Received: 24 August 2018 | Revised: 26 October 2018 | Accepted: 1 November 2018

DOI: 10.1111/dom.13573

WILEY

ORIGINAL ARTICLE

# CANadian CAnagliflozin REgistry: Effectiveness and safety of canagliflozin in the treatment of type 2 diabetes mellitus in Canadian clinical practice

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**Funding information**
This study was sponsored by Janssen Research and Development, LLC.

**Aim:** There is limited information concerning the effects of canagliflozin (CANA), a sodium-glucose co-transporter 2 inhibitor (SGLT2i) in a real-world clinical setting in Canada. CanCARE is a 12-month, prospective, observational analysis to demonstrate the effectiveness and safety of CANA in usual clinical practice in Canada.

**Materials and methods:** SGLT2i-naïve adult patients with type 2 diabetes mellitus (T2DM) (n = 527) on a stable antihyperglycemic agent (AHA) regimen with glycated hemoglobin (A1C) ≥ 7%, an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73m$^2$, were initiated on CANA as part of their usual treatment approach, and were followed for a period of 12 months. The primary effectiveness objective was the mean change in HbA1c from baseline to 6 and 12 months.

**Results:** Significant improvement from baseline in mean HbA1c levels were observed at 6 months (−0.90%; 95% CI, −1.02, −0.78) and at 12 months (−1.04%; 95% CI, −1.15, −0.92), regardless of duration of diabetes or background AHA treatment regimen. Similarly, significant decreases in systolic blood pressure (−4.65 mm Hg); body weight (−3.24 kg), waist circumference (−2.91 cm) and body mass index (−1.15 kg/m$^2$) were observed at 12 months. Additionally, 40.5% of patients achieved the double endpoint (≥0.5% HbA1c reduction and ≥ 3% weight loss), while 24.3% of patients achieved the triple composite endpoint (≥0.5% HbA1c reduction, ≥3% weight loss and ≥ 4 mm Hg systolic blood pressure reduction). No unexpected adverse events were reported.

**Conclusion:** CANA provided sustained clinically meaningful improvements in cardiometabolic parameters in this study in a real-world setting, confirming findings from randomized controlled trials.

KEYWORDS

Canadian, canagliflozin, effectiveness, prospective, real-world, SGLT2 inhibitor

## 1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disease with an increasing prevalence worldwide.[1,2] The International Diabetes Federation (IDF) estimated in 2015 that 415 million people had diabetes and projected that this figure will rise to 642 million by 2045.[3] Although the largest increase is expected to be in countries with developing economies, Canada will be impacted significantly as T2DM is one of the

fastest growing chronic diseases, with parallel increases in incident and prevalent obesity.[4,5] In 2015, the estimated prevalence of diabetes in Canada was 3.4 million, or 9.3% of the population, and is predicted to rise to 5 million, or 12.1% of the population, by 2025, which is a 44% increase from 2015 to 2025.[6]

The cornerstone of T2DM management is achievement of sustained glycaemic control in order to prevent diabetic complications. Despite the availability of multiple classes of antihyperglycaemic agents (AHAs), the results of the Diabetes Mellitus Status in Canada (DM-SCAN) survey highlighted the ongoing challenges faced by primary care physicians, with a persistent treatment gap associated with the management of TD2M in Canada, whereby only 50% of T2DM patients achieved HbA1c ≤ 7.0%.[7]

Since the DM-SCAN survey in 2013, new AHAs such as sodium-glucose co-transporter 2 inhibitors (SGLT2i) have been approved for use in the United States and Canada. In the recent 2018 updates of American Diabetes Association (ADA) Standards of Medical Care in Diabetes and Diabetes Canada (DC) Clinical Practice guidelines, the glycaemic and cardiovascular (CV) benefits of these newer agents have been recognized and integrated into the T2DM treatment algorithm.[8,9] These guidelines recommend a patient-centered approach to facilitate clinical decision making and selection of an AHA agent. As part of effective T2DM management, consideration of glycaemic efficacy, patient history of CV disease, vascular and renal benefits, impact on weight gain and hypoglycemia, as well as consideration of patient preferences, needs and values is suggested.[8,9]

Canagliflozin (CANA) is an orally active SGLT2i. Pharmacologic inhibition of SGLT2 is a unique mechanism that acts to decrease renal glucose reabsorption by lowering the renal threshold for glucose, leading to an increase in urinary glucose excretion (UGE) of 77-119 g/d for CANA. This enhanced UGE lowers plasma glucose in individuals with elevated glucose concentrations and results in a loss of 308-476 kcal/d.[10,11] The caloric loss leads to weight loss. Concomitantly, there is fluid loss, reflecting an osmotic diuresis and contributing to a reduction in both systolic and diastolic blood pressure.[10–20]

