DAPagliflozin for the attenuation of albuminuria in Patients with hEaRt failure and type 2 diabetes (DAPPER study): a multicentre, randomised, open-label, parallel-group, standard treatment-controlled trial

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Summary

Background Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the urinary albumin-to-creatinine ratio (UACR) in patients with elevated levels of albuminuria in the presence or absence of heart failure (HF) or type 2 diabetes mellitus (T2D). However, these effects have not yet been reported in the presence of both HF and T2D. This lack of evidence prompted us to conduct a clinical trial on the effects of dapagliflozin on UACR in patients with HF and T2D.

Methods DAPPER is a multicentre, randomised, open-labeled, parallel-group, standard treatment-controlled trial that enrolled patients at 18 medical facilities in Japan. Eligible participants with both HF and T2D and aged between 20 and 85 years were randomly assigned to a dapagliflozin or control (anti-diabetic drugs other than SGLT 2 inhibitors)

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group with a 1:1 allocation. The primary outcome was changes in UACR from baseline after a two-year observation, and secondary endpoints were cardiovascular (CV) events and parameters related to HF. This trial was registered with the UMIN-CTR registry, UMIN000025102 and the Japan Registry of Clinical Trials, jRCTs051180135.

Findings Between 12 May 2017 and 31 March 2020, 294 patients were randomly assigned to the dapagliflozin group (n = 146) or control group (n = 148). The mean age of patients was 72.1 years and 29% were female. The mean glycated hemoglobin value was 6.9%, mean NT-proBNP was 429.1 pg/mL, mean estimated GFR was 65.7 mL/min/1.73 m^2, and median UACR was 25.0 (8.8–74.6) mg/g Cr in the dapagliflozin group and 25.6 (8.2–95.0) mg/g Cr in the control group. Of the 146 patients in the dapagliflozin group, 122 completed the study, and 107 (87.7%) were taking 5 mg of dapagliflozin daily at the end of the observation period. The primary outcome did not significantly differ between the dapagliflozin and control groups. Among the secondary endpoints, the mean decrease in left ventricular end-diastolic dimensions as one of the echocardiographic parameters was larger in the dapagliflozin group than in the control group. The composite endpoint, defined as CV death or hospitalisation for CV events, hospitalisation for HF events, hospitalisation for all causes, and an additional change in prescriptions for heart failure in a two-year observation, was less frequent in the dapagliflozin group than in the control group.

Interpretation Although dapagliflozin at a dose of 5 mg daily did not reduce urinary albumin excretion in patients with HF and T2D from that in the controls, our findings suggest that dapagliflozin decreased CV events and suppressed left ventricular remodeling.

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Keywords: Sodium-glucose cotransporter 2; Dapagliflozin; Urinary albumin-to-creatinine ratio; Heart failure; Type 2 diabetes mellitus; Cardiovascular event

Research in context

Evidence before this study

We searched PubMed for publications in English between January 1 1990 and April 1 2023 using the search terms "SGLT2 inhibitor", "T2D", "HF", "UACR", and "randomised controlled clinical trial". In randomised controlled trials with a primary outcome that is a composite of the progression of kidney dysfunction or death from renal or CV causes, canagliflozin at 100 mg daily (CREDENCE), dapagliflozin at 10 mg daily (DAPA-CKD), and empagliflozin at 10 mg daily (EMPA-KIDNEY) were reported to reduce the primary outcomes.

Added value of this study

All patients in the present study had HF and T2D regardless of the baseline UACR value, and an RCT was conducted with the primary outcome being the mean change in UACR from baseline during the two-year observation. Nearly 90% of patients received 5 mg daily in the dapagliflozin group. The present results showed that the primary outcome did not significantly differ between the dapagliflozin and control groups and the cardiovascular endpoints in the two-year observation were more likely to be less frequent with a larger decrease in LVDd in the dapagliflozin group than in the control group.

Implications of all the available evidence

Although dapagliflozin at a dose of 5 mg daily did not reduce UACR in patients with HF and T2DM, it slightly decreased secondary CV outcomes, and its potentially suppressive effects on left ventricular remodeling were suggested to contribute to cardiovascular protection.

Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors were originally developed as blood glucose-lowering agents for patients with type 2 diabetes mellitus (T2D) and have been shown to reduce the risk of death and other adverse outcomes in patients with heart failure (HF) in the presence or absence of T2D.[1–4] Improvements in renal outcomes as a primary outcome have been achieved in patients with chronic kidney disease (CKD) in the presence or absence of T2D, even in those with a reduced estimated glomerular filtration rate (eGFR), such as 25 or 20 mL/min/1.73 m^2.[5,6] Following the findings of these randomised controlled trials (RCTs), the Kidney Disease Improving Global Outcomes (KDIGO) 2020 guidelines were issued and recommended SGLT2 inhibitors for patients with CKD and eGFR >30 mL/min/1.73 m^2,[7] while the updated guidelines recommend the initiation of SGLT2 inhibitor

therapy for patients with eGFR >20 mL/min/1.73 m^2.[8] To link the clinical hard and soft endpoints of CKD, RCTs using the urinary albumin-to-creatinine ratio (UACR) as the primary outcome were mainly conducted in the 2000s to obtain evidence for the efficacy of renin-angiotensin system inhibitors against diabetic nephropathy[9–13] because UACR is often used as a surrogate marker of CKD. Community-based cohort analyses revealed that increased UACR was associated with the development of HF with reduced and preserved ejection fractions (HFrEF and HFpEF, respectively),[14] while higher categories of UACR were associated with cardiovascular (CV) death and hospitalisation in patients with HF.[15] Furthermore, hospital admissions due to the worsening of HF were reduced in response to a reduction in UACR by medical treatment.[16] These findings suggest that SGLT2 inhibitors markedly reduce UACR and the incidence of CV in patients with both CKD and HF.

