Can J Diabetes 40 (2016) 247–257

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Original Research

Impact of Age and Estimated Glomerular Filtration Rate on the Glycemic Efficacy and Safety of Canagliflozin: A Pooled Analysis of Clinical Studies

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ARTICLE INFO

Article history:
Received 25 June 2015
Received in revised form
28 October 2015
Accepted 10 November 2015

Keywords:
clinical study
glycemic control
treatment
type 2 diabetes

ABSTRACT

Objective: Reduced efficacy has been reported in the elderly; it may be a consequence of an age-dependent decline in estimated glomerular filtration rate (eGFR) rather than ageing per se. We sought to determine the impact of these 2 parameters, as well as sex and baseline body mass index (BMI), on the efficacy and safety of canagliflozin, a sodium glucose co-transporter 2 inhibitor, in people with type 2 diabetes.
Methods: Data were pooled from 6 randomized, double-blind, placebo-controlled studies (18 or 26 weeks; N=4053). Changes in glycated hemoglobin (A1C) and systolic blood pressure (BP) from baseline with canagliflozin 100 mg and 300 mg and placebo were evaluated in subgroups by sex, baseline BMI, baseline age and baseline eGFR. Safety was assessed by reports of adverse events.
Results: Placebo-subtracted reductions in A1C with canagliflozin 100 mg and 300 mg were similar in men and women. A1C reductions with canagliflozin were seen across BMI subgroups and in participants aged <65 years and ≥65 years. Significantly greater placebo-subtracted reductions in A1C were seen with both canagliflozin doses in participants with higher baseline eGFR (≥90 mL/min/1.73 m^2). Reductions in systolic BP were seen with canagliflozin across subgroups of sex, BMI, age and eGFR. A1C reductions with canagliflozin were similar for participants aged <65 or ≥65 years who had baseline eGFR ≥60 mL/min/1.73 m^2 and were smaller in older than in younger participants with baseline eGFR 45 to <60 mL/min/1.73 m^2. The overall incidence of adverse events was similar across treatment groups regardless of sex, baseline BMI, baseline age or baseline eGFR.
Conclusions: Canagliflozin improved glycemic control, reduced BP and was generally well tolerated in people with type 2 diabetes across a range of ages, BMIs and renal functions.

Mots clés :
étude clinique
régulation de la glycémie
traitement
diabète de type 2

RÉSUMÉ

Objectif : Une réduction de l'efficacité a été signalée chez les personnes âgées. Cette réduction peut être la conséquence d'un déclin de l'estimation des débits de filtration glomérulaire (eDFG) lié à l'âge plutôt que le vieillissement en soi. Nous avons cherché à déterminer les répercussions de ces 2 paramètres, ainsi que celles du sexe et des indices de masse corporelle (IMC) initiaux, sur l'efficacité et l'innocuité de la canagliflozine, un inhibiteur du cotransporteur sodium-glucose de type 2, chez les personnes souffrant du diabète sucré de type 2.
Méthodes : Les données de 6 études comparatives contre placebo, à répartition aléatoire et à double insu (18 ou 26 semaines; N=4053) ont été regroupées. Nous avons évalué en sous-groupes par sexe, IMC initial, âge et eDFG les changements dans les valeurs initiales de l'hémoglobine glyquée (A1c) et de la pression artérielle (PA) systolique entre les personnes qui prenaient 100 mg et 300 mg de canagliflozine, et les

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1499-2671
http://dx.doi.org/10.1016/j.jcjd.2015.11.005

personnes qui prenaient le placebo. Les déclarations d'événements indésirables ont permis l'évaluation de l'innocuité.
Résultats : Les réductions soustraites du placebo dans les concentrations d'A1C étaient similaires chez les hommes et les femmes qui prenaient 100 mg et 300 mg de canagliflozine. Nous avons observé des réductions de la concentration d'A1C chez les personnes qui prenaient de la canagliflozine dans tous les sous-groupes par IMC et chez les participants de <65 ans et de ≥65 ans. Nous avons aussi observé des réductions soustraites du placebo significativement plus grandes dans les concentrations d'A1C pour les deux doses de canagliflozine chez les participants ayant une eDFG initiale plus élevée (≥90 ml/min/1,73 m^2). Nous avons observé des réductions de la PA systolique lors de la prise de canagliflozine parmi tous les sous-groupes par sexe, IMC, âge et eDFG. Les réductions de la concentration d'A1c lors de la prise de canagliflozine étaient similaires chez les participants de <65 ans ou de ≥65 ans qui avaient une eDFG initiale ≥60 ml/min/1,73 m^2 et étaient plus petites chez les participants plus âgés que chez les participants plus jeunes ayant une eDFG intiale de 45 à <60 ml/min/1,73 m^2. L'incidence globale des événements indésirables était similaire dans tous les groupes de traitement, quels que soient le sexe, l'IMC initial, l'âge ou l'eDFG.
Conclusions : La canagliflozine améliorait la régulation glycémique, réduisait la PA et était généralement bien tolérée par les personnes souffrant du diabète de type 2 à divers âges, IMC et fonctionnements rénaux.

Introduction

Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor developed to treat adults with type 2 diabetes (1–13). Canagliflozin inhibits renal glucose reabsorption by lowering the renal threshold for glucose (RT_G), thus reducing reabsorption of filtered glucose and increasing urinary glucose excretion (UGE), which results in lowered plasma glucose levels and a net caloric loss (1,14–16). Previous studies have reported a UGE of approximately 80 to 120 grams of glucose per day with canagliflozin treatment in people with type 2 diabetes (14,17,18).

In Phase 3 studies, canagliflozin provided reductions in glycated hemoglobin (A1C), body weight and systolic blood pressure (BP), and was generally well tolerated across a broad range of participants with type 2 diabetes (2–13). Clinical characteristics, such as sex, age and body mass index (BMI), may affect patients' responses to antihyperglycemic agent (AHA) therapy and should be considered when determining optimal treatment options for the management of type 2 diabetes. Canagliflozin has demonstrated greater effects in lowering A1C levels in participants with type 2 diabetes <65 years of age compared with participants 65 years of age or older (19). The rate of UGE is proportional to the glomerular filtration rate (GFR) and plasma glucose level (15,20), so the effect of canagliflozin on increasing UGE is expected to be attenuated in participants with lower GFRs. Consistent with this, the efficacy of canagliflozin has been shown to be dependent on renal function status (4,21). Thus, the differences in glycemic efficacy observed with canagliflozin between older and younger participants may be due to differences in baseline GFR. Of note, although GFR is considered to be the best measure of renal function, estimated GFR (eGFR) is typically used in clinical practice because of the difficulties and costs associated with obtaining actual GFR measurements (22).

In this analysis, the efficacy of canagliflozin in improving A1C and systolic BP and the safety of canagliflozin were assessed in subgroups by sex, baseline BMI, baseline age and baseline eGFR using pooled data from 6 randomized, double-blind, placebo-controlled, Phase 3 studies in people with type 2 diabetes.

