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SHORT COMMUNICATION

Effects of canagliflozin on body weight and relationship to HbA_{1c} and blood pressure changes in patients with type 2 diabetes

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Abstract
Aims/hypothesis Canagliflozin, a sodium glucose co-transporter 2 inhibitor, reduces HbA_{1c}, body weight and systolic BP (SBP) in patients with type 2 diabetes. As weight loss is known to reduce both HbA_{1c} and SBP, these analyses were performed to evaluate the contribution of weight loss resulting from treatment with canagliflozin to HbA_{1c} and SBP reductions in patients with type 2 diabetes.

Methods Pooled data from four placebo-controlled Phase 3 studies (N=2,250) in patients with type 2 diabetes were used in the analyses. In each study, patients were treated with placebo, canagliflozin 100 mg or canagliflozin 300 mg, once daily for 26 weeks. Changes from baseline in body weight, HbA_{1c} and SBP were measured at week 26, and the contribution of weight loss to the lowering of HbA_{1c} and SBP was obtained using ANCOVA.

Results Canagliflozin 100 and 300 mg reduced mean body weight, HbA_{1c} and SBP compared with placebo ($p<0.001$ for each), and more patients had body-weight reductions >0%, ≥5% and ≥10% with canagliflozin treatment than with placebo. Weight-loss-independent and weight-loss-associated mechanisms contributed to HbA_{1c} and SBP lowering with canagliflozin: ~85% of HbA_{1c} lowering and ~60% of SBP lowering was independent of weight loss.

Conclusions/interpretation In patients with type 2 diabetes, canagliflozin provided clinically meaningful body-weight reductions, and the weight loss contributed to reductions in HbA_{1c} and SBP.

Trial registration: ClinicalTrials.gov NCT01081834; NCT01106625; NCT01106677; and NCT01106690

Keywords Body weight · Canagliflozin · Sodium glucose co-transporter 2 (SGLT2) inhibitor · Type 2 diabetes mellitus

Abbreviations

AHA	Anti-hyperglycaemic agent
CVD	Cardiovascular disease
SBP	Systolic BP
SGLT2	Sodium glucose co-transporter 2
UGE	Urinary glucose excretion

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Introduction

Overweight/obesity confer additional comorbidities to individuals with type 2 diabetes mellitus, and most patients with type 2 diabetes are overweight or obese [1]. Recently, the American Medical Association recognised obesity as a complex disease associated with comorbidities, including type 2 diabetes and cardiovascular disease (CVD) [2]. In this regard, achieving weight loss of 5–10% can improve glycaemic control and CVD risk factors, including BP, HDL-cholesterol and triacylglycerol in patients with type 2 diabetes [1, 3–5]. In addition, clinically meaningful improvements in glycaemic control can be seen even with weight loss of 2–5% [5]. Unfortunately, it is difficult to both achieve and maintain weight loss, particularly as some anti-hyperglycaemic agents ([AHAs] e.g. sulfonylureas, insulin and pioglitazone) are associated with weight gain [1]. Even when lifestyle modifications lead to initial weight loss, weight regain is common [6–8]. Therefore, clinical strategies that help achieve and maintain weight loss remain unmet needs in type 2 diabetes management.

Newer AHAs, such as sodium glucose co-transporter 2 (SGLT2) inhibitors, have been proposed to address unmet clinical needs (e.g. weight loss) beyond improving glycaemic control. Canagliflozin is an SGLT2 inhibitor recently approved for the treatment of patients with type 2 diabetes that lowers the renal threshold for glucose and increases urinary glucose excretion (UGE). These actions result in decreased plasma glucose in patients with hyperglycaemia and a mild osmotic diuresis [9–12]. Canagliflozin as monotherapy and in combination with other AHAs improves glycaemic control and reduces body weight and BP in patients with type 2 diabetes [9–12].

