Efficacy and Safety of Canagliflozin, an Inhibitor of Sodium–Glucose Cotransporter 2, When Used in Conjunction With Insulin Therapy in Patients With Type 2 Diabetes

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Diabetes Care 2015;38:403–411 | DOI: 10.2337/dc14-1237

OBJECTIVE

There are limited data about the effects of sodium–glucose cotransporter 2 inhibitors when used with insulin. We report the efficacy and safety of canagliflozin in patients with type 2 diabetes using insulin.

RESEARCH DESIGN AND METHODS

The CANagliflozin CardioVascular Assessment Study is a double-blind, placebo-controlled study that randomized participants to placebo, canagliflozin 100 mg, or canagliflozin 300 mg once daily, added to a range of therapies. The primary end point of this substudy was the change in HbA_{1c} from baseline at 18 weeks among patients using insulin; 52-week effects were also examined.

RESULTS

Individuals receiving insulin at baseline were randomized to receive placebo (n = 690), canagliflozin 100 mg (n = 692), or canagliflozin 300 mg (n = 690). These individuals were 66% male and had a median age of 63 years, mean HbA_{1c} of 8.3% (67 mmol/mol), BMI of 33.1 kg/m^2, estimated glomerular filtration rate of 75 mL/min/1.73 m^2, fasting plasma glucose of 9.2 mmol/L, and a median daily insulin dose of 60 IU. Most individuals were using basal/bolus insulin. Reductions in HbA_{1c} with canagliflozin 100 and 300 mg versus placebo were −0.62% (95% CI −0.69, −0.54; −6.8 mmol/mol [95% CI −7.5, −5.9]; $P < 0.001$) and −0.73% (95% CI −0.81, −0.65; −8.0 mmol/mol [95% CI −8.9, −7.1]; $P < 0.001$) at 18 weeks and −0.58% (95% CI −0.68, −0.48; −6.3 mmol/mol [95% CI −7.4, −5.2]) and −0.73% (95% CI −0.83, −0.63; −8.0 mmol/mol [95% CI −9.1, −6.9]) at 52 weeks. There were significant falls in fasting plasma glucose, body weight, and blood pressure at both time points and there was a greater incidence of hypoglycemia, genital mycotic infections, and hypovolemia with both canagliflozin doses.

CONCLUSIONS

Canagliflozin added to insulin therapy improved glycemic control and decreased body weight. There was a greater frequency of several anticipated side effects, although few led to discontinuation of treatment.

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Received 15 May 2014 and accepted 29 October 2014.

Clinical trial reg. no. NCT01032629, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-1237/-/DC1.

**A complete list of the CANVAS Trial Collaborative Group and collaborating sites can be found in the Supplementary Data online.*

See accompanying articles, pp. 352, 355, 365, 373, 376, 384, 394, 412, 420, 429, and 431.

Type 2 diabetes causes a large burden of disease around the world (1). The control of blood glucose levels is central to the management of symptoms and the prevention of complications (2). There are a broad range of treatments that can be used to lower blood glucose levels, but many patients still fail to achieve targets (3). Accordingly, new therapies that can lower blood glucose levels with good safety and tolerability have significant potential in the future management of the condition.

Inhibition of the sodium–glucose cotransporter 2 (SGLT2) is a novel strategy for glucose control (4–9). SGLT2 is a high-capacity and low-affinity glucose transporter that is expressed in the luminal membranes of the proximal renal tubules and is responsible for the majority of glucose reabsorption from the tubular lumen. An inherited deficiency of SGLT2 can produce renal glucosuria, with some affected individuals excreting as much as 100 g of urinary glucose per day (5). Canagliflozin is an orally active inhibitor of SGLT2 that reduces proximal tubular glucose reabsorption and increases urinary glucose excretion (10–13). Treatment produces a significant loss of glucose, with beneficial effects on glycemic control, body weight, and blood pressure (12,14–22). Small increases in LDL and HDL cholesterol have been observed, with the ratio remaining unchanged (23).

Canagliflozin has a low risk of hypoglycemia in the absence of concomitant therapy, although rates may be increased when used in conjunction with insulin or insulin secretagogues (23,24). The risks of genitourinary infections and lower urinary tract infections are elevated with canagliflozin (23,25,26), but the risks of upper urinary tract infections are not and the rates of treatment discontinuation attributed to side effects are low (12,14–22). This report defines the effects of canagliflozin on indicators of glycemia, safety, and tolerability when used in conjunction with insulin therapy in a prespecified substudy of the CANagliflozin CardioVascular Assessment Study (CANVAS).

RESEARCH DESIGN AND METHODS

Overall Design of the CANVAS Trial

CANVAS is a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial. The study is ongoing and has randomized 4,330 individuals on a 1:1:1 basis to placebo, canagliflozin 100 mg, or canagliflozin 300 mg, with the primary objectives being to determine the efficacy and safety of canagliflozin compared with placebo.

Objectives and Specific Hypotheses for the Insulin Substudy

The purpose of the insulin substudy of the CANVAS trial was to define the 18-week effects of canagliflozin (when used in addition to insulin therapy at a dose of $\geq$20 IU/day) on a range of efficacy, safety, and tolerability outcomes in patients with type 2 diabetes with inadequate glycemic control. The objectives of the substudy were to assess separately the effects of each dose of canagliflozin compared with placebo on HbA_{1c}, safety, and tolerability at the 18-week follow-up. The primary hypothesis was that each dose of canagliflozin would produce a greater reduction in HbA_{1c} compared with placebo.