Methods

Study design, patient populations and treatments

This post hoc analysis was based on pooled data from 6 double-blind, placebo-controlled, Phase 3 studies of 18 or 26 weeks' duration in people with type 2 diabetes (N=4053), including studies of canagliflozin as monotherapy (2), add-on to metformin (9), add-on to metformin plus sulphonylurea (10), add-on to metformin plus pioglitazone (13), and the CANagliflozin cardioVascular Assessment Study (CANVAS) add-on to sulphonylurea and add-on to insulin substudies (23,24) (Table 1). In each study, participants were randomized to receive canagliflozin 100 mg or 300 mg or placebo once daily. Data for participants in the high glycemic substudy (baseline A1C >10.0% [86 mmol/mol] and ≤12.0% [108 mmol/mol]) of the monotherapy study (not placebo controlled) and the sitagliptin arm of the add-on to metformin study were not included in this analy-

Table 1
Study design and participant population

Study	Time point[b]	Inclusion criteria			Participants contributing data to pooled analysis, n[a]			
		Age, y	eGFR, mL/min/1.73 m^2	A1C, %	PBO	CANA 100 mg	CANA 300 mg	Total
Monotherapy	26 weeks	≥18 and ≤80	≥50	≥7.0 and ≤10.0	191	194	197	582
Add-on to MET	26 weeks	≥18 and ≤80	≥55	≥7.0 and ≤10.5	183	368	367	918
Add-on to MET+SU	26 weeks	≥18 and ≤80	≥55	≥7.0 and ≤10.5	155	157	156	468
Add-on to MET+PIO	26 weeks	≥18 and ≤80	≥55	≥7.0 and ≤10.5	115	113	114	342
CANVAS add-on to insulin substudy	18 weeks	≥30[c]	≥30	≥7.0 and ≤10.5	532	540	557	1629
CANVAS add-on to SU substudy	18 weeks	≥30[c]	≥30	≥7.0 and ≤10.5	39	39	36	114
Total, N					1215	1411	1427	4053

A1C, glycated hemoglobin; *CANA,* canagliflozin; *CANVAS,* CANagliflozin cardioVascular Assessment Study; *CV,* cardiovascular; *eGFR,* estimated glomerular filtration rate; *MET,* metformin; *PBO,* placebo; *PIO,* pioglitazone; *SU,* sulphonylurea.
[a] Data for participants with baseline eGFR <45 mL/min/1.73 m^2 were excluded from the analysis.
[b] Assessment time point.
[c] ≥30 years for patients with a history of CV disease or ≥50 years for patients with presence of CV risk factors.

sis. Data for participants with baseline eGFR <45 mL/min/1.73 m^2 were also excluded from this pooled analysis because canagliflozin is not indicated for use in these patients (25).

Eligible participants must have had inadequately controlled type 2 diabetes at screening and at the start of the placebo run-in period while on the protocol-specified background AHA therapy. Key inclusion criteria for most studies included A1C levels ≥7.0% (53 mmol/mol) and ≤10.5% (91 mmol/mol) at screening and repeated fasting plasma glucose (FPG) ≥15.0 mmol/L (270 mg/dL) during the pretreatment phase (Table 1). Common exclusion criteria included histories of type 1 diabetes; severe renal impairment; myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident with 3 months of screening; and uncontrolled hypertension. Details of the study design, as well as randomization and blinding, and glycemic rescue therapy have previously been reported for the individual studies included in this pooled dataset (2,9,10,13,23,24,26).

All studies included in this analysis were conducted in accordance with ethical principles that comply with the Declaration of Helsinki and were consistent with good clinical practices and applicable regulatory requirements. Study protocols and amendments were approved by institutional review boards and independent ethics committees at participating institutions. All participants provided written informed consent prior to participation in the studies.

Study endpoints and assessments

The primary endpoint for each study was the change in A1C from baseline at the primary assessment time point (week 18 for CANVAS substudies and week 26 for other studies). In this post hoc analysis, changes in A1C and systolic BP from baseline were evaluated in subgroups of participants based on sex (men [n=2301] and women [n=1752]); baseline BMI (<25 kg/m^2 [n=353], 25 to <30 kg/m^2 [n=1148], 30 to <35 kg/m^2 [n=1298] and ≥35 kg/m^2 [n=1250]); baseline age (<65 years [n=2905] and ≥65 years [n=1148]); and baseline eGFR (≥90 mL/min/1.73 m^2 [n=1369], 60 to <90 mL/min/1.73 m^2 [n=2295] and 45 to <60 mL/min/1.73 m^2 [n=389]). Baseline eGFR was calculated according to the Modification of Diet and Renal Disease Study (MDRD) equation (27,28). An additional exploratory analysis examined changes in A1C and systolic BP as a function of age and baseline eGFR. A separate analysis evaluated the change in A1C in participants with baseline eGFR <45 mL/min/1.73 m^2. Safety and tolerability were assessed based on adverse event (AE) reports. The overall incidence of AEs, as well as the incidence of specifically selected AEs related to the mechanism of action of canagliflozin, including genital mycotic infections, urinary tract infections (UTIs) and AEs related to osmotic diuresis (e.g. pollakiuria, polyuria) and volume depletion (e.g. postural dizziness, orthostatic hypotension) were evaluated. A comprehensive analysis of safety with canagliflozin has been reported previously (29).

Statistical analyses

Efficacy analyses were conducted using the modified intent-to-treat analysis set, which included all randomized participants who received ≥1 dose of double-blind study drug. Efficacy data were analyzed according to randomized treatment assignment using the last observation carried forward (LOCF) approach to impute missing data; for participants who received glycemic rescue therapy, the last postbaseline value prior to initiation of rescue therapy was used for analysis. An analysis of covariance (ANCOVA) model, with treatment and study as factors and the respective baseline value for each endpoint as a covariate, was used to assess primary endpoints. The least squares (LS) mean differences between groups and 2-sided 95% confidence intervals (CIs) were estimated. No formal hypothesis testing was conducted for the subgroup analyses; therefore, no *P* values are reported. Safety analyses included all reported AEs, regardless of rescue therapy, and included all randomized participants who received ≥1 dose of double-blind study drug.

Results

Participant disposition and baseline characteristics

Of the 4053 participants in the modified intent-to-treat population with baseline eGFR ≥45 mL/min/1.73 m^2, 3601 (88.8%) completed the respective primary assessment period. Baseline demographic and disease characteristics were generally similar across treatment groups in the overall population (Table 2). The majority of participants were men (56.8%) and <65 years of age (71.7%). A similar proportion of participants had baseline BMI 25 to <30 kg/m^2 (28.3%), 30 to <35 kg/m^2 (32.1%) and ≥35 kg/m^2 (30.9%); a small proportion had baseline BMI <25 kg/m^2 (8.7%). Most participants had baseline eGFR 60 to <90 mL/min/1.73 m^2 (56.6%) or eGFR ≥90 mL/min/1.73 m^2 (33.8%); 9.6% of participants had

Table 2
Baseline demographic and disease characteristics (overall population)[a]

Characteristic	PBO (n=1215)	CANA 100 mg (n=1411)	CANA 300 mg (n=1427)	Total (N=4053)
Sex, n (%)				
Men	714 (59)	793 (56)	794 (56)	2301 (57)
Women	501 (41)	618 (44)	633 (44)	1752 (43)
Age, years	59.1±9.3	58.6±9.7	58.8±9.5	58.8±9.5
Race, n (%)[b]				
White	910 (75)	1037 (73)	1071 (75)	3018 (74)
Black or African American	41 (3)	54 (4)	64 (4)	159 (4)
Asian	169 (14)	184 (13)	183 (13)	536 (13)
Other[c]	95 (8)	136 (10)	109 (8)	340 (8)
A1C, % (mmol/mol)	8.1±0.9 (65±9.8)	8.1±0.9 (65±9.8)	8.1±0.9 (65±9.8)	8.1±0.9 (65±9.8)
FPG, mmol/L (mg/dL)	9.4±2.5 (169.4±45.0)	9.4±2.5 (169.4±45.0)	9.4±2.6 (169.4±46.8)	9.4±2.5 (169.4±45.0)
BMI, kg/m^2	32.7±6.5	32.7±6.4	32.6±6.4	32.7±6.4
eGFR, mL/min/1.73 m^2	82.1±19.4	84.1±19.0	83.2±19.4	83.2±19.3
Duration of type 2 diabetes, years	11.4±8.1	11.0±8.0	11.0±7.9	11.1±8.0

A1C, glycated hemoglobin; *BMI,* body mass index; *CANA,* canagliflozin; *eGFR,* estimated glomerular filtration rate; *FPG,* fasting plasma glucose; *PBO,* placebo; *SD,* standard deviation.

