ORIGINAL RESEARCH

Canagliflozin improves risk factors of metabolic syndrome in patients with type 2 diabetes mellitus and metabolic syndrome

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Objective: Metabolic syndrome refers to a collection of risk factors associated with the development of cardiovascular disease and type 2 diabetes mellitus (T2DM). Canagliflozin, a sodium glucose co-transporter 2 inhibitor, improves glycemic control and reduces body weight and blood pressure (BP) in a broad range of patients with T2DM. This post hoc analysis assessed the effects of canagliflozin on the components of metabolic syndrome in patients with T2DM and metabolic syndrome.

Methods: This analysis was based on data from 2 head-to-head studies of canagliflozin in patients with T2DM on background metformin versus glimepiride (study 1) and background metformin plus sulfonylurea versus sitagliptin 100 mg (study 2). Changes from baseline in glycemic efficacy, anthropometric measures, BP, and lipids were evaluated with canagliflozin versus glimepiride and sitagliptin at week 52 in patients who met ≥2 of the criteria for metabolic syndrome (in addition to T2DM): triglycerides ≥1.7 mmol/L; high-density lipoprotein cholesterol (HDL-C) <1.0 mmol/L (men) or <1.3 mmol/L (women); waist circumference ≥102 cm (non-Asian men), ≥88 cm (non-Asian women), >90 cm (Asian men), or >80 cm (Asian women); diagnosis of hypertension or meeting BP-related criteria (systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg). Safety was assessed based on adverse event reports.

Results: In study 1, canagliflozin 100 and 300 mg provided similar and greater HbA1c reductions versus glimepiride, respectively. In study 2, canagliflozin 300 mg provided greater HbA1c lowering versus sitagliptin 100 mg. Canagliflozin also reduced fasting plasma glucose, body weight, body mass index, waist circumference, BP, and triglycerides, and increased HDL-C and low-density lipoprotein cholesterol versus glimepiride and sitagliptin. Canagliflozin was generally well tolerated in each study.

Conclusion: Canagliflozin was associated with improvements in all components of metabolic syndrome in patients with T2DM and metabolic syndrome, whereas glimepiride and sitagliptin only improved glycemic components over 52 weeks.

Keywords: canagliflozin, sodium glucose co-transporter 2, type 2 diabetes, metabolic syndrome

Introduction

Metabolic syndrome refers to a collection of risk factors associated with the development of cardiometabolic complications and type 2 diabetes mellitus (T2DM).[1] Criteria for the metabolic syndrome can vary, but typically include dyslipidemia (ie, increased triglycerides, reduced high-density lipoprotein cholesterol [HDL-C]), central obesity, hypertension, and glucose intolerance.[1,2] In the United States, the prevalence of metabolic syndrome has been estimated to be nearly 35% in adults, with a higher prevalence (~50%) in those aged ≥60 years.[3] Metabolic syndrome is also prevalent in Europe,

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affecting an estimated ~40%–80% of men and ~25%–65% of women, depending on criteria, age, and geographic region.[4]

Canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, increases urinary glucose excretion, leading to decreased plasma glucose levels and a net caloric loss in patients with T2DM.[5] Across phase 3 studies, canagliflozin improved glycemic control, body weight, and blood pressure (BP), and was generally well tolerated in a broad range of patients with T2DM.[6–23] In head-to-head trials, canagliflozin 300 mg demonstrated superiority in HbA1c lowering versus glimepiride as add-on to metformin[20] and versus sitagliptin 100 mg as add-on to metformin or metformin plus sulfonyl-urea at 52 weeks.[8,22] Canagliflozin also provided statistically significant reductions in body weight and BP compared with glimepiride and sitagliptin.[8,20,22] The improvements in HbA1c, body weight, and BP seen with canagliflozin sug-gest that it may be an effective treatment for improving the components of metabolic syndrome in patients with T2DM. The present analysis evaluated the effects of canagliflozin versus glimepiride and sitagliptin in patients with T2DM and metabolic syndrome.