Canagliflozin was previously shown to decrease UACR in patients with T2D in the CREDENCE trial,[17] while dapagliflozin reduced UACR in patients with CKD in the DAPA-CKD trial.[18] However, in the CREDENCE and DAPA-CKD trials, the coexistence of HF in eligible patients was as low as 10–15%. These trials were conducted on patients with albuminuria of 300 < UACR ≤ 5000 and 200 ≤ UACR ≤ 5000, with albumin measured in milligrams and creatinine in grams (mg/g Cr), respectively. Therefore, RCTs have not yet examined the effects of SGLT2 inhibitors on UACR in patients with HF and T2D. The KDIGO guidelines in 2022 recommended UACR >200 as an indication for the use of SGLT2 inhibitors,[8] suggesting that evidence for the effects of SGLT2 inhibitors irrespective of UACR values is lacking. Therefore, we conducted an RCT on DAPagliflozin for the attenuation of albuminuria in Patients with hEaRt failure and T2D (the DAPPER study) and investigated whether treatment with dapagliflozin for two years attenuated UACR and reduced CV events in 294 patients with HF and T2D with any range of UACR.

Methods

Trial design and oversight

The design of this multicentre, randomised, open-labeled, parallel-group, standard treatment-controlled trial was previously reported,[19] it was designed to evaluate whether dapagliflozin decreases albuminuria in patients with HF and T2D and exerts cardioprotective effects on the failing heart. The trial was sponsored by AstraZeneca and Ono Pharmaceutical Companies from the start of the trial to August 2021, was thereafter supported by until the end of the trial, and was conducted at 18 medical facilities in Japan between 12 May 2017 (First Patient In) and 24 March 2022 (Last Patient Last Visit). A Protocol Steering Committee consisting of nine members was responsible for the design and oversight of the trial and the reporting of results. The Independent Data Monitoring Committee, consisting of three members from outside the study site, evaluated safety data. The Event Evaluation Committee also comprised three members who belonged to a non-study site and centrally assessed the occurrence of events in secondary endpoints. Statistical analyses were performed by two clinical statisticians affiliated with the Data Science Department of the National Cardiovascular Centre. The first and last authors drafted the first version of the manuscript, and all authors contributed to revisions. The decision to submit the manuscript for publication was made jointly by all of the authors, who vouched for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. This trial was initially registered with the UMIN-CTR registry (UMIN000025102) on 15 December 2016 before enrollment and was also registered with the Japan Registry of Clinical Trials (jRCTs051180135) on 18 March 2019.

Patients

Patients with HF and T2D were eligible if they were aged between 20 and 85 years at the time of providing informed consent. All participants had HbA1c <10%, required the initiation of or modifications to diabetes medication or were deemed eligible for a change in their medication regimen, and had eGFR ≥45 mL/min/1.73 m^2. HF was defined as any of the following conditions within 3 months prior to providing informed consent: 1) patients presenting with New York Heart Association (NYHA) cardiac function class II or higher, 2) plasma BNP levels ≥100 pg/mL or plasma NT-proBNP levels ≥400 pg/mL, or 3) a history of HF requiring drug treatment. All participants provided written informed consent before the commencement of any trial-specific procedure. Exclusion criteria were as follows: 1) patients receiving insulin treatment at the time of consent, 2) a history of hypersensitivity to investigational drugs, 3) a history of diabetic ketoacidosis and/or hyperosmolar hyperglycemic syndrome, 4) patients with a mechanical circulatory support device, 5) patients awaiting a heart transplant, 6) patients awaiting a cardiac surgery, 7) a history or risk of dehydration, 8) patients had liver diseases [aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels three fold the upper limit of normal; however, high AST or ASL levels associated with heart disease were included], 9) patients with significant bilateral or unilateral renal artery stenosis, 10) patients with a serious condition with a life expectancy of less than 3 years, 11) patients who were suspected of abusing alcohol or illegal drugs, 12) pregnant patients or those suspected to be pregnant, 13) lactating patients, 14) patients who had been enrolled in another clinical trial, and 15) patients whose participation was considered to be inappropriate by the

principal investigator or a sub-investigator. Since we intended to investigate the reducing effects of dapagliflozin on UACR as well as its preventative effects against an increase in UACR, we did not define entry or exclusion criteria for the UACR value. Details on inclusion and exclusion criteria and sample size calculations for this study are provided in the Supplementary Materials, DAPPER study protocol.

UACR measurements

Urinary albumin concentrations were measured using a turbidimetric immunoassay, while creatinine concentrations were evaluated using an enzymatic colorimetric method. All urinary samples were collected and measured centrally at the same laboratory. UACR testing was performed at baseline and 8 and 96 weeks after the initiation of the study.

Randomisation and masking

A principal investigator or sub-investigator accessed the web-based enrollment system and uploaded the necessary information regarding patients. Participants were randomly assigned to a control (anti-diabetic drugs other than SGLT 2 inhibitors) or dapagliflozin group with a 1:1 allocation. Randomisation and data collection were performed centrally by a web system. Study group allocation was concealed using the secured web system. Since this was an open-labelled study, blinding to either the participants or attending physicians was not possible. Therefore, consideration was given to ensuring the objectivity of the secondary outcomes by conducting clinical event certification at a blinded Event Evaluation Committee.

Trial procedures

Among T2D drug-naïve patients in the dapagliflozin group, treatment with dapagliflozin was initiated at 5 mg/day and titrated to 10 mg/day as required. Patients in the control group were administered anti-diabetic drugs other than SGLT-2 inhibitors. When patients with diabetes who were receiving an SGLT2 inhibitor other than dapagliflozin were assigned to the dapagliflozin group, the drug was replaced with dapagliflozin at 5 or 10 mg once daily. In cases in which drugs other than SGLT2 inhibitors were being administered, one of the drugs was replaced with dapagliflozin at 5 or 10 mg once daily. On the other hand, when patients with diabetes who were receiving an SGLT2 inhibitor including dapagliflozin were assigned to the control group, the SGLT2 inhibitor was replaced with a drug that was not a SGLT2 inhibitor.

