ORIGINAL RESEARCH ARTICLE

Empagliflozin confers reno-protection in acute myocardial infarction and type 2 diabetes mellitus

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Abstract

Aims Although the reno-protective effects of sodium–glucose cotransporter 2 inhibitors are known in patients with heart failure or type 2 diabetes mellitus (T2DM), this effect has not been confirmed in patients with acute myocardial infarction (AMI).
Methods and results The prospective, multicentre, randomized, double-blind, placebo-controlled EMBODY trial investigated patients with AMI and T2DM in Japan. The eligible patients included adults aged 20 years or older, diagnosed with AMI and T2DM, and who could be discharged within 2–12 weeks after the onset of AMI. One hundred and five patients were randomized (1:1) to receive once daily 10 mg empagliflozin or placebo within 2 weeks of AMI onset. In this sub-analysis, we investigated the time course of renal functional parameters such as serum creatinine levels and estimated glomerular filtration rate (eGFR) from baseline to Weeks 4, 12, and 24. Ninety-six patients (64 ± 11 years, 78 male) were included in the full analysis (n = 46 and 50 in the empagliflozin and placebo groups, respectively). We used serum creatinine and eGFR as indicators of renal function. In the placebo group, eGFR decreased from 66.14 mL/min/1.73 m^2 at baseline to 62.77 mL/min/1.73 m^2 by Week 24 (P = 0.023) but remained unchanged in the empagliflozin group (from 64.60 to 64.36 mL/min/1.73 m^2, P = 0.843). In the latter group, uric acid improved from 5.8 mg/dL at baseline to 4.9 mg/dL at Week 24 ($P < 0.001$). In the earlier analysis of 56 patients with eGFR ≥ 60 mL/min/1.73 m^2, the eGFR decreased and the serum creatinine increased from baseline to 24 weeks in the placebo group, significantly different to the empagliflozin group (−6.61 vs. +0.22 mL/min/1.73 m^2, P = 0.008 and +0.063 vs. −0.001 mg/dL, P = 0.030, respectively). The changes in serum creatinine and eGFR from baseline to Week 24 were significantly correlated with those in uric acid in the placebo group (r = 0.664, $P < 0.001$ and r = −0.675, $P < 0.001$, respectively) but not in the empagliflozin group.
Conclusions Empagliflozin prevented the kidney functional decline in patients with AMI and T2DM, especially those with baseline eGFR ≥ 60 mL/min/1.73 m^2. Early administration of sodium–glucose cotransporter 2 inhibitors in these patients is considered desirable for renal protection.

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common diseases and the leading cause of end-stage renal and cardiovascular (CV) disease[1]; it has emerged as a social problem worldwide.[2] Sodium–glucose cotransporter 2 (SGLT2) inhibitors, released in the 2010s as a new class of glucose lowering drugs, reduce blood pressure (BP) and body weight (BW) in addition to improving blood glucose by urinary glucosuria.[3] SGLT2 inhibitors have been shown to be

beneficial in the reduction of CV events and improving renal outcomes in recent, large, randomized, placebo-controlled trials (EMPA-REG OUTCOME trial, CANVAS trial, and DECLARE–TIMI 58 study).[4–6] The effects of SGLT2 inhibitors such as empagliflozin as osmotic diuretics and on natriuresis may underlie the CV and renal benefits demonstrated in the recent EMPA-REG OUTCOME trial.[4] The reno-protective effect of SGLT2 inhibitors was demonstrated in the recent CREDENCE and DAPA-CKD trials.[7,8]

Although reno-protective effects of SGLT2 inhibitors have been recognized in patients with heart failure or T2DM, this protection has not been fully examined in patients with acute myocardial infarction (AMI). We therefore examined whether empagliflozin, an SGLT2 inhibitor, shows reno-protective effects in patients with AMI and T2DM. This study was a sub-analysis of the EMBODY trial, which showed that a decrease in cardiac sympathetic hyperactivity associated with empagliflozin may contribute to the prevention of CV events, including sudden cardiac death, in patients with T2DM and AMI treated with SGLT2 inhibitors in Japan.[9]

Methods

Trial design

The EMBODY trial is a recently published prospective, multicentre, randomized, double-blind, placebo-controlled trial comprising patients with AMI and T2DM in Japan.[10] One hundred and five patients were randomized (1:1) to receive once daily placebo or empagliflozin (10 mg) within 2 weeks of AMI onset. In the present sub-analysis, we specifically focused on the time course of renal function from baseline to Weeks 4, 12, and 24 after AMI. We used serum creatinine levels and estimated glomerular filtration rate (eGFR) as indicators of renal function.

Trial population and follow-up

The trial recruitment period was from February 2018 to March 2019, and the last visit of the last patient was completed in August 2019. The inclusion and exclusion criteria have been published previously.[10] Once each patient had provided written informed consent for participation, been randomized, and assigned to either the empagliflozin or placebo group, the follow-up visits were scheduled at 4, 12, and 24 weeks. Patients received standard treatment for their underlying diseases, T2DM, and AMI during the trial period. In this study, blood tests for all cases were performed on an empty stomach.

The left ventricular ejection fraction was calculated using the modified Simpson's method via transthoracic echocardiography. The tricuspid regurgitation velocity was obtained using continuous wave Doppler imaging in the right ventricular inflow or apical four-chamber views. The trans-tricuspid pressure gradient (TRPG) was calculated as follows:

$$TRPG = 4 \times (tricuspid\,regurgitation\,velocity)^2.$$

The peak early diastolic phase (E) and late diastolic phase (A) mitral inflow velocities and the E/A ratio were measured using pulsed-wave Doppler echocardiography with the sample volume between the mitral leaflet tips. The mitral annular velocity (E′) and mean E/E′ ratio were measured at the septal and lateral annuli using tissue Doppler imaging. The left atrial diameter was measured using B-mode during systole in the parasternal long-axis view.

Randomization and blinding

Patients with AMI and T2DM were randomly assigned to an empagliflozin (10 mg/day) group or a placebo group, both as add-ons to conventional therapy within 2 weeks of the onset of AMI, based on allocation factors, baseline glycated haemoglobin (HbA1c) values (<7.0% or ≥7.0%), and max creatine kinase levels (<3000 or ≥3000 IU/L) using a dynamic allocation method. Post-randomization follow-up visits were scheduled at 4, 12, and 24 weeks. This study was double-blinded. Patients also received post-AMI treatment with beta-blockers, anti-platelet therapy, statins, and renin–angiotensin system inhibitors in accordance with local guidelines.[11,12] Throughout the trial, investigators were encouraged to treat other CV risk factors (including dyslipidaemia and hypertension) to ensure the best available standard of care to patients.

