------------------|
| Blood chemistry/AST, ALT, ALP, γ-GTP, LDH, BUN, Cr, CPK, T-enzyme tests | Bil, TC, HDL-c, TG, FBS, HbA1c, UA |
| Blood test (central)          | HbA1c, IRI, hsCRP, cathecolamines, BNP, NT-pro-BNP, pro-BNP, ANP, TSH, ft4, ft3, enzyme tests, ketones |
| Urine test                    | U-prot, U-glu, U-ketone, pregnancy test |
| Urine chemistry               | Alb, Cr                                  |

Table 4

| Indication              | Class                                                                 |
|-------------------------|----------------------------------------------------------------------|
| PC 9                    | IRI, hsCRP, cathecolamines, BNP, NT-pro-BNP, pro-BNP, ANP, TSH, ft4, ft3, enzyme tests, ketones |
| Others                  | PCSK9, proprotein convertase subtilisin/kexin type 9.                  |

3 min. Details of the blood/urine sampling for on-site monitoring and central measurement are listed in Table 3. HbA1c is evaluated by on-site management of diabetes and by central measurement as an exploratory outcome. Following the screening period, patients still meeting the inclusion/exclusion criteria are randomized (1:1) to receive either empagliflozin of 10 mg or sitagliptin of 50 mg once daily in addition to their background therapy. Treatment allocation is centrally performed with a minimization algorithm implementing a random component by the data management group of the data centre. Baseline heart rate (<75 or ≥75 count/min), age (<50 or ≥50 years), HbA1c (<8% or ≥8%), and treatment centre are considered as balancing factors. Background glucose-lowering therapy is to remain unchanged for the 24 weeks after randomization if possible, although rescue therapy can be initiated. During this period, empagliflozin (10–25 mg/day) or sitagliptin (50–100 mg/day) can be adjusted to achieve desired glycaemic control at the investigator’s discretion for the best standard of care according to local guidelines. Twenty-four hours of Holter ECG and blood sampling (on-site/central measurement) are performed at 12 and 24 weeks of treatment (Table 4). HRV is analysed in the time-frequency domain as shown in Table 5.

Endpoints

The primary outcome of this study is the change in the LF/HF ratio from the baseline to the end of the study (24 weeks). The key secondary outcomes include the changes in LF, HF, and LF/HF ratio from baseline to 12 weeks and changes in LF and HF from baseline to 24 weeks. The following variables are evaluated for changes from baseline to 12 and 24 weeks: average of all N-N intervals, standard deviation of N-N intervals (SDNN), standard deviation of the averages of N-N intervals for all 5 min segments of a 24 h recording, mean of the standard deviations of N-N intervals for all 5 min segments of a 24 h recording, root mean square of successive differences between adjacent N-N intervals (rMSSD), percentage of differences between adjacent N-N intervals that are greater than 50 ms, incidence of premature heart-beat and arrhythmia events, body weight and body mass index, and HbA1c. The changes from baseline to 12 and 24 weeks in waist circumference, serum cathecolamines, thyroid-stimulating hormone, ft4, ft3, brain natriuretic peptide (BNP), N-terminal-pro-BNP, pro-BNP, and atrial natriuretic peptide (ANP) are investigated as exploratory outcomes. Details of the outcomes are described in Table 6.

Holter electrocardiogram

All data from 24 h Holter ECG are sent to the Core Laboratory for analysis by an unrelated physician in a blinded manner (MemCalc/CHIRAM, Suwa Trust GMS, Tokyo, Japan) to obtain the LF (0.04–0.15Hz) and HF (0.15–0.4Hz) components of HRV (measured in absolute units; i.e. ms²). The total power of HRV is also calculated for regression analysis as a global marker of cardiac autonomic function. From the electrocardiographic recordings, the statistical and geometric time domain indices are calculated from the N-N intervals noted earlier (Table 6). Frequency domain variables including the total, LF, and HF powers as well as the LF/HF ratio are derived from spectral analysis of successive N-N intervals.
Safety