[a] Data are mean ± SD unless otherwise indicated.

[b] Percentages may not total 100% due to rounding.

[c] Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, not reported, other and unknown.

baseline eGFR 45 to <60 mL/min/1.73 m^2. Baseline demographic and disease characteristics in subgroups based on age at baseline are shown in the Supplementary Table A1. Participants aged ≥65 years generally had longer known duration of type 2 diabetes and lower BMI and eGFR values at baseline than participants aged <65 years.

Glycemic efficacy

Across subgroups, canagliflozin 100 mg and 300 mg provided clinically meaningful, dose-related reductions in A1C that were consistently larger than those observed with placebo, regardless of sex, baseline BMI, baseline age or baseline eGFR (Figure 1). The 95% CIs for changes in A1C overlap between subgroups, based on sex, BMI or age, indicating no differences in A1C lowering related to sex, BMI or age. Participants with baseline eGFR ≥90 mL/min/1.73 m^2 had significantly greater A1C reductions compared with participants with lower baseline eGFR values.

Sex

Canagliflozin 100 mg and 300 mg were associated with placebo-subtracted LS mean reductions from baseline in A1C levels that were similar in men (–0.72% [–7.9 mmol/mol] and –0.84% [–9.2 mmol/mol], respectively) and women (–0.68% [–7.4 mmol/mol] and –0.84% [–9.2 mmol/mol], respectively) (Figure 2).

Body mass index

Placebo-subtracted reductions from baseline in A1C were generally similar across subgroups of baseline BMI with canagliflozin 100 mg and 300 mg (BMI <25 kg/m^2: –0.74% [–8.1 mmol/mol] and –0.78% [–8.5 mmol/mol]; 25 to <30 kg/m^2: –0.67% [–7.3 mmol/mol] and –0.82% [–9.0 mmol/mol]; 30 to <35 kg/m^2: –0.71% [–7.8 mmol/mol] and –0.83% [–9.1 mmol/mol]; ≥35 kg/m^2: –0.73% [–8.0 mmol/mol] and –0.91% [–9.9 mmol/mol], respectively) (Figure 3).

Age

Placebo-subtracted reductions from baseline in A1C were seen with canagliflozin 100 mg and 300 mg in participants aged <65 years (–0.72% [–7.9 mmol/mol] and –0.88% [–9.6 mmol/mol], respectively) and ≥65 years (–0.65% [–7.1 mmol/mol] and –0.76% [–8.3 mmol/mol], respectively) (Figure 4). Clinically meaningful A1C reductions were seen with both canagliflozin doses in both age groups.

Estimated glomerular filtration rate

Larger, placebo-subtracted reductions from baseline in A1C were seen with canagliflozin 100 mg and 300 mg in participants with baseline eGFR ≥90 mL/min/1.73 m^2 (–0.87% [–9.5 mmol/mol] and –1.01% [–11.0 mmol/mol], respectively) compared to those with lower baseline eGFRs (eGFR 60 to <90 mL/min/1.73 m^2: –0.63% [–6.9 mmol/mol] and –0.80% [–8.7 mmol/mol]; 45 to <60 mL/min/1.73 m^2: –0.57% [–6.2 mmol/mol] and –0.61% [–6.7 mmol/mol], respectively) (Figure 5). Participants with baseline eGFR <45 mL/min/1.73 m^2 (n=111) were not included in the pooled subgroup analysis because canagliflozin is not indicated for use in these patients (25). Among participants with baseline eGFR <45 mL/min/1.73 m^2, placebo-subtracted changes (95% CI) from baseline in A1C with canagliflozin 100 mg and 300 mg were –0.02% (–0.55, 0.51; –0.2 mmol/mol [–6.0, 5.6]) and –0.25% (–0.76, 0.26; –2.7 mmol/mol [–8.3, 2.8]).

Age by estimated glomerular filtration rate

Because a decline in eGFR may occur with aging, data were analyzed as a function of both age and eGFR. The majority of participants <65 years of age had baseline eGFR ≥90 mL/min/1.73 m^2 (n=1214; 42%) or 60 to <90 mL/min/1.73 m^2 (n=1522; 52%); 169 participants (6%) had baseline eGFR 45 to <60 mL/min/1.73 m^2. Among participants ≥65 years of age, most had baseline eGFR 60 to <90 mL/min/1.73 m^2 (n=773; 67%); fewer participants had baseline eGFR ≥90 mL/min/1.73 m^2 (n=155; 14%) or 45 to <60 mL/min/1.73 m^2 (n=220; 19%). Absolute mean and median eGFR values were similar across treatment groups in the age and eGFR subgroups (Figure 6); older participants generally had lower baseline eGFR.

The impact of age on A1C lowering was attenuated within eGFR subgroups (Figure 6). Placebo-subtracted changes from baseline in A1C with canagliflozin 100 mg and 300 mg were similar for older and younger participants in subgroups of baseline eGFR ≥90 mL/min/1.73 m^2 (<65 years: –0.86% [–9.4 mmol/mol]

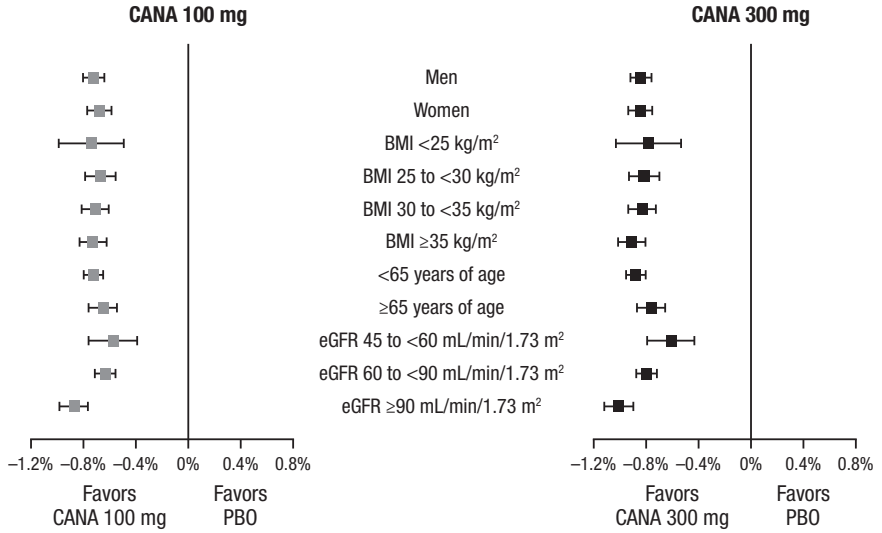

Figure 1. Differences (95% CIs) between canagliflozin 100 mg and 300 mg vs. placebo in the change in A1C from baseline by subgroup (LOCF).
A1C, glycated hemoglobin; *BMI*, body mass index; *CANA*, canagliflozin; *CI*, confidence interval; *eGFR*, estimated glomerular filtration rate; *LOCF*, last observation carried forward; *PBO*, placebo.