Secondary objectives of the substudy were to determine the effects, at the 18-week follow-up, of each dose of canagliflozin compared with placebo on body weight, fasting plasma glucose, proportion of participants reaching HbA_{1c} $<$7.0% (53 mmol/mol), systolic and diastolic blood pressure, and fasting plasma lipids (i.e., triglycerides, HDL cholesterol, LDL cholesterol, total cholesterol, and the ratio of LDL cholesterol to HDL cholesterol). For the 52-week assessment, the defined objectives were to determine the effects of each dose of canagliflozin compared with placebo on fasting plasma glucose, body weight, systolic and diastolic blood pressure, and fasting plasma lipids. The prespecified hypotheses for the secondary objectives were related to the 18-week effects on fasting plasma glucose, the proportion of participants reaching HbA_{1c} $<$7.0% (53 mmol/mol), and body weight.

Recruitment

Recruitment for the CANVAS study was performed at 386 centers in 24 countries, commencing in December 2009 and completing in March 2011 (clinical trial reg. no. NCT01032629, clinicaltrials.gov). The 12-month follow-up of the final participants included in this substudy was completed in March 2012. Regulatory approval for the conduct of the trial was obtained in each country, and ethics approval was received at every site prior to initiation of the trial.

Participant Inclusion and Exclusion Criteria

Participants in the CANVAS trial are men and women with type 2 diabetes who have inadequate glycemic control (HbA_{1c} $\geq$7.0% [53 mmol/mol] and $\leq$10.5% [91 mmol/mol]), despite current management with glucose-lowering strategies, and are at an elevated risk of cardiovascular disease. The subset included in the insulin substudy comprised participants that were using $\geq$20 IU/day insulin at baseline. All participants were required to provide informed consent, be willing and able to adhere to the study protocol requirements, and successfully complete the trial screening and run-in period. To ensure the recruitment of a broad population group, there were minimal restrictions on the use of background therapies. Patients using insulin pumps were not excluded from the study. All participants had an established or an elevated risk of cardiovascular disease and were either $\geq$30 years of age with a history of symptomatic atherosclerotic vascular disease (coronary, cerebrovascular, or peripheral) or $\geq$50 years of age with two or more of the following risk factors: $\geq$10 years duration of diabetes, systolic blood pressure $>$140 mmHg while receiving one or more or antihypertensive agents, current smoking, microalbuminuria or macroalbuminuria, or HDL cholesterol $<$1 mmol/L. Individuals with an estimated glomerular filtration rate (eGFR) $<$30 mL/min/1.73 m^2 at baseline were not eligible for inclusion in the study. Other exclusion criteria were typical of those usually invoked for a trial of this stage in this patient group (27).

Screening and Run-in Period

All potential participants completed a screening visit to establish initial eligibility and progressed to a 2-week, single-blind, placebo run-in period if the screening criteria were met. The primary purpose of the run-in period was to exclude, prior to randomization, those individuals who were unlikely to adhere to the long-term treatment and follow-up regimen required by the trial.

Randomization

Randomization was performed centrally through an interactive voice response system or an interactive web response system. Participants were randomly assigned on the basis of a computer-generated randomization schedule prepared by the study sponsor. Randomization was in a 1:1:1 ratio to one of three treatment groups, canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo, using randomly permuted blocks, with stratification by use of background glucose-lowering therapy at screening (i.e., insulin alone, insulin plus metformin, or insulin plus any other glucose-lowering agent).

Postrandomization Study Treatment and Control

Study treatment was provided in identical blister cards of canagliflozin 100 mg, canagliflozin 300 mg, or placebo. Participants took their study treatment once daily before the first meal of the day, with all participants and all study staff remaining blinded to individual treatment allocation.

Background Drug Treatments

Participants were required to be receiving stable background glucose-lowering therapy, including insulin, for 8 weeks before screening and to persist with this treatment regimen unchanged, if possible, for the first 18 weeks after randomization. The rationale for this strategy was the desire to evaluate the short-term (18-week) effects of canagliflozin on biomarkers while receiving constant background therapy. A stable dose of insulin was defined as no change in the type(s) of insulin used and no change of >15% in the total daily dose of insulin used (averaged over 1 week to account for day-to-day variability). Criteria for the institution of glycemic rescue therapy in the first 18 weeks after randomization were provided for patients with significant derangements of blood glucose levels during the initial 18-week period (Supplementary Table 3). After week 18, glycemic management was at the discretion of the responsible investigator, in line with applicable local guidelines. Likewise, the use of all other therapies was managed according to best practice and instituted according to local guidelines and policies throughout the study period.

Follow-up Schedule

Postrandomization follow-up was scheduled at 2, 4, 6, 9, 12, 18, 26, 39, and 52 weeks after randomization. The follow-up performed at 2, 4, and 9 weeks after randomization was by telephone, unless a face-to-face consultation was deemed necessary. Every follow-up contact included inquiry about adverse events (including safety outcomes) and concomitant therapies and a review of the patient diary entries and self-monitored blood glucose results. All face-to-face visits also included prescription of study medication and recording of physical measurements. Individuals who prematurely discontinued study treatment were encouraged to return for regular assessments to ensure full ascertainment of study outcomes and to support an intention-to-treat analysis for all outcomes.

Outcomes

The primary efficacy outcome for this substudy was the change in HbA_{1c}. The secondary efficacy outcomes were fasting plasma glucose, proportion of participants reaching HbA_{1c} <7.0% (53 mmol/mol), body weight, systolic and diastolic blood pressure, and fasting plasma lipids (i.e., triglycerides, HDL cholesterol, LDL cholesterol, total cholesterol, and the ratio of LDL cholesterol to HDL cholesterol).

