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STUDY PROTOCOL

Effect of Empagliflozin Versus Placebo on Cardiac Sympathetic Activity in Acute Myocardial Infarction Patients with Type 2 Diabetes Mellitus: Rationale

Yoshiaki Kubota · Takeshi Yamamoto · Shuhei Tara · Yukichi Tokita · Kenji Yodogawa · Yuki Iwasaki · Hitoshi Takano · Yayoi Tsukada · Kuniya Asai · Masaaki Miyamoto · Yasushi Miyauchi · Eitaro Kodani · Naoki Sato · Jun Tanabe · Wataru Shimizu

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ABSTRACT

Introduction: Protection from lethal ventricular arrhythmias leading to sudden cardiac death is one of the most important problems after myocardial infarction. Cardiac sympathetic hyperactivity is related to poor prognosis and fatal arrhythmias and can be non-invasively assessed with heart rate variability, heart rate turbulence, T-wave alternans, late potentials, and ^{123}I-*meta*-iodobenzylguanide (^{123}I-MIBG) scintigraphy. Sodium glucose cotransporter 2 (SGLT2) inhibitors potentially reduce sympathetic nervous system activity that is augmented in part due to the stimulatory effect of hyperglycemia. The EMBODY trial is designed to determine whether the suppression of cardiac sympathetic activity induced by the SGLT2 inhibitor is accompanied by protection against adverse cardiovascular outcomes.

Methods: The EMBODY trial is a prospective, multicenter, randomized, double-blind, placebo-controlled trial in patients with acute MI and type 2 diabetes in Japan. A total of 98 patients will be randomized (1:1) to receive once-daily placebo or empagliflozin, an SGLT2 inhibitor, 10 mg. The primary end point is the change from baseline to 24 weeks in heart rate variability. Secondary end points include the change from baseline for other sudden cardiac death surrogate-markers such as heart rate turbulence, T-wave alternans, late potentials, and ^{123}I-MIBG scintigraphy imaging. Adverse effects will be evaluated throughout the trial period.

Planned Outcomes: The EMBODY trial will evaluate the potential cardioprotective effect of empagliflozin and will provide additional important new data regarding its preventative effects on sudden cardiac death.

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Y. Kubota · T. Yamamoto · S. Tara · Y. Tokita · K. Yodogawa · Y. Iwasaki · H. Takano · Y. Tsukada · K. Asai · M. Miyamoto · W. Shimizu (✉)
Department of Cardiovascular Medicine, Nippon Medical School Hospital, 1-1-5, Sendagi, Bunkyo-ku, Tokyo 113-0022, Japan
e-mail: wshimizu@nms.ac.jp

Y. Miyauchi
Department of Cardiovascular Medicine, Nippon Medical School Chiba Hokusoh Hospital, 1715, Kamagari, Inzai, Chiba 270-1694, Japan

E. Kodani
Department of Cardiovascular Medicine, Nippon Medical School Tama-Nagayama Hospital, 1-7-1 Nagayama Tama-shi, Tokyo 206-8512, Japan

N. Sato
Department of Cardiovascular Medicine, Nippon Medical School Musashi Kosugi Hospital, 1-396 Kosugi-machi, Nakahara-ku, Kawasaki-shi, Kanagawa 211-8533, Japan

J. Tanabe
Department of Cardiovascular Medicine, Shizuoka Medical Center, 762-1 Nagasawa, Shimizu-cho, Sunto-gun, Shizuoka 411-8611, Japan

Trial Registration: Unique Trial Number, UMIN000030158 (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000034442).
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Keywords: Acute myocardial infarction; Cardiac sympathetic activity; Empagliflozin, sodium glucose cotransporter 2 (SGLT2) inhibitor; Type 2 diabetes mellitus (T2DM)

Abbreviations

AMI	Acute myocardial infarction
CAD	Coronary artery disease
CV	Cardiovascular
ECG	Electrocardiography
HF	High-frequency power
HRT	Heart rate turbulence
HRV	Heart rate variability
^{123}I-MIBG	^{123}I-*meta*-iodobenzylguanide
LF	Low-frequency power
LP	Late potentials
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
SCD	Sudden cardiac death
SGLT2	Sodium glucose cotransporter 2
T2DM	Type 2 diabetes mellitus
TWA	T-wave alternans