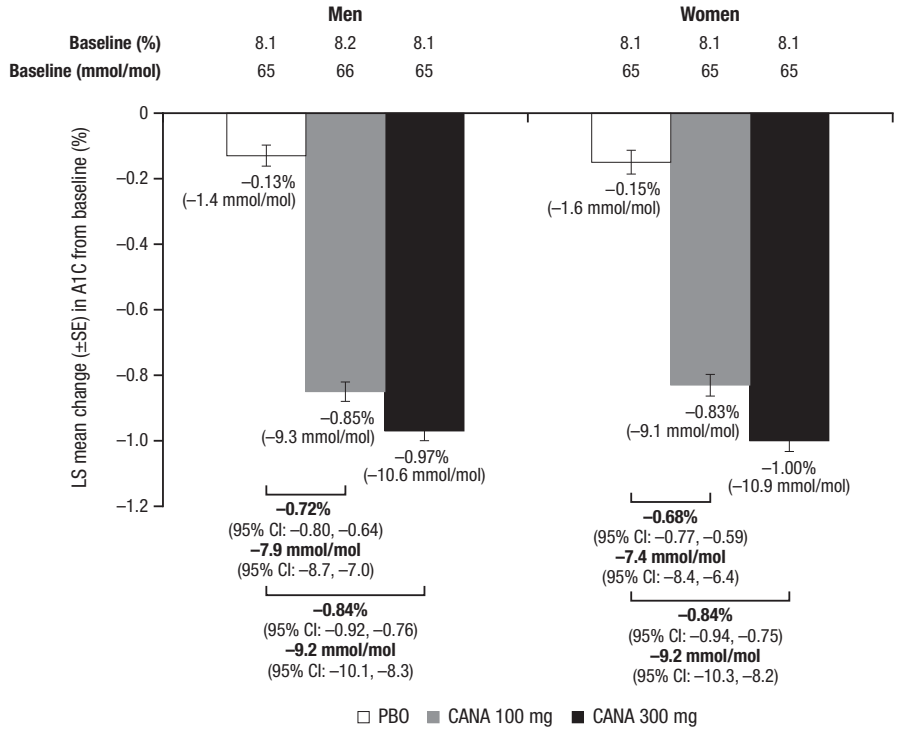

Figure 2. Change in A1C levels by sex (LOCF).
A1C, glycated hemoglobin; *CANA*, canagliflozin; *CI*, confidence interval; *LOCF*, last observation carried forward; *LS*, least squares; *PBO*, placebo; *SE*, standard error.

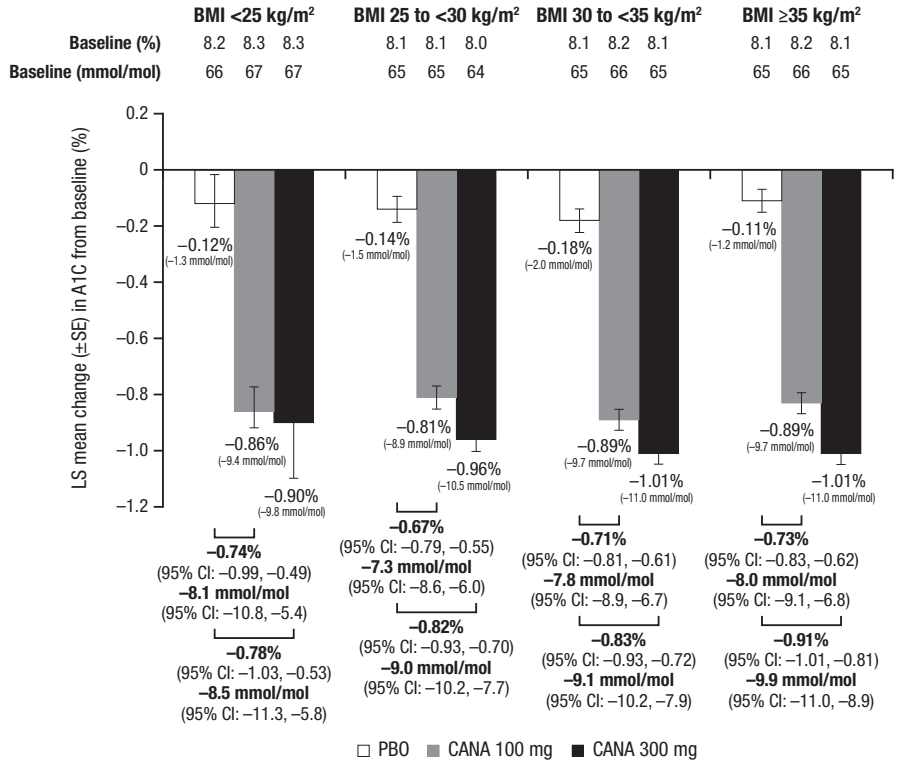

Figure 3. Change in A1C by baseline BMI (LOCF).
A1C, glycated hemoglobin; *BMI*, body mass index; *CANA*, canagliflozin; *CI*, confidence interval; *LOCF*, last observation carried forward; *LS*, least squares; *PBO*, placebo; *SE*, standard error.

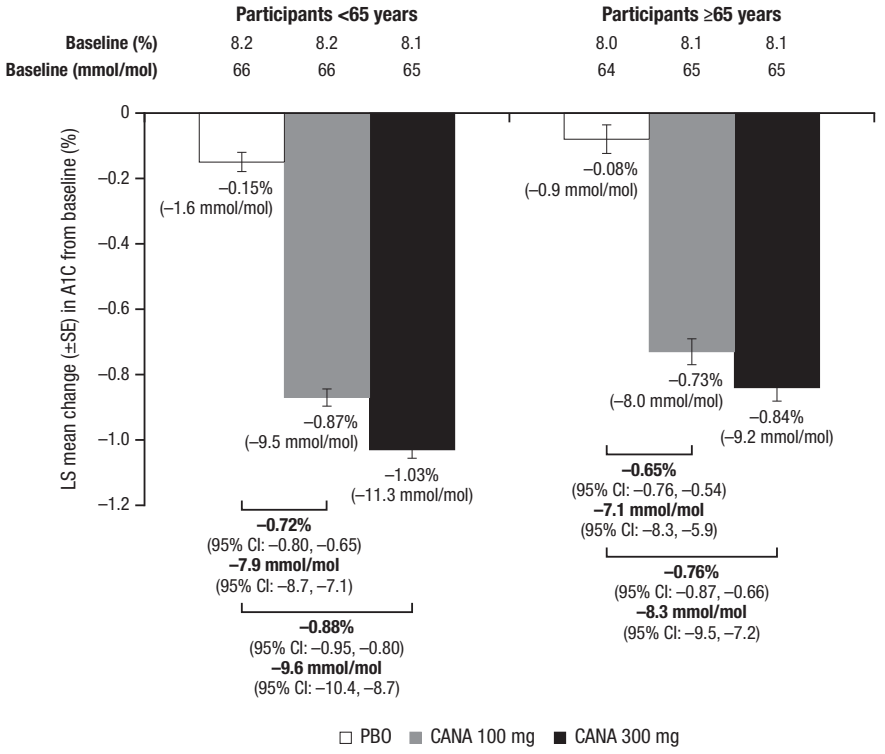

Figure 4. Change in A1C by age at baseline (LOCF).
A1C, glycated hemoglobin; *CANA*, canagliflozin; *CI*, confidence interval; *LOCF*, last observation carried forward; *LS*, least squares; *PBO*, placebo; *SE*, standard error.

