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ORIGINAL RESEARCH ARTICLE

Effects of canagliflozin in patients with type 2 diabetes and chronic heart failure: a randomized trial (CANDLE)

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Abstract

Aims Little is known about the impact of sodium glucose co-transporter 2 (SGLT2) inhibitors on cardiac biomarkers, such as natriuretic peptides, in type 2 diabetes (T2D) patients with concomitant chronic heart failure (CHF). We compared the effect of canagliflozin with glimepiride, based on changes in N-terminal pro-brain natriuretic peptide (NT-proBNP), in that patient population.

Methods and results Patients with T2D and stable CHF, randomized to receive canagliflozin 100 mg or glimepiride (starting-dose: 0.5 mg), were examined using the primary endpoint of non-inferiority of canagliflozin vs. glimepiride, defined as a margin of 1.1 in the upper limit of the two-sided 95% confidence interval (CI) for the group ratio of percentage change in NT-proBNP at 24 weeks. Data analysis of 233 patients showed mean left ventricular ejection fraction (LVEF) at randomization was 57.6 ± 14.6%, with 71% of patients having a preserved LVEF (≥50%). Ratio of NT-proBNP percentage change was 0.48 (95% CI, −0.13 to 1.59, $P = 0.226$) and therefore did not meet the prespecified non-inferiority margin. However, NT-proBNP levels did show a non-significant trend lower in the canagliflozin group [adjusted group difference; −74.7 pg/mL (95% CI, −159.3 to 10.9), $P = 0.087$] and also in the subgroup with preserved LVEF [−58.3 (95% CI, −127.6 to 11.0, $P = 0.098$]).

Conclusions This study did not meet the predefined primary endpoint of changes in NT-proBNP levels, with 24 weeks of treatment with canagliflozin vs. glimepiride. Further research is warranted to determine whether patients with heart failure with preserved ejection fraction, regardless of diabetes status, could potentially benefit from treatment with SGLT2 inhibitors.

Keywords Type 2 diabetes; Heart failure; SGLT2 inhibitor; NT-proBNP; Non-inferiority; Glimepiride

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Clinical Trial RegistrationURL: https://www.umin.ac.jp/ctr/index.htm Unique identifier: UMIN000017669.

Introduction

Accumulating evidence suggests that type 2 diabetes (T2D) is a major risk factor of cardiac dysfunction and heart failure (HF), independent of hypertension and coronary artery disease, and concomitant HF strongly contributes to a worsened prognosis.[1] Recent large-scale randomized trials on cardiovascular outcomes with newer glucose-lowering agents have shown some agents have a large impact on the components of cardiovascular diseases including HF.[2] Among T2D treatments, sodium glucose co-transporter 2 (SGLT2) inhibitors markedly reduced hospitalization for HF in patients with T2D at high risk for cardiovascular events, irrespective of cardiovascular disease history including HF.[3] In addition to the blood glucose-lowering effect, SGLT2 inhibitors have non-glycemic effects, such as reduction in blood pressure, body weight, excess plasma fluid, and the risk of cardiovascular and renal events.[4,5] However, those cardiovascular outcomes trials included few participants with concomitant HF, and their HF types were not phenotyped. More recently,

dapagliflozin also significantly reduced the risk of worsening HF or cardiovascular death even in both diabetic and non-diabetic patients with HF and a reduced ejection fraction.[6] These results suggest that SGLT2 inhibitors have favourable effects in patients with HF, irrespective of T2D, and have advantages for HF care. Nevertheless, the profound drivers of SGLT2 inhibitors for beneficial impact on HF are still uncertain.[7] Furthermore, the effects of SGLT2 inhibitors on cardiac function or neurohumoral factors, such as natriuretic peptides, are still not fully understood.

We therefore undertook a randomized trial comparing canagliflozin with glimepiride, which has been associated with decreases in HbA1c levels similar to canagliflozin 100 mg,[8] with the primary objective of assessing the effect of canagliflozin on N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in T2D patients with chronic HF (CHF).

Methods

Study design and participants

The CANDLE trial (UMIN000017669) was an investigator-initiated, multicentre, prospective, randomized, open-label, blinded-endpoint trial at 34 centres in Japan. The detailed rationale and design have been described previously.[9] Briefly, individuals aged 20 years or older with appropriately diagnosed T2D and New York Heart Association (NYHA) class I–III CHF were eligible. CHF was defined by skilled cardiologists according to the clinical signs or symptoms associated with the Framingham criteria for congestive HF, relevant findings based on physiological and laboratory tests, and a documented history of HF. Participants' NYHA class and medical treatment for CHF could not change up to 4 weeks prior to eligibility screening. Regarding glycemic control, patients with T2D who were under poor or suboptimal control were eligible. Key exclusion criteria were severe renal dysfunction (estimated glomerular filtration rate $<$ 45 mL/min/1.73m^2), CHF with NYHA class IV, and history of cardiovascular disease needing revascularization within 3 months of screening.

The trial was approved by individual sites' institutional review boards and independent ethics committees, in compliance with the Declaration of Helsinki and the current legal regulations in Japan. All enrolled patients provided written informed consent prior to eligibility screening.