CANA has been evaluated in a broad range of patients with T2DM on a background of various AHAs, including monotherapy, add-on therapy with metformin (Met), sulfonylurea (SU), Met and SU and Met and pioglitazone, as well as add-on therapy with insulin, with or without other AHAs.[18] In addition, two head-to-head studies comparing CANA 300 mg to a dipeptidyl peptidase-4 (DPP-4) inhibitor (sitagliptin) and to an SU (glimepiride) showed that it was significantly superior to these agents in reducing HbA1c over 12 months.[12,15] Clinical trials evaluating CANA in older patients, in patients with moderate chronic kidney disease and in those with established CV disease, or who are at high risk for it, consistently demonstrated clinically relevant reductions in HbA1c, body weight and blood pressure (BP).[16–19] In the CANVAS Program, CANA provided significant benefits in the reduction of CV events, in a decreased rate of hospitalization because of heart failure, and in a reduction in progression of albuminuria.[19] The CREDENCE trial, which was discontinued early because of positive efficacy findings,[20] will provide important insights concerning the effects of CANA in T2DM patients with diabetic nephropathy.[21]

CANA has been studied extensively in randomized controlled clinical trials,[13–21] and in retrospective real-world analyses in the United States.[22,23] However, there is limited information concerning prospective outcomes in patients receiving CANA in a real-world setting that reflects Canadian practice. The present study prospectively evaluated CANA effectiveness and safety in the treatment of T2DM in the context of usual clinical practice in Canada.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and patient population

The aim of this prospective, multicentre study (was to evaluate treatment of T2DM with CANA in the setting of usual clinical practice in Canada. CanCARE (clinicaltrials.gov NCT02688075) is an observational study with pre-specified analyses for primary, secondary and exploratory outcomes. The results are presented descriptively as no formal hypotheses were pre-specified.

To be eligible for the study, patients must have been SGLT2i-naïve and at least 18 years of age, with a diagnosis of T2DM and with inadequate glycaemic control (HbA1c ≥ 7%) at baseline. Patients who initiated CANA as part of an optimal treatment approach, were stable while undergoing an AHA regimen for at least 30 days prior to CANA initiation, wo had an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 $m^2$, and who gave informed consent could be enrolled in this prospective study. Exclusion criteria were history of use of SGLT2 inhibitors; history of diabetic ketoacidosis (DKA), autoimmune diabetes (eg, type 1 diabetes mellitus [T1DM] or latent autoimmune diabetes in adults [LADA]); history of pancreas or beta-cell transplantation; history of diabetes secondary to pancreatitis or pancreatectomy; receipt of an investigational drug within the 3 months prior to initiation of CANA; or any condition that, in the opinion of the investigator, would make participation contrary to the best interest of the participant or could prevent, limit or confound the protocol-specified assessments.

The primary data source was the patient's medical records. Patients who were willing to participate in the study signed a written informed consent form, confirming that they understood the procedures for data collection. Baseline data were collected at the study enrollment visit. As per study protocol, investigators reported diabetes-related complications (retinopathy, neuropathy, nephropathy, CAD, stroke or PVD) but were not required to provide further description or detailed history for this observational, real-world study.

The observational phase began at the time of CANA initiation and patients were followed for a maximum of 12 months. Data collection was performed during each visit at Months 3, 6 and 12 (±45 days) or until the time of early withdrawal or termination. Measures of effectiveness (ie, glycemic control, body weight, body mass index [BMI], waist circumference), patient reported outcomes (PROs) as well as safety and other data were collected at baseline and during the observational phase. Only data available from routine clinical practice were collected. Treatment adherence was evaluated at Visits 2, 3 and 4 based on the percentage of prescribed pills missed in the last 14 days as reported by patients. All aspects of treatment decisions and clinical management of patients were in accordance with clinical

practice and at the discretion of the treating physician. The protocol did not stipulate dose selection or changes in dose.

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practices. Additionally, each site received institutional review board approval.

### 2.2 | Effectiveness outcomes

The primary outcome of the study was an estimation of mean change in HbA1c from baseline at 6 and 12 months. For patients who discontinued CANA, only HbA1c values collected before discontinuation were included in the analyses. Patients who did not fill prescriptions for CANA were considered drop-outs. Secondary outcomes included measures of glycaemic control (mean change in HbA1c from baseline at 3, 6 and 12 months stratified by baseline HbA1c), proportion of patients achieving reduction in HbA1c ≥ 0.5% and of those reaching HbA1c < 7%, anthropometric endpoints (observed values for weight, BMI and waist circumference), and a double composite endpoint (proportion of patients with both ≥0.5% reduction in HbA1c and weight loss ≥3%). An exploratory analysis was undertaken to determine the proportion of patients with all three parameters: reduction in A1C ≥ 0.5%, weight loss ≥3% and reduction in systolic BP ≥ 4 mm Hg.

### 2.3 | Safety outcomes

The terms used by participating physicians to document adverse events (AE) were coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 19.1). AEs were summarized by system organ class and lowest-level term using the percentage of patients who experienced at least one occurrence of the given event.

