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Reasons for hospitalizations in patients with type 2 diabetes in the CANVAS programme: A secondary analysis

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Abstract

Aim: To determine the reasons for hospitalizations in the CANagliflozin cardioVascular Assessment Study (CANVAS) programme and the effects of the sodium-glucose co-transporter-2 inhibitor canagliflozin on hospitalization.

Materials and Methods: A secondary analysis was performed on the CANVAS programme that included 10 142 participants with type 2 diabetes randomized to canagliflozin or placebo. The primary outcome was the rate of total (first plus all recurrent) all-cause hospitalizations (ACH). Secondary outcomes were total hospitalizations categorized by the Medical Dictionary for Regulatory Activities hierarchy at the system organ class level, reported by investigators at each centre. Outcomes were assessed using negative binomial models.

Results: Of the 7115 hospitalizations reported, the most common reasons were cardiac disorders (23.7%), infections and infestations (15.0%), and nervous system disorders (9.0%). The rate of total ACH was lower in the canagliflozin group ($n = 5795$) compared with the placebo group ($n = 4347$): 197.9 versus 215.8 participants per 1000 patient-years, respectively (rate ratio [RR] 0.92; 95% confidence interval [CI] 0.86, 0.98). Canagliflozin reduced the rate of total hospitalizations because of cardiac disorders (RR 0.81; 95% CI 0.75, 0.88). There was no significant difference between the canagliflozin and placebo groups in the rates of total hospitalizations because of infections and infestations (RR 0.96; 95% CI 0.86, 1.02) or nervous system disorders (RR 0.96; 95% CI 0.88, 1.05).

Conclusions: In the CANVAS programme, the most common reasons for hospitalization were cardiac disorders, infections and infestations, and nervous system disorders. Canagliflozin, compared with placebo, reduced the rate of total ACH.

KEYWORDS

canagliflozin, cardiovascular outcomes, hospitalization, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Hospitalizations in patients with type 2 diabetes are common and lead to a significant burden on patients and the healthcare sector.¹ Trends of diabetes-related hospitalizations have not improved

over the last decade as hospitalizations because of short-term complications have increased and those attributable to long-term complications have plateaued.² Efforts to reduce hospitalizations in patients with type 2 diabetes are therefore a high priority for clinicians.

Recent large randomized controlled trials have shown that sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce cardiovascular and renal events and also have effects on reducing hospitalizations, particularly for heart failure (HF).³⁻⁸ However, as with many medications, SGLT2 inhibitors have known adverse effects. Because of their mechanism of reducing hyperglycaemia by increasing urinary glucose excretion, SGLT2 inhibitors have, for instance, been associated with increased genital infections and volume depletion that may result in increased rates of hypotensive events and thus hospitalizations.⁹ The reasons for hospitalizations in the context of SGLT2 inhibitors are unclear, and limited data are available.

The CANagliflozin cardioVascular Assessment Study (CANVAS) programme was composed of two separate randomized controlled trials (<https://clinicaltrials.gov>; CANVAS [NCT01032629] and CANVAS-Renal [CANVAS-R; NCT01989754]) evaluating canagliflozin on cardiovascular, kidney, and safety outcomes.¹⁰ The CANVAS programme included 10 142 participants with a median of 2.4 years of follow-up, providing an opportunity to investigate the reasons for hospitalization in a large cohort of patients taking an SGLT2 inhibitor.⁴ In the current study, we aimed to investigate the reasons for hospitalizations and the rate of hospitalizations in participants assigned canagliflozin compared with those assigned placebo. We also compared the reasons for hospitalizations in participants with and without known cardiovascular disease.

2 | MATERIALS AND METHODS

2.1 | Overview

This study is a secondary analysis of the CANVAS programme, for which the design, primary results, and results in the primary and secondary prevention groups have been published.^{4,10-13} Briefly, the CANVAS programme evaluated the safety and efficacy of canagliflozin versus placebo through a combination of two similarly designed large randomized controlled trials. A total of 667 centres in 30 countries enrolled participants from 2009 to 2017. Each centre obtained approval from their local institutional ethics committees and all participants provided informed consent. The CANVAS programme was sponsored by Janssen Research & Development, LLC, and was conducted jointly by the sponsor, an academic steering committee, and an academic research organization, George Clinical.