Randomization

All participants who met the enrolment criteria were randomly assigned (1:1) to treatment with canagliflozin or glimepiride. Treatment assignment was carried out with a web-based program with the minimization method with biassed coin assignment balancing for age ($<$65, $\geq$65 yr), HbA1c level ($<$6.5%, $\geq$6.5%), and left ventricular ejection fraction (LVEF; $<$40%, $\geq$40%) at the time of screening.

Procedures

After randomization, patients were started on canagliflozin 100 mg once daily or glimepiride 0.5 mg once daily. The intervention design spanned 24 weeks. Although no specific numerical goal for HbA1c level was set in this trial, all patients were treated according to the Japanese treatment guidelines for diabetes. For patients who could not achieve their glycemic goal, increasing the dose of background therapy or adding glucose-lowering agents other than SGLT2 inhibitors and sulfonylureas in both groups was allowed. In the glimepiride group, a dose increase of up to 6.0 mg daily was permitted. Given that these modes in principle and if possible, unchanged during the study period. However, the dose of diuretics could be tapered if considered clinically appropriate in order to avoid excess diuresis and subsequent dehydration caused by co-administration of canagliflozin. The intervention period was of 24 weeks duration.

Endpoints

The primary endpoint was the percentage change (post/pre -1) from baseline in NT-proBNP at Week 24. In the secondary endpoints, we evaluated the changes in parameters after 24 weeks of treatment or at early termination visits, including (1) NT-proBNP level, (2) vital signs (body weight, blood pressure, and heart rate), (3) glycemic control (HbA1c, fasting plasma glucose), (4) estimated plasma volume (ePV) calculated by the Strauss formula (*Method S1*),[10,11] (5) echocardiographic measures (LVEF and mitral inflow to mitral relaxation velocity ratio; E/e'), (6) NYHA functional classification, and (7) CHF-related quality of life evaluated by scaled responses to the Minnesota Living with Heart Failure (MLHF) questionnaire. As a safety endpoint, we also analysed the prevalence of prespecified and adjudicated clinical events, including hospitalization for HF, which were adjudicated according to the predefined evaluation criteria (*Method S2*) by an independent clinical event committee. We also assessed the incidence of adverse events throughout the study period.

NT-proBNP was assessed at baseline and Week 24 or at early termination visits and measured at a central laboratory (SRL, Inc. Tokyo, Japan) with an electrochemiluminescence immunoassay (Roche, Basel, Switzerland) under blindness for allocation.

Echocardiography was performed at screening, baseline, and Week 24 or at early termination visits to measure systolic and diastolic function at each local site. We used the mean e′ in the septal and lateral side.

Statistical analysis

In the power calculation, based on the previous study,[12] we assumed an 18% difference in the changes in NT-proBNP from baseline to 24 weeks between the two groups and a common standard deviation for the log scale of the ratio of 0.80. We estimated that it was necessary to recruit 125 patients in each group to demonstrate non-inferiority of canagliflozin vs. glimepiride, ensuring at least 80% power to detect 18% difference, using a one-sided *t*-test with an α level of 0.025 and a non-inferiority margin of 1.1 in the upper limit of the two-sided 95% confidence interval (CI) for the group ratio of the percentage changes from baseline to 24 weeks in NT-proBNP levels and a dropout rate of 10%.

We analysed the primary and secondary efficacy variables by comparing all patients who received at least one dose of treatment during the study period and had no serious protocol deviations (full analysis set), and changes in the variables were compared based on data from patients who had baseline and 24-week assessments. The incidence of adverse events was analysed with data collected after randomization (safety analysis set). To assess the primary endpoint, a group ratio of percentage changes in NT-proBNP and their 95% CI were calculated with Fieller's method. The baseline-adjusted means and 95% CIs estimated by analysis of covariance for the absolute change in NT-proBNP level at 24 weeks were compared between the two treatments. Post hoc responder analyses were also conducted to investigate the proportions of patients who had a clinically meaningful change (20% or greater) in NT-proBNP level from baseline to 24 weeks,[13] while a logistic regression model adjusted for corresponding baseline NT-proBNP values was used to assess the effect of canagliflozin vs. glimepiride. Other comparisons of the changes in parameters between the treatment groups were performed using Student's *t*-test or Wilcoxon rank-sum test for changes in NYHA classification. No adjustment for multiplicity was considered for the secondary and post hoc efficacy endpoints. Statistical testing was carried out at the two-sided significance level of 0.05 and estimated effect sizes and their 95% CIs, and all statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Results

Study population

Between August 2015 and June 2017, 253 patients were assessed for the study eligibility, of whom eight were excluded before randomization. A total of 245 patients were randomized, of whom 228 patients completed 24 weeks of treatment, and 241 and 233 were included in the safety analysis set and full analysis set, respectively (*Figure 1*). In the glimepiride group, the median daily dose of glimepiride at the final visit was 1.0 mg (interquartile range 0.5, 1.0).