INTRODUCTION

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are known to not only remove insulin-independent glycemic toxicity, but also reduce blood pressure, body weight, and visceral fat [1]. The SGLT2 inhibitors have the potential to reduce sympathetic nervous system activity, which is augmented in part because of the stimulatory effect of hyperglycemia [2, 3]. Recently, results of the EMPAREG OUTCOME trial, which aimed to evaluate the long-term cardiovascular (CV) safety and benefits of empagliflozin, one of the SGLT2 inhibitors, as an add-on to standard anti-diabetic care, was published [4]. In this trial, empagliflozin significantly reduced the relative risk of CV death by 38% (including sudden cardiac death, SCD) and all-cause death by 32% during a median follow-up of 3.1 years [4]. It is of particular importance that empagliflozin reduced deaths from CV in the early phase (0–6 months) [4]. Protection against lethal ventricular arrhythmias leading to SCD is one of the most important aims after prevention of myocardial infarction (MI) [5]. Compared with individuals without diabetes, those with diabetes are at a 56% greater risk of death from an ST elevation myocardial infarction heart attack and at a 39% greater risk of death from a non-ST elevation MI [6]. Cardiac sympathetic hyperactivity is related to poor prognosis and fatal arrhythmias [7]. To date, noninvasive techniques such as T-wave alternans (TWA), late potentials (LP), heart rate turbulence (HRT), and heart rate variability (HRV) have been developed for this purpose. Considering the above factors, it is quite important to evaluate the effect of empagliflozin on the suppression of the induction of lethal ventricular tachyarrhythmias in the early phase. Thus, the EMBODY trial may provide the possible mechanisms by which empagliflozin reduces CV deaths, including SCD in acute MI (AMI) patients with type 2 diabetes mellitus (T2DM). We hypothesized that empagliflozin will ameliorate the abnormal sympathetic activity that contributes to SCD after AMI in patients with T2DM.

METHODS AND DESIGN

Trial Overview

The EMBODY trial is a prospective, multicenter, randomized, double-blind, placebo-controlled trial in patients with AMI and T2DM in Japan. A total of 98 patients will be randomized (1:1) to receive once-daily placebo or once-daily empagliflozin (10 mg). We seek to assess the beneficial effect of empagliflozin on cardiac sympathetic activity in comparison with a placebo in relation to lethal ventricular tachyarrhythmias measured by ambulatory electrocardiography (ECG) (SCM-8000 Fukuda Denshi Co., Ltd. Tokyo, Japan) and ^{123}I-*meta*-iodobenzylguanide (^{123}I-MIBG) scintigraphy. The EMBODY trial was registered with the

University Hospital Medical Information Network in November 2017 (UMIN ID: 000030158). The trial drugs will be provided by Boehringer Ingelheim (Germany). Ethics approval was obtained from the local institutional review board of each participating center and the trial complies with the Declaration of Helsinki.

Trial Population and Follow-Up

We will recruit a total of 98 patients across five sites in Japan from February 2018 to March 2019. The criteria established for enrollment are detailed in Table 1. Briefly, eligible patients include those with a diagnosis of T2DM and AMI. A single anti-diabetic agent indicates that each physician decides based on the patient's individual characteristics or intolerance on metformin. After each patient has been provided written informed consent of the trial plan, randomized, and assigned to either the empagliflozin or placebo group, the follow-up visits will be scheduled at 4, 12, and 24 weeks (Table 2). They will receive standard treatment for their background disease, T2DM, and AMI during trial period (Fig. 1).

Randomization and Blinding

Patients with AMI and T2DM will be randomly assigned into an empagliflozin (10 mg/day) group or a placebo add-on to conventional therapy group 2 weeks after the onset of AMI based on allocation factors, baseline HbA1c value (less than 7.0% or ≧ 7.0%), and max CK (less than 3000 or ≧ 3000 IU/l) by a dynamic allocation method. All patients will receive a drug (empagliflozin 10 mg or placebo, once daily) and be followed up for 24 weeks after stratified randomization. Glucose-lowering therapy will remain unchanged for the first 12 weeks after randomization. After week 12, investigators will be encouraged to adjust glucose-lowering therapy, including metformin, sulfonylurea, alpha glucosidase inhibitors, thiazolidinediones, and dipeptidyl peptidase-4 inhibitors, at their discretion, to achieve glycemic control according to the Japan Diabetes Society guidelines [8].