2.2 | Participants

The inclusion criteria were men and women with type 2 diabetes (HbA1c $\geq 7.0\%$ and $\leq 10.5\%$) who were either aged 30 years or older with documented symptomatic atherosclerotic cardiovascular disease (including stroke, myocardial infarction, hospitalization for unstable angina, coronary artery bypass graft, percutaneous coronary intervention, peripheral revascularization, symptomatic with documented

haemodynamically significant carotid or peripheral vascular disease, or amputation secondary to vascular disease; secondary prevention cohort), or aged 50 years or older with two or more risk factors (including duration of diabetes ≥ 10 years, systolic blood pressure >140 mmHg while on ≥ 1 blood pressure-lowering treatment, current daily cigarette smoker, documented microalbuminuria or macroalbuminuria, or documented high-density lipoprotein cholesterol <1 mmol/L; primary prevention cohort). The primary prevention cohort comprised participants aged 50 years or older with two or more risk factors for cardiovascular events but with no prior cardiovascular event. The secondary prevention cohort comprised participants aged 30 years or older with a prior cardiovascular event.

2.3 | Randomization and follow-up

After a 2-week, single-blind, placebo run-in period, participants were randomized through a web-based computer-generated schedule. In CANVAS, participants were randomized in a 1:1:1 ratio to receive canagliflozin 100 mg daily, canagliflozin 300 mg daily, or placebo; in CANVAS-R, participants were randomized in a 1:1 ratio to receive canagliflozin 100 mg daily or placebo. At week 13, participants in CANVAS-R had an optional increase to 300 mg or matched placebo. In this study, all participants taking canagliflozin regardless of dose were pooled together, and thus randomization was not equal. All participants and trial staff were blinded to the treatment assignments until completion of the trial. Use of other background therapy for glycaemic control or cardiovascular risk management was determined by local guidelines' best practices.

Face-to-face follow-up was performed three times in the first year of enrolment and every 6 months thereafter with telephone follow-ups in between the face-to-face follow-ups. During every follow-up, primary and secondary outcome events and serious adverse events were assessed.

2.4 | Outcomes

The primary outcome for these analyses was the rate of total (first plus all recurrent) all-cause hospitalizations (ACH). Hospitalization data were obtained from adverse event reporting and the reasons for hospitalization were determined by site investigators. Adverse events requiring hospitalizations were categorized by system organ class by the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy, the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, and all analyses were performed at this level. Categories comprising less than 2% of the reasons for hospitalization were combined into an "other" category.

TABLE 1 Baseline characteristics stratified by hospitalization status

Characteristic	Overall (n = 10 142)	Hospitalized (n = 3486)	Not hospitalized (n = 6656)	P value*
Age, y, mean (SD)	63.3 (8.2)	64.5 (8.1)	62.7 (8.3)	<.001
Female, n (%)	3633 (35.8)	1086 (31.2)	2547 (38.3)	<.001
Race, n (%)				<.001
White	7944 (78.3)	2832 (81.2)	5112 (76.8)	
Asian	1284 (12.7)	399 (11.4)	885 (13.3)	
Black or African American	336 (3.3)	85 (2.4)	251 (3.8)	
Other	578 (5.7)	170 (4.9)	408 (6.1)	
Region, n (%)				<.001
North America	2430 (24.0)	834 (23.9)	1596 (24.0)	
Central/South America	1021 (10.1)	217 (6.2)	804 (12.1)	
Europe	3609 (35.6)	1425 (40.9)	2184 (32.8)	
Rest of the world	3082 (30.4)	1010 (29.0)	2072 (31.1)	
Any microvascular complications, n (%)	4667 (46.0)	1809 (51.9)	2858 (42.9)	<.001
Nephropathy	2129 (21.0)	706 (20.3)	1068 (16.0)	<.001
Neuropathy	1774 (17.5)	1226 (35.2)	1884 (28.3)	<.001
Retinopathy	3110 (30.7)	862 (24.7)	1267 (19.0)	<.001
Current smoker, n (%)	1806 (17.8)	534 (15.3)	1272 (19.1)	<.001
History of hypertension, n (%)	9125 (90.0)	3128 (89.7)	5997 (90.1)	.557
Duration of diabetes, y, mean (SD)	13.5 (7.8)	14.6 (8.1)	13.0 (7.5)	<.001
History of atherosclerotic vascular disease, n (%)				
Coronary	5721 (56.4)	2212 (63.5)	3509 (52.7)	<.001
Cerebrovascular	1958 (19.3)	773 (22.2)	1185 (17.8)	<.001
Peripheral	2113 (20.8)	826 (23.7)	1287 (19.3)	<.001
History of cardiovascular disease, ^a n (%)	6656 (65.6)	2506 (71.9)	4150 (62.3)	<.001
History of HF, n (%)	1461 (14.4)	558 (16.0)	903 (13.6)	.001
History of amputation, n (%)	238 (2.3)	117 (3.4)	121 (1.8)	<.001
BMI, kg/m ² , mean (SD)	32.0 (5.9)	32.5 (6.1)	31.7 (5.8)	<.001
SBP, mmHg, mean (SD)	136.6 (15.8)	137.3 (16.5)	136.3 (15.4)	.053
DBP, mmHg, mean (SD)	77.7 (9.7)	76.9 (10.0)	78.1 (9.5)	<.001
HbA1c, %, mean (SD)	8.2 (0.9)	8.2 (0.9)	8.3 (0.9)	.995
LDL cholesterol, mmol/L, mean (SD)	2.3 (0.9)	2.3 (0.9)	2.3 (0.9)	.007
LDL/HDL cholesterol ratio, mean (SD)	2.0 (0.9)	2.0 (0.9)	2.0 (0.9)	.206
eGFR, mL/min/1.73m ² , mean (SD)	76.5 (20.5)	73.8 (19.5)	77.9 (20.9)	<.001
UACR, mg/g, mean (SD)	12.3 (6.7, 42.1)	14.9 (7.1, 59.9)	11.3 (6.5, 36.0)	<.001
Medication, n (%)				
Diuretic	4490 (44.3)	1707 (49.0)	2783 (41.8)	<.001
Loop diuretic	1308 (12.9)	644 (18.5)	664 (10.0)	.031
RAAS antagonist	8116 (80.0)	2831 (81.2)	5285 (79.4)	<.001
β-blocker	5421 (53.5)	2013 (57.7)	3408 (51.2)	<.001
Statin	7600 (74.9)	2708 (77.7)	4892 (73.5)	<.001
Antithrombotic	7471 (73.7)	2784 (79.9)	4687 (70.4)	<.001
Insulin	5095 (50.2)	2028 (58.2)	3067 (46.1)	<.001
Metformin	7825 (77.2)	2519 (72.3)	5306 (79.7)	<.001
Sulphonylurea	4361 (43.0)	1412 (40.5)	2949 (44.3)	<.001
GLP-1 receptor agonist	407 (4.0)	163 (4.7)	244 (3.7)	.014