Outcomes

The primary outcome was changes in UACR from baseline after a two-year observation. Secondary endpoints were (1) the percentage of patients presenting with an albuminuria category shift in each group (dapagliflozin and control groups), (2) changes in eGFR during a two-year period, (3) the percentage of patients presenting with an eGFR category shift in each group, (4) changes in urinary kidney injury molecule-1 from baseline after a two-year observation, (5) changes in plasma aldosterone, plasma NT-proBNP, serum fibroblast growth factor 23, and plasma α-Klotho concentrations from baseline after a two-year observation, (6) the composite endpoint, defined as CV death or hospitalisation for CV events in a two-year observation, (7) the composite endpoint, defined as CV death or hospitalisation for HF in a two-year observation, (8) the onset of CV events in a two-year observation, (9) hospitalisation for CV events in a two-year observation, (10) hospitalisation for HF in a two-year observation, (11) death from all causes in a two-year observation, (12) hospitalisation for all causes in a two-year observation, (13) an additional change in prescriptions for HF in a two-year observation, (14) changes in echocardiographic parameters, including left ventricular end-diastolic dimensions (LVDd) and end-systolic dimensions, the left atrial volume index, and left atrial dimensions, (15) the ejection fraction, (16) fractional shortening from baseline after a two-year observation, (17) the category of the NYHA classification in a two-year observation, (18) changes in the echocardiographic parameters of the mitral peak E-wave (E) from baseline after a two-year observation, (19) changes in the echocardiographic parameters of early diastolic mitral annular velocity by tissue doppler echocardiography (e') from baseline after a two-year observation, (20) changes in the echocardiographic parameters of the E/mitral peak A velocity (A) ratio from baseline after a two-year observation, (21) changes in the echocardiographic parameters of the E/e' ratio from baseline after a two-year observation, (22) changes in the echocardiographic parameters of the E velocity deceleration time from baseline after a two-year observation, and (23) new-onset atrial fibrillation and/or atrial flutter in a two-year observation. Items (18)–(22) were added after the initiation of the study because we found that the items collected on echocardiographic findings were missing from the secondary endpoints and again received approval by the Ethics Committee. All secondary endpoints are listed in Supplementary Materials.

Ethics approval

The protocol was approved by the National Cerebral and Cardiovascular Centre Ethics Committee (approval ID M28-059) before the first registration with the UMIN-CTR registry (UMIN000025102), and the Certified Review Board of Hyogo College of Medicine approved this trial (approval ID C0006) before its registration with the Japan Registry of Clinical Trials (jRCTs051180135). The present study was performed in accordance with the Declaration of Helsinki and the Clinical Trials Act. Written informed consent was obtained from all patients before recruitment.

Statistical analysis

Efficacy analyses were performed on the full-analysis set of patients who were randomly assigned, received at least one dose of the study drug, and whose outcomes were observed at least at one time point. Safety analyses were conducted on patients who had received at least one dose of the study drug. As part of the analysis of the primary outcome, the mean change in UACR two years after the initiation of the study and its 95% confidence interval (95% CI) were calculated. The Student's *t*-test and an analysis of covariance, including the baseline value of UACR as a covariate, were used to compare changes between study groups. We adjusted for age, a history of diabetes, eGFR, a history of hypertension, and combination drugs in addition to baseline UACR in the analysis of covariance. A per-protocol analysis of the primary outcome was also performed. Regarding other efficacy endpoints, summary statistics of changes were calculated when analysing continuous variables; an ordinal logistic model was used to analyse the NYHA functional classification with a three-level response variable, and odds ratios for the effects of the study drug were calculated. Time-to-event data were analysed by the Kaplan–Meier estimator, the Log-rank test, and Cox proportional hazards model. Missing data were not completed and were excluded from the analysis. Statistical analyses were performed using R version 4.2.0.

Role of the funding source

Study sponsors did not participate in the study design, the collection, analysis, and interpretation of data, the writing of the manuscript, or the decision to submit the study for publication. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Results

Between 12 May 2017 and 31 March 2020, 294 patients were randomly assigned to the dapagliflozin (n = 146) or control (n = 148) group at 18 medical facilities in Japan (Fig. 1). Among the 146 patients in the dapagliflozin group, 122 completed the study (Fig. 1), and 107 (87.7%) were taking 5 mg daily of dapagliflozin at the end of the observation period. The baseline characteristics of patients were similar in both groups (Table 1). The mean age of patients was 72.1 years and 29% were female. The mean glycated hemoglobin value was 6.9%, mean NT-proBNP was 429.1 pg/mL, mean eGFR was 65.7 mL/min/1.73 m^2, and median UACR was 25.0 (8.8–74.6) mg/g Cr in the dapagliflozin group and 25.6 (8.2–95.0) mg/g Cr in the control group. The distributions of UACR categories in each group were 56 and 59% for category 1 (<30 mg/g Cr), 37 and 29% for category 2 (30–300 mg/g Cr), and 7 and 12% for category 3 (>300 mg/g Cr), respectively. The distributions of NYHA functional classes in each group were 9 and 12% for class I, 87 and 83% for class II, and 4 and 6% for class III, respectively. The prescription rates of an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, β-blocker, potassium-sparing diuretics, SGLT2 inhibitor, α-glucosidase inhibitor, biguanide, glinide, dipeptidyl peptidase 4 inhibitor, thiazolidinedione, sulphonyl urea, glucagon-like peptide-1 receptor agonist, and insulin before the study are shown in Table 1.

No significant differences were observed in the primary outcome, defined as the mean change in UACR from baseline during the two-year observation, between the dapagliflozin and control groups, evaluated both as crude values and log-transformed values (Table 2). Median UACR were 27.1 (12.1–75.4) and 32.7 (11.5–91.7) mg/g Cr in the dapagliflozin and control groups, respectively, at the end of the two-year observation.

Regarding secondary endpoints, the distribution of a shift to a better category of UACR and the mean change in eGFR from baseline during the two-year observation were similar in the dapagliflozin and control groups (Table 3). However, the mean decrease in LVDd as one of the echocardiographic parameters was larger in the dapagliflozin group than in the control group (Table 3). The distributions of a shift to a better class of NYHA during the two-year observation were 14.6 and 8.3% in the dapagliflozin and control groups, respectively (Table 3). The Event Evaluation Committee in the DAPPER trial confirmed 10 CV events in the dapagliflozin group (four of HF, two of stroke, two of arrhythmia, one of ischemic heart disease, and one of resistant hypertension) and 25 CV events in the control group (13 of HF, five of arrhythmia, three of ischemic heart disease, three of stroke, and one of aortic dissection). The composite endpoint, which was defined as CV death or hospitalisation for CV events in the two-year observation, was less frequent in the dapagliflozin group than in the control group (Fig. 2A), and the hazard ratio for comparisons of the dapagliflozin and control groups was 0.397 (95% CI, 0.174–0.907) (Table 4). Hospitalisation for CV events (Fig. 2B), hospitalisation for all causes (Fig. 2D), and an additional change in prescriptions for HF (Fig. 2E) in the two-year observation were less frequent in the dapagliflozin group than in the control group, and their hazard ratios were 0.397 (95% CI, 0.174–0.907), 0.591 (95% CI, 0.357–0.979), and 0.321 (95% CI, 0.161–0.642), respectively (Table 4). The probabilities of new-onset atrial fibrillation and/or atrial flutter in the two-year observation were similar between the dapagliflozin and control groups (Fig. 2F), and the hazard ratio was 1.952 (95% CI, 0.177–21.526) (Table 4). In the evaluation of CV event outcomes in the individual UACR categories, the rate of CV death or hospitalisation for CV events was significantly higher in the control group than in the dapagliflozin group in category 2 (microalbuminuria) only. The rate of additional changes in prescriptions for