Methods
Study design and patient populations

This post hoc analysis was based on data from 2 random-ized, double-blind, head-to-head, phase 3 studies that evaluated the efficacy and safety of canagliflozin in patients with T2DM. In study 1 (ClinicalTrials.gov identifier: NCT00968812), patients (N=1,450) received canagliflozin 100 or 300 mg or glimepiride as add-on to metformin for a 52-week core treatment period, followed by a 52-week extension period;[20,21] the current analysis was based on data from the 52-week core treatment period. In study 2 (ClinicalTrials.gov identifier: NCT01137812), patients (N=755) received canagliflozin 300 mg or sitagliptin 100 mg as add-on to metformin plus sulfonylurea for a 52-week core treatment period.[22] Details of the individual study designs and results have been published previously.[20,22]

The effects of canagliflozin versus glimepiride and sitagliptin on the components of metabolic syndrome were assessed in the subset of patients from each study who met ≥2 of the following criteria for metabolic syndrome (in addition to T2DM);[1,2] triglycerides ≥1.7 mmol/L; HDL-C <1.0 mmol/L in men or <1.3 mmol/L in women; waist cir-cumference ≥102 cm (non-Asian men), ≥88 cm (non-Asian women), >90 cm (Asian men), or >80 cm (Asian women); diagnosis of hypertension or meeting BP-related criteria (systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg).

The studies included in this analysis were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and followed Good Clinical Prac-tice and applicable regulatory requirements. Approval was obtained from institutional review boards and independent ethics committees for each participating center. Participants provided informed written consent prior to enrollment in the studies.

Endpoints/assessments

Changes from baseline in glycemic parameters (HbA1c and fasting plasma glucose [FPG]), anthropometric parameters (body weight, body mass index [BMI], and waist circumfer-ence), BP (systolic and diastolic), and lipids (low-density lipoprotein cholesterol [LDL-C], HDL-C, and triglycerides) were assessed at week 52. Safety and tolerability were assessed based on adverse event (AE) reports in the overall population of each study (not the subset of patients with metabolic syndrome), as the majority of patients in each study had metabolic syndrome.

Statistical analyses

Data were from the modified intent-to-treat (mITT) popula-tion, which consisted of all randomized patients who received ≥1 dose of study drug. The last observation carried forward (LOCF) approach was used to impute missing data. Efficacy endpoints were analyzed using an analysis of covariance model, with treatment, stratification factor, and frequently sampled mixed-meal tolerance test (study 2 only) as fixed effects and the corresponding baseline value as a covariate. Least squares mean differences and 2-sided 95% confidence intervals were estimated for the comparisons of canagliflozin versus glimepiride or sitagliptin. Statistical comparison of canagliflozin versus glimepiride or sitagliptin was not prespecified for these post hoc analyses; therefore, *P* values are not reported.

Results
Patients

At baseline, 81% (n=1,169) of 1,450 randomized patients with T2DM in study 1 and 78% (n=586) of the 755 ran-domized patients with T2DM in study 2 met the criteria for metabolic syndrome; proportions were similar across treatment groups in each study (study 1: 82%, 82%, and 79% with canagliflozin 100 and 300 mg and glimepiride, respectively; study 2: 77% and 79% with canagliflozin 300 mg and sitagliptin 100 mg, respectively). Baseline demographic characteristics were generally balanced across

Table 1 Baseline demographic characteristics of patients who met the criteria for metabolic syndrome

Characteristics	Study 1			Study 2	
	GLIM (n=379)	CANA 100 mg (n=394)	CANA 300 mg (n=396)	SITA 100 mg (n=297)	CANA 300 mg (n=289)
Mean (SD) age, year	56.1 (8.9)	56.3 (9.5)	55.9 (9.4)	56.6 (8.7)	56.9 (9.9)
Sex, n (%)[a]					
Male	182 (48)	199 (51)	187 (47)	165 (56)	150 (52)
Female	197 (52)	195 (50)	209 (53)	132 (44)	139 (48)
Race, n (%)					
White	266 (70)	277 (70)	283 (72)	199 (67)	196 (68)
Black or African American	18 (5)	17 (4)	13 (3)	32 (11)	26 (9)
Asian	60 (16)	69 (18)	72 (18)	45 (15)	50 (17)
Other[b]	35 (9)	31 (8)	28 (7)	21 (7)	17 (6)
Ethnicity, n (%)[a]					
Hispanic/Latino	61 (16)	63 (16)	54 (14)	56 (19)	60 (21)
Not Hispanic/Latino	316 (83)	329 (84)	341 (86)	240 (81)	229 (79)
Other[c]	2 (0.5)	2 (0.5)	1 (0.3)	1 (0.3)	0