Patients will not be able to use insulin, glucagon-like peptide-1 analog, or high doses of sulfonylurea (glimepiride > 2 mg, glibenclamide > 1.25 mg, glimicron > 40 mg) during

Table 1 Inclusion and exclusion criteria

Inclusion	Exclusion
1. Adults (aged ≥ 20 years)	1. Type 1 diabetes mellitus
2. Glycemic condition	2. Persistent atrial fiblilation
Subjects appropriately diagnosed as T2DM by the Japanese guideline[8]	3. Insulin and glucagon-like peptide-1 analog user
Drug-naïve subjects or taking single anti-diabetic agent	4. High dose of sulfonylurea (glimepiride > 2 mg, glibenclamide > 1.25 mg, glimicron > 40 mg)
T2DM patients who need to start or are possibly changing or adding an anti-diabetic agent	5. HbA1c ≥ 10%
3. Patients within 2–12 weeks after the onset of AMI, who can be discharged home	6. History of diabetic ketoacidosis or diabetic coma within 3 months prior to the randomization
	7. Renal dysfunction (eGFR < 45 ml/min/1.73 m^2)
	8. Heart failure graded at NYHA functional class IV
	9. Pregnancy or possible pregnancy and breast feeding
	10. Lack of informed consent
	11. Contraindications to empagliflozin according to the label

Table 2 Post-randomized follow-up visits at 4, 12, and 24 weeks

	Screening	0 W (Baseline)	4 W (± 4 W)	12 W (± 4 W)	24 W (± 4 W)
Assessment of eligibility and informed consent	[a]				
Randomization		[a]			
Investigator visit		[a]	[b]	[b]	[a]
Body weight		[a]	[b]	[b]	[a]
Blood pressure and heart rate		[a]	[b]	[b]	[a]
TWA,LP,HRT, and HRV by ambulatory ECG		[a]			[a]
^{123}I-MIBG scintigraphy		[b]			[b]
Blood sampling		[a]	[b]	[b]	[a]
Safety assessment, including events			[b]	[b]	[a]

W weeks(s), *TWA* T-wave alternans, *LP* late potentials, *HRT* heart rate turbulence, *HRV* heart rate variability, *ECG* electrocardiogram, *^{123}I-MIBG* ^{123}I-*meta*-iodobenzylguanide

[a] Primary or key secondary variables

[b] Optional

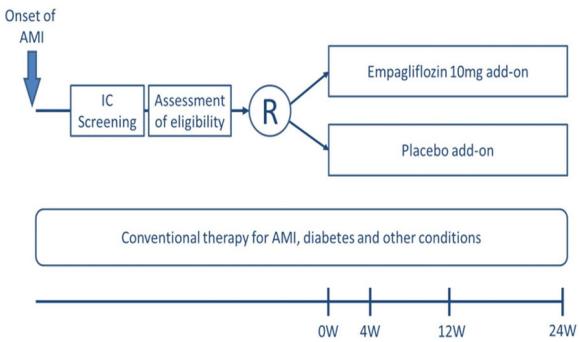

Fig. 1 Trial outline. Patients with acute myocardial infarction and type 2 diabetes mellitus will be randomly assigned to receive empagliflozin (10 mg/day) or placebo add-on to conventional therapy at 2 weeks after the onset of AMI. They will receive treatment for 24 weeks after stratified randomization

the trial period. Patients will also receive treatment post-AMI with beta-blockers, anti-platelet therapy, statins, and renin-angiotensin system inhibitors in accordance with local guidelines [9] [10]. Throughout the trial, investigators will be encouraged to treat other cardiovascular risk factors (including dyslipidemia and hypertension) to achieve the best available standard treatment. After the trial has been completed, all patients can continue any anti-diabetic treatments in accordance with their individual condition.