Throughout the study, safety information is collected by recording such serious adverse events as all-cause mortality, fatal events, and adverse conditions requiring admission or prolongation of admission regardless of the causal relationship with the trial drugs or protocol, in addition to pre-defined adverse events of special interest including hepatic injury, decreased renal function, metabolic acidosis, ketoacidosis, diabetic ketoacidosis, and events involving lower limb amputation. When investigators identify any adverse event, its severity or grade, procedures conducted, outcomes, and relationship to the study drug are recorded and assessed. Investigators promptly report the occurrence of adverse events to the secretariat who then immediately informs the principal investigator for relay to Nippon Boehringer Ingelheim and the Data and Safety Monitoring Board (DSMB). The DSMB consists of an authorized endocrinologist and clinical epidemiologists with relevant expertise. Blinded to treatment allocation, the DSMB independently evaluates safety during the trial, assesses the necessity for any revisions to the trial design, and validates any decisions to continue the trial. If needed, the DSMB makes recommendations on safety issues to the principal investigator.

Study monitoring

Risk-based monitoring of the study sites is implemented to ensure that this study is properly conducted. A monitoring protocol has been separately created for the detailed monitoring-related plan. Auditing by an independent third party is also conducted to ensure the reliability of study results. Auditing is performed according to a separately specified, documented procedure. Records and medical information identifying the patients are kept confidential during monitoring and auditing. When new safety information-related issues arise, the Protocol Steering Committee or the DSMB

Table 4  Scheduled visits and assessments in the EMPYREAN study

|                  | Screening                  | Randomization   |
|------------------|----------------------------|-----------------|
|                  | Step 1                     | Step 2          | Step 3          | Step 4          |
|                  | 4 weeks prior to randomization | 0 weeks         | 12 weeks        | 24 weeks        |
| Eligibility      | ○                         | ○               | ○               | ○               |
| Informed consent | ○                         | ○               | ○               | ○               |
| Patient characteristics | ○                | ○               | ○               | ○               |
| Physical examination | ○                                 | ○               | ○               | ○               |
| Blood test (on-site) | ○                                  | ○               | ○               | ○               |
| Schellong test   | ○                         | ○               | ○               | ○               |
| ECG              | ○                         | ○               | ○               | ○               |
| Holter ECG       | ○                         | ○               | ○               | ○               |
| Blood test (central) | ○                                   | ○               | ○               | ○               |
| Medication adherence | ○                             | ○               | ○               | ○               |
| Safety           | ○                         | ○               | ○               | ○               |

ECG, electrocardiogram.

Table 5  Heart rate variability indices assessed in the EMPYREAN study

| Time domain indices | Frequency domain indices |
|---------------------|-------------------------|
| AVNN, ms            | LF/ HF ratio            |
| SDNN, ms            | Total spectral power of all N-N intervals between 0.04 and 0.15 Hz |
| SDANN, ms           | Total spectral power of all N-N intervals between 0.15 and 0.4 Hz |
| SDNNIDX             | Ratio of low-frequency to high-frequency power |
| rMSSD, ms           |                         |
| pNN50, %            |                         |

Average of all N-N intervals
Standard deviation of all N-N intervals
Standard deviation of the averages of N-N intervals for all 5 min segments of a 24 h recording
Mean of the standard deviations of N-N intervals for all 5 min segments of a 24 h recording
Root mean square of successive differences between adjacent N-N intervals
Percentage of differences between adjacent N-N intervals that are greater than 50 ms
Table 6  Study endpoints

| Primary endpoint |
|------------------|
| Change in LF/HF ratio (from baseline to end of study) |

| Secondary endpoints |
|---------------------|
| Changes in LF, HF, and LV/HF ratio (from baseline to 12 weeks) |
| Changes in LF and HF (from baseline to 24 weeks) |
| Changes in the following variables (from baseline to 12 and 24 weeks): |
| HRV indices (AVNN, SDNN, SDANN, SDNNIDX, rMSSD, and pNN50), incidence of premature heartbeat and arrhythmia, body weight, body mass index, and HbA1c |

| Exploratory endpoints |
|-----------------------|
| Changes in the following variables (from baseline to 12 and 24 weeks): |
| Waist circumference, catecholamines, thyroid hormones (TSH, fT4, and fT3), plasma BNP, NT-pro-BNP, pro-BNP, and ANP |

Abbreviations are listed in Tables 3 and 5.

discuss the issue, including study discontinuation or continuation, and the ethical review committee at each study site confirms each patient’s intention to continue participation in the study.