Trial endpoints

The primary endpoints of this study were changes in renal functional markers (eGFR, serum creatinine, cystatin, and urinary albumin) from baseline to 24 weeks. The secondary endpoints were the correlations between these renal functional markers and other factors [systolic BP (SBP), serum uric acid, haematocrit, and ketones].

Renal functional markers

Estimated glomerular filtration rate
The glomerular filtration rate (GFR) is a key indicator of renal function. The eGFR is a mathematically derived value, based on a patient's serum creatinine level, age, sex, and race. Although the Modification of Diet in Renal Disease[13] and Chronic Kidney Disease Epidemiology Collaboration[14] equations are used internationally, the GFR estimation formula for the Japanese population based on the serum

creatinine value was used for eGFR calculations in this study, as the former tends to overestimate renal function in Japanese individuals.[15] The eGFR estimation formula used in this study is shown as follows:

$$eGFRcreatinine \ (mL/min/1.73 \ m^2)$$
$$= 194 \times serumcreatinine \ (mg/dL)^{-1.094} \times (age)^{-0.287}.$$

For women, the obtained value is multiplied by 0.739.

Chronic kidney disease stage

According to the Kidney Disease Outcome Quality Initiative[16] and Kidney Disease: Improving Global Outcome[13] guidelines, patients were defined as having chronic kidney disease (CKD) if they had abnormalities of kidney function or structure for more than 3 months. Kidney disease severity is classified into five stages according to the eGFR level. In this study, patients were classified for analysis as follows: eGFR ≥ 60 mL/min/ 1.73 m², which indicated normal kidney function to mild renal impairment (CKD Stage 1 or 2), and eGFR between 45 and 59 mL/min/1.73 m², which corresponded to early renal insufficiency (CKD Stage 3).

Statistical analyses

All continuous values and categorical variables are expressed as mean ± standard deviation and the number and percentage of patients, respectively. Mixed-effects model repeated measures analysis was used to compare changes in primary outcomes: BP, BW, HbA1c, eGFR, haematocrit, uric acid, glycaemic and lipid parameters, and serum ketone bodies, from baseline to 24 weeks. For other outcomes, a t-test was used to analyse continuous variables and the Wilcoxon signed-rank test was used for categorical variables. A two-sided probability value of $P < 0.05$ was considered statistically significant. In addition to the earlier analysis, the cohort was stratified into two groups based on baseline eGFR [45 mL/min/1.73 m² ≤ eGFR < 60 mL/min/1.73 m² (eGFR 45–59) and eGFR ≥ 60 mL/min/1.73 m² (eGFR ≥ 60)] for subgroup analysis. All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA).

Ethics approval and consent to participate

The EMBODY trial was registered at the UMIN in November 2017 (ID: 000030158). The local institutional review boards and independent ethics committees approved the trial protocol. The investigation conformed with the principles outlined in the Declaration of Helsinki and was performed according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labour, and Welfare and the Ministry of Education, Culture, Sports, Science, and Technology in Japan. After initial screening for eligibility using prior medical records, each patient received an adequate explanation of the trial plan before they provided written informed consent.

Results

A total of 105 AMI patients with T2DM met the inclusion criteria, consented to participate in the trial between February 2018 and March 2019, and were randomized into two groups. Six patients in the empagliflozin group and three in the placebo group withdrew their consent and were thus excluded before medication was initiated. Therefore, 96 patients were finally included in the full analysis (46 in the empagliflozin group and 50 in the placebo group) (Figure 1). Baseline characteristics were not significantly different between the treatment groups (Table 1).

In terms of changes in parameters from baseline to 24 weeks, SBP and BW were decreased in the empagliflozin group and increased in the placebo group, a significant difference between the groups (−6.6 ± 14.3 vs. 3.5 ± 18.6 mmHg, $P = 0.004$ and −2.23 ± 3.56 vs. 0.08 ± 2.25 kg, $P = 0.001$, respectively). Intergroup comparison showed that there was no significant difference between the treatment groups in terms of the amount of change in the serum creatinine levels and eGFR from baseline to 24 weeks ($P = 0.236$ and $P = 0.120$, respectively) (Figure 2). Although intra-group comparison showed that the creatinine values and eGFR had not changed significantly from baseline to 24 weeks in the empagliflozin group (0.922–0.937 mg/dL, $P = 0.456$ and 64.60–64.36 mL/min/1.73 m², $P = 0.843$, respectively), both parameters significantly worsened in the placebo group (0.887–0.935 mg/dL, $P = 0.008$ and 66.14–62.77 mL/min/1.73 m², $P = 0.023$, respectively). Intra-group and intergroup comparisons showed no significant differences in the change in cystatin C and urinary albumin concentrations from baseline to 24 weeks (Figure 2). Changes in other blood parameters from baseline to 24 weeks are shown in Table 2. Intergroup comparison showed that changes in serum uric acid and haematocrit levels from baseline to 24 weeks were significantly different between the empagliflozin group and the placebo group (−0.89 ± 1.11 vs. 0.03 ± 1.03 mg/dL, $P < 0.001$ and 3.70 ± 3.72% vs. 0.16 ± 4.52%, $P < 0.001$, respectively).

Subgroup analyses in the estimated glomerular filtration rate 45–59 group

Baseline characteristics were not significantly different between the empagliflozin and placebo subgroups in the eGFR 45–59 group (67.8 ± 10.0 years, male 80%, and $n = 18$ in the empagliflozin subgroup and $n = 22$ in the placebo