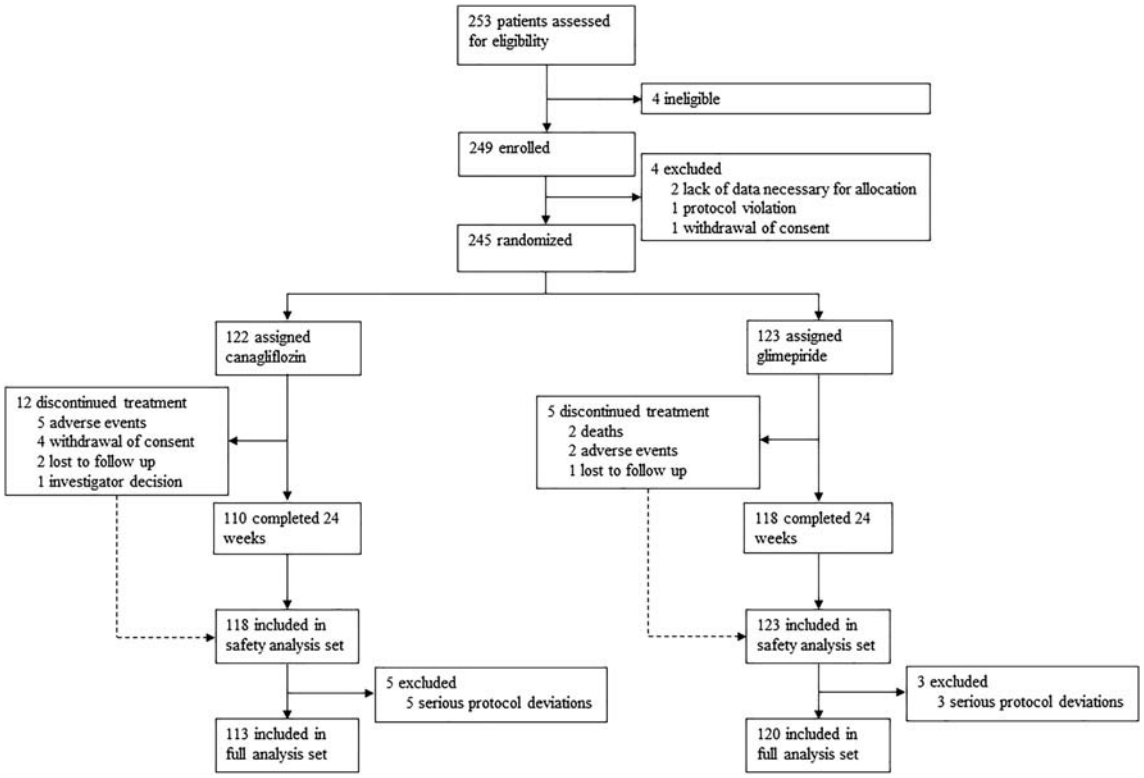
Baseline characteristics were comparable between treatment groups (*Table 1*). The patients were elderly (68.6 ± 10.1 yrs), and most were male patients (75%) and well controlled in blood pressure and NYHA functional class I (64%) or II (34%). Overall, 24% had a history of myocardial infarction, and the aetiology of CHF in 43% was ischemia. Mean LVEF at randomization was 57.6 ± 14.6%, with 71% of patients having a reduced LVEF (≥50%). Most patients had been taking renin–angiotensin–aldosterone system blockers and statins before enrolment. Approximately 40% had been prescribed diuretics. The baseline level of HbA1c was 7.0 ± 0.8%.

N-terminal pro-brain natriuretic peptide

The details of NT-proBNP levels at baseline and 24 weeks are shown in *Table S1*. The mean percentage changes were 10.4% (95% CI, −0.54 to 21.26) in the canagliflozin group and 21.5% (95% CI, 7.18 to 35.77) in the glimepiride group, with a group ratio of percentage changes (canagliflozin vs. glimepiride) of 0.48 (95% CI, −0.13 to 1.59, *P* = 0.226, *Figure 2A*). The responder analyses (*Figure 2B–D*) showed that a larger proportion of patients treated with canagliflozin, especially those with preserved LVEF (≥50%), had a ≥ 20% reduction in NT-proBNP levels. However, there was no significant difference in this proportion between the two treatment groups (*Table S2*). Similarly, a numerically smaller proportion of patients treated with canagliflozin, especially subjects with a reduced LVEF (<50%), had a ≥ 20% increase in NT-proBNP levels, with no significant difference in this proportion between the two groups.