Safety was defined based upon the occurrence of adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA), with data reported for all adverse events, serious adverse events, deaths, and adverse events prespecified as being of specific interest (i.e., genital mycotic infections in women and men, upper and lower urinary tract infections, fractures, and photosensitivity). Hypoglycemia episodes, defined as biochemically documented episodes (concurrent fingerstick or plasma glucose ≤3.9 mmol/L, irrespective of symptoms), and severe hypoglycemia episodes (i.e., requiring the assistance of another individual or resulting in seizure or loss of consciousness) were also reported. The proportion of participants permanently discontinuing randomized treatment was recorded.

Statistical Analyses

Efficacy and safety analyses were performed using the modified intent-to-treat population, consisting of all eligible randomized patients who received ≥1 dose of the study drug. The last observation carried forward (LOCF) approach was used to impute missing efficacy data. Efficacy end points of a continuous nature were assessed using an ANCOVA model, with treatment and stratification factor (i.e., background glucose-lowering therapy at screening) as fixed effects, and the corresponding baseline value as a covariate. Least squares mean differences between treatment groups and the associated two-sided 95% CIs were estimated based on this model. The categorical secondary efficacy end point (i.e., the proportion of patients reaching HbA_{1c} <7.0% [53 mmol/mol]) was analyzed using a logistic regression model, including terms for treatment and stratification factor and adjusting for baseline HbA_{1c} as a covariate. A prespecified, hierarchical testing sequence, which controls the type I error rate by ordering the hypotheses to undergo statistical testing, was used to evaluate the prespecified 18-week hypotheses (28). For all other outcomes where no hypothesis was prespecified, the data are presented as point estimates and 95% CIs with no *P* value. The primary efficacy analyses at 18 weeks were calculated censoring the data after the initiation of rescue therapy. All other analyses were computed regardless of the use of nonrandomized background therapies.

The constancy of effects in participant subgroups defined by sex, age, race, ethnicity, BMI, baseline HbA_{1c}, and baseline eGFR was explored for the 52-week time point. Analyses were undertaken for the primary outcome only, with the effects in subgroups compared using tests of the treatment by subgroup interaction to assess homogeneity. A series of sensitivity analyses was calculated to check the robustness of the study findings. First, the 18-week efficacy analyses were repeated including participants regardless of whether they required rescue therapy. Second, the efficacy analyses were repeated for all CANVAS trial participants who recorded any use of insulin at baseline (i.e., ≥1 IU/day, *n* = 2,168; see data in Supplementary Data) and, third, for the smaller group of participants using a baseline insulin dose of ≥30 IU/day (*n* = 1,718; data not shown, but conclusions not different). Finally, subsequent to locking the

substudy database, there were two individuals identified who had implausible low LDL cholesterol values at baseline (possibly because of laboratory errors), who were excluded from the lipid analyses but were included in all other analyses.

RESULTS

During a recruitment period of 15 months, there were 7,691 individuals who were screened and 4,330 who were randomized (Supplementary Fig. 1). There were 2,074 CANVAS trial participants who met the inclusion criteria for this substudy (insulin use at a dose of ≥20 IU/day), with 2 participants excluded from the final analysis since they received no dose of the randomized treatment. Furthermore, there were 94 individuals receiving treatment with insulin at baseline at a dose of 1–19 IU/day, and there were 1,718 individuals in the subset of participants receiving insulin at baseline at a dose ≥30 IU/day. Among the 2,072 individuals included in the primary analysis, there were 690 assigned to placebo, 692 assigned to canagliflozin 100 mg, and 690 assigned to canagliflozin 300 mg (Supplementary Fig. 1). Four percent of each active treatment group and 8% of the placebo group required rescue therapy during the first 18 weeks. At the end of 52 weeks, the change in the total daily dose of insulin from baseline was 4.4 IU/day (11%), −2.0 IU/day (−1%), and −4.3 IU/day (−4%) among individuals receiving placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. A total of 88% of participants completed the scheduled 52-week follow-up visits. At 18 weeks, there were an estimated 94% assigned to placebo, 95% assigned to canagliflozin 100 mg, and 94% assigned to canagliflozin 300 mg who were still receiving randomized treatment; the corresponding percentages at 52 weeks were 85%, 89%, and 89%, respectively.

Baseline Characteristics of Participants

At entry into the study, the median age of participants was 63 years, the mean HbA_{1c} was 8.3% (67 mmol/mol), the mean BMI was 33.1 kg/m^2, the mean eGFR was 75 mL/min/1.73 m^2, and the mean fasting plasma glucose was 9.2 mmol/L (Table 1). The median daily insulin dose was 60 IU, with most using basal/bolus insulin regimens. The mean duration of diabetes was 16 years. About one-quarter of participants were receiving background sulfonylurea therapy, two-thirds were receiving metformin therapy, and three-quarters each were receiving statin and antithrombotic therapy. All characteristics were balanced across randomized groups at baseline.

