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Effect of canagliflozin on white blood cell counts in patients with type 2 diabetes and heart failure: A subanalysis of the randomized CANDLE trial

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ABSTRACT

Aims/Introduction: Clinical evidence is lacking about the influence of sodium–glucose cotransporter 2 inhibitors on white blood cell (WBC) counts, a commonly used and widely available marker of inflammation. The aim of the present analysis was to assess the effect of canagliflozin relative to glimepiride on WBC counts.

Materials and Methods: This was a post-hoc subanalysis of the CANDLE trial (Effects of Canagliflozin in Patients with Type 2 Diabetes and Chronic Heart Failure: A Randomized Trial; UMIN000017669), an investigator-initiated, multicenter, open-label, randomized, controlled trial. A total of 233 patients with type 2 diabetes and concomitant heart failure were randomly assigned to either canagliflozin (n = 113) or glimepiride (n = 120) treatment for 24 weeks. Overall, patient baseline characteristics were as follows: mean ± standard deviation age, 68.6 ± 10.1 years; hemoglobin A1c, 7.0 ± 0.9%; left ventricular ejection fraction, 56.7 ± 14.4%; and median N-terminal pro-brain natriuretic peptide, 252 pg/mL (interquartile range 96–563 pg/mL). The mean baseline WBC counts were 6704 cells/μL (95% confidence interval 6,362–7,047) in the canagliflozin group and 6322 cells/μL (95% confidence interval 5,991–6,654) in the glimepiride group. There were no significant differences between treatment groups in terms of changes in WBC counts from baseline to weeks 4 and 12. In contrast, a group difference (canagliflozin minus glimepiride) from baseline to week 24 was significant (mean difference − 456 cells/μL [95% confidence interval −774 to −139, P = 0.005]).

Conclusions: Our findings suggest that 24 weeks of treatment with canagliflozin, relative to glimepiride, reduced WBC counts in patients with type 2 diabetes and heart failure.

INTRODUCTION

Systemic and chronic inflammation is known to be a key driver of most cardiovascular disease (CVD), mainly through excessive oxidative stress and adverse remodeling of cardiovascular tissues[1–5]. Recent randomized clinical trials assessing the therapeutic effects of anti-inflammatory therapies with canakinumab and colchicine in patients with myocardial infarction demonstrated that those medications significantly reduced the risk of cardiovascular events[6,7] Thus, establishing new therapeutic strategies to target inflammation in CVD has attracted considerable attention[8–13].

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Inflammatory pathways are also known to play a pivotal role in the pathogenesis of heart failure (HF)[14–16]. Elevated circulating levels of several pro-inflammatory cytokines, such as those in the interleukin family and tumor necrosis factor-alpha, are associated with the severity of HF[17]. Furthermore, a high white blood cell (WBC) count could predict the incidence of HF and/or adverse outcomes in population-based studies[18,19], in patients with coronary artery disease[20], and in patients with existing HF[21,22]. However, to date no randomized clinical trial shows any apparent clinical benefit of anti-inflammatory therapies, specifically in patients with HF[16]; accordingly, therapeutic strategies targeting inflammation in HF are yet to be established.

In keeping with the accumulated evidence from the recent cardiovascular outcome trials (CVOT)[23,24], sodium–glucose cotransporter 2 (SGLT2) inhibitors – originally approved as a glucose-lowering agent – have emerged as a newer pillar of HF medication. However, the precise mechanism(s) underpinning the therapeutic effects of SGLT2 inhibitors in HF are not fully understood, nor is their influence on markers of inflammation in the setting of clinical care certain. Therefore, we investigated the effects of canagliflozin, a SGLT2 inhibitor, on WBC counts using data obtained from the CANDLE trial (Effects of Canagliflozin in Patients with Type 2 Diabetes and Chronic Heart Failure: A Randomized Trial; UMIN000017669) for patients with type 2 diabetes and concomitant HF[25].