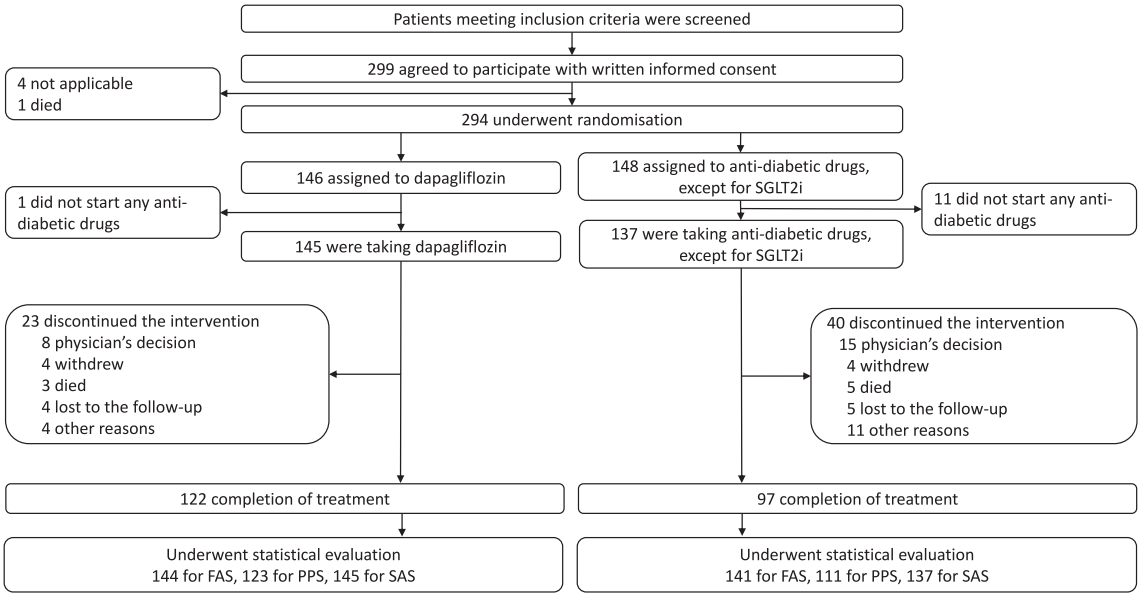

Fig. 1: **Randomisation and outcomes.**

HF was also significantly higher in the control group than in the dapagliflozin group in categories 1 (normal albuminuria) and 2 (Table 5). A summary of adverse events is listed in Table 6. The recorded number of patients with serious adverse events was 26 (17.8%) in the dapagliflozin group and 40 (29.0%) in the control group. Serious adverse events are listed in Supplementary Table S1 as Supplementary Material.

Discussion

The present study provides that dapagliflozin at the dose of 5 mg daily neither reduced UACR nor suppressed UACR increase, whereas decreased secondary CV outcomes, and suppressed left ventricular remodeling in patients with HF and T2DM.

The results obtained on the primary endpoint revealed no significant difference in renal dysfunction judged by UACR between the dapagliflozin and control groups, which is in contrast to previous findings from three RCTs showing the effects of SGLT2 inhibitors on the preservation of renal function as a primary outcome.[5,6,17] Therefore, attention was drawn to patient characteristics. We initially considered baseline UACR. The median values of UACR at baseline were 927 mg/g Cr in the CREDENCE trial,[17] 934 and 965 mg/g Cr for the placebo and dapagliflozin groups, respectively, in the DAPA-CKD trial,[5] and 327 and 331 mg/g Cr for the placebo and empagliflozin groups, respectively, in the EMPA-kidney trial.[6] On the other hand, in the present study, the median values of UACR were 25.6 and 25.0 mg/g Cr for the control and dapagliflozin groups, respectively, indicating that UACR was markedly lower than those in the three RCTs at baseline. The EMPA-kidney trial previously reported that the albuminuria reduction was more pronounced in higher UACR categories in the EMPA-pooled analysis.[20] One plausible explanation for the lack of a significant effect of dapagliflozin on renal protection, defined as a reduction in UACR, in the present study was low UACR in our trial patients.

Another important issue to consider is the dosage of dapagliflozin. In the present study, the initial dose of dapagliflozin was 5 mg daily and titrated to 10 mg daily as required in the protocol. Therefore, 5 mg daily accounted for 87.7% of doses at the end of the observation period, which markedly differed from the DAPA-CKD trial, in which dapagliflozin was administered at 10 mg daily to all patients. Since dapagliflozin in Japan was limited to patients with diabetes mellitus at the start of the DAPPER study, the initial oral dosage was 5 mg of dapagliflozin once daily, but was increased to 10 mg once daily if the effect was insufficient in the DAPPER study protocol. With an average HbA1c of 6.9% at baseline, it was not considered necessary to increase the dose of dapagliflozin from 5 to 10 mg in many cases based on blood glucose control. In a meta-analysis of dose differences, a dose of 5 mg daily of dapagliflozin was reported to reduce the risk of all-cause mortality significantly more than 2.5 mg daily; however, there was no information on renal outcomes.[21] Therefore, it is important to consider that nearly 90% of patients received 5 mg daily of dapagliflozin, which may explain the lack of a significant difference in renal outcomes as assessed by a change in UACR in the present study. We also speculate that dapagliflozin at 5 mg daily, the major