Individual subject listings were to be provided for patients who died and pations who experienced a serious AE (SAE), severe hypoglycaemia, defined requiring assistance of another person and/or unconsciousness and/or plasma glucose <2.8 mmol/L or DKA. The number and percentage of patients with AEs of special interest (AESI) were tabulated. These included genital mycotic infections, polyuria, intravascular volume-related AEs, urinary tract infections, severe hypoglycaemia and DKA. Fractures and amputations were not identified as adverse events of special interest at the time of protocol development, and therefore were categorized under reported AEs. All AESIs, irrespective of their relationship to therapy, were documented in the electronic case report form (eCRF). Clinical laboratory values and vital sign data from baseline over time were summarized by visit using descriptive statistics.

### 2.4 | Statistical methods

The study population comprised all patients enrolled in the study who used CANA. A sample size of 385 patients allowed an estimation of the 95% CI for change in HbA1c from baseline at 6 months with a precision $\delta = 0.10\ \sigma$, where $\sigma$ represents the value of the standard deviation of change in HbA1c from baseline in the population. It was assumed that the dropout rate would be approximately 15% every 6 months. Based on these estimates, a sample size of 535 patients was required to achieve the precision mentioned above.

The primary outcome of the study was an estimation of the mean change in HbA1c from baseline at 6 and 12 months. The 95% CIs were estimated for the change from baseline at 6 and 12 months using a mixed model, with the change from baseline as response, with month as main factor and with baseline HbA1c as covariate. In addition, pre-specified secondary outcomes were the effect of CANA on glycaemic control such as mean change in HbA1c from baseline at 3, 6 and 12 months and, stratified by baseline HbA1c (<7.5%, 7.5 to <8.5%, ≥8.5%), achievement of the composite endpoints BMI, weight and waist circumference.

For patients who discontinued use of CANA, only HbA1c values collected before discontinuation were included in the analyses. Analyses were carried out using the available data without any imputation of missing data. However, for sensitivity analysis of the primary outcome, interpolation and last observation carried forward (LOCF) were used to impute missing HbA1c values at 6 and 12 months. Primary outcome and all secondary continuous variables were summarized using descriptive statistics, including the number of observations, mean, standard deviations, ranges and 95% CIs for the mean. All secondary categorical variables were summarized using counts (n) and percentages (%).

## 3 | RESULTS

### 3.1 | Demographic and baseline characteristics

A total of 538 patients were screened for the CanCARE study, of whom 527 patients were enrolled at 28 Canadian sites and were included in the final analysis set for effectiveness and safety. Eleven (2.0%) patients were excluded from analysis because they did not meet one or more of the eligibility criteria. The number of participants for whom HbA1c data were available within the required reporting window of $\pm$45 days was: baseline, 509; 3 months, 435; 6 months, 376 and 12 months, 321. Patient demographics are summarized in Table 1. Overall baseline demographic and disease characteristics were consistent with eligibility criteria and were representative of the Canadian T2DM patient population.[5]

Mean baseline HbA1c was 8.5%, with a mean T2DM duration of 9.8 years. Patients enrolled in the study were treated by community specialists (39.3%) or primary care practitioners (60.7%). At baseline, CANA treatment was initiated, either as monotherapy or as add-on therapy to multiple AHAs, including one or more oral and injectable agents. With respect to dosing patterns, 83.1% (438/527) of patients received CANA 100 mg and 16.5% (87/527) received CANA 300 mg at study initiation. Two patients (0.7%) initially received CANA 200 mg. Among 351 participants who completed the 12-month study, 58.2% were receiving CANA 100 mg and 41.5% were receiving CANA 300 mg. A total of 77% percent of patients who completed the study reported not missing a single dose of CANA throughout the duration of the study. A very low percentage of patients (~4%) received CANA as monotherapy from baseline through Months 6 and 12. At initiation, most patients (75.9%) received CANA in combination with two AHAs. The proportion of patients receiving CANA according to different AHA regimens at baseline, and at 6 and 12 month was: insulin, with

**TABLE 1** Baseline characteristics of patients included in the study

| | Total (n = 527) |
|---|---|
| Gender (female); n (%) | 207 (39.3) |
| Age (y); mean (SD) | 60.7 (10.8) |
| BMI (kg/m$^2$); mean (SD) | 32.1 (6.37) |
| Race; n (%) | |
| Aboriginal | 10 (1.9%) |
| African/African American | 26 (4.9%) |
| Caucasian | 355 (67.4%) |
| East Asian | 28 (5.3%) |
| South Asian | 94 (17.8%) |
| Other/multiple/not reported | 14 (2.7%) |
| Systolic blood pressure (mm Hg); mean (SD) | 130.8 (12.70) |
| Diastolic blood pressure (mm Hg); mean (SD) | 78.3 (9.27) |
| eGFR (ml/min/1.73 m$^2$); mean (SD) | 85.80 (19.12) |
| HbA1c baseline (%); mean (SD) | 8. 5% |
| Strata n (%) | |
| <7% | 1 (0.2) |
| 7 to <7.5% | 96 (18.2) |
| 7.5 to <8.5% | 219 (41.6) |
| ≥ 8.5% | 193 (36.6) |
| Duration of diabetes (y); mean (SD) | 9.8 (7.3) |
| n (%) | |
| <5 yrs | 152 (28.8) |
| 5–10 y | 159 (30.2) |
| ≥10 y | 216 (41.0) |
| Microvascular disease; n (%) | |
| Diabetic retinopathy | 45 (8.5%) |
| Diabetic nephropathy | 61 (11.6%) |
| Diabetic neuropathy | 70 (13.3%) |
| Macrovascular disease; n (%) | |
| Cerebrovascular disease | 17 (3.2%) |
| Coronary artery disease | 67 (12.7%) |
| Peripheral vascular disease | 13 (2.5%) |
| Hypertension; n (%) | 406 (77.0%) |
| Hyperlipidaemia; n (%) | 452 (85.8%) |
| Vaginal yeast infections (n = 207); n (%) | 17 (8.2%) |