MATERIALS AND METHODS

Study design and participants

This report was a post-hoc subanalysis of the CANDLE trial, an investigator-initiated, multicenter, prospective, randomized, open-label clinical trial primarily designed to assess the effects of 24 weeks of add-on canagliflozin treatment versus glimepiride on *N*-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations in patients with type 2 diabetes and concomitant chronic HF[25]. Details of the original study design and participant eligibility criteria have been reported previously[26]. Briefly, eligible participants were adults with type 2 diabetes and chronic HF – excluding those with New York Heart Association (NYHA) class IV – who were clinically stable 4 weeks before study enrollment. Key exclusion criteria included severe renal dysfunction (estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m^2 or on dialysis), malnutrition, those in the perioperative period at the time of screening visit, severe infection or trauma at trial screening, a malignancy, or a recent history of CVD within 3 months before screening. Using a Web-based minimization method balanced for age (<65, ≥65 years), hemoglobin A1c (HbA1c) level (<6.5%, ≥6.5%) and left ventricular ejection fraction (<40%, ≥40%) at the time of screening, eligible participants were assigned randomly to either canagliflozin (100 mg daily) or glimepiride (starting dose 0.5 mg daily) treatment groups. All participants received the study treatment for 24 weeks, and were managed in accordance with local guidelines for type 2 diabetes and chronic HF. In the glimepiride group, increases in the dose of this agent were allowed for individuals according to their glycemic management and the investigator's judgment. The background medications of participants were, in principle and if possible, maintained during the study within clinically permissible ranges.

The CANDLE trial was approved by the institutional review boards of the individual sites and carried out in accordance with the Declaration of Helsinki. All participants provided written, informed consent before screening and randomization.

Measurements and end-points

The details of the original outcome measures in the CANDLE trial have been described previously[26]. In brief, vital signs were recorded, and blood samples were collected at baseline and at weeks 4, 12 and 24. WBC counts and other routine laboratory parameters were measured at each local site. Specific biomarkers, NT-proBNP, high-sensitivity C-reactive protein (hs-CRP) and high-sensitivity troponin I were measured at baseline and week 24 in a blinded manner at central commercial laboratories (NT-proBNP and hs-CRP at SRL Inc., Tokyo, Japan; high-sensitivity troponin I at Abbott Japan, Tokyo, Japan).

Statistical analysis

Analyses were carried out based on the full analysis set, which included all participants who received at least one dose of the study treatment during the study period and did not have any serious violation of the study protocol. The baseline demographics and clinical characteristics are expressed as numbers (%) for categorical variables, and as means ± standard deviation, median [interquartile range] or mean (95% confidence interval [CI]) for continuous variables. Mean WBC counts with 95% CIs at weeks 4, 12 and 24 were analyzed using a linear mixed model and compared between treatment groups. The consistency of the treatment effect on WBC counts was examined across subgroups stratified according to demographics and baseline clinical characteristics of interest. Some clinical factors associated with a change in WBC counts in the canagliflozin group were assessed by calculating Pearson's correlation coefficients. To investigate the influence of baseline WBC counts on treatment effects for clinical parameters of interest (body mass index [BMI], HbA1c, NT-proBNP and eGFR) at 24 weeks, data were analyzed using linear regression models in subgroups according to baseline WBC counts. NT-proBNP concentrations were expressed as a geometric mean (95% CI), and the proportional changes from baseline to week 24 were estimated using a natural logarithmic scale[27]. The effect of treatment on the NYHA class was analyzed using Wilcoxon rank-sum tests in subgroups according to baseline WBC counts. A *P*-value for the interaction between the treatment and baseline WBC count category on the NYHA class was calculated using an ordinal logistic regression model analysis. All statistical analyses were carried out using R software, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) at a two-sided significance level of 0.05. No adjustments for multiplicity were considered in the present analyses.

RESULTS

Baseline demographics and clinical characteristics

The flow of participants in the CANDLE trial has been reported previously[25]. Briefly, a total of 245 participants were randomly assigned to the canagliflozin group (n = 122) or the glimepiride group (n = 123), and the full analysis set comprised 113 and 120 patients, respectively. The baseline demographics and clinical characteristics for the present analysis were almost balanced between treatment groups and are shown in Table 1. Overall, baseline mean ± standard deviation values were 7.0 ± 0.9% for HbA1c and 56.7 ± 14.4% for left ventricular ejection fraction, and median (interquartile range [IQR]) results were 686 ng/mL (IQR 302–1,680 ng/mL) for hs-CRP, 5.4 pg/mL (IQR 3.3–10.8 pg/mL) for high-sensitivity troponin I and 252 pg/mL (IQR 96–563 pg/mL) for NT-proBNP. Before enrollment, 85 patients (36.5%) were not receiving any glucose-lowering agents, and >70% of all patients were receiving renin–angiotensin–aldosterone system blockers or beta-blockers.