Statistical considerations

Sample size estimation

To date, no data are available on the impact of SGLT-2 inhibitors on cardiac autonomic nerve activity. Thus, we referred to a previous study that evaluated the LF/HF ratio of patients treated with amlodipine or verapamil. The mean difference and standard deviation of the LF/HF ratio was 0.15 ± 0.25; thus, the effect size was 0.627 in the study. Accordingly, we considered a conservative effect size of 0.5, alpha error of 5%, and power of 80%. To allow for approximately 10% drop-out, 67 patients are required per group, that is, 134 participants in total.

Statistical analysis plan

The primary efficacy population has been defined as a full analysis set (patients who were randomly assigned to a group and received Holter ECG at least once). The change in the LF/HF ratio at 24 weeks is examined via mixed model repeated measures analysis for comparisons between the efficacy of the treatments (empagliflozin and sitagliptin). Inter-group comparisons of the least squares means at 24 weeks are performed as well. Missing data are not imputed. The covariates included in the model are as follows: treatment group, time point, interaction between treatment group and time point, baseline heart rate, age, and HbA1c. Additionally, unstructured correlation is assigned via the restricted maximum likelihood concerning the correlation structure, and the Kenward–Roger method is used to calculate the degree of freedom.28 When difficulties (e.g. convergence is not attained) arise, first-order autoregressive covariance is used followed by compound symmetry. Similar analytical methods are applied to the secondary endpoints. The safety population has been defined as a safety analysis set (patients who were randomly assigned to a group and received at least one dose of the study treatment). Descriptive analysis is performed for the frequency of adverse events. A two-sided P-value of <0.05 is considered statistically significant. All statistical analyses are performed using SAS Version 9.4 software (SAS Institute, Cary, NC).

Discussion

The EMPYREAN, identically designed, phase IV studies will shed light on the impact of empagliflozin on cardiac autonomic function in patients with T2DM in addition to conventional therapy. Although SGLT-2 inhibitors have been recommended for the treatment of T2DM and provide favourable cardiovascular outcomes, their mechanism of improving morbidity and mortality is not well investigated. Furthermore, while empagliflozin decreased systolic blood pressure and increased haematocrit after administration, substantial declines in HR were also observed in the EMPA-REG outcome study.23 This raised the possibility that empagliflozin might modulate cardiac autonomic function in patients with T2DM.

In the present ongoing study, a DPP4-I is being administered for treatment of the control group. An increasing number of patients with T2DM are receiving DPP4-I agents, which are a new therapeutic class of oral antihyperglycaemic drugs for T2DM. These agents have been shown to reduce HbA1c levels without increasing the risk of hypoglycaemia or weight gain.29 The use of DPP4-I drugs for T2DM has now been firmly established in clinical practice. However, in comparison with a placebo, the DPP4-I sitagliptin could not reduce cardiovascular mortality in the TECOS trial. Thus, comparing SGLT-2 and DPP4-I drugs enables us to evaluate the additional impact of SGLT-2 inhibition on the cardiovascular system with a sufficient decrease in HbA1c that is equivalent to that with a DPP4-I and with a low hypoglycaemic risk. In the EMPA-REG OUTCOME trial, an Asian cohort that underwent empagliflozin treatment displayed better cardiovascular outcomes than did a non-Asian cohort.23 Thus, our Japanese population appears preferable for investigation of the impact of empagliflozin on the cardiovascular system.