Notes: [a]Percentages may not total to 100% due to rounding. [b]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, and other (study 1) and American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported (study 2). [c]Includes not reported and unknown.
Abbreviations: CANA, canagliflozin; GLIM, glimepiride; SD, standard deviation; SITA, sitagliptin.

groups in the subset of patients with metabolic syndrome in each study (Table 1).

Efficacy

In study 1, canagliflozin 100 and 300 mg were associated with similar and greater reductions in HbA1c, respectively, and greater reductions in FPG compared with glimepiride at week 52 (Figure 1A). Relative to glimepiride, canagliflozin 100 and 300 mg also provided greater reductions in body weight, BMI, and waist circumference (Figure 2A), and systolic BP and diastolic BP (Figure 3A). Canagliflozin 100 and 300 mg were associated with larger increases in HDL-C and LDL-C versus glimepiride at 52 weeks; numeric reductions in triglycerides were seen with canagliflozin 100 and 300 mg relative to glimepiride (Figure 4A). After 52 weeks, the proportion of patients who met the criteria for metabolic syndrome diagnosis was 87%, 86%, and 93% in the canagliflozin 100 mg, canagliflozin 300 mg, and glimepiride groups, respectively.

In study 2, canagliflozin 300 mg provided greater reductions in HbA1c and FPG versus sitagliptin 100 mg at 52 weeks (Figure 1B). Treatment with canagliflozin 300 mg versus sitagliptin 100 mg was also associated with greater reductions in body weight, BMI, and waist circumference (Figure 2B), and systolic BP and diastolic BP (Figure 3B). Increases in HDL-C and LDL-C and reductions in triglycerides were seen with canagliflozin 300 mg versus sitagliptin 100 mg (Figure 4B). The proportion of patients who met

the criteria for metabolic syndrome at 52 weeks was 89% in the canagliflozin 300 mg group and 95% in the sitagliptin 100 mg group.

Safety

As the proportion of patients with metabolic syndrome was nearly 80% in each study, safety was assessed in the overall population of each study rather than in the subset of patients with metabolic syndrome. Canagliflozin was generally well tolerated in both studies, with a higher incidence of AEs related to the mechanism of SGLT2 inhibition (eg, genital mycotic infections, osmotic diuresis–related AEs).[20,22] In study 1, the overall incidence of AEs was 64.4%, 68.5%, and 68.5% with canagliflozin 100 and 300 mg and glimepiride, respectively, at week 52.[20] Incidences of genital mycotic infections (male: 6.7% and 8.3% vs 1.1%; female: 11.3% and 13.9% vs 2.3%), urinary tract infections (6.4% and 6.4% vs 4.6%), and osmotic diuresis–related AEs (5.6% and 6.2% vs 1.7%) were higher with canagliflozin 100 and 300 mg compared with glimepiride.[20,24] In addition, the incidence of documented hypoglycemia was significantly lower with canagliflozin 100 and 300 mg versus glimepiride (5.6% and 4.9% vs 34.2%).[20]