Effect of treatments on WBC counts

The changes in WBC counts from baseline to weeks 4, 12 and 24 are shown in Figure 1 and Table S1. The mean baseline WBC counts were 6,704 cells/μL (95% CI 6,362–7,047) in the canagliflozin group, and 6,322 cells/μL (95% CI 5,991–6,654) in

Table 1 | Baseline demographic and clinical characteristics

Variables	Overall (n = 233)	Canagliflozin (n = 113)	Glimepiride (n = 120)
Age (years)	68.6 ± 10.1	68.3 ± 9.8	68.9 ± 10.4
Women	59 (25.3)	25 (22.1)	34 (28.3)
BMI (kg/m^2)	25.5 ± 3.9	25.3 ± 3.6	25.7 ± 4.2
HbA1c (%)	7.0 ± 0.9	6.9 ± 0.7	7.1 ± 0.9
eGFR (mL/min/1.73 m^2)	63.7 ± 15.1	64.1 ± 15.3	63.3 ± 14.9
<60 mL/min/1.73 m^2	125 (53.9)	65 (57.5)	60 (50.4)
hs-CRP (ng/mL)	686.0 [302.0–1680.0]	760.5 [278.0–1820.0]	663.0 [309.5–1340.0]
LVEF (%)	56.7 ± 14.4	56.7 ± 14.5	56.6 ± 14.4
<50%	67 (28.9)	34 (30.4)	33 (27.5)
hs-TnI (pg/mL)	5.4 [3.3–10.8]	5.4 [3.4–10.75]	5.4 [3.1–10.75]
NT-proBNP (pg/mL)	252.0 [96.0–563.0]	245.5 [113.0–519.75]	263.0 [82.5–651.0]
NYHA class			
I	148 (63.5)	72 (63.7)	76 (63.3)
II	79 (33.9)	39 (34.5)	40 (33.3)
III	5 (2.1)	2 (1.8)	3 (2.5)
Unknown	1 (0.4)	0	1 (0.8)
Complications			
Hypertension	102 (43.8)	49 (43.4)	53 (44.2)
Dyslipidemia	100 (42.9)	46 (40.7)	54 (45.0)
Myocardial infarction	56 (24.0)	32 (28.3)	24 (20.0)
Smoking status			
Current smoker	32 (13.7)	19 (16.8)	13 (10.8)
Past smoker	98 (42.1)	47 (41.6)	51 (42.5)
Never	103 (44.2)	47 (41.6)	56 (46.7)
Medication for T2D			
Insulin	7 (3.0)	4 (3.5)	3 (2.5)
Metformin	44 (18.9)	18 (15.9)	26 (21.7)
DPP-4 inhibitor	127 (54.5)	64 (56.6)	63 (52.5)
Others	41 (17.6)	16 (14.2)	25 (20.8)
Medication-naïve	85 (36.5)	39 (34.5)	46 (38.3)
Medication for HF			
ACE inhibitor or ARB	177 (76.0)	89 (78.8)	88 (73.3)
Beta-blocker	164 (70.4)	82 (72.6)	82 (68.3)
MRA	86 (36.9)	42 (37.2)	44 (36.7)
Diuretic	99 (42.5)	46 (40.7)	53 (44.2)
Digitalis	20 (8.6)	12 (10.6)	8 (6.7)

Data are mean ± standard deviation, median [interquartile range], or n (%). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; hs-TnI, high-sensitivity troponin I; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; T2D, type 2 diabetes.