Figure 1 Flow chart of the study patients. A total of 105 patients met the inclusion criteria and were randomized in this study. Six patients in the empagliflozin group and three patients in the placebo group were excluded because of consent withdrawal before medication began. Therefore, 96 patients were included in the final analysis (46 in the empagliflozin group and 50 in the placebo group). Additional stratified analysis was performed according to baseline estimated glomerular filtration rate (eGFR).
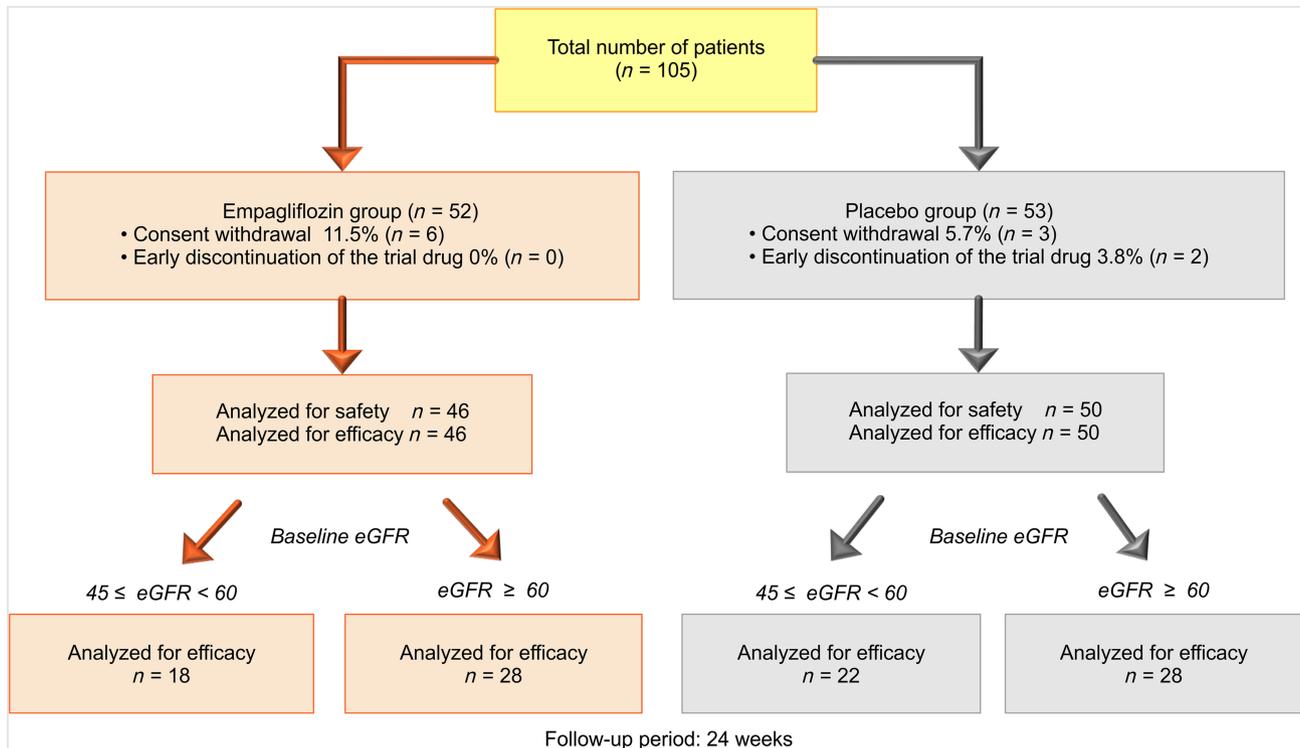
subgroup) (Supporting Information, Table S1). Although intra-group and intergroup comparisons showed that there was no significant difference in the change in renal functional markers between these subgroups from baseline to 24 weeks (*Figure* 3A–3D), upon intra-group comparison, the serum uric acid level had significantly decreased in the empagliflozin subgroup from baseline to 24 weeks (6.54 ± 1.34 to 5.47 ± 1.07 mg/dL, *P* = 0.014) but not in the placebo subgroup (5.93 ± 1.66 to 5.73 ± 1.48 mg/dL, *P* = 0.682). Upon intergroup comparison, the uric acid level decreased significantly more in the empagliflozin subgroup than in the placebo subgroup (−1.08 ± 0.94 vs. −0.20 ± 1.01 mg/dL, *P* = 0.009). Changes in other parameters studied in this sub-analysis are shown in Supporting Information, Table S1.

Subgroup analyses in the estimated glomerular filtration rate ≥60 group

Supporting Information, Table S2 shows the baseline characteristics of patients in the eGFR ≥ 60 group (61.8 ± 10.9 years, male 80.4%, and *n* = 28 in the empagliflozin subgroup and *n* = 28 in the placebo subgroup). Baseline characteristics were not significantly different between the empagliflozin and placebo subgroups, except for cystatin C (1.02 ± 0.17 vs.

0.88 ± 0.15 mg/L, *P* = 0.039). In the placebo subgroup, the eGFR decreased and the serum creatinine increased from baseline to 24 weeks, significantly different compared with those in the empagliflozin subgroup (−6.61 vs. +0.22 mL/min/1.73 m^2, *P* = 0.008 and +0.063 vs. −0.001 mg/dL, *P* = 0.030, respectively) (*Figure* 4A and 4B). Regarding the serum uric acid level, the same tendency as that of the eGFR 45–59 group was obtained; in the intra-group comparison, the serum uric acid level had significantly decreased in the empagliflozin subgroup from baseline to 24 weeks (5.24 ± 1.21 to 4.47 ± 1.35 mg/dL, *P* = 0.031) but not in the placebo subgroup (5.57 ± 1.24 to 5.79 ± 1.40 mg/dL, *P* = 0.553), and in the intergroup comparison, the uric acid level decreased in the empagliflozin subgroup and increased in the placebo subgroup, a significant difference (−0.78 ± 1.17 vs. 0.23 ± 0.99 mg/dL, *P* = 0.001). Changes in other parameters in this sub-analysis are shown in Supporting Information, Table S2.

Correlation between renal functional markers and various parameters

Table 3 shows correlation between the renal functional markers and various clinical parameters in the entire study