Given the observed weight loss with canagliflozin, an unanswered question relates to the weight-loss-associated mechanisms with this therapy. We used a pooled dataset of four placebo-controlled Phase 3 studies to characterise the changes in body weight, HbA_{1c} and systolic BP (SBP) observed with canagliflozin treatment and estimated the relative contributions of weight-loss-associated mechanisms to the overall reductions in HbA_{1c} and SBP in patients with type 2 diabetes.

Methods

Study design, patient population and treatments Data were pooled from patients with type 2 diabetes enrolled in four randomised, double-blind, placebo-controlled Phase 3 studies with similar designs. Each study had a primary assessment at 26 weeks and evaluated canagliflozin 100 and 300 mg vs placebo as monotherapy, add-on to metformin, add-on to metformin plus sulfonylurea, or add-on to metformin plus pioglitazone [9–12]. Eligible patients were aged 18–80 years, and generally had HbA_{1c} ≥7.0% (53 mmol/mol) and ≤10.5% (91 mmol/mol) and estimated glomerular filtration rate ≥55 ml min^{-1} 1.73 m^{-2} at screening.

All studies were conducted in accordance with ethical principles that comply with the Declaration of Helsinki and are consistent with Good Clinical Practice and applicable regulatory requirements. Study protocols and amendments were approved by ethical committees or institutional review boards at participating institutions. All patients provided written informed consent prior to participation.

Study assessments Change in body weight, HbA_{1c} and SBP were assessed at several time points between baseline and week 26 in each study [9–12]. The proportion of patients achieving >0%, ≥5% and ≥10% weight loss and changes in body weight by quartiles of weight loss at week 26 were assessed. The last observation carried forward (LOCF) approach was used to impute any missing data at week 26.

Statistical analyses Mean per cent change from baseline in body weight and mean changes from baseline in HbA_{1c} and SBP at week 26, as well as corresponding cumulative distribution plots, are reported for each variable. For the analysis of weight-loss-independent and weight-loss-associated effects of canagliflozin on HbA_{1c} and SBP, patients within each treatment group were divided into deciles based on weight change, and mean change in HbA_{1c} and SBP were calculated within each decile. ANCOVA models were used with HbA_{1c} or SBP change as the response variable and body-weight change as a covariable. The slope of the relationship between body-weight change and HbA_{1c} or SBP change was determined and the differences in slopes between each treatment group were calculated. If the slopes were not statistically different ($p<0.05$) between treatment groups, a single slope was used for all groups. Weight-loss-independent components of HbA_{1c} and SBP changes were calculated as placebo-subtracted least squares (LS) mean differences from ANCOVA models (i.e. between-group differences observed at the same weight loss). All analyses were performed in Matlab, v8.4 (MathWorks, Natick, MA, USA).

Results

Patients Baseline demographic and disease characteristics are summarised in electronic supplementary material (ESM) Table 1. Patients had mild to moderate hyperglycaemia at baseline (mean HbA_{1c}, 8.0% [64 mmol/mol] across groups). Of the patients included in these analyses, ≥30% of patients were overweight (BMI ≥25 and <30 kg/m^2) and ≥50% of patients in each study were obese (BMI ≥30 kg/m^2).

Changes in body weight, HbA_{1c} and SBP Dose-dependent reductions were seen in body weight, HbA_{1c} and SBP with

canagliflozin compared with placebo (Fig. 1a–c). Most patients treated with canagliflozin 100 and 300 mg had a reduction in HbA_{1c}: 86% and 92%, respectively, compared with 55% of patients treated with placebo (Fig. 1d). Similarly, most canagliflozin-treated patients experienced weight loss with canagliflozin 100 and 300 mg: 82% and 85%, respectively, compared with 55% of placebo-treated patients (Fig. 1e and ESM Fig. 1). More patients treated with canagliflozin 100 and 300 mg vs placebo had ≥ 5% weight loss (25%, 33% and 6%, respectively) and ≥ 10% weight loss (3%, 3% and 1%, respectively; ESM Fig. 1). Body-weight reductions were seen in the highest three quartiles of weight loss with canagliflozin 100 and 300 mg compared with a small increase in the lowest quartile (ESM Fig. 2). Decreases in body weight vs placebo were seen with both canagliflozin doses across quartiles. The proportions of patients experiencing some reduction in SBP were also greater with canagliflozin 100 and 300 mg compared with placebo (64%, 67% and 50%, respectively; Fig. 1f).