	The dapagliflozin group (n = 144)	The control group (n = 141)
Age (years)	72.1 (9.4)	72.2 (9.5)
Female sex	40 (28%)	42 (30%)
Body mass index (kg/m^2)	25.3 (4.2)	24.8 (4.4)
History of diabetes (≥5 years)[a]	93 (65%)	87 (62%)
History of diabetes (<5 years)[b]	45 (31%)	47 (33%)
Smoking habit		
Past	50 (35%)	54 (38%)
Current	28 (19%)	17 (12%)
Alcohol	81 (56%)	68 (48%)
Medical history		
Hypertension	118 (82%)	121 (86%)
Dyslipidemia	120 (83%)	113 (80%)
Stroke	18 (13%)	33 (23%)
Chronic kidney disease	20 (14%)	25 (18%)
Previous myocardial infarction	36 (25%)	37 (26%)
Admission for heart failure	29 (20%)	30 (21%)
Heart failure etiology		
Hypertensive heart disease	79 (55%)	80 (57%)
Ischemic heart disease	63 (44%)	58 (41%)
Valvular heart disease	18 (13%)	17 (12%)
Cardiomyopathy	13 (9%)	16 (11%)
Heart failure medication		
Angiotensin converting enzyme inhibitor	24 (17%)	19 (14%)
Angiotensin II receptor blocker	73 (51%)	66 (47%)
Beta-blocker	67 (47%)	73 (52%)
Potassium-sparing diuretics	17 (12%)	25 (18%)
Diabetes medication before the study		
SGLT2 inhibitor	34 (24%)	19 (14%)
Alpha-glucosidase inhibitor	25 (17%)	23 (16%)
Biguanide	69 (48%)	79 (56%)
Glinide	7 (5%)	8 (6%)
DPP-4 inhibitor	109 (76%)	103 (73%)
Thiazolidinedione	29 (20%)	26 (18%)
Sulphonyl urea	33 (23%)	32 (23%)
GLP-1 receptor agonist	1 (0.7%)	0 (0%)
Insulin	5 (4%)	6 (4%)
Physiological measurements		
Systolic blood pressure (mmHg)	131.2 (13.1)	129.2 (13.3)
Diastolic blood pressure (mmHg)	70.1 (10.7)	69.5 (10.9)
Heart rate (beats per min)	71.2 (11.1)	69.4 (11.0)
NYHA class	(n = 141)	(n = 139)
I	12 (8.5%)	16 (11.5%)
II	123 (87.2%)	115 (82.7%)
III	6 (4.3%)	8 (5.8%)
IV	0 (0%)	0 (0%)
Laboratory measurements		
Serum creatinine (mg/dL)	0.85 (0.21)	0.86 (0.19)
eGFR	66.9 (17.7)	64.6 (15.4)
Category 1 (≥90 mL/min/1.73 m^2)	13 (9%)	12 (9%)
Category 2 (60 to <90 mL/min/1.73 m^2)	74 (51%)	70 (50%)
Category 3 (45 to <60 mL/min/1.73 m^2)	50 (35%)	54 (38%)
Category 4 (<45 mL/min/1.73 m^2)	7 (5%)	5 (4%)
UACR, number of patients	138	136
UACR	25.0 (8.8–74.6)	25.6 (8.2–95.0)

(Table 1 continues on next page)

	The dapagliflozin group (n = 144)	The control group (n = 141)
(Continued from previous page)		
Category 1 (<30 mg/g Cr)	77 (56%)	80 (59%)
Category 2 (30–300 mg/g Cr)	51 (37%)	40 (29%)
Category 3 (>300 mg/g Cr)	10 (7%)	16 (12%)
Urinary KIM-1 (ng/mL)	2.13 (2.16)	1.74 (1.69)
Blood sugar (mg/dL)	150.1 (44.5)	153.0 (53.1)
HbA1c (%)	6.9 (0.7)	6.9 (0.8)
Plasma aldosterone (pg/mL)	126.0 (58.8)	128.8 (86.5)
Serum NT-proBNP (pg/mL)	357.8 (398.5)	501.5 (705.6)
Serum FGF23 (pg/mL)	55.9 (18.5)	59.2 (24.7)
Plasma alpha-Klotho (pg/mL)	629.6 (239.2)	618.5 (203.4)
Echocardiographic measurements		
LVDd (mm)	49.7 (7.4)	49.6 (7.3)
LVDs (mm)	34.4 (8.8)	34.3 (8.9)
LAVI (mL/m^2)	42.4 (24.7)	43.2 (24.0)
LAD (mm)	41.4 (9.2)	41.0 (8.1)
LVEF (%)	58.1 (11.9)	58.3 (11.6)
E (cm/sec)	72.3 (33.0)	73.5 (26.4)
e′ (cm/sec)	7.2 (2.4)	7.1 (2.3)
E/A	0.82 (0.39)	0.91 (0.51)
E/e′	9.8 (3.3)	11.1 (5.3)
Dct (m sec)	223.1 (63.6)	220.5 (48.8)

SD = standard deviation; IQR = interquartile range; SGLT2 = sodium-glucose co-transporter 2; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide-1; NYHA = New York Heart Association; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio; KIM-1 = kidney injury molecule-1; NT-proBNP = N-terminal B-type natriuretic peptide; FGF23 = fibroblastic growth factor 23; LVDd = left ventricular end-diastolic dimension; LVDs = left ventricular end-systolic dimension; LAVI = left atrial volume index; LAD = left atrial dimension; LVEF = left ventricular ejection fraction; E = mitral peak E-wave velocity; e′ = early diastolic mitral annular velocity by tissue Doppler echocardiography; E/A = E/mitral peak A velocity ratio; Dct = E velocity deceleration time. Data are n (%), means (SD), or medians (IQR). Hypertension was defined as office blood pressure of 140/90 mmHg or higher systolic/diastolic pressure or both. Dyslipidemia was defined as LDL cholesterol of 140 mg/dL or higher, HDL cholesterol lower than 40 mg/dL, or triglycerides of 150 mg/dL or higher. Alcohol use was defined as drinking more than 30 g/day for men and more than 20 g/day for women. [a]History of diabetes ≥5 years: patients who have had diabetes for five years and longer. [b]History of diabetes <5 years: patients who have had diabetes for less than five years.

Table 1: **Baseline characteristics of participants in the DAPPER trial.**

dose of the present study, may not have attenuated renal dysfunction or reduced UACR further in patients with both HF and T2D. In a sub-analysis of DAPA-CKD reported by McMurry et al., 10 mg of dapagliflozin reduced the risk of kidney failure and CV death/HF hospitalisation in patients with CKD with or without T2DM, independently of a history of HF.[22] The mean baseline eGFR was 43.2 mL/min/1.73 m^2, and the median UACR was 940 mg/g Cr in the DAPA-CKD trial, indicating that urinary albumin levels were higher and renal function was lower than in patients in the DAPPER study. Dapagliflozin was characterised by a reduction in CV events, even at the main dose of 5 mg in patients in the DAPPER study.

