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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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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
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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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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.