Table 1 Clinical characteristics of the study population

Variable	Empagliflozin n = 46	Placebo n = 50	P value
Men, n (SD)	38 (82.6)	39 (78.0)	0.616
Age, years (SD)	63.9 (10.4)	64.6 (11.6)	0.734
Body weight, kg (SD)	70.1 (13.7)	68.1 (14.4)	0.493
BMI, kg/m^2 (SD)	25.2 (3.7)	25.2 (4.1)	0.992
DM duration, months (SD)	38.3 (43.4)	32.4 (43.3)	0.507
Current smoker, n (%)	24 (52.2)	27 (54.0)	0.913
Medical history			
Cerebrocardiovascular disease, n (%)	7 (15.2)	11 (22.0)	0.442
Hypertension, n (%)	38 (82.6)	39 (78.0)	0.617
Dyslipidaemia, n (%)	34 (73.9)	36 (72.0)	1.000
NYHA classification			
I/II, %	92.6/7.4	83.9/16.1	0.309
Killip's classification at admission			
I/II, %	77.8/7.4	58.1/22.6	0.087
III/IV, %	11.1/3.7	9.7/9.7	0.429
Contrast medium usage, mL (SD)	157.4 (50.4)	147.8 (74.0)	0.582
Blood sampling test			
Max CK, IU/L (SD)	2080.7 (2461.6)	2358.7 (2829.1)	0.610
HbA1c, % (SD)	6.82 (1.00)	6.89 (0.92)	0.735
Uric acid, mg/dL (SD)	5.8 (1.4)	5.7 (1.5)	0.935
Creatinine, mg/dL (SD)	0.922 (0.19)	0.887 (0.20)	0.392
eGFR, mL/min/1.73 m^2 (SD)	64.60 (14.95)	66.14 (15.72)	0.624
Urinary albumin amount, mg/g Cr (SD)	130.88 (333.8)	56.65 (112.3)	0.181
Cystatin C, mg/L (SD)	1.132 (0.27)	1.110 (0.34)	0.784
Haematocrit, % (SD)	40.5 (4.6)	40.3 (4.2)	0.858
NT-proBNP, pg/mL (SD)	1028.7 (1105.6)	1270.6 (1521.0)	0.450
Transthoracic echocardiography			
LVEF, % (SD)	55.13 (14.19)	55.01 (13.65)	0.972
E/A (SD)	0.94 (0.49)	1.01 (0.69)	0.645
Average E/E$\prime$ (SD)	13.47 (7.24)	13.73 (6.26)	0.883
Left atrial dimension, mm (SD)	36.36 (8.61)	36.71 (5.56)	0.854
TRPG, mmHg (SD)	17.59 (7.48)	20.71 (11.49)	0.234
Medical therapy			
Beta-blocker, n (%)	41 (89.1)	38 (76.0)	0.11
ARB, n (%)	22 (47.8)	19 (38.0)	0.41
ACE-I, n (%)	23 (50.0)	28 (56.0)	0.68
Statin, n (%)	44 (95.7)	48 (96.0)	1.00
Spironolactone, n (%)	11 (23.9)	12 (24.0)	1.00
Diuretics, n (%)	8 (17.4)	11 (22.0)	0.62
Metformin, n (%)	7 (15.2)	6 (12.0)	0.77
DPP-4 inhibitor, n (%)	20 (43.5)	23 (46.0)	0.84
ASA/P2Y12 inhibitor, n (%)	46 (100)	50 (100)	1.00
DOAC, n (%)	3 (6.5)	3 (6.0)	1.00
NSAIDs, n (%)	4 (8.7)	2 (4.0)	0.35

A, late diastolic phase mitral inflow velocity; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; CK, creatine kinase; DM, diabetes mellitus; DOAC, direct oral anticoagulant; DPP-4, dipeptidyl peptidase-4; E, peak early diastolic phase mitral inflow velocity; E$\prime$, mitral annular velocity; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; LVEF, left ventricular ejection fraction; NSAIDs, non-steroidal anti-inflammatory drugs; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; TRPG, trans-tricuspid pressure gradient.

population. In the entire study population, the changes in serum creatinine and eGFR from baseline to Week 24 were significantly correlated with those in uric acid (*Figure* 5B) and SBP in the placebo group, but not in the empagliflozin group (*Figure* 5A). In the eGFR ≥ 60 subgroup, the changes in serum creatinine and eGFR from baseline to Week 24 were also significantly correlated with those in uric acid (*Figure* 5D) and SBP in the placebo group but not in the empagliflozin group (*Figure* 5C and Supporting Information, Table S4). However, this was not the case in the eGFR 45–59 group (*Figure* 5E and 5F and Supporting Information, Table S3).

Discussion

In summary, for the sub-analysis of the EMBODY trial in the entire study population, serum creatinine and eGFR at Week 24 did not change when compared with their baseline values in the empagliflozin group but were significantly worse over time in the placebo group. The serum uric acid level was significantly decreased in the empagliflozin group but remained unchanged in the placebo group. In the placebo group, there was a significant correlation between the deterioration of renal function and changes in uric acid levels and SBP. These

Figure 2 Changes from baseline in (A) creatinine, (B) estimated glomerular filtration rate (eGFR), (C) cystatin C, and (D) urinary albumin. In the analysis within each group, though changes in creatinine values and eGFR at 24 weeks compared with those in baseline values were not significantly different in the empagliflozin group, both were significantly worse at 24 weeks in the placebo group.
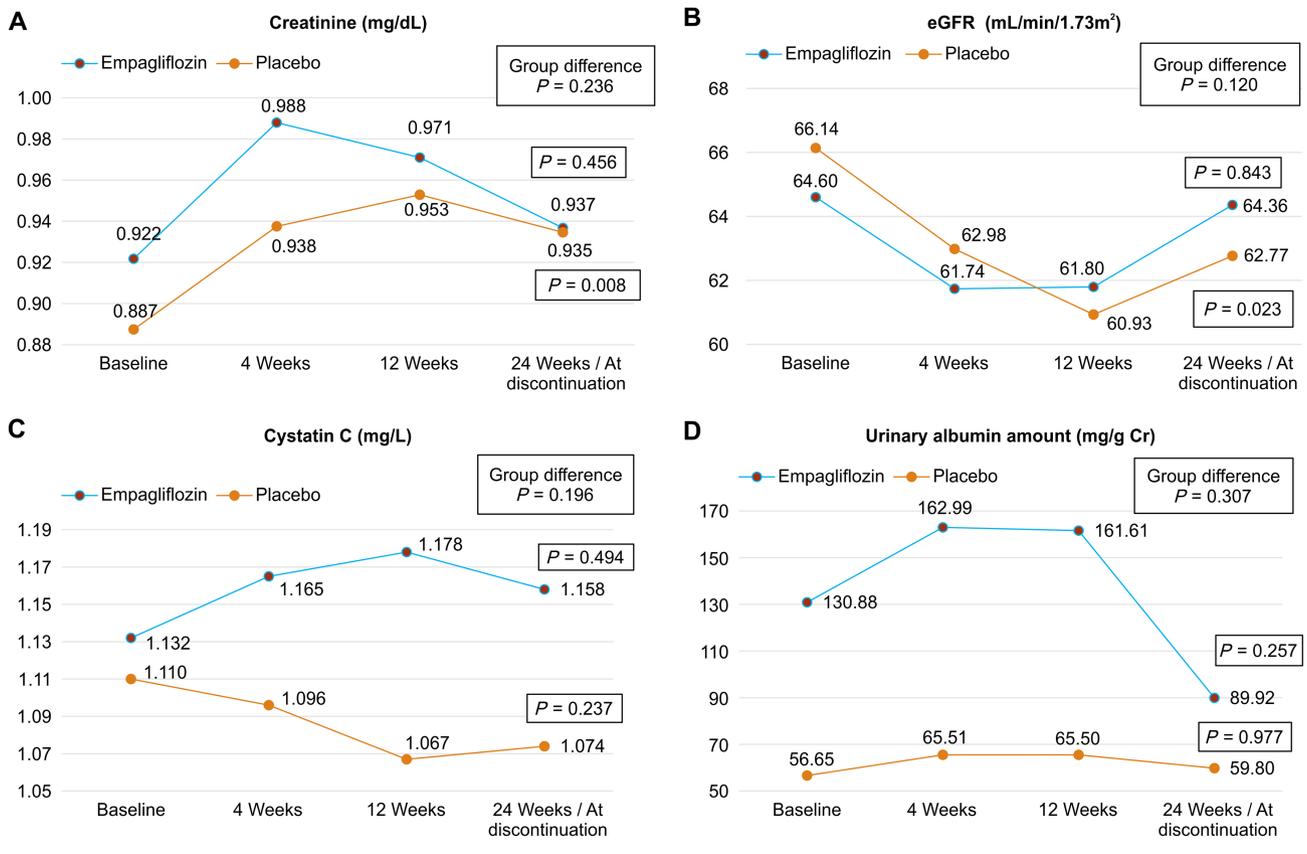
tendencies were more pronounced in the eGFR ≥ 60 subgroup but not in the eGFR 45–59 subgroup. In previous studies,[7,8] decreases in the GFR in the acute phase after administration of SGLT2 inhibitors were observed. Such a decrease was also observed early on in this study, and the eGFR decreased in the first 4 weeks after administration of empagliflozin but increased thereafter and recovered to baseline eGFR levels at 24 weeks. In a previous study of Japanese subjects,[17] the eGFR was retained from 12 to 52 weeks after SGLT2 inhibitor administration despite an initial decrease, and a high eGFR at baseline was associated with a larger initial decrease, which is consistent with the results of this study. The DAPA-CKD trial,[8] in contrast to this study, revealed a more sensitive renal protective effect of SGLT2 inhibitors in the group with a low baseline eGFR. A possible reason for the discrepancy is that, in this study, drugs were used from the acute stage after the onset of AMI and the follow-up period was 24 weeks. If our follow-up period was 72 weeks, as in the DAPA-CKD trial, we may have discovered a renal protective effect even in patients with a low baseline eGFR. While the DAPA-CKD trial was targeted at patients who were already taking renin–angiotensin–aldosterone system inhibitors, renin–angiotensin–aldosterone system inhibitors were introduced during hospitalization in about half of the cases in this study, which may also have affected the results.