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HDL, high-density lipoprotein; HF, heart failure; LDL, low-density lipoprotein; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SD, standard deviation; UACR, urinary albumin: creatinine ratio.

^aDefined as history of symptomatic atherosclerotic vascular disease (coronary, cerebrovascular, or peripheral).

*Comparison between participants who were hospitalized and those who were not.

2.5 | Statistical analysis

Categorical variables were reported as the number of participants with corresponding percentages, and continuous variables were reported as mean and SD or median and interquartile range. Analyses of the outcome variables were reported based on an intention-to-treat analysis.

All analyses were planned post hoc. Analysis of the rate of total hospitalizations was performed using negative binomial models to understand the nature of all hospitalizations in the CANVAS programme, and rate ratios (RRs) with 95% confidence intervals (CIs) were estimated. In addition, we also performed analyses using Anderson-Gill models and Wei-Lin-Weissfeld models as sensitivity analyses.¹⁴ A supplementary analysis of the rate of first hospitalizations was also performed using Cox regression models. Annualized incidence rates were calculated per 1000 patient-years of follow-up. To improve the performance and validity of our statistical models, a bundling approach was used, whereby multiple adverse events requiring hospitalizations occurring on the same day were counted as one event. The CANVAS programme was not powered to detect differences between canagliflozin and placebo for causes of hospitalization; *P* values are provided for descriptive purposes without adjustment for multiplicity. We assessed for constancy of RRs across subgroups by fitting an interaction term. *P* values less than .05 were considered significant. All analyses were performed using SAS Enterprise Guide version 7.1.

3 | RESULTS

3.1 | Participant characteristics

Of the 10 142 participants enrolled in the CANVAS programme, 5795 were randomized to canagliflozin and 4347 to placebo. A total of 3486 (34.4%) participants were hospitalized. Mean follow-up was 3.6 years; median follow-up was 2.4 years. Participants who were hospitalized, compared with those who were not, were more probable to be older (64.5 vs. 62.7 years of age, respectively), be male (69% vs. 62%), have microvascular complications (60% vs. 43%), have a longer duration of diabetes (14.6 vs. 13.0 years), be using insulin (58% vs. 46%), have a history of cardiovascular disease (72% vs. 62%), or have a history of HF (16% vs. 14%) (Table 1). Participants who were hospitalized were more probable to have a history of atherosclerotic vascular disease (coronary [64% vs. 53%], cerebrovascular [22% vs. 18%], or peripheral [24% vs. 19%]). When participants were further stratified by canagliflozin versus placebo, similar trends were seen in those who were hospitalized and those who were not (Table S1).