Trial End Points

The primary end point of this trial is the change in HRV from baseline to 24 weeks. The HRV provides important information about the sympathovagal balance (low-frequency power, LF; high-frequency power, HF) of the heart. Traditionally, the HRV is analyzed using time and frequency domain methods.

- Time domain analysis:
  1. Mean RR interval for 24 h (mean NN)
  2. Standard deviation of normal RR intervals (SDNN)
  3. Standard deviation of all 5-min mean normal RR intervals (SDANN)
  4. Square root of the mean of the sum of the squares of differences between adjacent RR intervals (r-MSSD)

5. Percentage of adjacent RR intervals differing by > 50 ms (pNN50)

- Frequency domain analysis:
  1. Total power (TP 0–0.4 Hz)
  2. HF (0.15–0.4 Hz)
  3. LF (0.04–0.15 Hz)
  4. Sympathovagal balance (LF/HF ratio)

Secondary end points are to evaluate the change from baseline in the following measurements after add-on empagliflozin treatment with conventional therapy compared to the placebo throughout the trial period.

(1) TWA, LP, and HRT assessed by ambulatory ECG (SCM-8000)

2) Cardiac sympathetic activity assessed by ^{123}I-MIBG scintigraphy

Additionally, we will compare the changes from baseline in other variables, including glycemic and lipid profiles, uric acid, estimated glomerular filtration rate, body weight, blood pressure, and safety parameters, including adverse events (hypoglycemic episode, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) after 24 weeks of treatment. We will provide results at each follow-up period (Table 2).

Statistical Considerations

Sample Size Estimation

Sample size was calculated for the LF/HF ratio, one of the parameters of the primary end point. As no previous studies have examined the effect of SGLT2 inhibitors on cardiac sympathetic activity, it is estimated that the mean difference in change between the empagliflozin and standard treatment from baseline to 24 weeks in the Ln LF/HF (ms^2) will be 0.3 and the SD will be 0.5 (taken from previous studies using a similar approach) [11] [12] [13]. When the significance level is 5% (two sided), a sample size of 88 patients per arm will provide a power of 80% for the comparison. It is estimated that at least 10% of randomized patients will not be treated or will have a baseline value or at least one post-baseline value missing, so will be removed from the analysis. Consequently, we assume that a total of 98 patients should be enrolled in this trial.

Statistical Analyses

Continuous variables will be expressed as mean ± standard deviation (SD), while categorical variables will be expressed as number (percentage). To compare characteristics in the empagliflozin and placebo groups, chi-square tests and independent t tests will be used for categorical and continuous variables, respectively. The relationships between the changes in HRV and each measurement listed will be evaluated using Pearson's correlation coefficient. The principal investigator and a biostatistician will create a statistical analysis plan before patient recruitment and database locking have been completed. $p \leq 0.05$ will be considered statistically significant. SAS version 9.4 (SAS Institute, Cary, NC, USA) will be used for statistical analyses.

DISCUSSION

The mechanisms by which empagliflozin has a beneficial impact on the prevention of SCD and CV outcomes in AMI patients with T2DM have not yet been established. The EMBODY trial aims to reveal whether suppression of cardiac sympathetic activity is accompanied by protection from SCD.

Assessment by Ambulatory ECG

The evidence connecting the autonomic nervous system to life-threatening arrhythmias and to cardiovascular mortality is well established. There is a clear link between increasing sympathetic activity and/or decreasing vagal activity and a greater tendency for lethal ventricular arrhythmias during myocardial ischemia [14]. The HRV is a physiologic phenomenon characterized by beat-to-beat variation in cardiac cycle length, which is influenced by autonomic tone. Depressed HRV is currently considered a strong predictor of mortality and lethal ventricular

arrhythmias in post-MI patients [15]. In many previous reports, depressed HRV was reported to be associated with adverse outcomes in survivors of acute MI [16–21]. Depressed HRV compared with depressed left ventricular ejection fraction (LVEF) predicts arrhythmic rather than nonarrhythmic mortality [22, 23]. The integration of traditional risk stratifiers, such as LVEF and non-sustained ventricular tachycardia, with autonomic markers, such as HRV, provides a powerful approach to the ever-daunting problem of early identification of post-MI patients at a risk of cardiac and arrhythmic mortality [15, 24].