Effect of body-weight change on HbA_{1c} and SBP Patients with greater weight loss had greater reductions in HbA_{1c} and SBP; slopes for the effect of weight loss on HbA_{1c} and SBP were similar across groups (Fig. 2). Each 1% reduction in body weight was associated with a 0.045% (0.5 mmol/mol) reduction in HbA_{1c} and a 0.62 mmHg reduction in SBP. The weight-loss-independent and weight-loss-associated effects of canagliflozin were evaluated using the ANCOVA models, as illustrated in Fig. 2. Approximately 85% of the placebo-subtracted reductions in HbA_{1c} with canagliflozin were weight-loss-independent, and 15% were weight-loss-associated

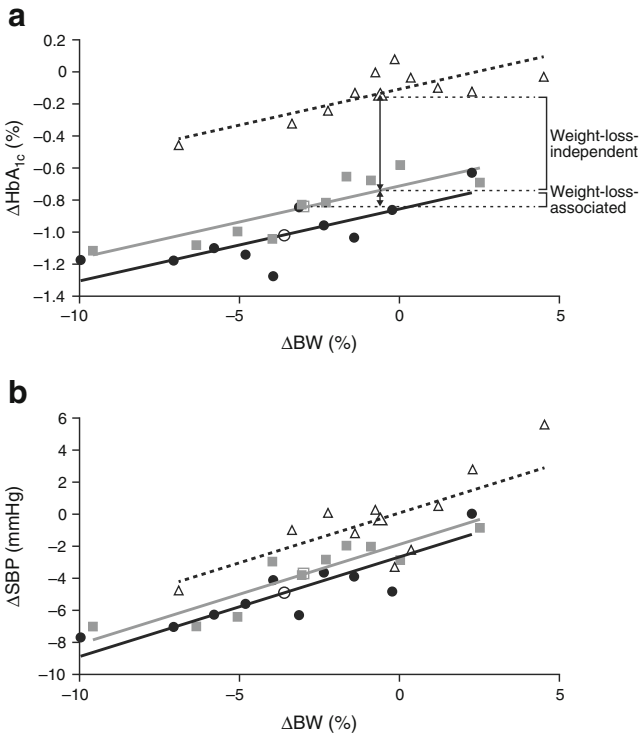

Fig. 2 Relationship between changes in body weight and (**a**) HbA_{1c} and (**b**) SBP at week 26. Larger open symbols represent the mean change for the entire treatment group, and smaller symbols represent mean changes within each decile of weight change; white triangles, placebo; grey squares, canagliflozin 100 mg; black circles, canagliflozin 300 mg. To convert values for change in HbA_{1c} in % into mmol/mol, multiply by 10.929. BW, body weight

(Fig. 2). Approximately 58% of the placebo-subtracted reductions in SBP with canagliflozin were weight-loss-independent, with 42% being weight-loss-associated.