Reno-protective effects of empagliflozin in patients with acute myocardial infarction and type 2 diabetes mellitus

Although the protective effects of SGLT2 inhibitors on renal function have been demonstrated in the EMPA-REG OUTCOME study, four patients who developed acute coronary syndrome within 2 months were excluded. The DAPA-CKD study[8] also demonstrated that the dapagliflozin group showed a significant advantage over the placebo group in terms of renal functional progression or death, which was defined as the primary composite endpoint. However, the population in the DAPA-CKD study included patients with CKD with or without T2DM but excluded the patients with acute coronary syndromes. The patients in our EMBODY trial were randomly assigned to an empagliflozin (10 mg/day) group or a placebo group within 2 weeks of AMI onset and were administered a drug during the relatively acute

Table 2 Comparison of changes in parameters between the two treatment groups

	Empagliflozin group				Placebo group				
	n	Average	SD	P value[a]	n	Average	SD	P value[a]	P value[b]
SBP (mmHg)									
Baseline	46	129.7	11.9		50	123.1	15.7		
24 weeks	46	123.1	12.7		49	126.2	17.8		
Changes	46	−6.6	14.3	0.003	49	3.5	18.6	0.190	0.004
DBP (mmHg)									
Baseline	46	75.3	9.2		50	71.9	9.9		
24 weeks	46	73.	9.1		49	73.7	11.3		
Changes	46	−1.5	10.9	0.343	49	1.8	13.3	0.360	0.191
BW (kg)									
Baseline	46	70.08	13.74		50	68.10	14.40		
24 weeks	46	67.85	12.58		50	68.19	14.16		
Changes	46	−2.23	3.56	<0.001	50	0.08	2.25	0.836	0.001
BMI (kg/m^2)									
Baseline	46	25.18	3.69		50	25.17	4.07		
24 weeks	46	24.39	3.39		50	25.21	4.04		
Changes	46	−0.78	1.22	<0.001	50	0.04	1.12	0.809	<0.001
RBC (× 10^4/μL)									
Baseline	46	449.9	52.8		50	439.6	52.7		
24 weeks	46	492.8	45.6		50	444.7	56.6		
Changes	46	42.9	46.8	<0.001	50	5.1	54.9	0.513	<0.001
WBC (/μL)									
Baseline	46	6679.8	2062.8		50	7173	2029.7		
24 weeks	46	6394.6	1654.3		50	6658.8	1338.1		
Changes	46	−285.2	1857.2	0.303	50	−514.2	1818.3	0.051	0.543
Hb (g/dL)									
Baseline	46	13.53	1.85		50	13.58	1.48		
24 weeks	46	14.69	1.52		50	13.66	1.58		
Changes	46	1.16	1.31	<0.001	50	0.08	1.54	0.702	<0.001
Ht (%)									
Baseline	46	40.50	4.55		50	40.34	4.21		
24 weeks	46	44.20	3.86		50	40.50	4.22		
Changes	46	3.70	3.72	<0.001	50	0.16	4.52	0.806	<0.001
Plt (×10^4/μL)									
Baseline	46	25.11	9.92		50	23.30	6.81		
24 weeks	46	23.55	9.74		50	21.10	4.83		
Changes	46	−1.57	5.53	0.061	50	−2.21	5.96	0.012	0.586
AST (U/L)									
Baseline	46	24.7	7.9		50	24.4	10.3		
24 weeks	46	23.2	8.5		50	25.4	13.9		
Changes	46	−1.5	9.6	0.280	50	1.0	14.8	0.629	0.322
ALT (U/L)									
Baseline	46	26.4	14.8		50	26.6	16.4		
24 weeks	46	22.3	13.1		50	24.2	11.9		
Changes	46	−4.1	12.9	0.039	50	−2.4	16.9	0.320	0.594
γ-GTP (U/L)									
Baseline	46	39.6	29.1		50	32.4	18.9		
24 weeks	46	40.0	40.2		50	39.2	38.1		
Changes	46	0.3	28.3	0.934	50	6.8	31.9	0.136	0.296
Uric acid (mg/dL)									
Baseline	46	5.75	1.43		50	5.73	1.46		
24 weeks	46	4.86	1.35		49	5.76	1.45		
Changes	46	−0.89	1.11	<0.001	49	0.03	1.03	0.815	<0.001
Creatinine (mg/dL)									
Baseline	46	0.922	0.187		50	0.887	0.204		
24 weeks	46	0.937	0.245		50	0.935	0.214		
Changes	46	0.015	0.135	0.456	50	0.047	0.121	0.008	0.236
eGFR (mL/min/1.73 m^2)									
Baseline	46	64.60	14.95		50	66.14	15.72		
24 weeks	46	64.36	16.84		50	62.77	15.44		
Changes	46	−0.24	8.19	0.843	50	−3.37	10.12	0.023	0.120
NT-proBNP (pg/mL)									
Baseline	33	1028.7	1105.6		36	1270.6	1521.2		
24 weeks	32	370.3	530.9		33	673.7	1151.1		
Changes	32	−633.6	822.9	<0.001	33	−603.9	1180.1	0.006	0.907