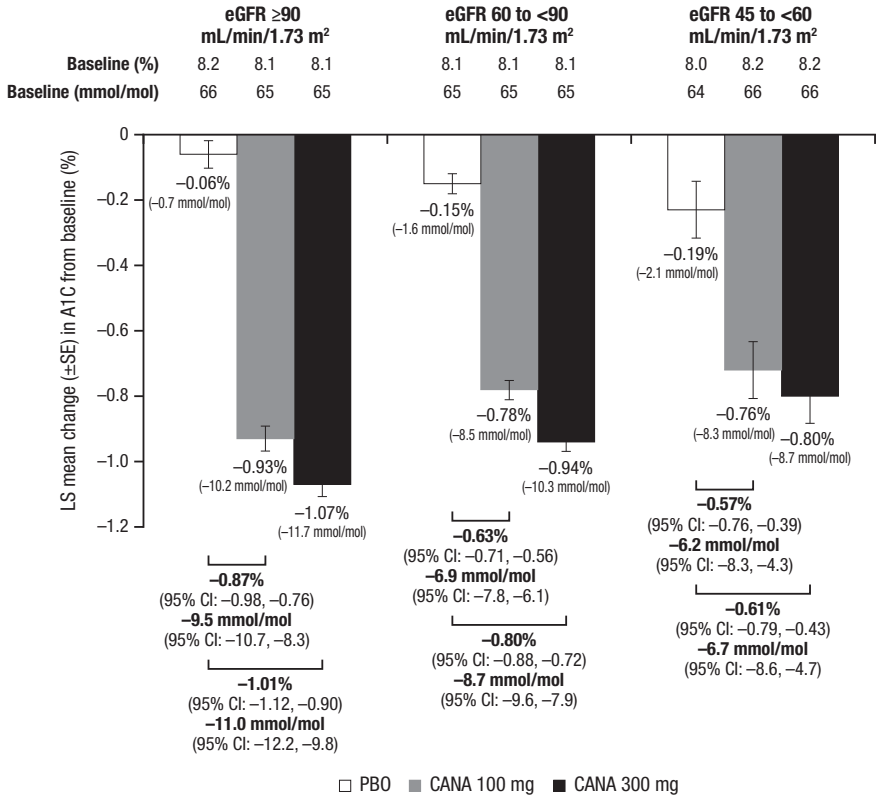

Figure 5. Change in A1C by baseline eGFR (LOCF).
A1C, glycated hemoglobin; *CANA*, canagliflozin; *CI*, confidence interval; *eGFR*, estimated glomerular filtration rate; *LOCF*, last observation carried forward; *LS*, least squares; *PBO*, placebo; *SE*, standard error.

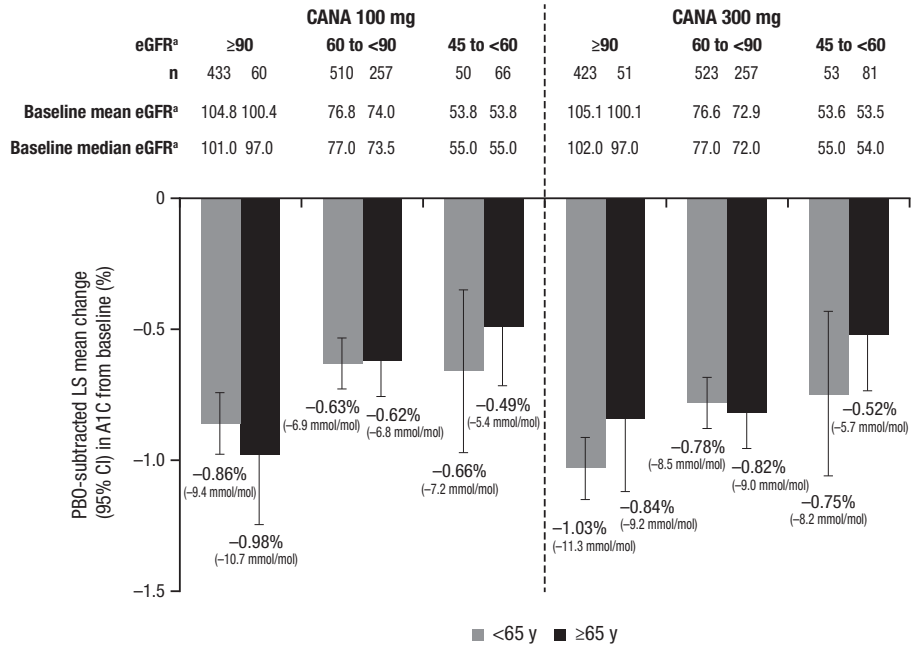

Figure 6. Placebo-subtracted LS mean changes in A1C by age at baseline and baseline eGFR (LOCF).
A1C, glycated hemoglobin; *CANA,* canagliflozin; *CI,* confidence interval; *eGFR,* estimated glomerular filtration rate; *LOCF,* last observation carried forward; *LS,* least squares; *PBO,* placebo; *SE,* standard error.
[a]Unit of mL/min/1.73 m^2 for eGFR.

and –1.03% [–11.3 mmol/mol]; ≥65 years: –0.98% [–10.7 mmol/mol] and –0.84% [–9.2 mmol/mol], respectively) and eGFR 60 to <90 mL/min/1.73 m^2 (<65 years: –0.63% [–6.9 mmol/mol] and –0.78% [–8.5 mmol/mol]; ≥65 years: –0.62% [–6.8 mmol/mol] and –0.82% [–9.0 mmol/mol], respectively). Among the small subgroup of participants with baseline eGFR 45 to <60 mL/min/1.73 m^2, placebo-subtracted changes in A1C with canagliflozin 100 mg and300 mg were –0.66% (–7.2 mmol/mol) and –0.75% (–8.2 mmol/mol), respectively, in participants aged <65 years, and were –0.49% (–5.4 mmol/mol) and –0.52% (–5.7 mmol/mol), respectively, in participants aged ≥65 years.

Changes in blood pressure

Canagliflozin 100 mg and 300 mg provided dose-related reductions in systolic BP that were larger than those observed with placebo across most subgroups (Supplementary Figure A1). The 95% CIs for changes in systolic BP overlap between subgroups based on sex, BMI, age and eGFR, indicating that the reductions in systolic BP provided by canagliflozin are not related to these baseline patient characteristics. Because age and eGFR may affect BP, changes in systolic BP were analyzed as a function of both age and eGFR (Supplementary Figure A2). Across eGFR subgroups, placebo-subtracted changes from baseline in systolic BP with canagliflozin 100 mg and 300 mg ranged from –2.8 to –5.6 mmHg in patients aged <65 years and from –0.8 to –5.3 mmHg in patients aged ≥65 years. There was no clear trend in systolic BP reduction across subgroups; however, the wide CIs make it difficult to interpret differences based on age and eGFR.

Safety

The overall incidence of AEs was similar across treatment groups (60.2%, 60.9% and 58.9% with canagliflozin 100 mg and 300 mg and placebo, respectively). The incidence of AEs leading to discontinuation (3.3%, 4.3% and 2.6% with canagliflozin 100 mg and 300 mg and placebo, respectively) and the incidence of serious AEs (4.0%, 3.9% and 4.7% with canagliflozin 100 mg and 300 mg and placebo, respectively) were low and were similar across treatment groups.