Effects of Canagliflozin on Efficacy Outcomes

Both doses of canagliflozin significantly reduced the primary outcome of HbA_{1c} relative to placebo at week 18 (both $P < 0.001$), with comparable reductions also seen at week 52 (Table 2, Fig. 1). There were also reductions in the secondary outcomes of body weight and fasting plasma glucose (all $P < 0.001$, Table 2) and increases in the proportion of patients achieving HbA_{1c} <7.0% (53 mmol/mol) (both $P < 0.001$, Fig. 1) with both canagliflozin doses versus placebo at week 18. Similar effects were seen for all outcomes at week 52. Canagliflozin 100 and 300 mg also provided dose-dependent reductions in systolic blood pressure compared with placebo at both time points (Table 2). The higher dose of canagliflozin raised HDL cholesterol levels compared with placebo at both 18 and 52 weeks, but the lower dose raised levels only at 52 weeks. Canagliflozin 100 and 300 mg caused an elevation in LDL cholesterol at 18 and 52 weeks, but there was no detectable change in the ratio of LDL cholesterol to HDL cholesterol at either time point for either dose. There was a reduction in triglycerides only with the 300-mg dose at 52 weeks. Where effects were apparent, they were mostly numerically greater for the higher dose. Analyses that did not censor individuals requiring rescue therapy in the first 18 weeks showed almost identical results (Supplementary Table 1). Likewise, sensitivity analyses that included patients using insulin at any dose (Supplementary Table 2) or only at doses ≥30 IU (data not shown) did not change the conclusions. Subgroup analyses identified greater effects on HbA_{1c} only for younger individuals compared with older individuals (P = 0.02) and for more obese individuals compared with less obese individuals (P = 0.05), but there was no evidence of an interaction between treatment effect and the other baseline characteristics studied (all P values >0.17; Supplementary Fig. 2). Active treatment was observed to reduce albuminuria at both doses at 12- and 52-week time points compared with placebo, with mean reductions in the albumin-to-creatinine ratio of −9.6 (95% CI −13.0, −6.1) for the 100-mg dose and −9.5 (95% CI −12.9, −6.0) for the 300-mg dose at 52 weeks.

Effects of Canagliflozin on Safety and Tolerability Outcomes

At 52 weeks of follow-up, adverse events were reported for 77%, 78%, and 81% of participants treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively (Table 3). The corresponding percentages for serious adverse events were 17%, 14%, and 15%, respectively. Adverse events leading to discontinuation of treatment were significantly more frequent with canagliflozin treatment compared with placebo, as were genital mycotic infections in men and women, and volume-related adverse events. Genital mycotic infections were more common with both doses of canagliflozin for women and men, but there was no evidence of an increased rate of upper or lower urinary tract infections. Adverse events attributable to volume depletion were mostly postural hypotension and dizziness. The rates of documented hypoglycemia were not significantly greater with canagliflozin than placebo, and the proportion of cases defined as severe hypoglycemia was low and was not significantly different across treatment groups (Table 3). There was a decline in the mean eGFR at 52 weeks of −1.2 mL/min/1.73 m^2 (95% CI −2.3, −0.1) with the 100-mg dose and −2.1 mL/min/1.73 m^2 (95% CI −3.2, −0.9) with the 300-mg dose. These effects were attenuated compared with the 18-week findings of a decline in mean eGFR of −2.6 mL/min/1.73 m^2 (95% CI −3.6, −1.6) with the 100-mg dose and −3.2 mL/min/1.73 m^2 (95% CI −4.2, −2.2) with the 300-mg dose.

CONCLUSIONS

There were clear beneficial effects on HbA_{1c} of adding canagliflozin to background insulin therapy. These benefits were apparent at 18 weeks and were sustained through 52 weeks for both

Table 1—Baseline characteristics of randomized participants using insulin (≥20 IU/day) at baseline

	Placebo (*n* = 690)	Canagliflozin 100 mg (*n* = 692)	Canagliflozin 300 mg (*n* = 690)
Age (years), median (range)	63.0 (38–82)	62.0 (32–83)	63.0 (37–85)
Female (%)	34	33	35
Race (%)*			
White	75	76	76
Asian	18	15	15
Black	3	2	3
Other†	5	7	6
Current smoker, *n* (%)	114 (17)	96 (14)	99 (14)
Duration of diabetes (years), mean (SD)	16.0 (7.8)	16.4 (7.3)	16.3 (7.4)
Insulin dose (IU/day), median	58	60	60
Insulin therapy, *n* (%)‡			
Basal plus bolus	427 (62)	443 (64)	428 (62)
Basal alone	178 (26)	189 (27)	182 (26)
Bolus alone	76 (11)	49 (7)	66 (10)
Other drug therapy, *n* (%)			
Sulfonylurea	170 (25)	165 (24)	156 (23)
Metformin	438 (64)	435 (63)	430 (62)
Statin	521 (76)	538 (78)	513 (74)
Antithrombotic	504 (73)	501 (72)	506 (73)
Microvascular disease, *n* (%)			
Retinopathy	193 (28)	189 (27)	213 (31)
Nephropathy	146 (21)	141 (20)	133 (19)
Neuropathy	277 (40)	260 (38)	293 (43)
Atherosclerotic vascular disease, *n* (%)§			
Coronary	350 (51)	343 (50)	378 (55)
Cerebrovascular	110 (16)	107 (16)	118 (17)
Peripheral	109 (16)	115 (17)	135 (20)
Any	436 (63)	434 (63)	470 (68)
BMI (kg/m^2), mean (SD)	33.1 (6.5)	33.0 (6.5)	33.3 (6.2)
Body weight (kg), mean (SD)	94.8 (22.3)	94.4 (21.6)	94.8 (21.3)
SBP (mmHg), mean (SD)	137.8 (16.2)	136.9 (16.7)	137.1 (16.7)
DBP (mmHg), mean (SD)	77.2 (10.3)	76.2 (9.9)	76.3 (9.8)
HbA_{1c}, mean (SD)			
%	8.3 (0.9)	8.3 (0.9)	8.3 (0.9)
mmol/mol	67.0 (9.8)	67.0 (9.8)	67.0 (9.8)
FPG (mmol/L), mean (SD)	9.2 (2.7)	9.2 (2.7)	9.2 (2.8)
Total cholesterol (mmol/L), mean (SD)	4.3 (1.2)	4.3 (1.2)	4.3 (1.0)
Triglycerides (mmol/L), mean (SD)	2.0 (1.9)	2.0 (1.3)	1.9 (1.3)
HDL cholesterol (mmol/L), mean (SD)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
LDL cholesterol (mmol/L), mean (SD)	2.2 (0.9)	2.2 (0.9)	2.3 (0.9)
LDL-to-HDL cholesterol ratio, mean (SD)	2.0 (0.9)	1.9 (0.8)	2.0 (0.9)
eGFR (mL/min/1.73 m^2), mean (SD)	74.9 (19.2)	76.2 (19.1)	73.7 (18.7)
eGFR $<$60 mL/min/1.73 m^2, *n* (%)	140 (20)	130 (19)	149 (22)
ACR (mg/g), mean (SD)	139.5 (459.6)	105.8 (418.2)	113.3 (344.8)
Microalbuminuria, *n* (%)	159 (23)	188 (27)	156 (23)
Macroalbuminuria, *n* (%)	69 (10)	46 (7)	54 (8)