(*Continues*)

Table 2 (continued)

	Empagliflozin group				Placebo group				
	n	Average	SD	*P* value[a]	*n*	Average	SD	*P* value[a]	*P* value[b]
Blood ketone bodies (μmol/L)									
Baseline	29	119.8	187.9		33	62.1	47.2		
24 weeks	32	119.3	169.2		33	61.2	35.7		
Changes	32	49.7	175.4	0.120	33	−16.6	73.5	0.203	0.055
High-sensitivity CRP (mg/dL)									
Baseline	27	0.300	0.526		30	0.152	0.214		
24 weeks	27	0.175	0.208		30	0.093	0.160		
Changes	27	−0.126	0.564	0.257	30	−0.059	0.211	0.138	0.547

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BW, body weight; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; Ht, haematocrit; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Plt, platelet; RBC, red blood cell; SBP, systolic blood pressure; SD, standard deviation; WBC, white blood cell; γ-GTP, γ-glutamyl transpeptidase.
[a]Within-group comparisons, 24 weeks compared with baseline.
[b]Between-group comparisons of changes over time.

Figure 3 Amount of change in (A) creatinine, (B) estimated glomerular filtration rate (eGFR), (C) cystatin C, and (D) urinary albumin at 24 weeks from baseline in patients with baseline eGFR 45–59 and eGFR ≥ 60, respectively. In the eGFR 45–59 group, there was no significant difference between the two groups, but in the eGFR ≥ 60 group, creatinine and eGFR were maintained in the empagliflozin group but not in the placebo group, a significant difference.
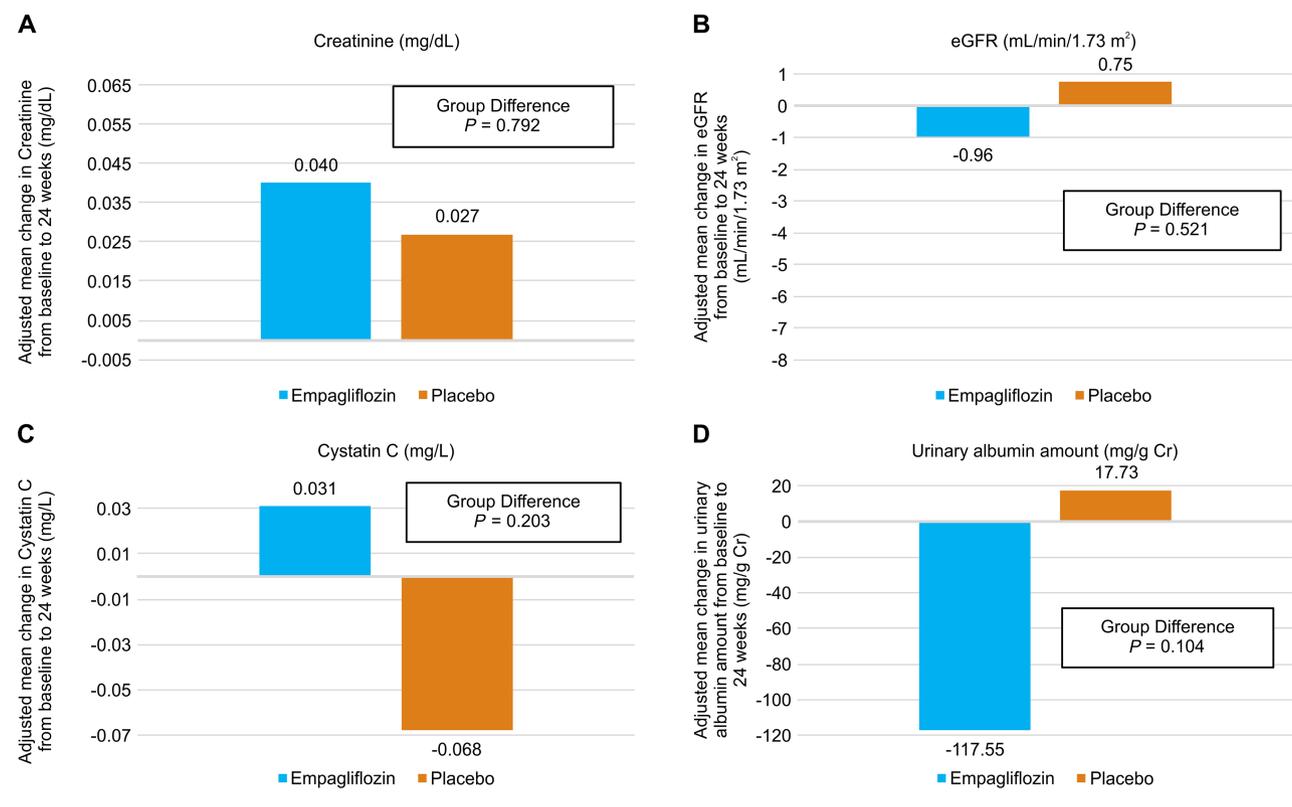
phase of AMI, within 2–12 weeks of onset. Therefore, this sub-analysis of the EMBODY trial is the first published study to investigate the reno-protective effect of an SGLT2 inhibitor in patients with T2DM and AMI. The present study also showed the renal protective effect of empagliflozin, an SGLT2 inhibitor, in patients with T2DM and AMI, similar to previous, large, randomized, placebo-controlled trials, suggesting that early administration of SGLT2 inhibitors after the onset of AMI is recommended for renal protection.