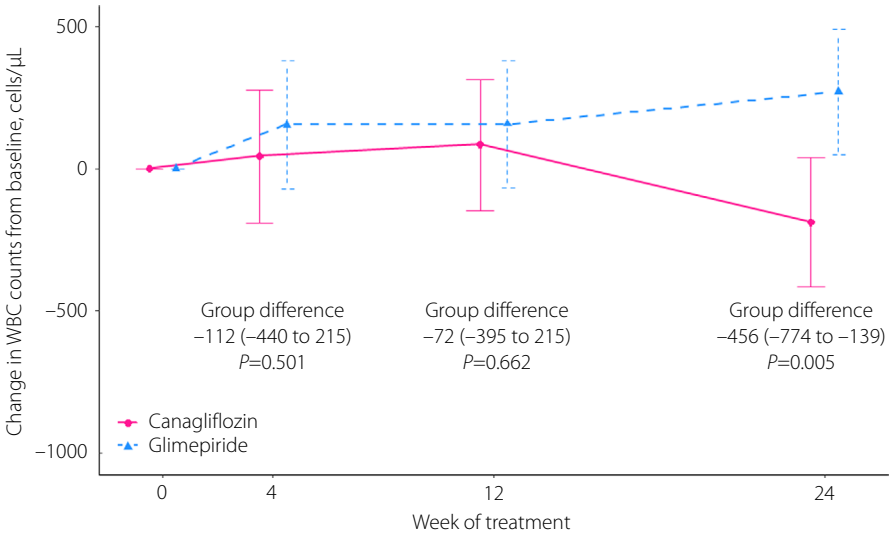

Figure 1 | Changes in white blood cell (WBC) counts from baseline to weeks 4, 12 and 24. The data are expressed as the mean group difference (canagliflozin minus glimepiride) with the 95% confidence interval.

the glimepiride group. There were no significant differences in the changes in WBC counts from baseline to weeks 4 and 12. In contrast, significant differences from baseline to week 24 were observed (Figure 1), and the difference from week 12 to week 24 was also significant (mean group difference − 384 cells/μL, 95% CI −725 to −44; $P = 0.027$).

The effect of canagliflozin relative to glimepiride on the WBC counts was mostly consistent across the subgroups stratified by baseline clinical characteristics, including diabetes, HF and smoking statuses (Figure 2). Of interest, the reduction in WBC counts in the subgroups with a median WBC count of ≥6,275 cells/μL and baseline use of diuretic was numerically greater than that in each opposite subgroup, although the *P* values (0.072 and 0.068) for the interaction were non-significant.

A group ratio (canagliflozin vs glimepiride) of proportional changes from baseline to week 24 in the geometric means of hs-CRP concentration was 0.973 (95% CI 0.665–1.424; $P = 0.887$).

Correlations between changes in the WBC counts and clinical parameters

Pearson's correlations between changes in the WBC count and clinical parameters of interest from baseline to week 24 are shown for the canagliflozin group (Table S2) and for the glimepiride group (Table S3). In the canagliflozin group, changes in the WBC count were positively associated with the concentration of triglycerides and hs-CRPs (Figure 3). These associations were also observed in the glimepiride group. In contrast, there were no significant associations between changes in the WBC counts and other clinical variables examined in both treatment groups.

Effect of baseline WBC count on changes in clinical measures

Changes from baseline to week 24 for clinical measures of interest (BMI, HbA1c, NT-proBNP and eGFR) in a subgroup according to the baseline WBC count (median 6,275 cells/μL) are shown in Table S4. The treatment effects on BMI, HbA1c and NT-proBNP were consistent between subgroups with baseline WBC counts <6,275 and ≥6,275 cells/μL. Although a reduction in the eGFR was more apparent in the subgroups with a baseline WBC count <6,275 cells/μL as opposed to ≥6,275 cells/μL, the interaction was non-significant ($P = 0.070$).

Categorical changes in the NYHA class at week 24, according to the median WBC count, are shown in Figure 4. A significant difference in the changes of the NYHA class between treatment groups was only observed in the subgroup with the low WBC count at baseline; however, the interaction between the treatment and baseline WBC count category was non-significant ($P = 0.169$).

DISCUSSION

To the best of our knowledge, this is the first report to assess the clinical effects of a SGLT2 inhibitor on WBC count, and show that add-on canagliflozin, relative to glimepiride, reduces the WBC count in patients with HF and type 2 diabetes, suggesting an anti-inflammatory effect of canagliflozin treatment. Although this observation might be partly related to the clinical benefit observed in recent CVOTs with SGLT2 inhibitors, the actual influence of canagliflozin-induced WBC count-lowering on the pathogenesis of HF itself remains uncertain. Additionally, the absolute changes in WBC counts were modest, and the relationship between those changes and clinical outcomes was not assessed in the present study. Thus, the present findings might still be hypothesis-generating; therefore, further