In study 2, the overall incidence of AEs was 76.7% and 77.5% with canagliflozin 300 mg and sitagliptin 100 mg, respectively.[22] Incidences of genital mycotic infections (male: 9.2% vs 0.5%; female: 15.3% vs 4.3%) and osmotic diuresis–related AEs (5.0% vs 2.4%) were higher with
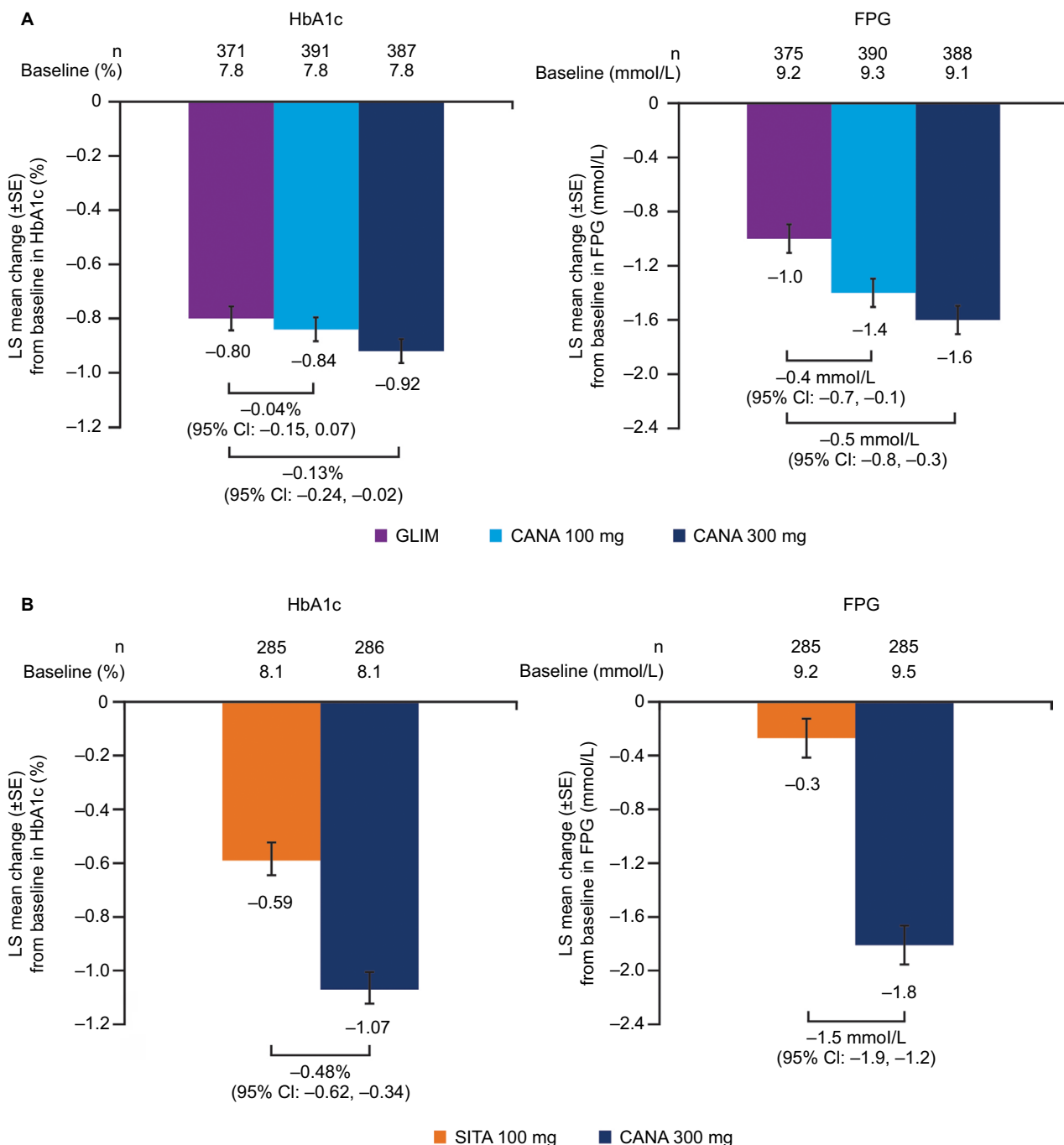
A

B

Figure 1 Effects on glycemic efficacy at week 52 in (**A**) study 1 and (**B**) study 2.
Abbreviations: CANA, canagliflozin; CI, confidence interval; FPG, fasting plasma glucose; GLIM, glimepiride; LS, least squares; SE, standard error; SITA, sitagliptin.

canagliflozin 300 mg compared with sitagliptin 100 mg, whereas the incidence of urinary tract infections was similar between groups (4.0% vs 5.6%).[22] When added to a background of metformin and sulfonylurea, the incidence of documented hypoglycemia was similar with canagliflozin 300 mg and sitagliptin 100 mg (43.2% vs 40.7%), despite the larger reduction in HbA1c with canagliflozin in the overall study population.