A greater reduction in NT-proBNP levels was observed in all the patients treated with canagliflozin, although there was no significant difference in baseline-adjusted mean changes in NT-proBNP levels between canagliflozin and glimepiride [−78.7 pg/mL (95% CI, −139.9 to −17.5) vs. −4.5 pg/mL (95% CI, −63.4 to 54.4), *P* = 0.087]. Data stratified according to baseline NT-proBNP levels using the overall median value of 252 pg/mL and guideline-recommended cut-off values for diagnosing HF[14,15] showed canagliflozin treatment reduced NT-proBNP levels to a greater extent than in subgroups with elevated levels of NT-proBNP, especially the subgroup with a baseline NT-proBNP level ≥ 125 pg/mL [−121.5 pg/mL (95% CI, −201.7 to −41.2) vs. −6.1 pg/mL (95% CI, −86.9 to 74.7), *P* = 0.047; *Figure 3A* and *Table 2*]. Subgroup analyses based on the baseline LVEF showed the group difference in adjusted mean change in NT-proBNP level was 10.0 pg/mL in patients with reduced LVEF (95% CI, −204.2 to 224.3, *P* = 0.926) and −58.3 pg/mL (95% CI, −127.6 to 11.0, *P* = 0.098) in patients with preserved LVEF (*Figure 3B,C*). The reduction in NT-proBNP levels driven by canagliflozin in subgroups with elevated levels of the hormone was more apparent in patients

Figure 1 Flow chart of the study.



with preserved LVEF than in those with a reduced LVEF (*Table S3*).

Clinical parameters of interest

The changes in clinical and laboratory parameters of interest are summarized in *Table S4*. A larger reduction in HbA1c level was observed in the glimepiride group. Differences in changes in blood pressures and heart rate were not significant between treatment groups. The body weight reduction in the canagliflozin group was significantly larger than that in the glimepiride group. Canagliflozin treatment increased haemoglobin and haematocrit levels to a greater extent than glimepiride. In addition, 24 weeks of canagliflozin treatment significantly reduced ePV to a greater extent than that observed with glimepiride, irrespective of the baseline LVEF levels (*Figure 4A*).

Cardiac function, New York Heart Association class, and Minnesota Living with Heart Failure score

We measured no significant changes in echocardiographic parameters related to the left ventricular systolic and diastolic function (*Table S5*). Overall, changes in the NYHA class were comparable between groups ($P = 0.061$), whereas in the subgroup with a baseline LVEF ≥50% canagliflozin caused a significant improvement in NYHA classes compared with that found for glimepiride treatment ($P = 0.027$; *Figure 4B*). Although the total MLHF scores at baseline were not balanced and were lower in the canagliflozin group than in the glimepiride group (11.5 ± 12.7 vs. 16.5 ± 16.8, $P = 0.012$). However, there was no significant difference in baseline-adjusted mean changes in the total score at 24 weeks between canagliflozin and glimepiride (*Table S6*).

Adjudicated clinical and adverse events

Any adverse events were reported in nine patients (10 events) in the canagliflozin group and 13 patients (17 events) in the glimepiride group (*Table S7*). In the canagliflozin group, two patients (1.7%) had the prespecified and adjudicated clinical events, one non-fatal stroke and one investigator-reported worsening of HF; in the glimepiride group, five patients (4.1%) experienced those events, three investigator-reported worsening of HF events, leading to hospitalization in one patient, and two all-cause deaths. In the canagliflozin group, neither hypoglycemia nor urinary tract/genital infection was reported, but two adverse events possibly associated with

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Table 1 Baseline demographic and characteristics

Variable	Canagliflozin (n = 113)	Glimepiride (n = 120)
Age, year	68.3 ± 9.8	68.9 ± 10.4
Female	25 (22.1)	34 (28.3)
Body mass index, kg/m^2	24.1 ± 6.4	25.4 ± 4.8
Systolic blood pressure, mm Hg	124.9 ± 14.3	124.5 ± 18.0
History		
Hypertension	49 (43.4)	53 (44.2)
Dyslipidemia	46 (40.7)	54 (45.0)
Myocardial infarction	32 (28.3)	24 (20.0)
Angina pectoris	24 (21.2)	27 (22.5)
Coronary artery bypass grafting	12 (10.6)	10 (8.3)
Stroke	11 (9.7)	5 (4.2)
Heart failure cause*		
Ischemia	54 (47.8)	46 (38.3)
Hypertension	32 (28.3)	30 (25.0)
Valve	19 (16.8)	17 (14.2)
Dilated cardiomyopathy	17 (15.0)	19 (15.8)
Arrhythmia	29 (25.7)	33 (27.5)
Heart failure status		
NYHA functional class		
I	72 (63.7)	76 (63.9)
II	39 (34.5)	40 (33.6)
III	2 (1.8)	3 (2.5)
Unknown	0 (0.0)	1
LVEF <50%	35 (31.0)	33 (27.5)
Medication		
Non-diabetic		
ACE inhibitor or ARB	89 (78.8)	88 (73.3)
Beta-blocker	82 (72.6)	82 (68.3)
Calcium channel blocker	46 (40.7)	44 (36.7)
MRA	42 (37.2)	44 (36.7)
Diuretic	46 (40.7)	53 (44.2)
Digitalis	12 (10.6)	8 (6.7)
Statin	87 (77.0)	86 (71.7)
Anti-platelet or anti-coagulant	71 (62.8)	66 (55.0)
Diabetic		
Insulin	4 (3.5)	3 (2.5)
Metformin	18 (15.9)	26 (21.7)
Alpha-glucosidase inhibitor	16 (14.2)	24 (20.0)
DPP-4 inhibitor	64 (56.6)	63 (52.5)
GLP-1RA	1 (0.9)	1 (0.8)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association. Data are mean ± standard deviation or n (%).
*Multiple answers were allowed.

the study drug were observed: one osmotic diuresis-related symptom and one hypovolemia-related symptom.