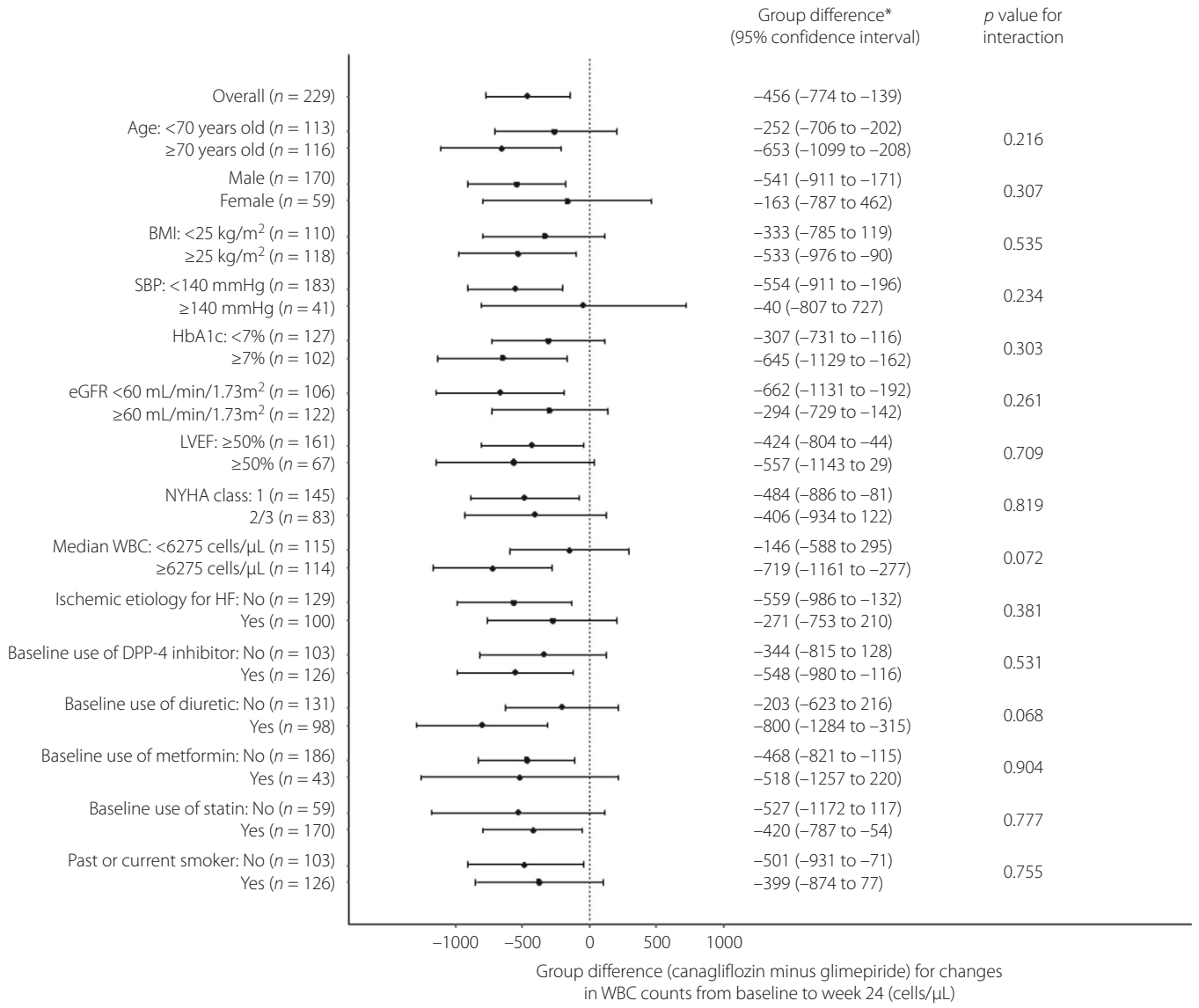

Figure 2 | Subgroup analysis of the change in white blood cell (WBC) counts at week 24. *Canagliflozin minus glimepiride. BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; T2D, type 2 diabetes, WBC white blood cell.

studies are required to validate our findings and assess their significance in HF therapy.

The inflammation pathway is one of the key and seminal pathophysiological players in disease development and progression across a wide spectrum of disease entities. Inflammation is also associated with complications and adverse outcomes. Even a low-grade inflammatory status and/or exposure to chronic inflammation can deteriorate the biological homeostasis and result in age-dependent disease, metabolic syndrome and CVD[28–31]. Thus, inflammation has been recognized as both a marker of risk for CVD and a therapeutic target[1,8,9,11,13,32], and accordingly, several clinical trials have examined the effect of anti-inflammatory therapy on cardiovascular outcomes[6,7].