or without an oral AHA (24.3%, 24.4% and 23.9%, respectively), metformin alone (19.7%, 18.6% and 19.8%, respectively), metformin and DPP-4 inhibitors (17.1%, 16.5% and 16.0%, respectively), metformin and sulfonylureas (12.7%, 13.1%, and 13.9%, respectively) or metformin + sulfonylureas + DPP-4 inhibitors (12.3%, 12.7%, and 16.0%, respectively).

## 3.2 | Analyses of effectiveness

Significant improvements from baseline in mean HbA1c levels (Figure 1(A)) were observed at 6 months (−0.90%, 95% CI [−1.02, −0.78]) and at 12 months (−1.04%, 95% CI [−1.15, −0.92]) (Figure 1(A)).

Results from sensitivity analysis of the primary outcome, using LOCF together with interpolation of data between visits to determine the response at target visits, were similar. In this analysis, the mean change in HbA1c from baseline at 6 and 12 months was −0.81 (95% CI, −0.91, −0.72) and − 0.85 (95% CI, −0.96, −0.75), respectively; Hence, significant reductions in HbA1c were observed at each available time point in the cohorts in which participants dropped out prior to the Month 12 reporting window.

The observed change in HbA1c at the pre-defined timepoints of 3 and 6 months among those participants for whom subsequent HbA1c data were not available within the required reporting window of ±45 days was −0.66 [−0.98, −0.35) and − 0.77 [−1.07, −0.47]), respectively.

The proportion of patients achieving a target HbA1c < 7% increased steadily over time, reaching 38.6% by the end of study treatment (Figure 2(A)).

Relative to baseline, mean body weight (Figure 1(B)), mean waist circumference (Figure 1(C)) and mean BMI (Figure 1(D)) consistently decreased at 3, 6 and 12 months. Over 80% of patients experienced weight loss, with approximately 30% experiencing weight loss ≥5% after 12 months of treatment (Figure 3(A)).

Mean changes from baseline in HbA1c at 3, 6 and 12 months, stratified by baseline HbA1c, are shown in Figure 2(C). A significant improvement in mean HbA1c values was observed over time from baseline in all three strata. At Month 12%, 72% of patients achieved HbA1c reduction ≥0.5% and 53% of patients with low HbA1c at baseline (7.0%-7.5%) reached this target. (Figure 2(B)). Furthermore, significant reduction in HbA1c was observed, regardless of the background AHA used (Figure 2(D)).

There were improvements in several measures of cardiovascular and metabolic parameters over the 12-month study (Table S1). In addition to individual efficacy endpoints, several composite endpoints were met, with an increasing proportion of patients over the 12-month period. The double composite endpoint (≥0.5% reduction in HbA1c and weight loss ≥3%) was achieved by 24.8%, 35.4% and 40.5% of patients receiving CANA at Months 3, 6 and 12, respectively (Figure 3(B)). *Post-hoc* analysis revealed that the triple composite endpoint (reduction in HbA1c ≥ 0.5%, weight loss ≥3% and reduction in SBP ≥ 4 mm Hg) was achieved by 15.2%, 21.0% and 24.3% of participants at Months 3, 6 and 12, respectively (Figure 3(C)). Exploratory analysis concerning the final CANA dose achieved at 12 months showed, from baseline, a mean reduction in HbA1c of 0.94% (−1.09, −0.79) and 1.23% (−1.44, −1.02) and a mean reduction in weight of 3.38 kg (−3.97, −2.79) and 3.68 kg (−4.48, −2.88) for doses of 100 and 300 mg, respectively.

## 3.3 | Analyses of safety

A summary of AE incidence reported in this study is presented in Table 2. In total, 200 of 527 patients (38.0%) reported 372 AEs. Four patients (0.7%) experienced fatal AEs (arrhythmia, cardiac arrest, esophageal varices and suicide), none of which was considered by the investigator to be related to the study drug. Among 527 patients, 54 (10.2%) discontinued study treatment; this was attributed mainly to genital fungal infections and polyuria which were the most frequently reported AEs.