3.2 | Reasons for hospitalization

There were 7115 total ACH in the CANVAS programme. The most common reasons for hospitalization in the entire cohort were cardiac

disorders (23.7%), followed by infections and infestations (15.0%), then nervous system disorders (9.0%) (Figure 1).

In the primary prevention cohort, there were 1894 (26.6% of the 7115) hospitalizations. The most common reasons for hospitalization in this cohort were infections and infestations (17.5%), cardiac disorders (16.1%), and nervous system disorders (8.7%). In the secondary prevention cohort, there were 5221 (73.4%) hospitalizations. The most common reasons for hospitalization in this cohort were cardiac disorders (26.5%), infections and infestations (14.0%), and nervous system disorders (9.1%). Figure 2 shows the reasons for hospitalization stratified by cohort.

3.3 | Hospitalization outcomes

Using negative binomial models to analyse the rates of total ACH, participants in the canagliflozin group, compared with the placebo group, had a lower rate of total ACH (197.9 vs. 215.8 participants per 1000 patient-years, respectively [RR 0.92; 95% CI 0.86, 0.98]). There was no statistical evidence of heterogeneity in the proportional treatment effects (*P* = .66) between the primary (RR 0.90; 95% CI 0.80, 1.02) and secondary (RR 0.93; 95% CI 0.86, 1.01) prevention cohorts (Figures 3 and S1). Similarly, participants in the canagliflozin group also had a lower rate of total hospitalizations because of cardiac disorders (48.9 vs. 60.0 participants per 1000 patient-years [RR 0.81; 95% CI 0.75, 0.88]) without statistical evidence of heterogeneity (*P* = .489) between the primary (RR 0.88; 95% CI 0.76, 1.02) and secondary (RR 0.82; 95% CI 0.74, 0.90) prevention cohorts.

Participants in the canagliflozin, compared with the placebo group, did not have an increased rate of hospitalizations because of infections and infestations (31.7 vs. 33.9 participants per 1000 patient-years, respectively [RR 0.94; 95% CI 0.86, 1.02]), and there was no statistical evidence of heterogeneity (*P* = .198) between the primary (RR 0.86; 95% CI 0.75, 1.00) and secondary (RR 0.98; 95% CI 0.88, 1.08) prevention cohorts. Participants in the canagliflozin group did not have a significantly different rate of hospitalization due to nervous system disorders (9.5 vs. 20.4 participants per 1000 patient-years [RR 0.96; 95% CI 0.88, 1.05]), but there was evidence of statistical evidence for heterogeneity (*P* < .001) between the primary (RR 0.76; 95% CI 0.65, 0.89) and secondary (RR 1.05; 95% CI 0.94, 1.17) prevention cohorts.

Using Andersen-Gill models and Wei-Lin-Weissfeld for recurrent event analyses, similar results were obtained (Figure S2, Table S2).

Canagliflozin, compared with placebo, did not significantly reduce the rate of first ACH in the CANVAS programme (118.7 vs. 131.1 participants per 1000 patient-years [HR 0.94; 95% CI 0.88, 1.00]). The rate of first hospitalizations because of cardiac disorders was reduced by canagliflozin (29.3 vs. 37.1 participants per 1000 patient-years [HR 0.82; 95% CI 0.72, 0.94]), but was not reduced for hospitalizations because of infections and infestations (17.3 vs. 20.5 participants per 1000 patient-years [HR 0.87; 95% CI 0.73, 1.04]) or nervous system disorders (13.6 vs. 14.1 participants per 1000 patient-years