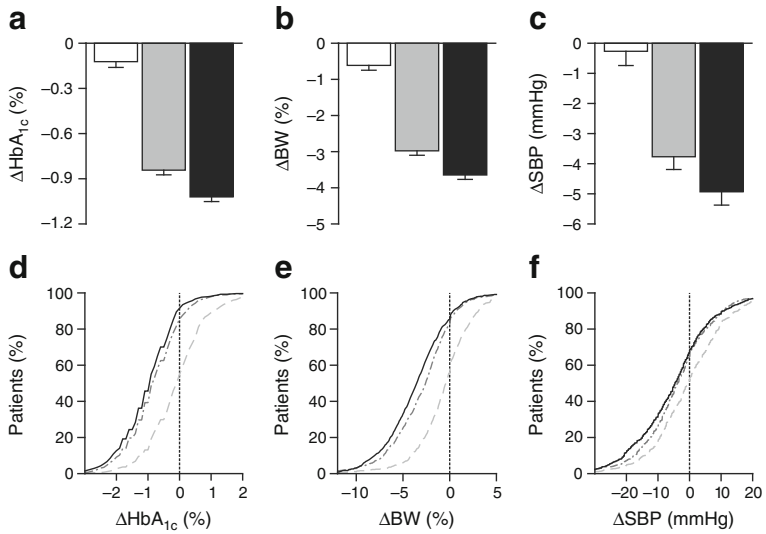

Fig. 1 Mean (SE) reduction in (**a**) HbA_{1c}, (**b**) body weight and (**c**) SBP. White bars, placebo; grey bars, canagliflozin 100 mg; black bars, canagliflozin 300 mg. (**d**–**f**) The cumulative distribution of change from baseline values for each measure. In each of these figures, the *y* coordinate represents the percentage of patients whose change from baseline value is lower than the change from baseline value represented by the *x* coordinate. Light grey dashed line, placebo; medium grey dashed–dotted line, canagliflozin 100 mg; solid black line, canagliflozin 300 mg. To convert values for change in HbA_{1c} in % into mmol/mol, multiply by 10.929. BW, body weight

Discussion

Most AHA therapies are considered to be either weight-loss neutral (e.g. biguanides, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors, bile acid sequestrants, bromocriptine) or to potentially increase body weight (e.g. sulfonylureas, insulin, glinides, pioglitazone) [1]. Thus, prior to the introduction of SGLT2 inhibitors, glucagon-like peptide-1 receptor agonists were the only class consistently associated with body-weight reduction in patients with type 2 diabetes [1]; however, patient-to-patient variability in weight loss has been observed [1, 13]. In this pooled analysis, we demonstrate that canagliflozin treatment provided dose-dependent reductions in body weight in patients with type 2 diabetes. Of note, patients in the highest weight-loss quartile had weight loss of ~7.4–8.0%, demonstrating some variability in canagliflozin-associated weight loss. In addition, consistent HbA_{1c} reductions were observed, whereas SBP changes were more variable.

HbA_{1c} and SBP reductions have previously been associated with weight loss in patients with type 2 diabetes [14]. In this analysis, greater HbA_{1c} and SBP reductions with canagliflozin were seen in patients with greater body-weight reductions over 26 weeks and occurred through both weight-loss-associated and weight-loss-independent mechanisms. Most of the HbA_{1c}-lowering effect of canagliflozin (~85%) was independent of weight loss, and is likely attributable to increased UGE. Weight loss contributed ~40% to the overall reduction in SBP seen with canagliflozin. The estimated effects of weight loss on HbA_{1c} and SBP in this analysis are slightly lower than corresponding estimates obtained following intensive diet/exercise modification for 1 year in the Look AHEAD study (estimated mean reductions of 0.074% [0.8 mmol/mol] in HbA_{1c} and 0.79 mmHg in SBP per each 1% reduction in body weight [7]). Differences in estimated effects of weight loss on HbA_{1c} and SBP may be attributable to different study durations; a comparable analysis was not performed for canagliflozin at 52 weeks because the placebo groups in most of the canagliflozin studies were switched to an active comparator for the 26 week extension. In addition, these differences may also be related to potential study effects to reduce HbA_{1c} and SBP independent of weight loss in the Look AHEAD study.

The exact mechanism of weight-loss-independent BP reduction is not completely understood, but may partially be related to the mild osmotic diuresis or alterations in sodium reabsorption. If osmotic diuresis was considered as a major mechanism, it might be expected that the BP-lowering effect would be less in patients with renal impairment. Interestingly, we have observed that in patients with stage 3 chronic kidney disease, canagliflozin was associated with less weight loss and HbA_{1c} lowering, but similar SBP lowering. However, the contribution of weight loss to HbA_{1c} and SBP reductions was similar to the present analysis (unpublished data).