Figure 4 Amount of change in (A) creatinine, (B) estimated glomerular filtration rate (eGFR), (C) cystatin C, and (D) urinary albumin at 24 weeks from baseline in patients with baseline eGFR 45–59 and eGFR ≥ 60, respectively. In the eGFR 45–59 group, there was no significant difference between the two groups, but in the eGFR ≥ 60 group, creatinine and eGFR were maintained in the empagliflozin group but not in the placebo group, a significant difference.
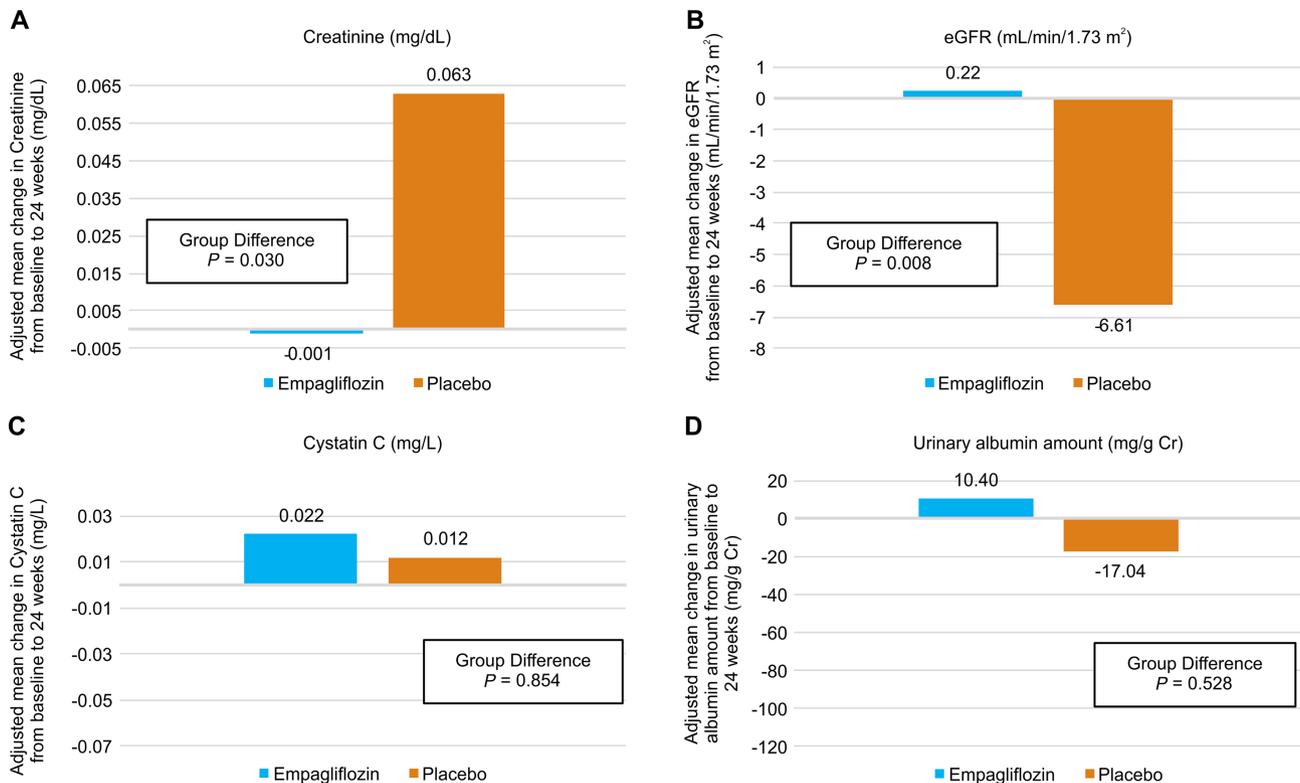
Table 3 Correlation between renal functional markers and various parameters in the entire study population

		Creatinine (mg/dL)		eGFR (mL/min/1.73 m^2)	
		r	P value	r	P value
SBP (mmHg)	All cohort	−0.131	0.209	0.129	0.214
	Empagliflozin group	−0.001	0.993	−0.090	0.558
	Placebo group	−0.331	0.020	0.352	0.013
HbA1c (%)	All cohort	0.051	0.623	−0.011	0.911
	Empagliflozin group	−0.038	0.800	0.114	0.452
	Placebo group	0.139	0.335	−0.098	0.500
Uric acid (mg/dL)	All cohort	0.251	0.014	−0.317	0.002
	Empagliflozin group	0.077	0.610	−0.079	0.603
	Placebo group	0.378	0.007	−0.438	0.002

eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; SBP, systolic blood pressure.

Mechanisms underlying the reno-protective effects of sodium–glucose cotransporter 2 inhibitors

A previous paper reported that the urinary glucose excretion effect of SGLT2 inhibitors indirectly lowered serum uric acid levels by inhibiting glucose transporter (GLUT) 9, which acts on uric acid reabsorption in the proximal tubules of the kidney.[18] SGLT2 inhibitors increase the concentration of glucose in the proximal tubules and inhibit glucose reabsorption into the lumen, resulting in transfer of glucose from the proximal tubules to the vasculature by a glucose concentration gradient via GLUT9. Uric acid reabsorption is then inhibited via a potential-dependent urate transporter 1 in the lumen.[18] A previous meta-analysis concluded that uric acid-lowering therapy may be effective in retarding the