We found that the treatment with dapagliflozin resulted in a reduction in our secondary composite endpoint of CV events compared with controls. We need to compare these results with the findings of three

	The dapagliflozin group	The control group	Difference in changes in UACR from baseline after a 2-year observation[a] mg/g Cr, (95% CI)	p
Crude values	3.7 (−9.3 to 24.6)	6.9 (−1.4 to 27.8)	−13.0 (−105.3 to 79.2)	0.78
Log-transformed values	3.2 (2.2–4.3)	3.2 (2.1–4.6)	−0.10 (−0.38 to 0.18)	0.48

UACR = urine albumin-to-creatinine ratio; Cr = creatinine; CI = confidence interval; IQR = interquartile range. Data are medians (IQR), unless stated otherwise. [a]Adjusting factors for an analysis of covariance: baseline UACR, age, history of diabetes (<5 years), namely, patients with diabetes for less than five years, eGFR, concomitant medication use[b]. [b]Concomitant medication 1: an angiotensin-converting enzyme inhibitor, angiotensin 2 receptor blocker, renin inhibitor or potassium-sparing diuretic Concomitant medication 2: use of a β-blocker (including an αβ-blocker).

Table 2: **Primary outcome of the DAPPER trial: changes in UACR from baseline after a 2-year observation.**

	The dapagliflozin group (n = 144)	The control group (n = 141)	Difference in changes from baseline after a 2-year observation (95% CI)	p
UACR	(n = 118)	(n = 112)		
Shift to a better category	23 (19%)	16 (14%)		0.29
No shift and shift to a worse category	95 (81%)	96 (86%)		
eGFR	(n = 139)	(n = 136)		
Changes in eGFR from baseline after a 2-year observation	−2.7 (11.2)	−3.2 (10.4)	0.5 (−2.1 to 3.1)	0.69
Shift to a better category	14 (10%)	17 (13%)		0.52
No shift and shift to a worse category	125 (90%)	119 (88%)		
Changes from baseline after a 2-year observation				
Urinary KIM-1	−0.55 (2.15)	−0.06 (1.88)	−0.49 (−1.04 to 0.06)	0.08
Plasma aldosterone	2.0 (64.9)	−6.9 (60.9)	9.0 (−7.4 to 25.3)	0.28
Serum NT-proBNP	90.6 (360.6)	106.6 (458.3)	−15.9 (−122.3 to 90.4)	0.77
Serum FGF23	8.4 (24.0)	4.9 (28.6)	3.5 (−3.3 to 10.3)	0.32
Plasma alpha-Klotho observation	15.0 (172.2)	25.6 (161.9)	−10.6 (−53.5 to 32.3)	0.63
LVDd	−0.9 (4.2)	0.7 (4.2)	−1.6 (−2.6 to −0.5)	0.01
LVDs	−0.5 (3.8)	0.6 (4.7)	−1.1 (−2.2 to 0.03)	0.06
LAVI	−0.3 (11.8)	−1.1 (12.5)	0.8 (−2.9 to 4.5)	0.68
LAD	−1.3 (5.6)	−0.4 (5.0)	−0.9 (−2.3 to 0.5)	0.21
LVEF	0.3 (6.7)	−0.9 (7.3)	1.3 (−0.6 to 3.1)	0.18
E	−2.1 (19.6)	0.1 (16.6)	−2.2 (−7.1 to 2.7)	0.38
e′	−0.2 (2.0)	−0.3 (1.8)	0.1 (−0.5 to 0.8)	0.64
E/A	0.03 (0.34)	0.00 (0.40)	0.03 (−0.09 to 0.15)	0.61
E/e′	0.3 (3.4)	0.6 (3.4)	−0.3 (−1.4 to 0.8)	0.63
Dct	11.7 (68.2)	0.2 (70.6)	11.6 (−7.6 to 30.7)	0.23
NYHA	(n = 137)	(n = 133)		
Shift to a better category	20 (14.6%)	11 (8.3%)	1.88 (0.95–3.72)	0.07
No shift in category	113 (82.5%)	115 (86.5%)		
Shift to a worse category	4 (2.9%)	7 (5.3%)		

Data are n (%) or medians (IQR), unless stated otherwise. IQR = interquartile range; UACR = urinary albumin-to-creatinine ratio; eGFR = estimated glomerular filtration rate; KIM-1 = kidney injury molecule-1; NT-proBNP = N-terminal B-type natriuretic peptide; FGF23 = fibroblastic growth factor 23; LVDd = left ventricular end-diastolic dimension; LVDs = left ventricular end-systolic dimension; LAVI = left atrial volume index; LAD = left atrial dimension; LVEF = left ventricular ejection fraction; E = mitral peak E-wave velocity; e′ = early diastolic mitral annular velocity by tissue Doppler echocardiography; E/A = E/mitral peak A velocity ratio; Dct = E velocity deceleration time.

Table 3: **Secondary outcomes of the DAPPER trial.**

previous RCTs from the viewpoint of entry criteria in order to characterise this trial. One of the inclusion criteria for patients was T2D in the CREDENCE trial and CKD in both the DAPA-CKD and EMPA-kidney trials. Therefore, 14.8% of patients in the CREDENCE trial concomitantly had HF, 67.4–67.6% had diabetes mellitus, and 10.8–10.9% had HF in the DAPA-CKD trial, while 45.8–46.2% had T2D, and 10% had a history of HF in the EMPA-kidney trial. In the post hoc analysis in the CREDENCE trial, the composite of any CV event, including myocardial infarction, stroke, hospitalisation for HF, hospitalisation for unstable angina, and CV death, was less frequent in the canagliflozin group than in the placebo group.[23] The prespecified analysis of the DAPA-CKD trial revealed that the risk for a composite of CV death or hospital admission for HF and all-cause mortality was lower in the dapagliflozin group than in the placebo group.[24] When we employed the enrollment criterion of HF with T2D in the present study, we found that the treatment with dapagliflozin resulted in a reduction in the secondary CV endpoints, suggesting the effectiveness of dapagliflozin for CV protection despite the limited number of patients examined, which was similar to the findings of the DAPA-CKD trial.[24]