In terms of the observation period of the EMPYREAN study, 24 weeks have been considered necessary. In the TAKEDA INSIGHT trial, patients showed body weight loss until 24 weeks under SGLT-2 inhibition by dapagliflozin. In those patients, weight loss with diuresis was obvious in the first 4 weeks, followed next by body weight loss with visceral fat reduction. Arterial blood pressure and HbA1c decreased from 12 weeks after the treatment, which was maintained until 24 weeks.
Conclusions

The results of the current EMPYREAN study are expected to provide key pathophysiological insights regarding the cardioprotective effect of empagliflozin. Findings from the EMPYREAN study will greatly facilitate clinical decision-making for patients with T2DM.

Acknowledgement

The authors sincerely thank Trevor Ralph for his English editorial assistance.

Conflict of interest

Dr. Hiramitsu has received lecture fee from MSD and Boehringer Ingelheim. Dr. Onishi has received lecture fee from Boehringer Ingelheim. Dr. Kuwahara has received lecture fee from Boehringer Ingelheim. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

References

1. Fitchett DH, Udell JA, Inzucchi SE. Heart failure outcomes in clinical trials of glucose-lowering agents in patients with diabetes. *Eur J Heart Fail* 2017; 19: 43–53.
2. Mentz RJ, Kelly JP, von Lueder TG, Voors AA, Lam CS, Cowie MR, Kjeldsen K, Jankowska EA, Atar D, Butler J, Fuzziat M, Zannad F, Pitt B, O’Connor CM. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol* 2014; 64: 2281–2293.
3. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974; 34: 29–34.
4. Al V, Ziegler D. Diabetec cardiovascular autonomic neuropathy. *Circulation* 2007; 115: 387–397.
5. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham study. *Am Heart J* 1987; 113: 1489–1494.
6. Porta A, Girardengo G, Bari V, George AL Jr, Brink PA, Goosen A, Crotti L, Schwartz PJ. Autonomic control of heart rate and QT interval variability influences arrhythmic risk in long QT syndrome type 1. *J Am Coll Cardiol* 2015; 65: 367–374.
7. Camm AJ, Prat C, Schwartz PJ, Al-Khalidi HR, Spyt MJ, Holroyde MJ, Karam R, Sonnenblick EH, Brum JM, AzimiLide post Infarct survVial Evaluation (ALIVE) Investigators. Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. *Circulation* 2004; 109: 990–996.
8. Wichterle D, Simek J, La Rovere MT, Schwartz PJ, Camm AJ, Malik M. Prevalent low-frequency oscillation of heart rate: novel predictor of mortality after myocardial infarction. *Circulation* 2004; 110: 1183–1190.
9. Seravalle G, Peperno A, Mariani R, Pelloni I, Facchetti R, Dell’Oro R, Cuspidi C, Mancia G, Grassi G. Alterations in sympathetic nerve traffic in genetic haemochromatosis before and after iron depletion therapy: a microneurographic study. *Eur Heart J* 2007; 37: 988–995.
10. Radaelli A, Cazzaniga M, Viola A, Balestri G, Janetti MB, Signorini MG, Ferruci AU. Enhanced baroreceptor control of the cardiovascular system by polyunsaturated fatty acids in heart failure patients. *J Am Coll Cardiol* 2006; 48: 1600–1606.
11. Mancia G, Parati G, Castiglioni P, di Rienzo M. Effect of sinoaortic denervation on frequency-domain estimates of baroreflex sensitivity in conscious cats. *Am J Physiol* 1999; 276: H1987–H1993.
12. Casolo GC, Stroder P, Signorini C, Calzolari F, Zucchini M, Balli E, Sulla A, Lazzeroni S. Heart rate variability during the acute phase of myocardial infarction. *Circulation* 1992; 85: 2073–2079.
13. Schwartz PJ, Vanoli E, Stramba-Badiale M, De Ferrari GM, Billman GE, Foreman RD. Autonomic mechanisms and sudden death: new insights from the analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. *Circulation* 1988; 78: 969–979.
14. Sands KE, Appel ML, Lilly LS, Schoen FJ, Mudge GH Jr, Cohen RJ. Power spectrum analysis of heart rate variability in human cardiac transplant recipients. *Circulation* 1989; 79: 76–82.
15. Kienzle MG, Ferguson DW, Birkett CL, Myers GA, Berg WJ, Mariano DJ. Clinical hemodynamic and sympathetic neural correlates of heart rate variability in congestive heart failure. *Am J Cardiol* 1992; 69: 761–767.
16. Kinney RP, Byrne S, Edmonds ME, Watkins PJ, Roberts VC. Heart rate variability in the assessment of autonomic diabetic neuropathy. *Auton Medica* 1982; 4: 155–167.
17. Pagani M, Mallattato G, Pierini S, Casati R, Masu AM, Poli M, Guzzetti S, Lombardi F, Cerutti S, Malliani A. Spectral analysis