Figure 5 Correlation of the change from baseline to 24 weeks in the estimated glomerular filtration rate (eGFR) vs. that of serum uric acid levels in the empagliflozin (A, C, E) and placebo (B, D, F) subgroups. The placebo group showed a negative correlation between eGFR and uric acid levels, whereas no such correlation was observed in the empagliflozin group.
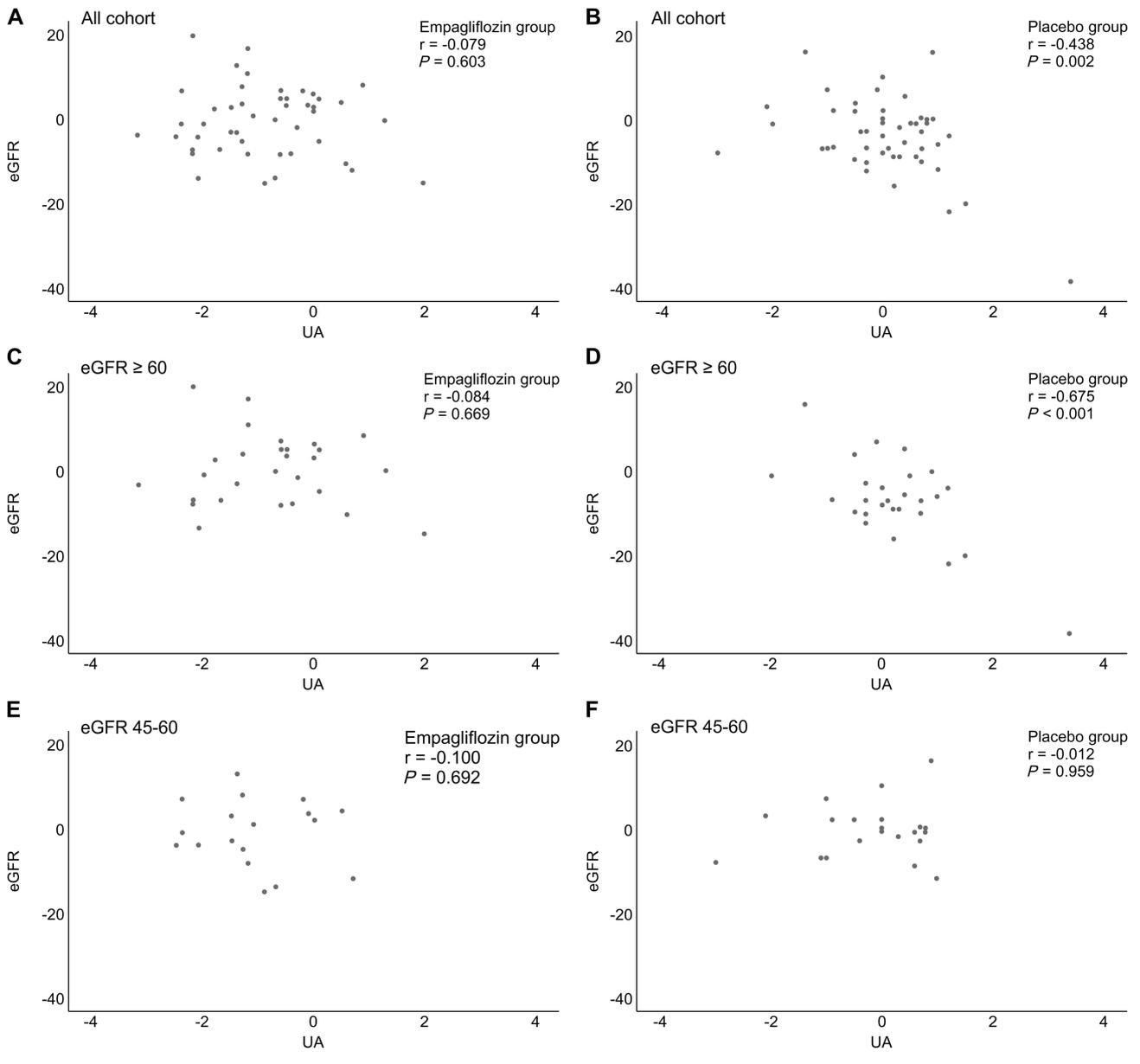
progression of CKD.[19,20] The results of this study showed that, regardless of baseline eGFR, the introduction of empagliflozin significantly reduced serum uric acid levels: upon stratified analysis of the baseline eGFR ≥ 60 group, empagliflozin demonstrated reno-protective effects when compared with placebo; furthermore, there was a significant correlation between serum uric acid levels and renal functional markers, which are consistent with previous papers.[19,20]

In addition to the earlier mechanism of lowering of serum uric acid levels, secondary factors such as suppression of the sympathetic nervous system and decreased BP and BW may contribute to the improvement of renal function.[21] The EMBODY trial and previous studies have shown that SGLT2 inhibitors have a sympathetic depressant effect, and reduced central sympathetic nervous system activation is thought to be an important mechanism for reducing renal SGLT2 expression.[22]

The concept of tubulo-glomerular feedback (TGF) is one of the mechanisms underlying the reno-protective effects of SGLT2 inhibitors.[23] Increased SGLT2 induces increased proximal tubular reabsorption of not only glucose but also sodium.[24] This reduces sodium chloride and fluid delivery from the proximal tubule to the macula densa present downstream, thereby causing glomerular hyperfiltration via impaired TGF. Glomerular hyperfiltration increases sodium transport and oxygen consumption in the kidney, particularly in the proximal tubules,[25] consequently causing kidney damage. Therefore, diabetes-induced glomerular hyperfiltration is a major risk factor for the subsequent development of diabetic kidney disease.[26] Furthermore, contraction of afferent arterioles and dilation of efferent arterioles via the TGF mechanism by SGLT2 inhibitors lead to correction of glomerular hypertension.[27,28] Our findings of significant renal protection in the eGFR $\geq$ 60 group and the correlation between serum uric acid level and eGFR are consistent with this mechanism. The reno-protective effect of SGLT2 inhibitors has been shown to be more pronounced in the group of patients with relatively maintained GFR, that is, those with early nephropathy.

Trial limitations

This study had several limitations. First, this study included a small number of cases and a relatively short follow-up period of 24 weeks. This may be why, regarding renal functional markers, there was a significant difference in the intra-group comparison but not in the intergroup comparison. If the follow-up period was further extended, the slopes and trends in the transition of renal function markers may have been different. Larger-scale randomized controlled trials for patients with AMI are desired in the future. Second, we excluded patients treated with insulin, glucagon-like peptide 1 analogues, or high doses of sulfonylureas and patients with HbA1c $\geq$ 10%. Third, optimal medical therapy, including use of renin–angiotensin system inhibitors, was at the discretion of the attending physician. However, there was no difference among research institutes. Fourth, the EMBODY trial was not designed with renal function as the primary endpoint; therefore, results of this sub-analysis are not sufficient to confirm the renal protective effect of SGLT2 inhibitors, considering the sample size.

Conclusions

Our study findings suggested that early administration of empagliflozin to patients with T2DM and AMI, particularly those in whom the initial eGFR is relatively preserved at 60 mL/min/1.73 m^2 or higher, suppresses the progression of renal dysfunction. The mechanism underlying the reno-protective effect of SGLT2 inhibitors may involve a reduction of serum uric acid levels. Larger prospective studies are needed to confirm whether early introduction of SGLT2 in patients with T2DM and AMI improves long-term renal outcomes and prognosis.

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Conflict of interest

Funding

Supporting information

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

Table S1. Comparison of parameters between groups with eGFR 45–59.

Table S2. Comparison of parameters between groups with eGFR ≥ 60.

Table S3. Correlation between renal function markers and various parameters in the eGFR 45–59 group.

Table S4. Correlation between renal function markers and various parameters in the eGFR ≥ 60 group.

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