ACR, albumin-to-creatinine ratio; DBP, diastolic blood pressure; FPG, fasting plasma glucose; SBP, systolic blood pressure. *Percentages may not total 100% due to rounding. †Including American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, multiple, other, and unknown. ‡Data on dosing regimen are missing for 1–2% of individuals. §Some participants had more than one type of atherosclerotic disease at baseline.

doses of canagliflozin compared with placebo. The reductions in HbA_{1c} were accompanied by favorable effects on body weight and blood pressure, which were also observed for both doses and over 52 weeks. These benefits were accompanied by the adverse effects anticipated for the drug class (24). Effects on lipid metabolism were inconsistent, but the broad pattern was similar to that reported previously (23). The net impact of the changes in lipid parameters produced by canagliflozin is uncertain, with the elevation in LDL cholesterol accompanied by a rise in HDL cholesterol that leaves the ratio of LDL cholesterol to HDL cholesterol unchanged. The hazard ratio for cardiovascular events reported during the regulatory review process prior to marketing was not suggestive of harm and

Table 2—Effects of each dose of canagliflozin compared with placebo on primary, secondary, and other efficacy outcomes at 18 and 52 weeks in patients using insulin (≥20 IU/day)

	18 weeks*		52 weeks†	
	Canagliflozin 100 mg vs. placebo (*n* = 661 vs. 636)‡	Canagliflozin 300 mg vs. placebo (*n* = 660 vs. 636)‡	Canagliflozin 100 mg vs. placebo (*n* = 664 vs. 639)‡	Canagliflozin 300 mg vs. placebo (*n* = 664 vs. 639)‡
Change in HbA_{1c}§				
%	−0.62 (−0.69, −0.54)‖	−0.73 (−0.81, −0.65)‖	−0.58 (−0.68, −0.48)	−0.73 (−0.83, −0.63)
mmol/mol	−6.8 (−7.5, −5.9)	−8.0 (−8.9, −7.1)	−6.3 (−7.4, −5.2)	−8.0 (−9.1, −6.9)
Change in body weight (%)§	−1.9 (−2.2, −1.6)‖	−2.4 (−2.7, −2.1)‖	−2.8 (−3.3, −2.4)	−3.5 (−3.9, −3.0)
Change in FPG (mmol/L)§	−1.2 (−1.4, −0.9)‖	−1.6 (−1.8, −1.3)‖	−1.1 (−1.4, −0.9)	−1.5 (−1.7, −1.2)
Change in SBP (mmHg)	−2.3 (−3.7, −1.0)	−4.1 (−5.5, −2.8)	−3.1 (−4.6, −1.7)	−6.2 (−7.7, −4.8)
Change in DBP (mmHg)	−1.0 (−1.8, −0.2)	−1.7 (−2.5, −0.9)	−1.2 (−2.0, −0.3)	−2.4 (−3.2, −1.5)
Proportion with HbA_{1c} <7.0% (%)§	11.5 (7.6, 15.4)‖	17.4 (13.3, 21.5)‖	13.3 (9.3, 17.4)	18.7 (14.5, 23.0)
Change in HDL cholesterol (%)	1.1 (−0.8, 3.0)	4.5 (2.6, 6.4)	2.3 (0.5, 4.1)	5.0 (3.3, 6.8)
Change in triglycerides (%)	−1.0 (−5.5, 3.4)	−2.7 (−7.1, 1.8)	−1.6 (−6.5, 3.3)	−5.6 (−10.5, −0.7)
Change in LDL cholesterol (%)¶	5.5 (−0.9, 11.9)	4.9 (−1.5, 11.3)	3.5 (−2.0, 8.9)	6.8 (1.3, 12.2)
Change in total cholesterol (%)	1.1 (−0.7, 3.0)	2.8 (0.9, 4.7)	1.6 (−0.5, 3.7)	3.1 (1.0, 5.2)
Change in LDL-to-HDL cholesterol ratio (%)§	4.0 (−2.5, 10.4)	0.4 (−6.0, 6.8)	1.1 (−4.6, 6.8)	0.7 (−5.0, 6.4)
Change in non-HDL cholesterol (%)	1.0 (−1.6, 3.6)	2.2 (−0.4, 4.8)	1.8 (−1.3, 4.9)	2.7 (−0.5, 5.7)

Data are presented as difference (95% CI). DBP, diastolic blood pressure; FPG, fasting plasma glucose; SBP, systolic blood pressure. *For patients not requiring rescue therapy. †For all participants regardless of need for rescue therapy. ‡Exact *n* for the primary outcome or patients with missing data, the last observation was carried forward. §Indicates end points that were prespecified for hypothesis testing at week 18. ‖$P < 0.001$ vs. placebo for all prespecified hypotheses. ¶Outlying data from two subjects were excluded at week 52. Differences (95% CI) vs. placebo for canagliflozin 100 mg and 300 mg with outliers included the following: LDL cholesterol, 16.7% (0.3, 33.0) and 7.4% (−9.1, 23.8), respectively; LDL-to-HDL cholesterol ratio, 11.2% (−2.2, 24.7) and 0.8% (−12.7, 14.3), respectively.

ruled out large adverse effects of the compound (23).