Discussion

In this trial we observed that (1) canagliflozin treatment given for 24 weeks to Japanese elderly patients with T2D and stable CHF did not meet the predefined primary endpoint (non-inferiority for the group ratio of percentage change in NT-proBNP level) possibly because of the large variation in these levels; (2) the reduction in NT-proBNP, a key secondary endpoint, was numerically greater in the canagliflozin group than in the glimepiride group, especially in patients with elevated NT-proBNP levels; (3) in the subgroup with HFpEF canagliflozin reduced NT-proBNP level and improved NYHA functional class to a greater extent than glimepiride; (4) canagliflozin significantly reduced ePV irrespective of baseline LVEF levels, although there was no significant effect on MLHF score.

At the time of designing the current trial, no one knew if SGLT2 inhibitors could reduce NT-proBNP and even improve HF-related outcomes. There was also no direct evidence showing that sulfonylureas can increase or decrease the risk of HF. Therefore, we speculated that canagliflozin might be non-inferior to glimepiride in regard to the effect on NT-proBNP and performed this trial.

Recent cardiovascular outcome trials with SGLT2 inhibitors in patients with T2D at high risk of cardiovascular events have demonstrated beneficial effects of SGLT2 inhibitors on HF-related outcomes, which have become a centre of attention.[16] Intriguingly, those trials showed a consistent risk reduction in HF-related outcomes, and such beneficial effects

Figure 2 Percentage changes in NT-proBNP levels between baseline and 24 weeks and responder analyses. (A) Percentage changes in NT-proBNP levels from baseline to 24 weeks and the group ratio (canagliflozin vs. glimepiride). (B–D) Proportion of all patients showing a clinically meaningful change in NT-proBNP levels at 24 weeks. (B) Overall. (C) HFrEF (defined as baseline LVEF <50%). (D) HFpEF (defined as baseline LVEF ≥50%). HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

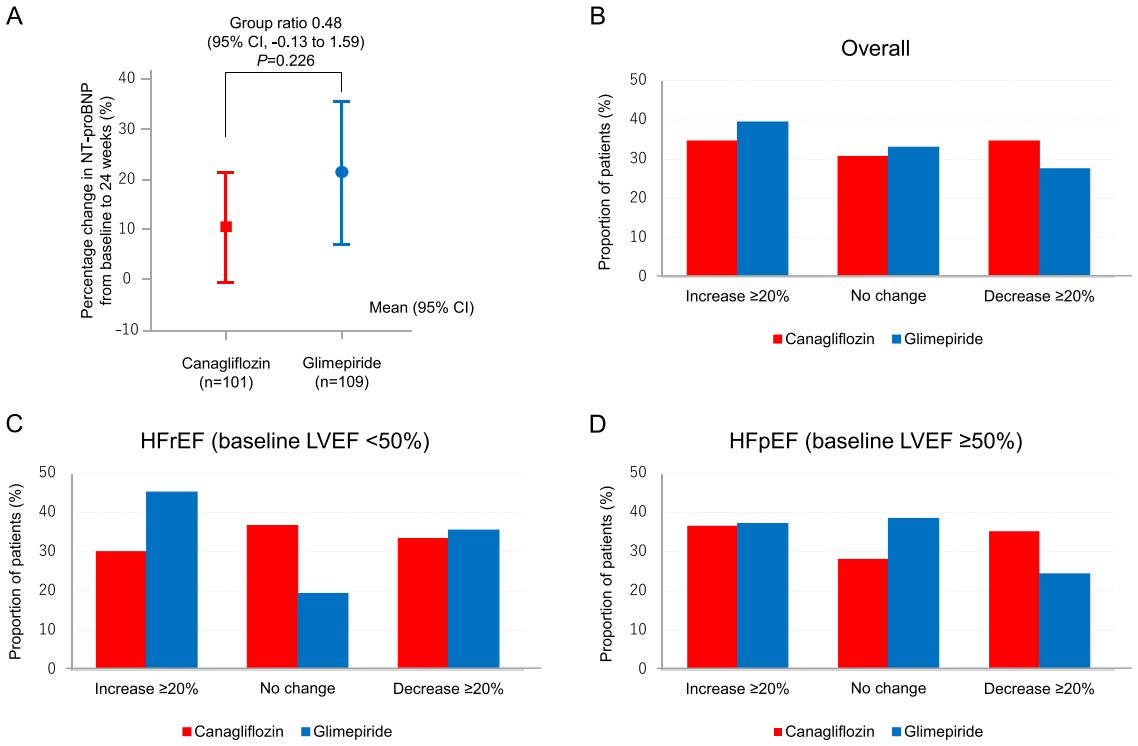

Figure 3 Adjusted mean change in NT-proBNP levels. (A) Adjusted mean change in NT-proBNP levels in all the patients and subgroups stratified according to baseline NT-proBNP levels. Detailed values and statistics are shown in *Table 2*. (B–C) Adjusted mean change in NT-proBNP levels and group differences (canagliflozin–glimepiride) in HFrEF (B) and HFpEF (C).