Discussion

Canagliflozin improved all components of metabolic syndrome (glycemic control, BP, anthropometric measures, and dyslipidemia) in patients with T2DM and metabolic syndrome in both studies. Glycemic improvements were also seen with glimepiride and sitagliptin, albeit to a lesser extent than those seen with canagliflozin. Furthermore, neither glimepiride nor sitagliptin showed meaningful
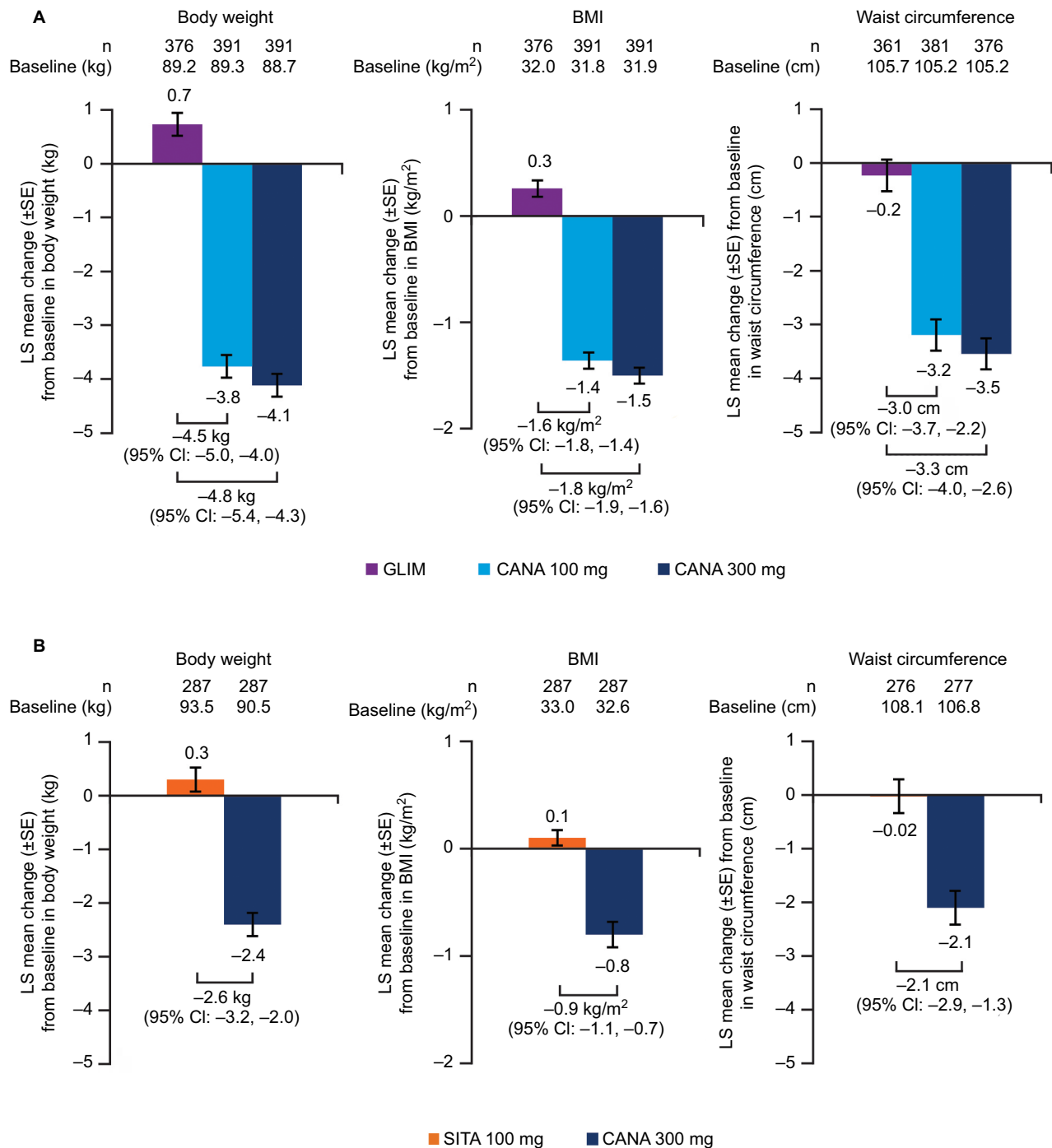
A