The overall incidence of AEs with canagliflozin 100 mg and 300 mg and placebo was generally similar in men (59.1%, 61.1% and 57.1%, respectively) and women (61.7%, 60.7% and 61.5%, respectively) and across baseline BMI subgroups (BMI <25 kg/m^2: 57.7%, 57.1% and 51.0%; 25 to <30 kg/m^2: 55.5%, 55.9% and 59.1%; 30 to <35 kg/m^2: 59.4%, 60.8% and 58.1%; ≥35 kg/m^2: 66.2%, 67.0% and 61.7%). A higher incidence of genital mycotic infections and osmotic diuresis–related AEs (e.g. pollakiuria [increased urine frequency], polyuria [increased urine volume]) was seen with canagliflozin compared with placebo in both men and women. Genital mycotic infections and osmotic diuresis–related AEs were more frequently reported with canagliflozin in participants with BMI ≥35 kg/m^2. The incidence of UTIs was higher across treatment groups in women compared with men and was low and similar across BMI subgroups. The incidence of AEs related to volume depletion (e.g. postural dizziness, orthostatic hypotension) was low and similar across treatment groups in men and women and across BMI subgroups.

The incidence of any AE, including AEs leading to discontinuation and serious AEs, was generally similar across treatment groups, regardless of age or baseline eGFR (Table 3). Across treatment groups, the incidence of serious AEs was generally higher in participants with baseline eGFR 45 to <60 mL/min/1.73 m^2 compared to those with higher baseline eGFR (60 to <90 and ≥90 mL/min/1.73 m^2), regardless of age. The incidence of genital mycotic infections in men and women was generally higher with canagliflozin than with placebo across age and eGFR subgroups. The incidence of UTIs and osmotic diuresis– and volume depletion–related AEs was generally low across treatment groups in the age and eGFR subgroups. The incidence of osmotic diuresis–related AEs was generally lower with canagliflozin compared with placebo, except in participants aged <65 years with eGFR 45 to <60 mL/min/1.73 m^2. The incidence of volume depletion–related AEs was higher with both canagliflozin doses compared with placebo in participants aged ≥65 years with eGFR 60 to <90 mL/min/1.73 m^2 or 45 to <60 mL/min/

Table 3
Summary of overall safety and selected adverse events by age and baseline eGFR

	Participants <65 years, n (%)								
	eGFR ≥90 mL/min/1.73 m^2			eGFR 60 to <90 mL/min/1.73 m^2			eGFR 45 to <60 mL/min/1.73 m^2		
	PBO (n=338)	CANA 100 mg (n=444)	CANA 300 mg (n=432)	PBO (n=465)	CANA 100 mg (n=522)	CANA 300 mg (n=535)	PBO (n=61)	CANA 100 mg (n=52)	CANA 300 mg (n=56)
Any AE	194 (57.4)	283 (63.7)	268 (62.0)	267 (57.4)	305 (58.4)	325 (60.7)	42 (68.9)	27 (51.9)	32 (57.1)
AEs leading to discontinuation	6 (1.8)	14 (3.2)	12 (2.8)	10 (2.2)	12 (2.3)	17 (3.2)	3 (4.9)	1 (1.9)	4 (7.1)
AEs related to study drug[a]	48 (14.2)	96 (21.6)	108 (25.0)	53 (11.4)	107 (20.5)	144 (26.9)	11 (18.0)	13 (25.0)	9 (16.1)
Serious AEs	14 (4.1)	15 (3.4)	14 (3.2)	14 (3.0)	14 (2.7)	14 (2.6)	11 (18.0)	1 (1.9)	8 (14.3)
Deaths	2 (0.6)	0	1 (0.2)	1 (0.2)	1 (0.2)	0	1 (1.6)	0	1 (1.8)
UTIs	13 (3.8)	21 (4.7)	18 (4.2)	12 (2.6)	24 (4.6)	16 (3.0)	1 (1.6)	2 (3.8)	1 (1.8)
Genital mycotic infections									
Men[b,c]	1 (0.5)	11 (4.6)	9 (4.4)	3 (1.1)	10 (3.6)	20 (6.5)	0	0	1 (2.7)
Women[d,e]	10 (6.8)	33 (16.3)	38 (16.6)	2 (1.1)	31 (12.7)	29 (12.9)	0	3 (16.7)	3 (15.8)
Osmotic diuresis–related AEs[f]	2 (0.6)	24 (5.4)	19 (4.4)	1 (0.2)	19 (3.6)	20 (3.7)	1 (1.6)	1 (1.9)	0
Volume depletion–related AEs[g]	3 (0.9)	3 (0.7)	11 (2.5)	3 (0.6)	5 (1.0)	11 (2.1)	2 (3.3)	1 (1.9)	1 (1.8)
	Participants ≥65 years, n (%)								
	eGFR ≥90 mL/min/1.73 m^2			eGFR 60 to <90 mL/min/1.73 m^2			eGFR 45 to <60 mL/min/1.73 m^2		
	PBO (n=42)	CANA 100 mg (n=60)	CANA 300 mg (n=53)	PBO (n=243)	CANA 100 mg (n=262)	CANA 300 mg (n=268)	PBO (n=66)	CANA 100 mg (n=71)	CANA 300 mg (n=83)
Any AE	23 (54.8)	32 (53.3)	35 (66.0)	153 (63.0)	163 (62.2)	161 (60.1)	37 (56.1)	40 (56.3)	48 (57.8)
AEs leading to discontinuation	1 (2.4)	2 (3.3)	3 (5.7)	8 (3.3)	12 (4.6)	15 (5.6)	3 (4.5)	6 (8.5)	10 (12.0)
AEs related to study drug[a]	4 (9.5)	8 (13.3)	16 (30.2)	30 (12.3)	59 (22.5)	70 (26.1)	15 (22.7)	12 (16.9)	24 (28.9)
Serious AEs	1 (2.4)	4 (6.7)	1 (1.9)	11 (4.5)	17 (6.5)	11 (4.1)	6 (9.1)	6 (8.5)	8 (9.6)
Deaths	0	0	0	2 (0.8)	1 (0.4)	0	1 (1.5)	1 (1.4)	1 (1.2)
UTIs	1 (2.4)	2 (3.3)	3 (5.7)	10 (4.1)	8 (3.1)	13 (4.9)	0	3 (4.2)	3 (3.6)
Genital mycotic infections									
Men[c,h]	0	0	4 (12.1)	0	10 (6.0)	10 (6.4)	0	1 (2.4)	3 (5.5)
Women[e,i]	1 (6.7)	3 (11.1)	2 (10.0)	0	11 (11.5)	14 (12.5)	1 (3.3)	2 (6.7)	2 (7.1)
Osmotic diuresis–related AEs[f]	0	1 (1.7)	0	1 (0.4)	11 (4.2)	6 (2.2)	0	0	2 (2.4)
Volume depletion–related AEs[g]	0	0	0	3 (1.2)	8 (3.1)	6 (2.2)	1 (1.5)	3 (4.2)	4 (4.8)

AE, adverse event; *eGFR,* estimated glomerular filtration rate; *CANA,* canagliflozin; *PBO,* placebo; *UTI,* urinary tract infection.

[a] Possibly, probably or very likely related to the study drug, as assessed by investigator.

[b] eGFR ≥90 mL/min/1.73 m^2: PBO, n=191; CANA 100 mg, n=241; CANA 300 mg, n=203; eGFR 60 to <90 mL/min/1.73 m^2: PBO, n=278; CANA 100 mg, n=278; CANA 300 mg, n=310; eGFR 45 to <60 mL/min/1.73 m^2: PBO, n=34; CANA 100 mg, n=34; CANA 300 mg, n=37.

[c] Including balanitis, balanitis candida, balanoposthitis and genital infection fungal.