The observed additive effects of canagliflozin on top of insulin are anticipated on the basis of the different mechanism of action of the compound. Because canagliflozin acts independently of insulin, it should be an effective treatment choice at most stages of the disease and also when used in conjunction with most other glucose-lowering therapies. Furthermore, the combination of canagliflozin with insulin may offer advantages compared with the combination of insulin with other oral agents because the use of canagliflozin may mitigate against the risks of hypoglycemia and weight gain that can be exacerbated by some other drug classes (29). The subset of patients among whom glucose-lowering efficacy might be reduced is those with renal impairment (23), and this might explain the lesser effect of canagliflozin among older individuals in this study. Alternatively, this may also be a chance finding because, as for the observed interaction with obesity, the *P* value was not extreme and age and obesity have not been identified as effect modifiers in larger data sets (23).

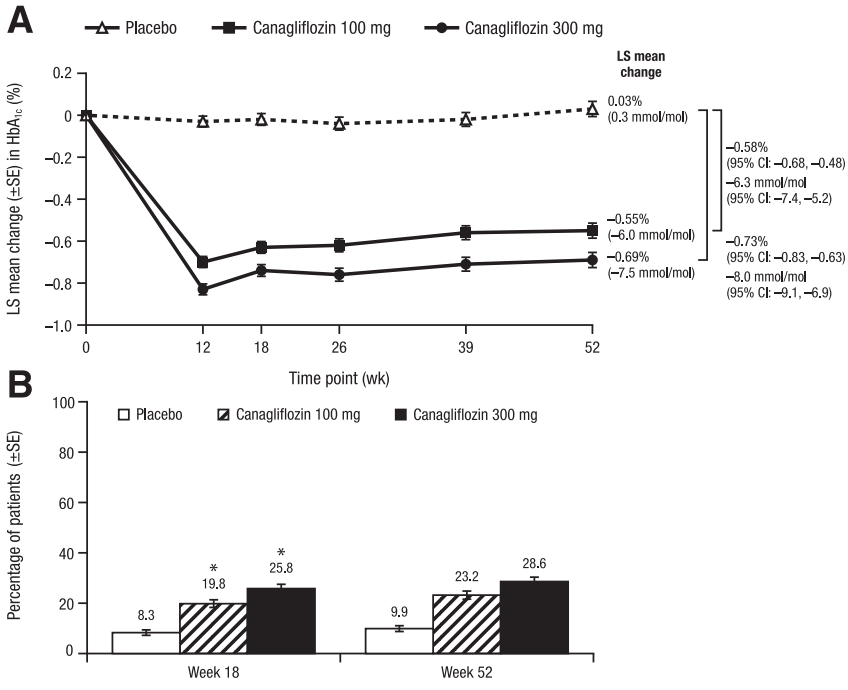

Figure 1—Effects of each dose of canagliflozin compared with placebo on measures of glycemia in patients using insulin (≥20 IU/day). *A*: LS mean change in HbA_{1c} from baseline to week 52. For patients with missing data, the last observation was carried forward. *B*: Proportion of patients reaching HbA_{1c} <7.0% (53 mmol/mol) at 18 and 52 weeks. LS, least squares. *$P < 0.001$ vs. placebo.

The 300-mg dose of canagliflozin was associated with numerically greater effects on most efficacy outcomes, although the incremental changes were moderate when compared against the differences between the 100-mg dose of canagliflozin and placebo. The additional efficacy effects conferred by the higher dose were achieved at the

Table 3—Effects of each dose of canagliflozin compared with placebo on safety outcomes at 52 weeks

	Placebo (*n* = 690)	Canagliflozin 100 mg (*n* = 692)	Canagliflozin 300 mg (*n* = 690)
All adverse events	533 (77)	540 (78)	558 (81)
Serious adverse events	115 (17)	94 (14)	104 (15)
Deaths	10 (1)	6 (1)	7 (1)
Event leading to discontinuation	34 (5)	29 (4)	48 (7)
Events related to study drug	144 (21)	233 (34)	267 (39)
Infections			
Genital mycotic infections in women*	7 (3)	41 (18)	32 (13)
Genital mycotic infections in men†	7 (2)	35 (8)	55 (12)
Upper urinary tract infections	4 (1)	4 (1)	0
Lower urinary tract infections	36 (5)	36 (5)	42 (6)
Documented hypoglycemia	333 (48)	409 (59)	396 (57)
Severe hypoglycemia	27 (4)	31 (5)	38 (6)
Osmotic diuresis–related adverse events	17 (2)	59 (9)	69 (10)
Volume-related adverse events	14 (2)	25 (4)	42 (6)
Renal-related adverse events	6 (1)	5 (1)	7 (1)
Photosensitivity events	1 (0.1)	1 (0.1)	3 (0.4)
Fractures	11 (2)	18 (3)	8 (1)

Data are presented as *n* (%). *Women: placebo, *n* = 232; canagliflozin 100 mg, *n* = 227; canagliflozin 300 mg, *n* = 244. †Men: placebo, *n* = 458; canagliflozin 100 mg, *n* = 465; canagliflozin 300 mg, *n* = 446.

expense of an increased risk of drug-related adverse events, driven primarily by a dose-related increase in side effects attributable to volume depletion. The balance of risks and benefits associated with each dose will need to be determined on an individual basis by the prescribing physician.