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Figure 2 Effects on anthropometric measures at week 52 in (**A**) study 1 and (**B**) study 2.
Abbreviations: BMI, body mass index; CANA, canagliflozin; CI, confidence interval; GLIM, glimepiride; LS, least squares; SE, standard error; SITA, sitagliptin.

improvements in any of the other components of metabolic syndrome. Canagliflozin was generally well tolerated, with an increased incidence of AEs related to the mechanism of SGLT2 inhibition (ie, genital mycotic infections, osmotic diuresis–related AEs) in both studies.

The observed results are likely attributable to the mechanism of action for canagliflozin versus sitagliptin or glimepiride. By inhibiting SGLT2, canagliflozin increases urinary glucose excretion in an insulin-independent manner, thereby lowering plasma glucose levels and resulting in a mild osmotic diuresis and net caloric loss.[25] Consequently, canagliflozin confers multiple benefits in patients with T2DM, including glycemic improvement, weight loss, and BP reduction.[5] In contrast, dipeptidyl peptidase-4 inhibitors (eg, sitagliptin) have shown neutral effects on weight and BP, and sulfonylureas (eg, glimepiride) have been associated with weight gain and decreased efficacy over time.[26]
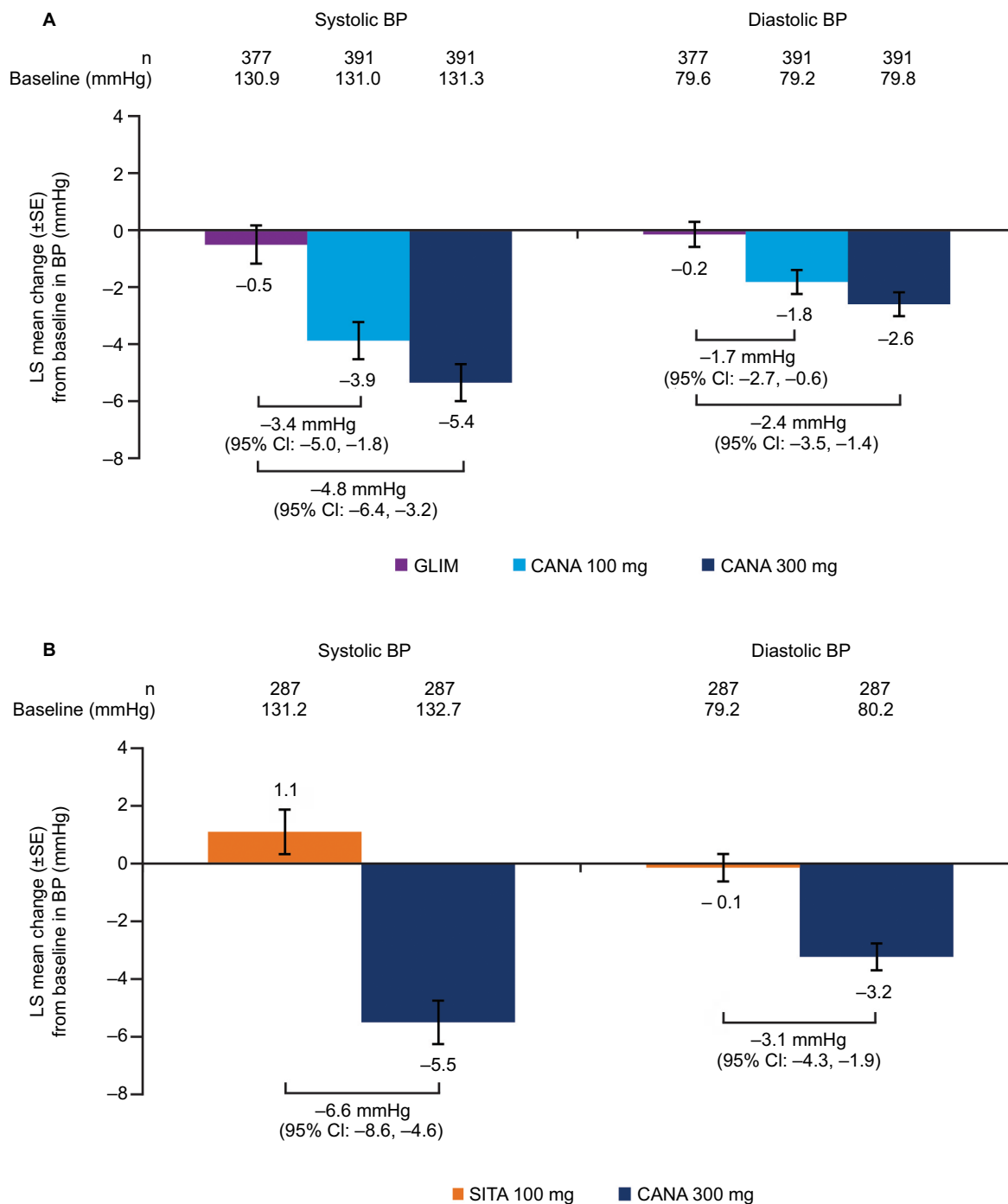
Figure 3 Effects on BP at week 52 in (**A**) study 1 and (**B**) study 2.
Abbreviations: BP, blood pressure; CANA, canagliflozin; CI, confidence interval; GLIM, glimepiride; LS, least squares; SE, standard error; SITA, sitagliptin.