The incidence of AESIs reported during the study was 14.8% and included severe hypoglycaemia (0.9%), genital mycotic infections

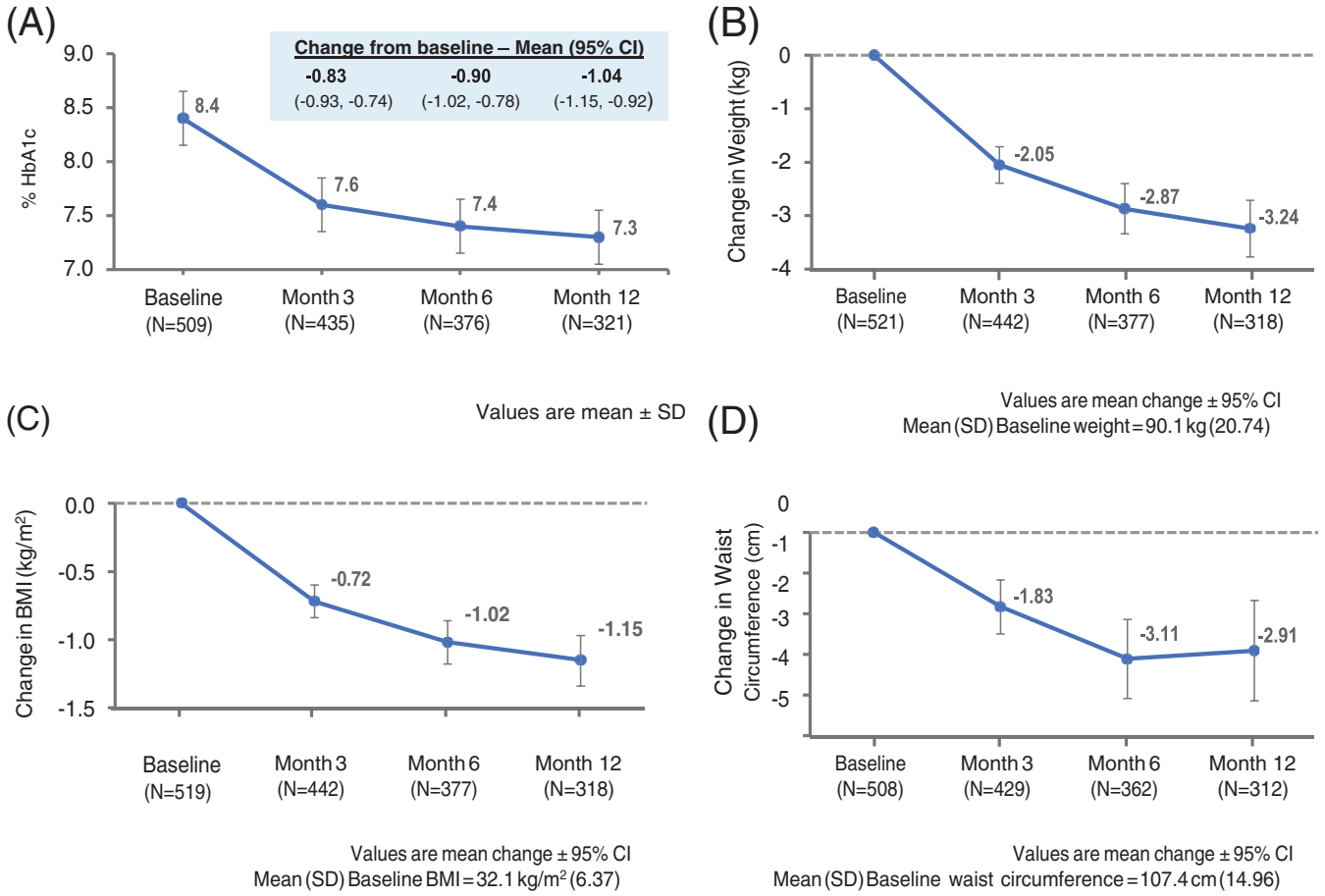


**FIGURE 1** Change from baseline in A, HbA1c. B, Body weight, C, Waist circumference and (D) BMI over duration of study, based on observed available data

(9.7%), polyuria (3.8%), intravascular volume related AEs (0.7%) (eg, hypotension, postural dizziness, orthostatic hypotension, syncope and dehydration), urinary tract infections (1.5%) and DKA (0.0%). Four traumatic fractures were reported, all of which were assessed by the investigators as unrelated to study drug. No amputation was reported during the study.

## 4 | DISCUSSION

In this prospective, multicentre study of SGLT2-naïve patients with T2DM, conducted in the context of usual Canadian clinical practices, CANA significantly lowered HbA1c from baseline at 6 and 12 months (mean changes of −0.90% and − 1.06%, respectively), regardless of the duration of diabetes or of combination treatment regimens involving other AHAs. Greater reductions in HbA1c were seen among the patients receiving CANA who had higher baseline HbA1c values. Overall, at Month 12, 38.8% of patients achieved the HbA1c target of <7.0% and 72% of patients achieved a reduction in HbA1c of ≥0.5%. Notably, 53% of patients with low HbA1c at baseline (7.0%-7.4%) achieved more than a half-point in HbA1c reduction. HbA1c reductions are more difficult to achieve in such patients compared to those with higher HbA1c levels, suggesting that CANA decreases HbA1c, even in patients with relatively low levels of hyperglycaemia.