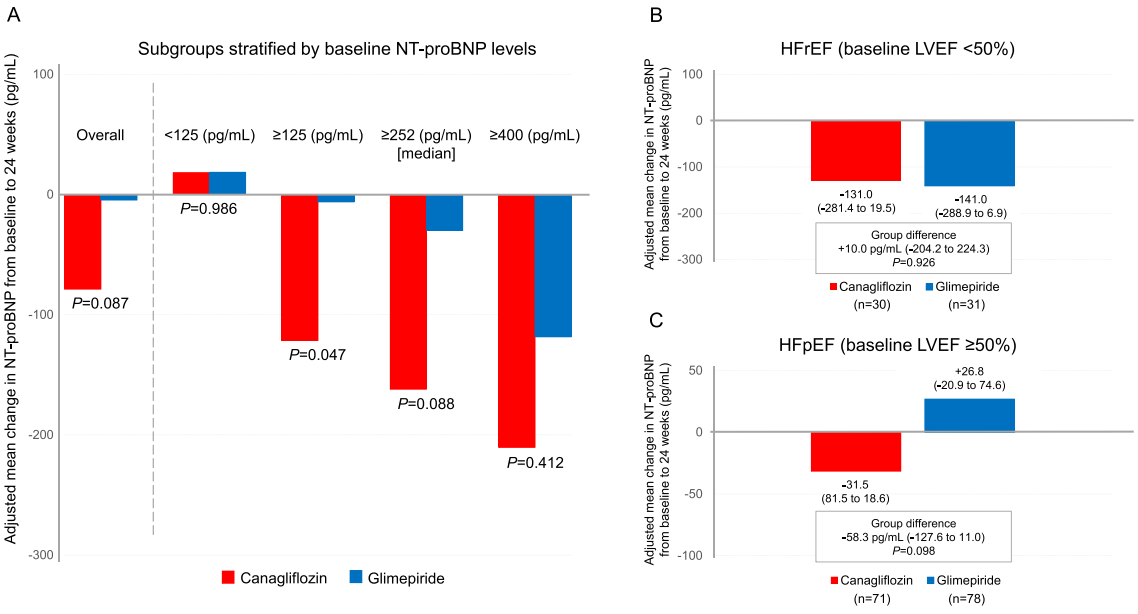

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Table 2 Adjusted mean changes in NT-proBNP from baseline to 24 weeks and group differences

Group	Treatment	*N*	Adjusted mean change from baseline to 24 weeks*	95% CI	Mean group difference (canagliflozin–glimepiride)	95% CI	*P* Value
Overall	Canagliflozin	101	−78.7	−139.9 to −17.5	−74.7	−159.3 to 10.9	0.087
	Glimepiride	109	−4.5	−63.4 to 54.4			
Baseline NT-proBNP <125 (pg/mL)	Canagliflozin	26	18.2	−2.6 to 39.1	−0.2	−27.8 to 27.3	0.986
	Glimepiride	35	18.5	0.5 to 36.5			
Baseline NT-proBNP ≥125 (pg/mL)	Canagliflozin	75	−121.5	−201.7 to −41.2	−115.4	−229.4 to −1.3	0.047
	Glimepiride	74	−6.1	−86.9 to 74.7			
Baseline NT-proBNP ≥252 (pg/mL)	Canagliflozin	52	−162.0	−270.7 to −53.3	−132.1	−284.3 to 20.1	0.088
	Glimepiride	55	−29.9	−135.6 to 75.8			
Baseline NT-proBNP ≥400 (pg/mL)	Canagliflozin	32	−210.4	−373.5 to −47.3	−92.0	−314.5 to 130.6	0.412
	Glimepiride	39	−118.4	−265.8 to 29.0			

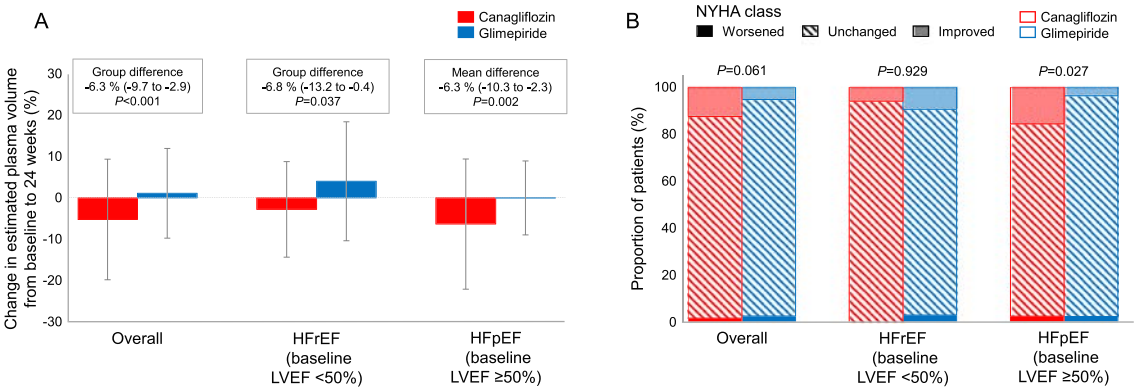
NT-proBNP, N-terminal pro-brain natriuretic peptide.
*Adjusted for corresponding baseline N-proBNP values.