The adverse effects of canagliflozin observed in this subset of patients using background insulin are those anticipated for the drug class (24). Genital mycotic infections were common but were generally mild or moderate in intensity, were managed with topical or oral antifungal drugs, and led to few discontinuations of randomized treatment. Rates of urinary tract infections were not clearly higher, although pooled analyses of larger data sets show that this is an adverse effect of this drug class when used in patients with diabetes (24). Symptoms attributable to volume depletion were dose related but did not cause serious adverse outcomes. There have been reports (24) of adverse effects of blood pressure–lowering agents on fall-related fractures attributed to volume depletion, and this also may be an effect of the SGLT2 drug class. The few fracture events recorded in this substudy were, however, balanced across groups. The observed decline in eGFR occurred relatively early (i.e., within the first 3–6 weeks after initiating therapy with canagliflozin), was attenuated over time, and was not associated with an excess of renal adverse events. The time course of the decline in eGFR parallels that of reduced numbers of intravascular volume adverse events, which also start early after initiating therapy with canagliflozin (30). The reduction in the albumin-to-creatinine ratio could be attributed to the effects of canagliflozin on blood pressure or blood glucose, and there is also some evidence to support a mechanism based upon tubuloglomerular feedback (31). The mechanism for weight loss was not explored in this trial, but other studies (15) have reported that about two-thirds of the effect is due to a reduction in fat.

A key strength of this study is its large size and its robust randomized and controlled design. The conduct of analyses at both 18 and 52 weeks provides estimates of both short- and medium-term effects, although the long-term impact of canagliflozin in this group remains to be established. The completeness of follow-up for the main efficacy and safety outcomes was good and the findings were robust to a series of sensitivity analyses. It is possible that some individuals may have been unblinded because of the effects of active treatment on diuresis or glucosuria, but this is unlikely to have substantively impacted the main trial conclusions, which are based mostly on fairly objective outcome measures. The absence of clear evidence about the effects of canagliflozin on definitive clinical outcomes in either this population using insulin or in broader patient groups with diabetes remains a significant shortcoming of the existing evidence base, although this should be rectified as a series of large ongoing trials are completed over the coming years. The enrollment of a high-risk patient group in the CANVAS trial was performed both to ensure that the study had power to address its efficacy and safety objectives and to increase the diversity of participants in the broader canagliflozin development program. While aspects of the results obtained here cannot be generalized directly to other patient populations, it is likely that the proportionate effects observed here are more broadly applicable. Older patients may have individualized HbA_{1c} targets above the 7.0% level defined as a secondary outcome for this study. It is of note that similarly large and significant benefits of canagliflozin compared with placebo were also observed when effects on target levels of 7.5% and 8.0% were examined.

In conclusion, canagliflozin appears to offer significant benefits when used in conjunction with insulin therapy. However, additional data are required for the subset of patients using insulin and for patients with diabetes more broadly to objectively define the effects of canagliflozin on major clinical outcomes.

Acknowledgments. The authors thank Kimberly Dittmar, of MedErgy, for technical editorial assistance. The authors also acknowledge the following committees and sponsor of the CANagliflozin CardioVascular Assessment Study: Steering Committee—D. Matthews (Co-chair), B. Neal (Co-chair), G. Fulcher, K. Mahaffey, V. Perkovic, G. Meininger, and D. de Zeeuw; Independent Data Monitoring Committee—P. Home (Chair), J. Anderson, I. Campbell, J. Lachin, D. Scharfstein, S. Solomon, and R. Uzzo; Endpoint Adjudication Committee—G. Fulcher, J. Amerena, C. Chow, G. Figtree, J. French, G. Hillis, B. Jenkins,

R. Lindley, B. McGrath, A. Street, and J. Watson; Sponsor—Janssen Research & Development, LLC.

Funding. B.N. is supported by an Australian Research Council Future Fellowship and a National Health and Medical Research Council Senior Research Fellowship. V.P. is supported by a Senior Research Fellowship from the Australian National Health and Medical Research Council.

Duality of Interest. The CANVAS trial is funded by Janssen Research & Development, LLC. Technical editorial assistance was funded by Janssen Global Services, LLC. B.N. holds a research grant for this study from Janssen, and for other large-scale cardiovascular outcome trials from Roche, Servier, and Merck/Schering-Plough. B.N. has received honoraria or travel support for contributions to the continuing medical education programs of Abbott, Novartis, Pfizer, Roche, and Servier. V.P. has served on advisory boards and/or spoken at scientific meetings sponsored by Janssen, Baxter, AbbVie, Astellas, Boehringer Ingelheim, AstraZeneca, Merck, and GlaxoSmithKline and has a policy of honoraria going to his employer. D.d.Z. has served as a consultant to AstraZeneca, Amgen, Abbot, Merck, Bristol-Myers Squibb, Novartis, Vitae, Takeda, HemoCue, Johnson & Johnson, Reata, Astellas, AbbVie, and ChemoCentryx. K.W.M. has provided continuing medical education on behalf of and/or has served as a consultant to the American College of Cardiology, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Johnson & Johnson, Medtronic, Merck, Spring Publishing, The Medicines Company, and WebMD. G.F. has served on advisory boards for Johnson & Johnson and as a consultant to Janssen. K.W., G.C., F.V., and G.M. are full-time employees of Janssen Research & Development, LLC, and are shareholders of Johnson & Johnson. M.D., W.S., M.A., and J.J. are full-time employees of Janssen Research & Development, LLC. D.M. has served on advisory boards or as a consultant for Novo Nordisk, GlaxoSmithKline, Novartis, Eli Lilly, Sanofi Aventis, Janssen, and Servier and has given lectures for Novo Nordisk, Servier, Sanofi Aventis, Eli Lilly, Novartis, Janssen, and Aché Laboratories. D.M. receives current research support from Janssen and the National Institute for Health Research. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. B.N. contributed to the design and conduct of the study and the interpretation of the data, wrote the first draft of the manuscript, and reviewed and approved the manuscript. V.P., D.d.Z., K.W.M., G.F., and D.M. contributed to the design and conduct of the study and the interpretation of data and reviewed and approved the manuscript. K.W. contributed to the design of the study and the analysis and interpretation of data and reviewed and approved the manuscript. M.D. and F.V. contributed to the conduct of the study and the acquisition and interpretation of data and reviewed and approved the manuscript. W.S. contributed to the design and conduct of the study and the acquisition of data and reviewed and approved the manuscript. G.C. and J.J. contributed to the analysis and interpretation of the data and reviewed and approved the manuscript. M.A. contributed to the interpretation of the data and reviewed and approved the manuscript. G.M. contributed to the design and conduct of the study and the acquisition, analysis, and interpretation of the data and reviewed and approved the manuscript. B.N. and M.D. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were previously presented in abstract form at the 48th Annual Meeting of the European Association for the Study of Diabetes, Berlin, Germany, 1–5 October 2012; and at the World Diabetes Congress of the International Diabetes Federation, Melbourne, Victoria, Australia, 2–6 December 2013.