Body weight, BMI and waist circumference were markedly reduced over time with use of CANA in this real-world study, which is consistent with published literature documenting the effects of CANA on body weight and modulation of visceral fat.[24] Abdominal or visceral adiposity is recognized as an independent predictor of metabolic and CV comorbidities.[25] Clinical studies concerning weight loss have shown the positive impact of weight reduction on lower cardiovascular risk factors such as lipids, BP and inflammatory markers.[26,27] Findings from the STENO-2 study emphasized the importance of focusing on multifactorial risk reduction in T2DM management, on reduction of CV disease and renal impairment, as well as on improvement in treatment compliance in T2DM patients.[28,29] Glycaemic control, weight loss and SBP reduction are known to markedly lower modifiable metabolic and CV-related risk factors, and are recognized as valid composite endpoints in assessing T2DM management.[30–32] In addition, changes in anthropometric measures are important and relevant to patients, and they have been associated with improvements in patient adherence to medication.[33,34] Over the 12-month study period, 40% of patients achieved the double composite endpoint and approximately 25% of patients achieved triple target control (Figure 3 (B),(C)).

Findings of the CanCARE study suggest that, in usual practice in Canada, CANA may facilitate achievement of multifactorial risk reduction (glycaemic, weight and BP goals) in patients with T2DM as