were consistent across a broad spectrum of clinical characteristics, irrespective of baseline HF.[3] In our study, canagliflozin treatment, compared with glimepiride, reduced NT-proBNP in patients with elevated levels of NT-proBNP. In a recent substudy from the DECLARE-TIMI 58 trial,[17] dapagliflozin treatment also showed a significantly greater absolute risk reduction in cardiovascular death or hospitalization for HF in patients with higher baseline NT-proBNP levels [>75 pg/mL (median)]. This suggested SGLT2 inhibitors have greater clinical benefit in patients with elevated NT-proBNP levels irrespective of overt HF.

Few randomized clinical trials have to date investigated the effect of SGLT2 inhibitors on NT-proBNP as a measure of treatment impact on HF. Januzzi *et al*. first reported that canagliflozin slowed the rise in NT-proBNP, relative to placebo, over 2 years in older patients with T2D.[18] Because the baseline levels of NT-proBNP in those patients were markedly lower than patients in our trial, only a few patients with overt CHF were likely to have been enrolled in that study. More recently, the use of dapagliflozin over 12 weeks did not affect NT-proBNP levels in patients with HFrEF, although it increased the proportion of patients who experienced clinically meaningful improvements in HF-related health status or natriuretic peptides levels.[13] Nevertheless, the DAPA-HF trial in a similar population demonstrated that the risk of worsening HF or cardiovascular death was lower in the dapagliflozin group than placebo.[6] Therefore, despite having limited effects on NT-proBNP levels, SGLT2 inhibitors improved clinical outcomes in patients with HFrEF. These conflicting findings should be interpreted as indicating a possible disconnect between short-term changes in NT-proBNP levels and clinical outcomes.

A recent subanalysis from the CANVAS program showed a greater canagliflozin-mediated risk reduction in HFrEF events compared with that observed in HFpEF events.[19] Furthermore, in the DECLARE-TIMI 58 trial, dapagliflozin appeared to be more effective for reducing the risk of cardiovascular death and all-cause death in patients with HFrEF (LVEF <45%) at baseline compared with those without HFrEF.[20] These data suggest that the impact of SGLT2 inhibitors on cardiovascular outcomes differs according to HF phenotype, with patients with HFrEF being more affected by SGLT2 inhibitors than those with HFpEF. In our study, the adjusted mean reduction in NT-proBNP associated with canagliflozin treatment was also relatively smaller in patients with HFpEF compared with those with HFrEF. Interestingly, canagliflozin treatment reduced NT-proBNP levels more than glimepiride in patients with HFpEF, and more patients with HFpEF had improvement in NYHA status in the canagliflozin group compared with glimepiride. These findings suggest that patients with HFpEF can also benefit from SGLT2 inhibitors. However, whether or not SGLT2 inhibitors improve HF-related outcomes in HFpEF remains to be determined by ongoing clinical

Figure 4 Changes in ePV and NYHA Class. (A) Percentage changes in ePV between baseline and 24 weeks, calculated by the Strauss formula and the group differences (canagliflozin vs. glimepiride) in all the patients and those with HFrEF or HFpEF. (B) Proportion of patients who worsened, remained unchanged, or improved their NYHA class in all the patients and those with HFrEF or HFpEF.



trials. These trials will provide profound insights into the effects of SGLT2 inhibitors according to HF phenotypes.

The beneficial effects of SGLT2 inhibitors on risk reduction in HF-related outcomes are primarily thought to result from hemodynamic effects derived from glycosuria and natriuresis.[4] Specifically, SGLT2 inhibitor-induced reductions in body weight are likely to be associated with a subsequent reduction in other components, such as interstitial fluid and fat mass.[21] Regarding the effects on cardiac structure and function, Verma *et al*. found that short-term of empagliflozin treatment was associated with significant reduction in left ventricular mass indexed to body surface area and improvement of diastolic function in patients with T2D and established cardiovascular disease.[22,23] Interestingly, as shown in the sub-analysis from the EMPA-REG OUTCOME trial,[24] increased haematocrit might help to supply oxygen to peripheral tissues and mitigate HF-related symptoms. In our trial, canagliflozin treatment was also associated with hemoconcentration and a resultant decrease in ePV, suggesting potential clinical benefits in T2D patients with concomitant CHF. However, the detailed mechanisms by which SGLT2 inhibitors exert their beneficial effects on HF remain to be determined,[7] because of the recent striking findings from the DAPA-HF trial that showed a marked reduction in risk for HF-related outcomes even in patients with established HFrEF regardless of T2D.[6] Further studies to elucidate drug-specific pathophysiological protection against myocardial injury and cardiomyocyte death are therefore warranted.[25]