Among the effects on UACR and CV events evaluated in this trial, we observed no significant difference in the primary outcome of a decrease in UACR, but noted a reduction in the secondary composite endpoint of CV events. Previous studies demonstrated that an increase in UACR was associated with the development of HF with HFrEF and HFpEF[14] and CV death and hospitalisation for HF in patients with HF,[15] while a reduction in UACR by drug treatment was associated with a decrease in the rate of hospitalisation for HF.[16] SGLT2 inhibitors were also shown to enhance renoprotective effects in patients with high HbA1c and UACR,[25] while the suppression of CV death and

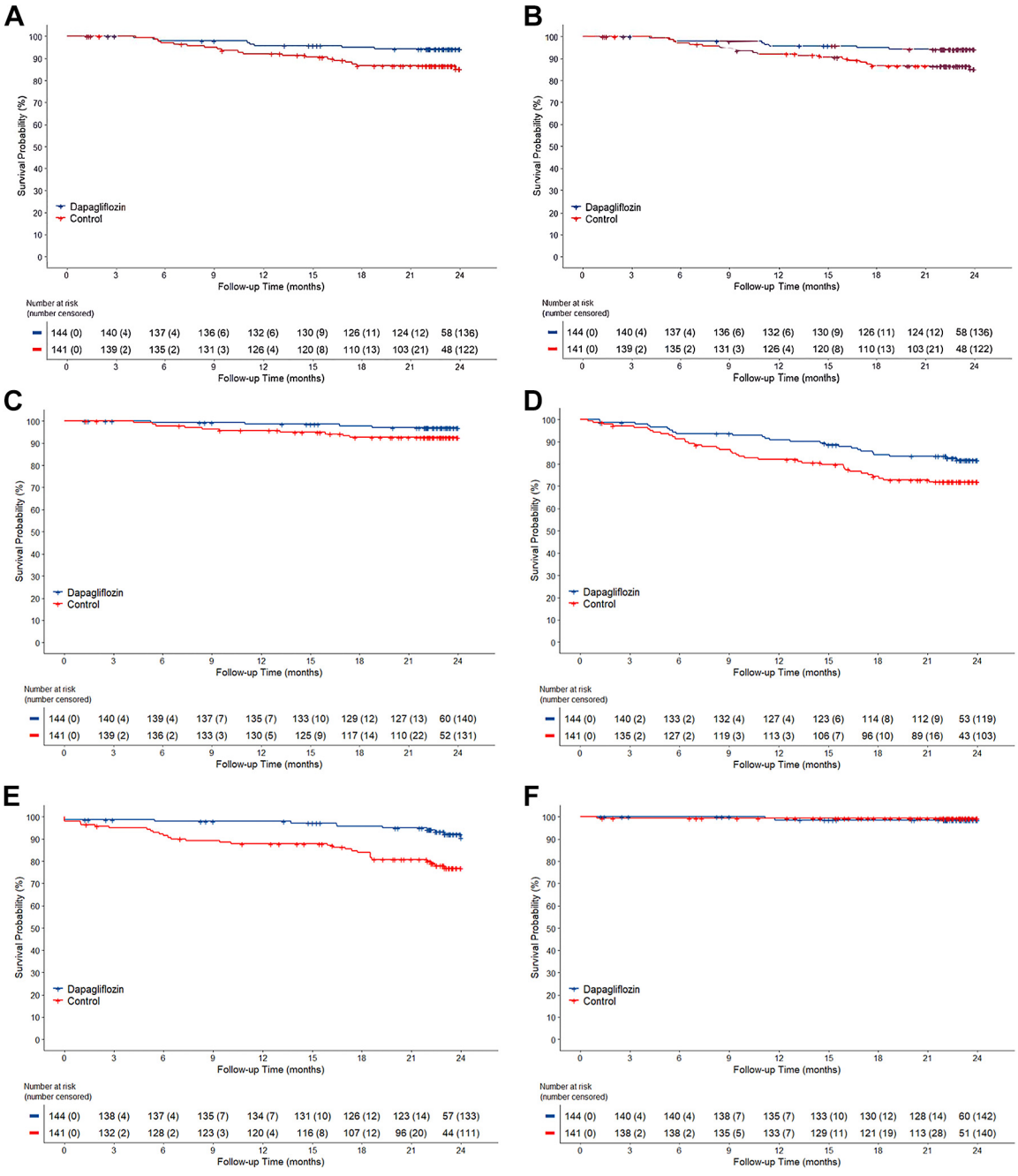

***Fig. 2:* (A) The composite endpoint, defined as CV death or hospitalisation for CV events in a two-year observation.** Log-rank test: p = 0.023 between the dapagliflozin and control groups. (B) Hospitalisation for CV events in a two-year observation. Log-rank test: p = 0.023 between the dapagliflozin and control groups. (C) Hospitalisation for HF in a two-year observation. Log-rank test: p = 0.09 between the dapagliflozin and control groups. (D) Hospitalisation for all causes in a two-year observation. Log-rank test: p = 0.039 between the dapagliflozin and control groups. (E) An additional change in prescriptions for HF in a two-year observation. Log-rank test: p < 0.001 between the dapagliflozin and control groups. (F) New-onset atrial fibrillation and/or atrial flutter in a two-year observation. Log-rank test: p = 0.58 between the dapagliflozin and control groups.

hospitalisation for HF were more frequent in patients with reduced eGFR with albuminuria.[26] Furthermore, in patients with CKD and T2D, a decrease in UACR by SGLT2 inhibitors was identified as an independent factor for the suppression of renal and CV events.[27] These findings may lead to the simplistic idea of

Events	The dapagliflozin group	The control group	Hazard ratio (95% CI)	p
CV death or for CV events hospitalisation	8/144	19/141	0.397 (0.174–0.907)	0.028
CV death or hospitalisation for HF	4/144	10/141	0.383 (0.120–1.222)	0.100
Onset of CV death	0/144	2/141	NA	
Hospitalisation for CV events	8/144	19/141	0.397 (0.174–0.907)	0.028
Hospitalisation for HF	4/144	10/141	0.383 (0.120–1.222)	0.100
Death from all causes	3/144	5/141	0.566 (0.135–2.369)	0.440
Hospitalisation for all causes	25/144	38/141	0.591 (0.357–0.979)	0.040
Additional change in prescriptions for HF	11/144	30/141	0.321 (0.161–0.642)	0.001
New-onset atrial fibrillation and/or atrial flutter	2/144	1/141	1.952 (0.177–21.526)	0.590

CV = cardiovascular; HF = heart failure; CI = confidence interval.