[d] eGFR ≥90 mL/min/1.73 m^2: PBO, n=147; CANA 100 mg, n=203; CANA 300 mg, n=229; eGFR 60 to <90 mL/min/1.73 m^2: PBO, n=187; CANA 100 mg, n=244; CANA 300 mg, n=225; eGFR 45 to <60 mL/min/1.73 m^2: PBO, n=27; CANA 100 mg, n=18; CANA 300 mg, n=19.

[e] Including pruritus genital, vaginal infection, vaginal inflammation, vulvitis, vulvovaginal burning sensation, vulvovaginal candidiasis, vulvovaginal discomfort, vulvovaginal dryness, vulvovaginal mycotic infection, vulvovaginal pain, vulvovaginal pruritus and vulvovaginitis.

[f] Including dry mouth, dry throat, micturition urgency, nocturia, pollakiuria, polydipsia, polyuria, thirst and urine output increased.

[g] Including dehydration, dizziness postural, hypotension, orthostatic hypotension, orthostatic intolerance, presyncope and syncope.

[h] eGFR ≥90 mL/min/1.73 m^2: PBO, n=27; CANA 100 mg, n=33; CANA 300 mg, n=33; eGFR 60 to <90 mL/min/1.73 m^2: PBO, n=148; CANA 100 mg, n=166; CANA 300 mg, n=156; eGFR 45 to <60 mL/min/1.73 m^2: PBO, n=36; CANA 100 mg, n=41; CANA 300 mg, n=55.

[i] eGFR ≥90 mL/min/1.73 m^2: PBO, n=15; CANA 100 mg, n=27; CANA 300 mg, n=20; eGFR 60 to <90 mL/min/1.73 m^2: PBO, n=95; CANA 100 mg, n=96; CANA 300 mg, n=112; eGFR 45 to <60 mL/min/1.73 m^2: PBO, n=30; CANA 100 mg, n=30; CANA 300 mg, n=28.

1.73 m^2. The incidence of volume depletion–related AEs was similar with canagliflozin 100 mg and placebo and higher with canagliflozin 300 mg in participants aged <65 years with eGFR ≥90 mL/min/1.73 m^2 or 60 to <90 mL/min/1.73 m^2. The overall incidence of AEs in participants with baseline eGFR <45 mL/min/1.73 m^2 with canagliflozin 100 mg and 300 mg and placebo was 77.4%, 73.0% and 76.7%, respectively. The safety profile of canagliflozin was similar to that seen in patients with baseline eGFR ≥45 mL/min/1.73 m^2, with increased incidence of UTIs, genital mycotic infections and volume depletion–related AEs compared with placebo.

Discussion

Findings from this post hoc analysis of pooled data from Phase 3 studies show that canagliflozin provides glycemic improvement and reductions in BP compared with placebo in people with type 2 diabetes, regardless of sex, baseline BMI, baseline age or baseline eGFR. Reductions in A1C were similar across subgroups by sex and baseline BMI. Greater reductions in A1C were generally seen in younger participants and in those with higher baseline eGFR, consistent with previous studies of canagliflozin (19,21). The reduced glycemic efficacy observed in older participants is likely related to lower baseline eGFR because, among participants aged <65 years and ≥65 years of age, A1C reductions were similar in the baseline eGFR ≥90 mL/min/1.73 m^2 and eGFR 60 to <90 mL/min/1.73 m^2 subgroups. In the small subgroup of participants with baseline eGFR 45 to <60 mL/min/1.73 m^2, A1C reductions were smaller in participants aged ≥65 years compared with those aged <65 years; however, any apparent differences may be due to variability, given the small sample size of this subgroup, as evidenced by the wide CIs observed for these comparisons.

Because of its mechanism of action, the efficacy of canagliflozin is expected to be dependent on the renal function status of participants. In a pooled analysis of data in participants with stage 3 chronic kidney disease (eGFR ≥30 and <60 mL/min/1.73 m^2), canagliflozin 100 mg and 300 mg provided greater reductions in A1C in the subgroups of participants with eGFR 45 to <60 mL/min/1.73 m^2 compared to those with eGFR 30 to <45 mL/min/1.73 m^2 (21). A separate study (12) demonstrated that canagliflozin improves glycemic control better than placebo in people with type 2 diabetes and eGFR ≥30 and <50 mL/min/1.73 m^2; reductions in A1C with canagliflozin were smaller than those reported in participants with normal or mildly impaired renal function (3,7–11). These results are consistent with those seen in the current analysis, which demonstrated that the A1C lowering response to canagliflozin was reduced in participants with lower eGFR (45 to <60 mL/min/1.73 m^2) irrespective of age, albeit slightly less in participants aged ≥65 years than in those aged <65 years. Thus, eGFR, rather than age, per se, largely determines the glycemic efficacy of canagliflozin in people with type 2 diabetes.

Canagliflozin was generally well tolerated across subgroups by sex and baseline BMI, baseline age and baseline GFR. The overall incidence of AEs and AEs leading to discontinuation were similar across treatment groups in all subgroups. The incidence of genital mycotic infections and osmotic diuresis–related AEs was generally higher in men and women treated with canagliflozin vs. placebo, consistent with previous studies (30); reports of genital mycotic infections and UTIs were more common in women than in men, regardless of treatment. The rate of genital mycotic infections with canagliflozin treatment tended to increase with increasing baseline BMIs. The incidence of serious AEs was higher across treatment groups in participants with eGFR 45 to <60 mL/min/1.73 m^2, regardless of age. The incidence of genital mycotic infections was higher with canagliflozin treatment in younger and older participants across eGFR subgroups. Although low overall, the incidence of volume depletion–related AEs was higher with canagliflozin than with placebo in older participants with lower baseline eGFR.

The studies included in this pooled analysis enrolled a large, diverse population of participants with type 2 diabetes and a variety of baseline characteristics that are typically encountered in a clinical setting. A limitation of the analysis is the exclusion of data from participants with baseline eGFR 30 to <45 mL/min/1.73 m^2 because canagliflozin is not indicated for use in people with baseline eGFR <45 mL/min/1.73 m^2 (25). An additional limitation is the use of eGFR instead of direct GFR measurements. Although the eGFR is often used as a more practical means of determining renal function, the measurement is less accurate when eGFR is ≥60 mL/min/1.73 m^2 (22). Furthermore, because age is a variable in the MDRD equation used to calculate eGFR, age is a confounding factor (27,28). Last, longer-term assessment of the subgroup factors influencing the glycemic efficacy and safety of canagliflozin would be helpful in evaluating the durability of canagliflozin treatment.

Overall, the findings from these subgroup analyses support canagliflozin as a therapeutic option for people with type 2 diabetes, including men and women across a broad range of ages, BMIs and varying degrees of renal impairment.

Acknowledgements

This study was sponsored by Janssen Research & Development, LLC. Medical writing support was provided by Kimberly Fuller, PhD, of MedErgy, and was funded by Janssen Global Services, LLC. Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation. The authors thank all investigators, study teams and patients for participating in these studies. Dr. Richard Gilbert is the Canada Research Chair in Diabetes Complications, and his participation in this work is thanks to the Canada Research Chairs Program. This study was previously presented, in part, in abstract form at the 74th Scientific Sessions of the American Diabetes Association, June 13 to 17, 2014, San Francisco, California, USA.

Author Disclosures

REG has received compensation from Boehringer Ingelheim, Janssen and AstraZeneca and has received research support from Boehringer Ingelheim and AstraZeneca. MRW has served as a scientific advisor for Akebia, Janssen, AstraZeneca, Otsuka, Merck Sharp & Dohme, AbbVie, Novartis, Boston Scientific, ZS Pharma, Relypsa, Amgen and Sandoz; has served as a steering committee member for Relypsa, Amgen and Sandoz; and has served as PI of a clinical trial for Relypsa. PF has served on advisory boards for Janssen and AstraZeneca. GL, MD, IK, WS and GM are current or former full-time employees of Janssen Research & Development, LLC.