Inflammation also contributes to the pathogenesis of HF[16], particularly in patients with HF and a preserved ejection fraction that is often characterized by the presence of inflammation-related multimorbidities, such as obesity and diabetes, and a subsequent systemic pro-inflammatory state[33]. In such a HF setting, in addition to activation of neurohumoral factors, excess inflammation and oxidative stress are co-induced. This forms a vicious cycle that accelerates the left ventricular remodeling and impairs the cardiac functional reserves, resulting in a poor prognosis. Although pharmacological

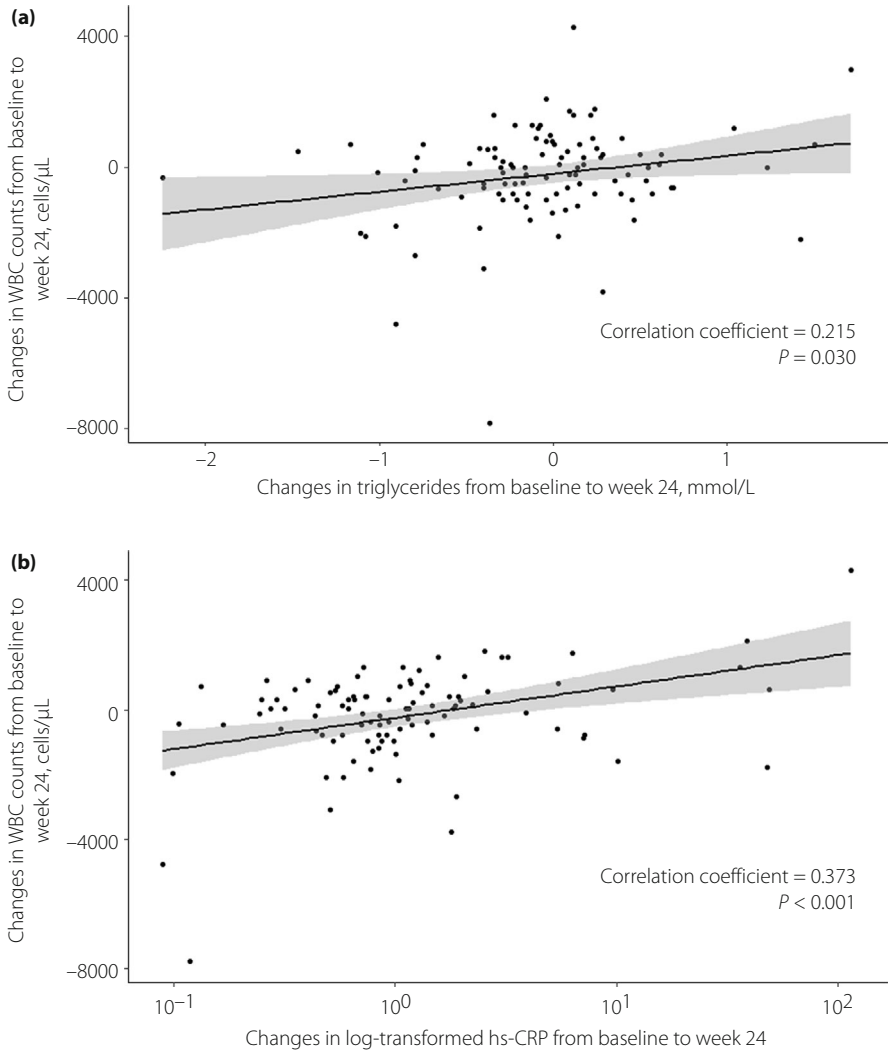

Figure 3 | Correlations with changes in white blood cell (WBC) counts at week 24 in the canagliflozin treatment group. Scatterplot detailing the correlation between changes in WBC counts from baseline to week 24 and corresponding changes in (a) triglycerides and (b) log-transformed high-sensitivity C-reactive protein (hs-CRP) concentrations.

interventions against activated neurohumoral factors have been established as a standard therapy for HF, little evidence of anti-inflammatory therapies specific to HF are currently available[16]. This scenario is indicative of one of the current unmet needs in HF care.

In recent CVOTs, the use of SGLT2 inhibitors consistently reduced the risk of HF worsening to the extent that hospitalization was required and/or cardiovascular death occurred in patients with a wide spectrum of CVD risk, irrespective of their diabetes and HF status[23,24,34]. Given the immediate diuretic effect of SGLT inhibitors through natriuresis, regulation of the excess fluid volume likely contributes to the early clinical benefit that precludes the worsening of HF events[35–37]. However, the precise mechanisms underpinning the medium- to long-term clinical benefits of SGLT2 inhibitors remain uncertain, and their clinical influence on inflammatory pathways/markers and their associations with clinical outcomes are also poorly understood. Although a number of experimental studies have shown the anti-inflammatory actions of SGLT2 inhibitors, limited clinical data are currently available to be able to elucidate their effect on inflammatory markers[38]. In a post-hoc exploratory analysis of the Canagliflozin Treatment and Trial Analysis versus Sulfonylurea (CANTATA-SU) study[39], 52 weeks of canagliflozin treatment (300 mg daily) relative to glimepiride in patients with type 2 diabetes increased serum adiponectin levels, and decreased serum concentrations of leptin and biomarkers of inflammation, such as interleukin-6 and tumor necrosis factor-alpha, suggesting beneficial effects of canagliflozin on adipose tissue function and insulin sensitivity. Importantly, because no inflammation-related markers were measured