In summary, we have provided novel observations regarding the clinical effect of SGLT2 inhibition. As previously reported, canagliflozin treatment was associated with reductions in body weight, HbA_{1c} and SBP. However, in this report, we provide data that show reductions in HbA_{1c} and SBP with canagliflozin occurred by both weight-loss-independent and weight-loss-associated mechanisms, with a greater proportion of the reduction in HbA_{1c}, relative to SBP, determined to be independent of weight loss.

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Duality of interest WTC has served as principal investigator on clinical research grants received by his institutions from AstraZeneca, Janssen, MannKind Corporation, GlaxoSmithKline, Sanofi and Lexicon Pharmaceuticals; served as a consultant for Intarcia Therapeutics, Inc; and served as a consultant to Sanofi through an institutional agreement. KS has no proprietary interest in the tested product, does not have a significant equity interest in the sponsor of the covered study and has not received significant payments of other sorts from the sponsor. LAL has received research funding from, has provided continuing medical education on behalf of, or has served as a consultant to AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, GlaxoSmithKline, Janssen, Merck, Novo Nordisk, Sanofi, Servier and Takeda. JPHW has served as a consultant for Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen and Novo Nordisk; served as a speaker for AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly and Novo Nordisk; and received research support from AstraZeneca, Lilly, Novo Nordisk and Merck Sharp & Dohme. LB has served as an investigator for Lilly, Novo Nordisk and Sanofi; served as a speaker for Novo Nordisk, Sanofi, Merck, Janssen and AstraZeneca; and served as a consultant for Novo Nordisk, Sanofi, Merck, Janssen, Quest Diagnostics, AstraZeneca and GlaxoSmithKline. DP, JX, DS, KU, WC and GM are current or former full-time employees of Janssen Research & Development, LLC.

Contribution statement WTC, KS, LAL, JPHW and LB contributed to the conduct of the study and the acquisition, analysis and interpretation of data, and drafted, reviewed and approved the manuscript. DP, KU, WC and GM contributed to the design and conduct of the study and the acquisition, analysis and interpretation of data, and drafted, reviewed and approved the manuscript. JX and DS contributed to the analysis and interpretation of data, and drafted, reviewed and approved the manuscript. All authors approved the final version of the manuscript. WTC and GM are the guarantors of this work.

References

1. Inzucchi SE, Bergenstal RM, Buse JB et al (2012) Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 35:1364–1379
2. American Medical Association House of Delegates (2013) Resolution 420 (A-13). Recognition of obesity as a disease. www.ama-assn.org/assets/meeting/2013a/a13-addendum-refcomm-d.pdf. Accessed 22 July 2013
3. Jensen MD, Ryan DH, Apovian CM et al (2014) 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation 129:S102–S138
4. Noria SF, Grantcharov T (2013) Biological effects of bariatric surgery on obesity-related comorbidities. Can J Surg 56:47–57
5. Wing RR, Lang W, Wadden TA et al (2011) Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care 34:1481–1486
6. The Diabetes Prevention Program Research Group (2012) Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. Diabetes Care 35:731–737
7. Pi-Sunyer X, Blackburn G, Brancati FL et al (2007) Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care 30:1374–1383
8. Wing RR, Bolin P, Brancati FL et al (2013) Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 369:145–154
9. Stenlöf K, Cefalu WT, Kim K-A et al (2013) Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 15:372–382
10. Lavalle-González FJ, Januszewicz A, Davidson J et al (2013) Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia 56:2582–2592
11. Wilding JP, Charpentier G, Hollander P et al (2013) Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. Int J Clin Pract 67:1267–1282
12. Forst T, Guthrie R, Goldenberg R et al (2014) Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. Diabetes Obes Metab 16:467–477
13. Monami M, Dicembrini I, Marchionni N, Rotella CM, Mannucci E (2012) Effects of glucagon-like peptide-1 receptor agonists on body weight: a meta-analysis. Exp Diabetes Res 2012:672658
14. de las Cruces Souto-Gallardo M, Bacardi Gascon M, Jimenez Cruz A (2011) Effect of weight loss on metabolic control in people with type 2 diabetes mellitus: systematic review. Nutr Hosp 26:1242–1249