Author Contributions

REG, MRW, PF and GL contributed to the analysis and interpretation of data and drafted, reviewed and approved the manuscript. MD and GM contributed to the design and conduct of the analysis; the acquisition, analysis and interpretation of data; and drafted, reviewed and approved the manuscript. IK and WS contributed to the conduct of the analysis; the acquisition, analysis and interpretation of the data; and drafted, reviewed and approved the manuscript.

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Appendix

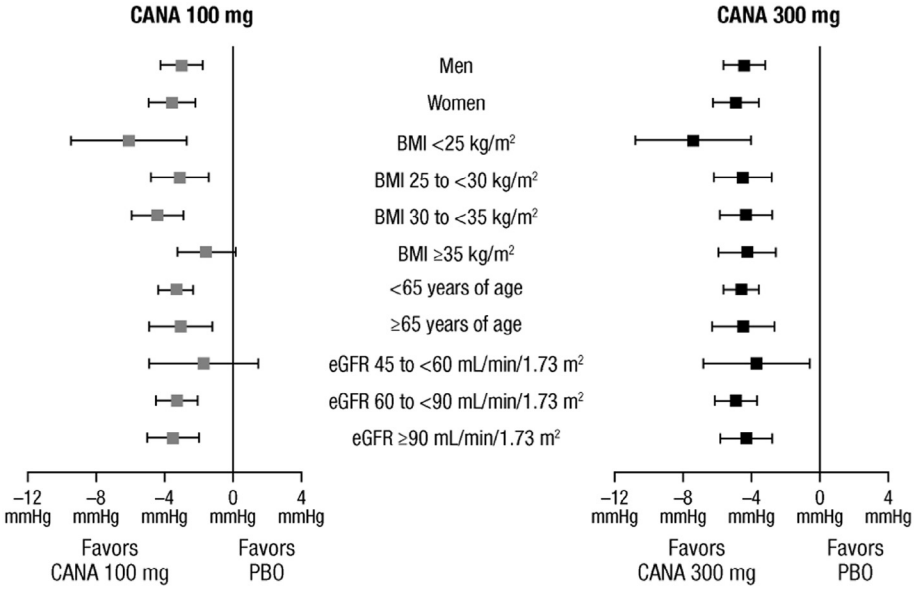
Supplementary Table A1
Baseline demographic and disease characteristics by age[a]

Characteristic	<65 years			≥65 years		
	PBO (n=864)	CANA 100 mg (n=1018)	CANA 300 mg (n=1023)	PBO (n=351)	CANA 100 mg (n=393)	CANA 300 mg (n=404)
Sex, n (%)						
Men	503 (58)	553 (54)	550 (54)	211 (60)	240 (61)	244 (60)
Women	361 (42)	465 (46)	473 (46)	140 (40)	153 (39)	160 (40)
Age, years	54.9±7.4	54.2±7.5	54.5±7.4	69.5±3.9	69.8±3.9	69.7±4.0
Race, n (%)						
White	618 (72)	710 (70)	737 (72)	292 (83)	327 (83)	334 (83)
Black/African American	31 (4)	46 (5)	55 (5)	10 (3)	8 (2)	9 (2)
Asian	142 (16)	157 (15)	150 (15)	27 (8)	27 (7)	33 (8)
Other[b]	73 (8)	105 (10)	81 (8)	22 (6)	31 (8)	28 (7)
eGFR, mL/min/1.73 m^2	85.9±19.6	87.8±18.9	87.4±19.3	72.8±15.4	74.4±15.7	72.5±15.3
eGFR ≥90 mL/min/1.73 m^2, n (%)	338±39	444±44	432±42	42±12	60±15	53±13
eGFR 60 to <90 mL/min/1.73 m^2, n (%)	465±54	522±51	535±52	243±69	262±67	268±66
eGFR 45 to <60 mL/min/1.73 m^2, n (%)	61±7	52±5	56±5	66±19	71±18	83±21
BMI, kg/m^2	32.9±6.8	33.0±6.7	32.8±6.6	32.2±5.5	31.9±5.6	32.1±5.9
Duration of type 2 diabetes, years	9.9±7.2	9.3±7.1	9.4±7.1	15.1±9.2	15.4±8.5	15.0±8.5

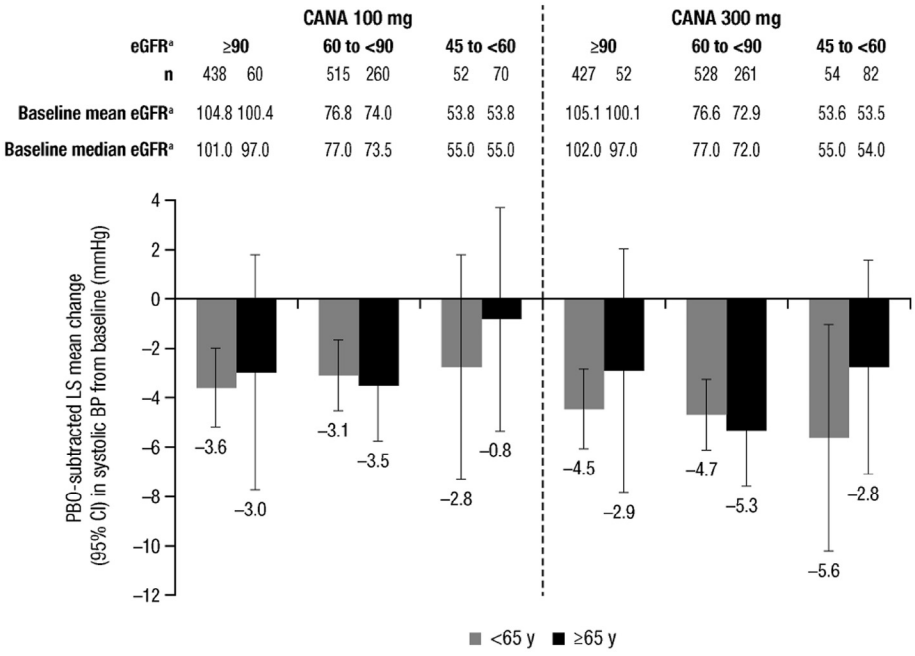
BMI, body mass index; *CANA,* canagliflozin; *eGFR,* estimated glomerular filtration rate; *PBO,* placebo; *SD,* standard deviation.

[a] Data are mean ± SD unless otherwise indicated.

[b] Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, not reported, other and unknown.



Supplementary Figure A1. Differences (95% CIs) between canagliflozin 100 mg and 300 mg vs. placebo in the change in systolic BP from baseline by subgroup (LOCF). *BMI*, body mass index; *BP*, blood pressure; *CANA*, canagliflozin; *CI*, confidence interval; *eGFR*, estimated glomerular filtration rate; *LOCF*, last observation carried forward; *PBO*, placebo.



Supplementary Figure A2. Placebo-subtracted LS mean changes in systolic BP by age at baseline and baseline eGFR (LOCF).
BP, blood pressure; *CANA*, canagliflozin; *CI*, confidence interval; *eGFR*, estimated glomerular filtration rate; *LOCF*, last observation carried forward; *LS*, least squares; *PBO*, placebo.
[a]Unit of mL/min/1.73 m^2 for eGFR.