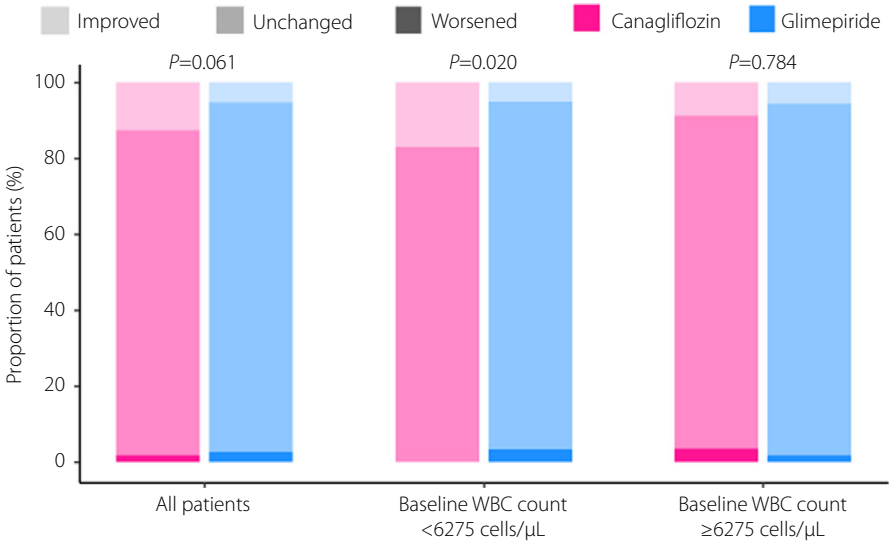

Figure 4 | Changes from baseline in New York Heart Association class at week 24 in subgroups stratified by the baseline median white blood cell (WBC) count. All *P* values were for the comparisons between treatment groups.

in the recent CVOTs with SGLT2 inhibitors, the extent to which potential anti-inflammatory effects influence the prognostic role of SGLT2 inhibitors remains unclear.

In patients with HF, neutrophils activated by chronic inflammation play pivotal roles in the maladaptive recruitment of immune cells and further promote proinflammatory responses in the cardiovascular systems[40]. Total neutrophil count and the neutrophil/lymphocyte ratio are known to be associated with the presence of HF and adverse outcome in patients with HF[40]. WBC counts are among the most convenient and widely used inflammatory biomarkers in clinical practice, and high WBC counts can also predict hospitalization for HF in patients with type 2 diabetes and coronary artery disease[20], as well as adverse outcomes, particularly in patients with HF and a preserved ejection fraction[21,22]. Thus, WBC counts are a predictive marker and a potential surrogate maker of HF treatment. However, no studies have examined the clinical effectiveness of HF treatment based on WBC counts, and its clinical significance has not been established.

Few data are currently available from which the effects of SGLT2 inhibitors on leukocyte lineage can be elucidated in patients with HF, whereas several reports exist about the effects of SGLT2 inhibitors on erythropoiesis primarily caused by an immediate increase in serum erythropoietin concentrations[41–43]. The direct effects of SGLT2 inhibitors on bone marrow, and the production, differentiation and maturation of the leukocyte lineage also continues to be poorly understood. Recently, an observation study for patients with type 2 diabetes and acute myocardial infarction undergoing percutaneous coronary intervention showed that levels of some leukocyte-related indices, such as WBC and neutrophils counts, and neutrophil/lymphocyte ratio, in the SGLT2 inhibitor users were lower than those in the non-SGLT2 inhibitor users, and SGLT2 inhibitor use was associated with reduced inflammatory response and smaller infarct size[44]. In contrast, off-label use of a SGLT2 inhibitor empagliflozin was reported to improve neutropenia and neutrophil dysfunction in the rare inherited metabolic disorder glycogen storage disease type Ib[45,46]. This favorable effect might be due to an increased urinary excretion of 1,5-anhydroglucitol through renal SGLT2 inhibition, which subsequently suppresses the accumulation of 1,5-anhydroglucitol-6-phosphate within neutrophils seen in patients with glycogen storage disease type Ib[45]. These results suggest that the effects of SGLT2 inhibitor on neutrophils vary largely depending on the pathophysiology of the medical conditions.