Funding

This work is supported by a research grant obtained through Boehringer Ingelheim and Eli Lilly and company. This is an investigator-driven trial designed by the steering committee (Supplementary Table) and conducted by the trial bureau and local investigators. The authors are solely responsible for the design and conduct of this study, all study analysis, the drafting and editing of the paper, and its final contents.

Supporting information

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

Data S1. Supporting Information
of heart rate variability in the assessment of autonomic diabetic neuropathy. *J Auton Nerv Syst* 1988; 23: 143–153.

18. Freemen R, Saul JP, Roberts MS, Berger RD, Broadbridge C, Cohen RJ. Spectral analysis of heart rate in diabetic neuropathy. *Arch Neurol* 1991; 48: 185–190.

19. Bernardi L, Ricordi L, Lazzari P, Solda P, Calciati A, Ferrari MR, Vande I, Finardi G, Frantino P. Impaired circulation modulation of sympathovagal modulation of sympathovagal activity in diabetes. *Circulation* 1992; 86: 1443–1452.

20. Boudet G, Walther G, Courteix D, Obert P, Lesourd B, Pereira B, Chapier D, Vinet A, Chamoux A, Naughton G, Poirier P, Dutheil F. Paradoxical dissociation between heart rate and heart rate variability following different modalities of exercise in individuals with metabolic syndrome: the RESOLVE study. *Eur J Prev Cardiol* 2017; 24: 281–296.

21. Benichou T, Pereira B, Mermillod M, Tauveron I, Pfibigan D, Maqdasy S, Dutheil F. Heart rate variability in type 2 diabetes mellitus: a systematic review and meta-analysis. *PLoS One* 2018; 13: e0195166.

22. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; 93: 1043–1065.

23. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi E. Investigators EMPA-REGOUTCOME. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128.

24. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology* 1996; 46: 1470.

25. Masaki KH, Schatz LJ, Burchfiel CM, Sharp DS, Chiu D, Foley D, Curb JD. Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. *Circulation* 1998; 98: 2290–2295.

26. Haneda M, Noda M, Origasa H, Noto H, Yabe D, Fujita Y, Goto A, Kondo T, Araki E. Japanese clinical practice guideline for diabetes 2016. *Diabetology International* 2018; 9: 1–45.

27. Sahin I, Kosar F, Altunkan S, Gunaydin M. Comparison of the effects of amlodipine and verapamil on autonomic activity in hypertensive patients. *Eur J of Intern Med* 2004; 15: 225–230.

28. Kenward MG, Roger JH. An improved approximation to the precision of fixed effects from restricted maximum likelihood. *Computational Statistics and Data Analysis* 2009; 53: 2583–2595.

29. Deacon CF. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes Obes Metab* 2011; 13: 7–18.

30. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR, TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015; 373: 232–242.

31. Masuda I, Nakamae K, Azuma N, Iwasaki A, Hige H, Toda K, Imai M, Ayukawa H, Toda K, Hamada Y, Sensui M, Hirata M, Takeda T, Kuzuya H. Effect of Dapagliflozin on body composition and glycemic control in type 2 diabetes mellitus patients. *Therapeutic Research* 2015; 36: 581–591 Japanese.