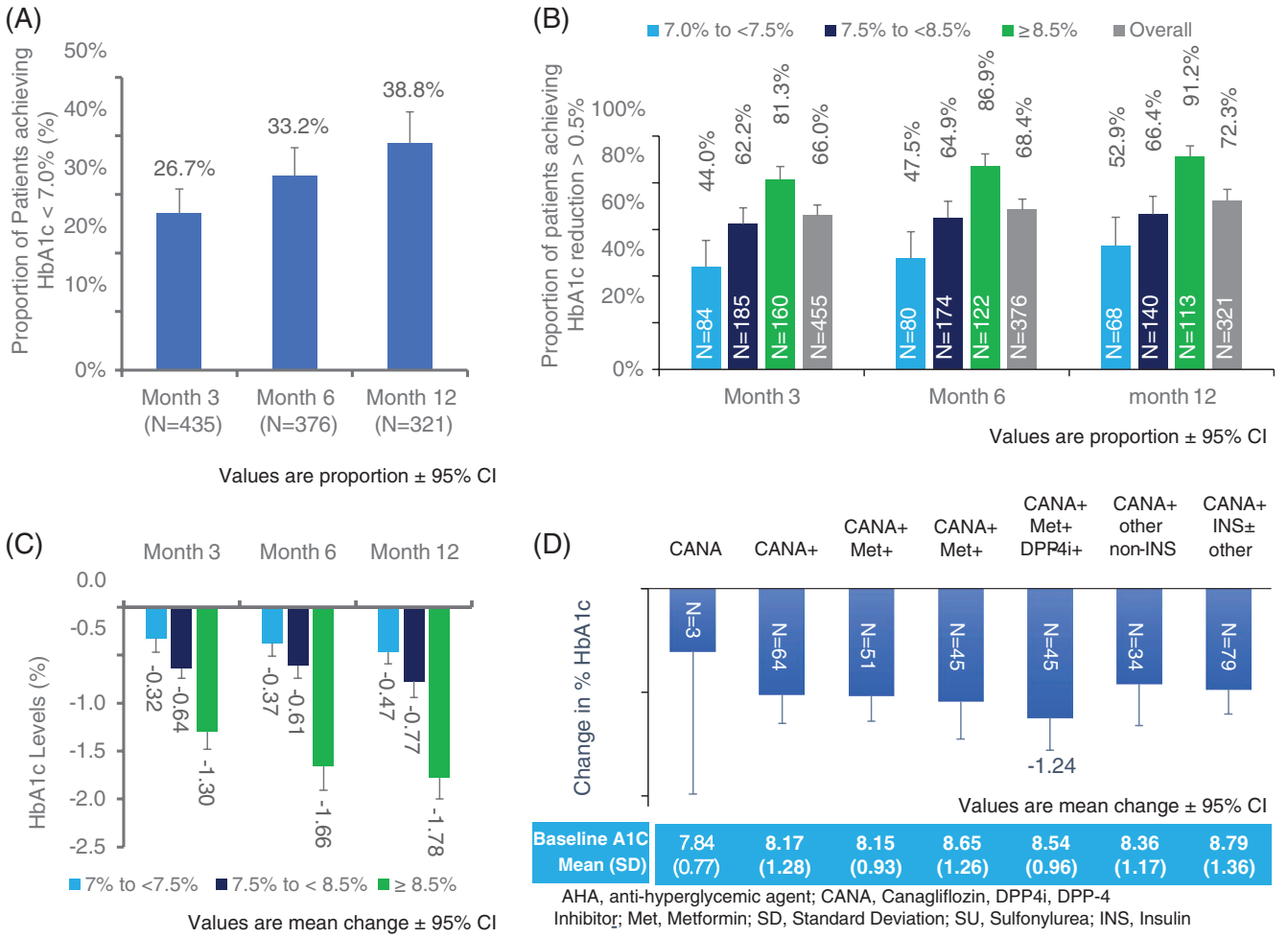


**FIGURE 2** Secondary HbA1c-related outcomes based on observed available data. A, Proportion of patients achieving HbA1c < 7.0% at 3, 6 and 12 months. B, Proportion of patients achieving HbA1c reduction ≥0.5% by baseline HbA1c strata. Baseline HbA1c strata represented by bars, from left to right: 7% to <7.5%, 7.5% to <8.5%, ≥8.5%, all patients. C, Change from baseline in HbA1c (%) by baseline HbA1c strata. Baseline HbA1c strata represented by bars, from left to right: 7% to <7.5% (N = 96; mean [SD] baseline HbA1c, 7.2% [0.13]); 7.5% to <8.5% (N = 219; mean [SD] baseline HbA1c, 7.9% [0.29]); ≥ 8.5% (N = 193; mean [SD] baseline HbA1c, 9.6% [1.14]). D, Change in HbA1c (%) from baseline after 12 months of treatment with canagliflozin by anti-hyperglycaemic agent (AHA) combination

adjunct therapy to multiple AHA regimens, including oral and injectable agents.

Consistent with the safety findings observed in CANA clinical trials,[12–18] the overall incidence of AEs was low, with most being either mild or moderate in severity. The vast majority of GMI and polyuria events occurred during the first 3 months after initiation of CANA treatment (Figure S2) and declined over time in both men and women, similar to findings from Phase 3 clinical trials.[35] The study discontinuation rate associated with AEs was approximately 10%, with the most frequent reasons cited being genital fungal infection and polyuria (Table 2). The recent Diabetes Canada 2018 clinical practice guidelines underscore the importance of avoiding weight gain and hypoglycaemia with treatment selection in the management of T2DM.[10] Hypoglycaemia is a potential side effect of antihyperglycaemic therapies, particularly therapy with insulin and sulfonylureas, and is recognized as a major clinical consequence associated with falls, fractures and traffic accidents; it has also proven to be traumatic by causing fear, stress and anxiety for both the T2DM patient and the caregiver.[36,37]

The observed renal threshold for glucose ($RT_G$) values with CANA treatment are above the usual threshold for hypoglycaemia (≤70.0 mg/dL or 3.9 mmol/L), a level above the plasma glucose concentration at which hypoglycaemic symptoms occur.[38] In our study, irrespective of different background AHA regimens (mono, dual or triple therapy, and in combination with insulin or other AHAs), the incidence of severe hypoglycaemia was very low (<1%) and occurred mainly in patients using insulin. This finding is in line with the clinical trial data available for CANA, in which hypoglycaemia was reported infrequently, and at rates similar to report rates for study comparator drugs.[13–19]

A potential limitation of this prospective, observational registry is the open-label study design, which may have introduced selection bias related to the inclusion of patients who would most likely benefit from the CANA treatment. The lack of a control group is another limitation of the study; however, the findings from the current study supplement the growing body of evidence concerning significant real-world outcomes with CANA.