In our present analysis, the reduction in WBC counts in the canagliflozin group exceeded those in the glimepiride group, and it was observed after week 12. In contrast, baseline WBC counts did not influence the effect of canagliflozin on clinical parameters, such as NT-proBNP and NYHA class. Given the positive association between changes in the WBC counts and hs-CRP concentrations, we speculated that the anti-inflammatory effects of canagliflozin treatment would exceed those with glimepiride treatment. At the same time, obesity is known to be one of the key contributors to elevate the WBC counts through inflammatory pathways[47]. In the CANDLE trial, the reductions in both bodyweight and BMI in the canagliflozin group were significantly larger than those in the glimepiride group[25,48]. Thus, the bodyweight loss by canagliflozin treatment might have partly affected the change in WBC counts, although there were no significant correlations between changes in BMI and WBC counts in the present analysis. Furthermore, the positive associations between changes in WBC counts and triglyceride and hs-CRP levels might be also partly

explained by the canagliflozin-induced bodyweight loss. In contrast, because there was no correlation of WBC counts with NT-proBNP concentrations, the potential for canagliflozin-induced WBC count-lowering on the pathogenesis of HF itself remains uncertain. We previously proposed the complex effects after SGLT2 inhibitor initiation, based on the biaxial effects of initial hemodynamic and subsequent metabolic actions[36]. Taken together, a reduction in WBC counts might represent a candidate mid-term marker reflecting the effects that follow initial hemodynamic actions immediately after SGLT2 inhibitor treatment, and longer-term observations might be required to elucidate the clinical significance of these effects.

The present analysis had several potential limitations. First, this was a post-hoc analysis of the CANDLE trial that was not designed or powered to assess the effect on WBC counts. Hence, the clinical significance of modest changes in WBC counts was uncertain, as is their relationship with outcomes. In addition, the reasons for the discrepancy between the effects of canagliflozin on WBC counts and hs-CRP concentrations are still unclear. Second, we have no data on WBC fractionation, including neutrophils and lymphocytes. Third, no detailed clinical information was available on comorbidities and events that might affect WBC counts during the follow-up period, although we implemented several exclusion criteria, such as patients in the perioperative period and with severe infection or trauma at the timing of screening to counteract this confounding aspect. In addition, urinary tract or genital infections were not observed in either group, and the frequency of other infectious diseases reported was similar in both groups (1.7% in the canagliflozin group and 1.6% in the glimepiride group)[25]. However, we were unable to exclude the possibility that other subclinical events affected WBC counts during the follow-up period. Finally, the patients with type 2 diabetes and HF (almost resembling the HF and a preserved ejection fraction phenotype) included in the CANDLE trial were clinically stable; therefore, it is uncertain whether the present findings are applicable to different clinical situations and patient populations.

In conclusion, the present findings suggest that 24 weeks of treatment with canagliflozin relative to glimepiride reduced WBC counts in patients with type 2 diabetes and HF. However, the clinical impact of that observation on the pathogenesis of HF and its prognosis remains uncertain, and thus the present findings might still be hypothesis-generating. Given that inflammation plays an important role in the pathogenesis of HF, further studies are required to validate the clinical effects of SGLT2 inhibitors on markers of inflammation and their significance in HF therapy.

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DISCLOSURE

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Approval of the research protocol: Approved by the institutional review boards of the individual sites.
Informed consent: All participants provided written, informed consent before screening and randomization.
Registry and the registration no. of the study/trial: 25 May 2015 (UMIN000017669).
Animal studies: N/A.

DATA AVAILABILITY STATEMENT

The datasets that support the findings of this study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

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

Table S1 | Changes in white blood cell counts at weeks 4, 12 and 24.

Table S2 | Pearson's correlations between changes in white blood cell counts and clinical parameters of interest from baseline to week 24 in the canagliflozin group.

Table S3 | Pearson's correlations between changes in white blood cell counts and clinical parameters of interest from baseline to week 24 in the glimepiride group.

Table S4 | Changes from baseline to week 24 in clinical measures of interest in subgroups stratified by median baseline white blood cell counts.