Table 4: **Cox proportional hazards regression analysis of secondary outcomes.**

withholding the prescription of SGLT2 inhibitors to patients with HF and T2D with low urinary albumin and preserved renal function when considering drug treatment regimens for these patients. The present results demonstrated that although dapagliflozin did not affect UACR or changes in UACR categories, differences were observed in CV outcomes between the dapagliflozin and control groups, suggesting that SGLT2 inhibitors directly reduced the incidence of CV outcomes and encouraging the prescription of dapagliflozin to patients with HF and T2D with low urinary albumin and preserved renal function in order to effectively reduce CV events. Furthermore, among our prespecified echocardiographic parameters, the mean decrease in LVDd was larger in the dapagliflozin group than in the control group, which is consistent with previous findings showing that SGLT2 inhibitors improved echocardiographic parameters in patients with T2D.[28] The effectiveness of dapagliflozin for CV protection may be attributed to its suppressive effects on left ventricular remodeling.

The present study has several limitations that need to be addressed. Since we included patients with relatively mild renal dysfunction (eGFR ≥45 mL/min/1.73 m^2), the generalisation of results for patients with lower eGFR was constrained. Furthermore, albuminuria was measured in single urine samples. High day-to-day variations in urine albumin levels may have affected the accuracy of these measurements. The percentages of SGLT2 inhibitors used at baseline were 24% in the dapagliflozin group and 14% in the control group, which may have affected baseline UACR levels. When patients with diabetes who were being treated with an SGLT2 inhibitor were assigned to a control group, an SGLT2 inhibitor, including dapagliflozin, was replaced with a drug that was not an SGLT2 inhibitor; however, we did not evaluate the impact of the discontinuation of SGLT2 inhibitors on changes in UACR and CV events. Moreover, all participants in the DAPPER study were residents of Japan, which may have affected the results obtained, such as the mean body mass index (BMI) being lower in the DAPPER study (25.0 kg/m^2) than in the CREDENCE trial (31.3 kg/m^2), the participants of which were from 34 countries. Although this limits the generalizability of the present results to patients with a higher BMI, they are still valuable for physicians and patients living in Japan. The frequency of women was low at 30% of enrolled patients. This may be due to the prevalence of diabetes[29] and HF[30] in Japan being higher in men and the lack of an adjustment for sex at the time

	Category 1		Category 2		Category 3	
CV death or hospitalisation for CV events	–	+	–	+	–	+
Dapagliflozin (n = 138)	73	4	49	2	8	2
Control (n = 136)	72	8	32	8	13	3
Chi-square p value	0.257		0.015		0.937	
Fisher p value	0.370		0.020		1.000	
Additional change in prescriptions for HF	–	+	–	+	–	+
Dapagliflozin (n = 138)	70	7	50	1	8	2
Control (n = 136)	62	18	32	8	12	4
Chi-square p value	0.022		0.004		0.768	
Fisher's p value	0.029		0.009		1.000	

CV = cardiovascular; HF = heart failure; UACR = urinary albumin-to-creatinine ratio.

Table 5: **CV event outcomes in individual UACR categories.**

	The dapagliflozin group (n = 146)	The control group (n = 138)
Any adverse events	158	171
Serious adverse events[a]	26 (17.8)	40 (29.0)
Diabetic ketoacidosis	0	0
Hyperosmolar hyperglycemic syndrome	0	0
Drug-related serious adverse events (investigator-defined)[a]	5 (3.4)	2 (1.4)
Fracture[a]	1 (0.7)	3 (2.2)
Amputation	0	0
Volume depletion	0	1 (0.7)

Data are n (%). [a]Patients with multiple events in the same category were counted only once in that category; Patients with events in more than 1 category were counted once in each of these categories.

Table 6: **Adverse events.**

of allocation. Another limitation is the open-label trial design; neither participants nor staff were blinded to allocations. Although efforts were made to ensure the objectivity of the secondary outcomes, it was considered difficult to ensure objectivity equivalent to that of double-blind controlled trials. Urine samples were collected and UACR, the primary endpoint in this trial, was centrally measured to eliminate differences between facilities due to measurement equipment and conditions. The evaluation of secondary endpoints was conducted under the non-disclosure of the allocation status. Clinical events were assessed by an Event Evaluation Committee blinded to allocations and structured to be as objective as possible. Therefore, physician subjectivity and variability in measurements among facilities were minimised as much as possible. Moreover, comparisons of the 23 secondary outcomes listed may increase the erroneous change for false positive results as a statistical limitation. Due to the simultaneous evaluation of multiple secondary endpoints in the present study, there is a concern regarding multiplicity in hypothesis testing. However, we positioned this research to have an exploratory nature, and, thus, did not plan for adjustments for multiplicity. In addition, due to uncertainty regarding the Missing at Random assumption in our dataset, we refrained from imputation procedures. This limitation may also have affected the analysis results of the data.

Although dapagliflozin at a dose of 5 mg daily, the major dose of the present study, did not reduce urinary albumin excretion in patients with HF and T2D irrespective of the urinary level of albumin, the effectiveness of dapagliflozin for CV protection with suppressive effects on left ventricular remodeling was suggested.

Contributors

FY, MI, MA, SI, and MK designed the study protocol. IS c), YH, HH, OO, CI f), CI g), TN, TS, NN, KF, KI, OT, KK, MT, KY, HT, TH p), IS q), TM, KW, KS, TH u), SA, and SH shared comments on study design, collected data, and performed quality control. FY, MI, SI, MK, TK, and KO directly accessed and verified the underlying data of the manuscript. TK, together with KO, performed statistical analyses and reporting. KO, with input from FY, MI, SI, and MK, wrote the statistical analysis plan. The first draft of the manuscript was written by FY and MI. All authors had full access to all the data in the study, commented on the manuscript and accepted responsibility for the decision to submit it for publication.

Data sharing statement

The data analysed in the present study are available from the corresponding author upon reasonable request. It is planned that decisions on data sharing will be made in accordance with the provisions of the research protocol, depending on the nature of the request.

Declaration of interests

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Appendix A. Supplementary data

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