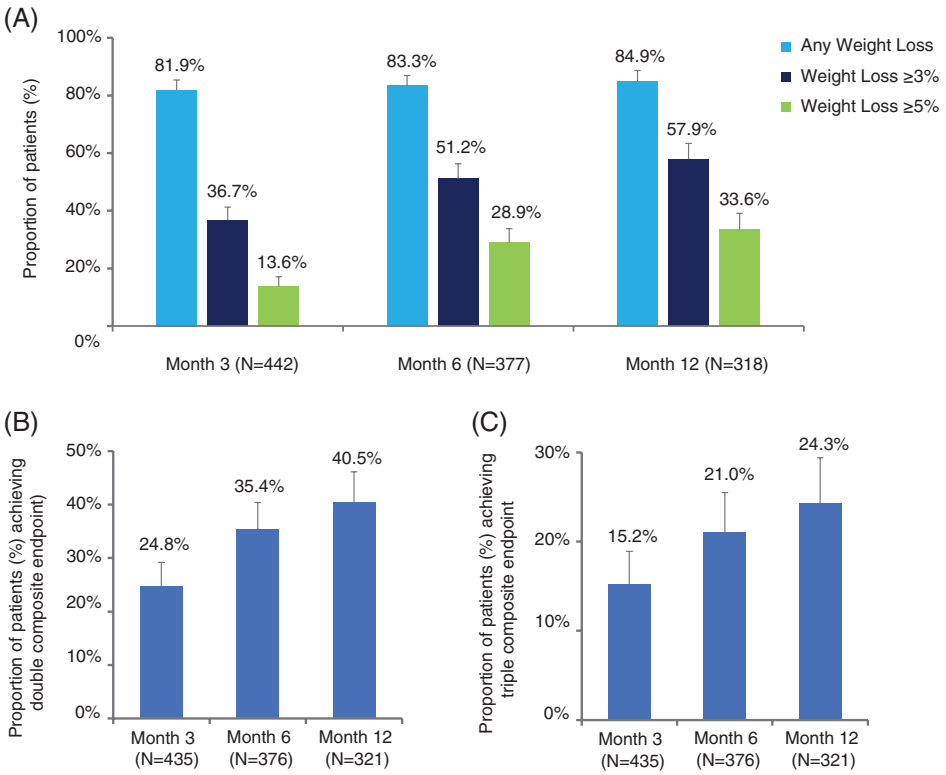


**FIGURE 3** Additional study outcomes. A, Proportion of patients achieving weight loss. B, Proportion of patients achieving double composite endpoint: Reduction in HbA1c ≥ 0.5% and weight loss ≥3%. C, Proportion of patients achieving triple composite endpoint: Reduction in HbA1c ≥ 0.5%, weight loss ≥3% and SBP reduction ≥4 mm Hg

**TABLE 2** Safety outcomes

| | % Patients n = 527 |
|---|---|
| ≥1 Adverse event (AE) | 38.0 |
| Serious AEs | 3.5 |
| Withdrawal because of AEs | 10.2 |
| AEs of special interest* | 14.5 |
| Genital mycotic infections (GMIs) | 9.5 |
| Polyuria | 3.7 |
| Urinary tract infections (UTIs) | 1.5 |
| Severe hypoglycaemia | 0.9 |
| Intravascular volume-related AEs (eg, hypotension, postural dizziness, orthostatic hypotension, syncope, dehydration) | 0.7 |
| Diabetic ketoacidosis | 0.0 |
| **Fracture:** Four traumatic fractures were reported by investigators as AEs and assessed by investigators as unrelated to CANA. | |
| **Amputation**: None reported | |

In conclusion, the CanCARE study demonstrated that CANA treatment was effective in optimal management of T2DM patients in real-world clinical practices in Canada. Following CANA initiation, significant mean reductions in HbA1c were observed at 6 and 12 months, and statistically significant improvements were noted in weight, waist circumference and BP. The efficacious improvement in cardiometabolic parameters with CANA that was observed in this real-world evidence study, confirms results from Phase 3 randomized controlled trials. CANA was well tolerated in T2DM patients, with a low incidence of reported AEs, a low incidence of hypoglycaemia and a high rate of persistence. These findings support the effectiveness and safety of CANA as a viable treatment option in Canadian clinical practice when administered either as monotherapy or in combination with other AHAs.

## ACKNOWLEDGMENTS

The authors thank all investigators, study teams and patients for participating in this study. Editorial support was provided by Liv Medical Agency, and Stat-Tu Inc. Canagliflozin was developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation. This study was previously presented, in part, in abstract form at the 77th Scientific Sessions of the American Diabetes Association, 9-13 June 2017, San Diego, California; at the 53rd Annual Meeting of the European Association for the Study of Diabetes, September 2017, Lisbon, Portugal; at the 20th Anniversary of Diabetes Canada/CSEM Professional Conference 1-4 November 2017, Edmonton, Alberta, Canada; and at the 78th Scientific Sessions of the American Diabetes Association, 22-26 June 2018, Orlando, Florida.

## CONFLICTS OF INTEREST

V. W. served as an investigator and received grant support from Janssen Inc. (Canada) during the conduct of the study; is involved in clinical trials for Eli Lilly, Locemia, BMS, Astra Zeneca, Janssen,

Merck, Novo Nordisk and Sanofi; and serves on advisory boards for Eli Lilly, Merck, Astra Zeneca, Novo Nordisk, Janssen and Sanofi.

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M. T. served as an investigator and received grant support from Janssen Inc. (Canada) during the conduct of the study; and is involved in clinical trials for Eli Lilly, Astra Zeneca, Novo Nordisk and Sanofi.

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## Author contributions

A. B., M. C., H. S. B., V. W., N. G., S. T., J. B. R. were involved with study concept, design and protocol, with statistical analysis and plan development, and with review. F. C. was involved with statistical analysis and plan development, and with review. A B., M. C., H. S. B., V. W., N. G., S. T., F. C., M. T., L. N., J. B. R. and W. R. were involved in interpreting data as well as drafting the manuscript. All authors were involved in reviewing the manuscript and approved the final draft of the manuscript for submission.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** Woo V, Bell A, Clement M, et al. CANadian CAnagliflozin REgistry: Effectiveness and safety of canagliflozin in the treatment of type 2 diabetes mellitus in Canadian clinical practice. *Diabetes Obes Metab*. 2019;21:691–699. https://doi.org/10.1111/dom.13573