The TWA is a periodic beat-to-beat variation in the amplitude or morphology of the T wave on ECG. Beat-to-beat TWA is believed to reflect increased dispersion of ventricular repolarization, and it is known to often precede the development of lethal ventricular tachyarrhythmias [25–27]. Recent clinical trials have shown that a positive TWA result is associated with serious ventricular arrhythmic events and SCD [28–30]. It is currently recommended as a class IIa, level of evidence A, risk-stratification tool for post-MI patients [31].

HRT is characterized by fluctuations in electrocardiographic cycle length after a ventricular premature contraction. To date, HRT has been examined mainly in post-MI patients, and it is suggested that abnormal HRT is associated with increased mortality after MI [32–34]. Impaired HRT, abnormal TWA, and an ejection fraction < 0.50 beyond 8 weeks after MI reliably identifies patients at risk of serious events [29].

LPs are characterized by a high-frequency, low-amplitude signal at the tail of a QRS complex attributable to fragmented and delayed electrical conduction through the borders of a myocardial scar. Delayed conduction represented by LP allows reentry of electrical impulses and susceptibility to ventricular tachyarrhythmias. Previous studies have reported that LP is useful for identifying patients with ventricular tachycardia after MI [35–37].

Assessment By ^{123}I-MIBG Scintigraphy

To explore the intracardiac sympathetic activity in detail, we will perform ^{123}I-MIBG scintigraphy. Cardiac sympathetic activity can be noninvasively assessed with cardiac ^{123}I-MIBG scintigraphy. ^{123}I-MIBG uptake will be determined, specifically the early and late heart/mediastinal (H/M) ratio and cardiac washout rate. Cardiac sympathetic hyperactivity is reflected by a decreased ^{123}I-MIBG late H/M ratio and increased washout rate. Both are associated with increased fatal arrhythmia and cardiac mortality [38].

After AMI, patients should be carefully managed with conventional therapy for T2DM and post-MI to prevent future CV events. To investigate the additional effect of empagliflozin on lethal ventricular tachyarrhythmias, we adopted a trial design comparing the effects of empagliflozin with a placebo on top of conventional therapy. Coronary artery disease (CAD) is prevented by interventions including statins against dyslipidemia. However, the reduction in the risk of CAD by statins has been reported to be only 30% [39]. Therefore, there has been a focus on further managing of the residual risk other than dyslipidemia. One of the few reports on this is the EMPAREG OUTCOME report [4], which reported improved prognosis in patients with DM and CAD including a history of MI.

This concept highlights the importance of developing a clinically feasible approach to select post-infarction patients who are at particularly high risk of predominantly arrhythmic death who would benefit from SGLT2 inhibitor therapy.

Trial Limitations

The main limitations of this trial will be the relatively small sample size. Although this research is a trial to examine the mechanisms by which empagliflozin has a beneficial impact on the prevention of SCD, to verify the results, real-world data accumulation is needed. Second, the trial period is 24 weeks. In the EMPAREG OUTCOME report, the reduction of CV death was

observed during an early follow-up period (0–-6 months), which may be attributable to decreased SCD with empagliflozin during this period. Thus, we expect that the 24-week assessment period will adequately demonstrate the effect of empagliflozin on cardiac sympathetic activity as a surrogate of lethal ventricular tachyarrhythmias. In addition, we will evaluate the effect of empagliflozin on the cardiac sympathetic activity during the chronic phase after AMI to avoid the potential confounding factor during the acute and sub-acute phase of AMI. Third, this trial will only be conducted in the Japanese population. Japanese patients with CAD generally receive adequate conventional therapy, including statins. Therefore, it is possible to determine the exact therapeutic effect of empagliflozin against residual risk. Fourth, beta-blockers will be not restricted during the trial period. Patients with LVEF < 40% and depressed HRV benefit from prophylactic antiarrhythmic treatment with beta-blockers [40]. Therefore, we will evaluate beta-blocker doses in the two groups. Fifth, tight glycemic control influenced the risk of cardiac autonomic neuropathy in T2DM patients [41–43]; we will evaluate glycemic control levels in the two groups.

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Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later

amendments or comparable ethical standards. All study participants will provide informed consent.

Data Availability. The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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