Most patients (~80%) in each study met the criteria for metabolic syndrome diagnosis at baseline. A limitation of this analysis was its post hoc nature, as patients were not randomized based on the presence of metabolic syndrome. However, baseline characteristics were generally similar across treatment groups within each study. Changes in efficacy parameters related to metabolic syndrome were generally consistent with observations from the overall population in each study.[20,22] Although further analyses based on patient characteristics were not done, the efficacy and safety of canagliflozin have been shown to be generally consistent in patients with T2DM in subgroups based on baseline demographic and disease characteristics (eg, sex, age, race, ethnicity, HbA1c, and T2DM duration).[27–32] Results from this analysis are consistent with findings from preclinical studies demonstrating the beneficial effects of treatment with other

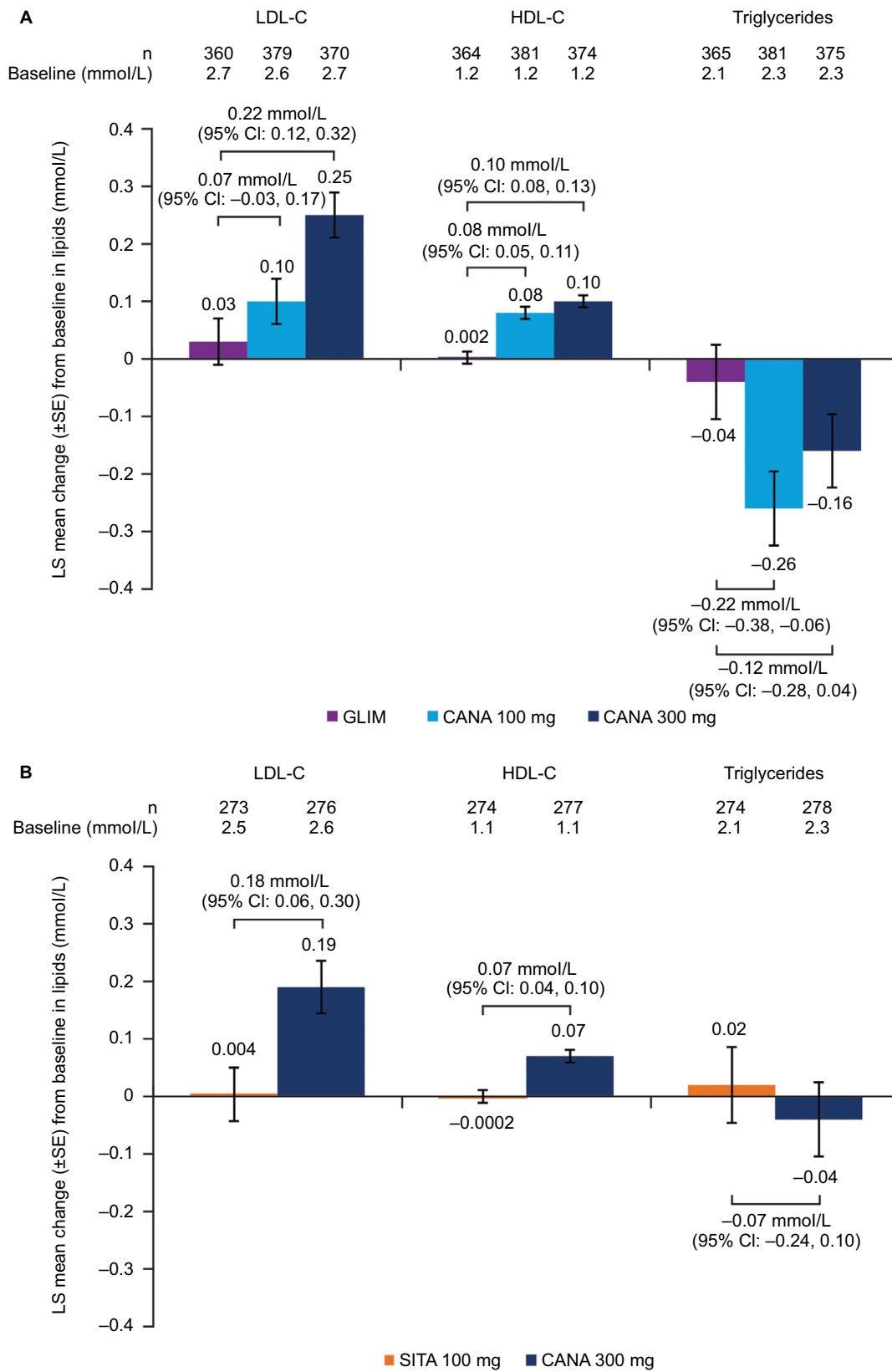**Figure 4** Effects on fasting plasma lipids at week 52 in (**A**) study 1 and (**B**) study 2.
Abbreviations: CANA, canagliflozin; CI, confidence interval; GLIM, glimepiride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LS, least squares; SE, standard error; SITA, sitagliptin.

SGLT2 inhibitors in the setting of metabolic syndrome.