Limitations

First, the trial was an open-label design and not placebo controlled and accordingly there might have been bias towards the assessment of outcomes resulting from the investigators' choice of background treatment and subjective manner. Second, the analysis was not based on the intention-to-treat manner, and the sample size was small, and the relatively short follow-up period of 24 weeks may have limited the effects of the outcomes measured. Third, the CHF status at baseline was evaluated by local investigators based solely on the clinical manifestations and documented history of HF. Because we did not use cut-off levels of NT-proBNP to avoid unforeseen misdiagnosis of CHF, it was therefore difficult to exclude patients with low levels of NT-proBNP and further confirm baseline CHF status. Furthermore, no robust effects on HF-related parameters may have resulted as a consequence of the mild and stable CHF status at baseline. Fourth, natriuretic peptides have substantial biological and analytic variation, and outliers may have had a potential influence on the statistical analyses. Furthermore, the absolute value of natriuretic peptide levels in outpatients reflects the cardiac load because of the latest activity rather than the state of CHF, and therefore, this value does not necessarily reflect the severity of CHF. It might also have been insufficient to evaluate the therapeutic impact of the study drugs on CHF at only one study visit, thereby limiting the use of biomarkers as a surrogate endpoint in relevant clinical trials.[26] Finally, because the trial included only Japanese patients, we cannot generalize the findings to other ethnicities. Moreover, the dose of canagliflozin used was limited to 100 mg daily.

Conclusions

The present study did not meet the predefined primary endpoint with respect to the percentage change in NT-proBNP levels, with 24 weeks of canagliflozin treatment, relative to glimepiride, showing no robust effects on NT-proBNP in patients with T2D and clinically stable CHF. Further research is warranted to determine whether patients with HF with preserved

ejection fraction, regardless of diabetes status, could potentially benefit from treatment with SGLT2 inhibitors.

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Conflict of interest

A.T. has received modest honoraria from Astellas, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Fukuda Denshi, MSD, Mitsubishi Tanabe, Novo Nordisk, Ono, Taisho Toyama, and Takeda research funding from GlaxoSmithKline. I.T. has received grants and personal fees from Mitsubishi Tanabe, AstraZeneca, Bristol-Myers Squibb, Bayer, Takeda, Daiichi Sankyo, Otsuka, MSD, Shionogi, Kowa, Sumitomo Dainippon, Boehringer Ingelheim, Mitsubishi Tanabe, and Mochida. H.T. has received grants from Omron Health Care, Asahi Calpis Wellness, Teijin, and Fukuda Denshi. M.S. has received grants and personal fees from Mitsubishi Tanabe, Takeda, Daiichi Sankyo, Astellas, Pfizer, Novartis, Boehringer Ingelheim, Bayer, MSD, Kowa, and AstraZeneca. S.U. has received grants from Kowa, Bristol-Myers Squibb, Bayer, honoraria from MSD, Boehringer Ingelheim, and Chugai. J.O. belongs to the endowed department of Fukuda Denshi. M.K. has received grants from Japanese government, Japan Heart Foundation, Japan Cardiovascular Research Foundation, Novartis, Nihon Kohden, and Kureha, grants and personal fees from Astellas, Pfizer, Ono, Mitsubishi Tanabe, and AstraZeneca, personal fees from Daiichi Sankyo. T.M. has received grants from Mitsubishi Tanabe, and Boehringer Ingelheim, personal fees from Mitsubishi Tanabe, Boehringer Ingelheim, Eli Lilly, AstraZeneca, Ono, and Kowa. K.N. has received grants from Mitsubishi Tanabe, during the conduct of the study; personal fees from MSD, Astellas, Amgen Astellas, AstraZeneca, Eli Lilly, Otsuka, Daiichi Sankyo, Takeda, Boehringer Ingelheim, Bayer, Pfizer, Ono, and Mitsubishi Tanabe, grants from Asahi Kasei, Astellas, Mitsubishi Tanabe, Teijin, Terumo, Boehringer Ingelheim, and Bayer, scholarship from Bayer, Daiichi Sankyo, Teijin, Astellas, Takeda, and Bristol-Myers Squibb. All other authors declare no competing interests.

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Supporting information

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

Method S1. Strauss formula.
Method S2. Evaluation criteria for clinical events.
Table S1. NT-proBN*P* values at baseline and 24 weeks in overall, HFrEF, and HFpEF.
Table S2. Binary outcomes of responder/non-responder analyses for patients treated with canagliflozin vs. glimepiride.
Table S3. Adjusted mean changes in NT-proBNP from baseline to 24 weeks and group differences in baseline-stratified subgroups with HFrEF and HFpEF.
Table S4. Changes in clinical and laboratory parameters of interest from baseline to 24 weeks.
Table S5. Changes in echocardiographic parameters at 24 weeks.
Table S6. Adjusted mean changes in MLHF total score from baseline to 24 weeks and group differences.
Table S7. Clinical and adverse events.

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