References

1. Unwin N, Gan D, Mbanya J, et al. *Diabetes Atlas*. Brussels, Belgium, International Diabetes Federation, 2009
2. Turnbull FM, Abraira C, Anderson RJ, et al.; Control Group. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288–2298
3. American Diabetes Association. Executive summary: standards of medical care in diabetes—2010. Diabetes Care 2010;33(Suppl. 1): S4–S10
4. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care 2009;32:650–657
5. Wright EM. Renal Na(+)-glucose cotransporters. Am J Physiol Renal Physiol 2001;280:F10–F18
6. Bailey CJ. Renal glucose reabsorption inhibitors to treat diabetes. Trends Pharmacol Sci 2011;32:63–71
7. Mogensen CE. Maximum tubular reabsorption capacity for glucose and renal hemodynamcis during rapid hypertonic glucose infusion in normal and diabetic subjects. Scand J Clin Lab Invest 1971;28:101–109
8. Mather A, Pollock C. Glucose handling by the kidney. Kidney Int Suppl 2011:S1–S6
9. Rahmoune H, Thompson PW, Ward JM, Smith CD, Hong G, Brown J. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. Diabetes 2005;54: 3427–3434
10. Devineni D, Morrow L, Hompesch M, et al. Canagliflozin improves glycaemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin. Diabetes Obes Metab 2012;14:539–545
11. Polidori D, Sha S, Ghosh A, Plum-Mörschel L, Heise T, Rothenberg P. Validation of a novel method for determining the renal threshold for glucose excretion in untreated and canagliflozin-treated subjects with type 2 diabetes mellitus. J Clin Endocrinol Metab 2013;98:E867–E871
12. Rosenstock J, Aggarwal N, Polidori D, et al.; Canagliflozin DIA 2001 Study Group. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care 2012;35:1232–1238
13. Sha S, Devineni D, Ghosh A, et al. Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, dose dependently reduces calculated renal threshold for glucose excretion and increases urinary glucose excretion in healthy subjects. Diabetes Obes Metab 2011;13:669–672
14. Bode B, Stenlöf K, Sullivan D, Fung A, Usiskin K. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hosp Pract (1995) 2013;41: 72–84
15. Cefalu WT, Leiter LA, Yoon K-H, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet 2013;382:941–950
16. Lavalle-González FJ, Januszewicz A, Davidson J, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia 2013;56:2582–2592
17. Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. Diabetes Care 2013;36:2508–2515
18. Stenlöf K, Cefalu WT, Kim KA, et al. Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. Curr Med Res Opin 2014;30:163–175
19. Stenlöf K, Cefalu WT, Kim K-A, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 2013;15:372–382
20. Wilding JP, Charpentier G, Hollander P, et al. 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 2013;67: 1267–1282
21. Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab 2013;15:463–473
22. Inagaki N, Kondo K, Yoshinari T, Maruyama N, Susuta Y, Kuki H. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. Diabetes Obes Metab 2013;15:1136–1145
23. Janssen Research & Development, LLC; Endocrinologic and Metabolic Drugs Advisory Committee. Canagliflozin as an adjunctive treatment to diet and exercise alone or coadministered with other antihyperglycemic agents to improve glycemic control in adults with type 2 diabetes mellitus. JNJ-28431754 (Canagliflozin). NDA 204042 [Internet], 2013. Available from http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm334551.pdf. Accessed 15 January 2014

24. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013;159:262–274
25. Nicolle LE, Capuano G, Fung A, Usiskin K. Urinary tract infection in randomized phase III studies of canagliflozin, a sodium glucose co-transporter 2 inhibitor. Postgrad Med 2014;126:7–17
26. Nyirjesy P, Sobel JD, Fung A, et al. Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. Curr Med Res Opin 2014;30:1109–1119
27. Neal B, Perkovic V, de Zeeuw D, et al. Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)—a randomized placebo-controlled trial. Am Heart J 2013;166:217–223, e11
28. Koch G, Gansky S. Statistical considerations for multiplicity in confirmatory protocols. Drug Inf J 1996;30:523–534
29. Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). 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 2012;35:1364–1379
30. Usiskin K, Kline I, Fung A, Mayer C, Meininger G. Safety and tolerability of canagliflozin in patients with type 2 diabetes mellitus: pooled analysis of phase 3 study results. Postgrad Med 2014;126:16–34
31. Abdul-Ghani MA, Norton L, Defronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. Endocr Rev 2011;32:515–531