[33–35] Despite these beneficial effects on all components of metabolic syndrome, there were small changes in the proportion of patients meeting the criteria for metabolic syndrome at week 52 in both studies. This is likely due to the continued diagnosis and treatment of T2DM, hypertension, and dyslipidemia following treatment in these studies. Furthermore, the present studies were not designed to ascertain the regression of metabolic syndrome.

The multifactorial nature of metabolic syndrome makes it a challenging condition to manage using currently available therapeutic agents.[36] Because canagliflozin has positive effects on multiple parameters (eg, glycemic, body weight, BP), it may be particularly beneficial for patients with metabolic syndrome and ultimately contribute to a decreased risk of cardiovascular disease. Results from the EMPA-REG OUTCOME trial have demonstrated reductions in cardiovascular risk in patients with T2DM treated with the SGLT2 inhibitor empagliflozin.[37] The potential benefits of canagliflozin on cardiometabolic outcomes are currently being assessed in the CANagliflozin cardioVascular Assessment Study (CANVAS) program, which consists of 2 ongoing trials in patients with T2DM and a history or high risk of cardiovascular disease (ie, CANVAS [ClinicalTrials.gov identifier: NCT01032629] and CANVAS-R [renal endpoints; ClinicalTrials.gov identifier: NCT01989754]).

Conclusion

These findings demonstrate that canagliflozin has beneficial effects on the multiple components of metabolic syndrome compared with glimepiride or sitagliptin in patients with T2DM and metabolic syndrome.

Acknowledgments

Disclosure

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