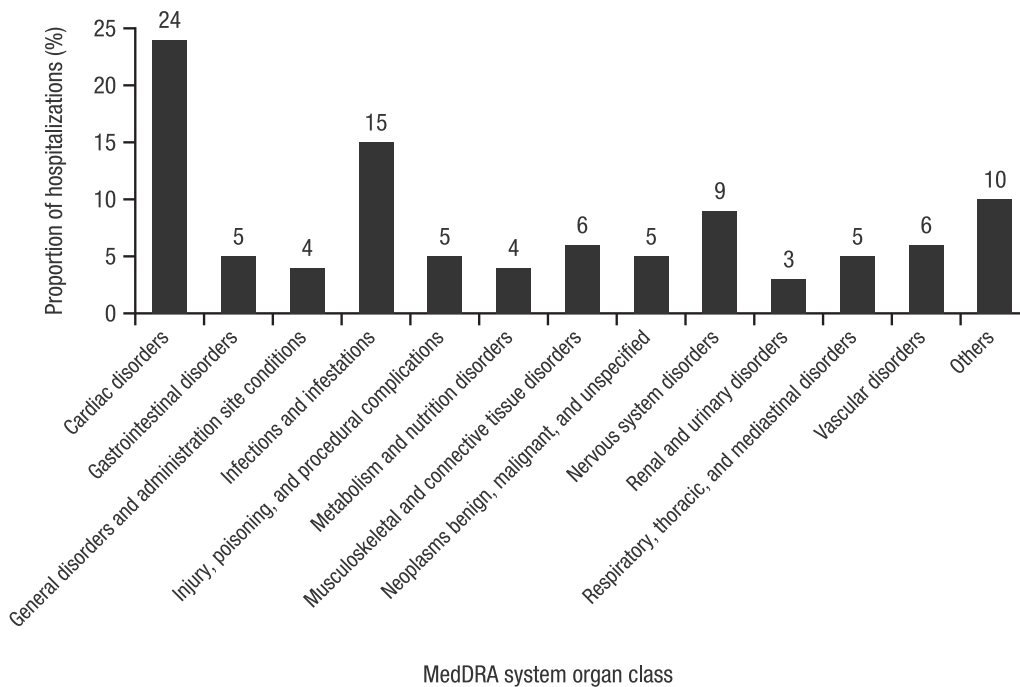


FIGURE 1 Reasons for hospitalizations in the CANVAS programme. Proportion of all hospitalizations (n = 7115) organized by MedDRA system organ class. Categories with less than 2% were grouped into the “other” category. The most common reasons for hospitalization were cardiac disorders, infections and infestations, and nervous system disorders. CANVAS, CANagliflozin cardioVascular Assessment Study; MedDRA, medical dictionary for regulatory activities

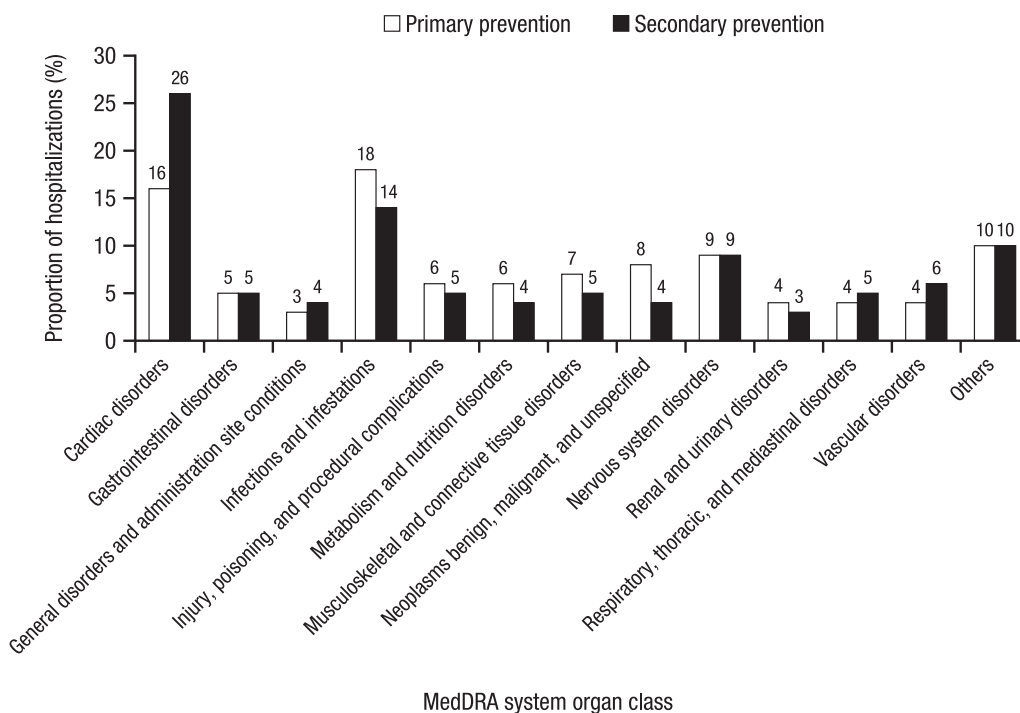


FIGURE 2 Reasons for hospitalizations in the CANVAS programme separated by cohort. Proportion of all hospitalizations within the primary prevention cohort (n = 1894) and secondary prevention cohort (n = 5221) organized by MedDRA system organ class. Categories with less than 2% were grouped into the “other” category. The most common reasons for hospitalization were similar between the two cohorts, although cardiac disorders were most common in the secondary prevention cohort whereas infections and infestations were most common in the primary prevention cohort. CANVAS, CANagliflozin cardioVascular Assessment Study; MedDRA, medical dictionary for regulatory activities

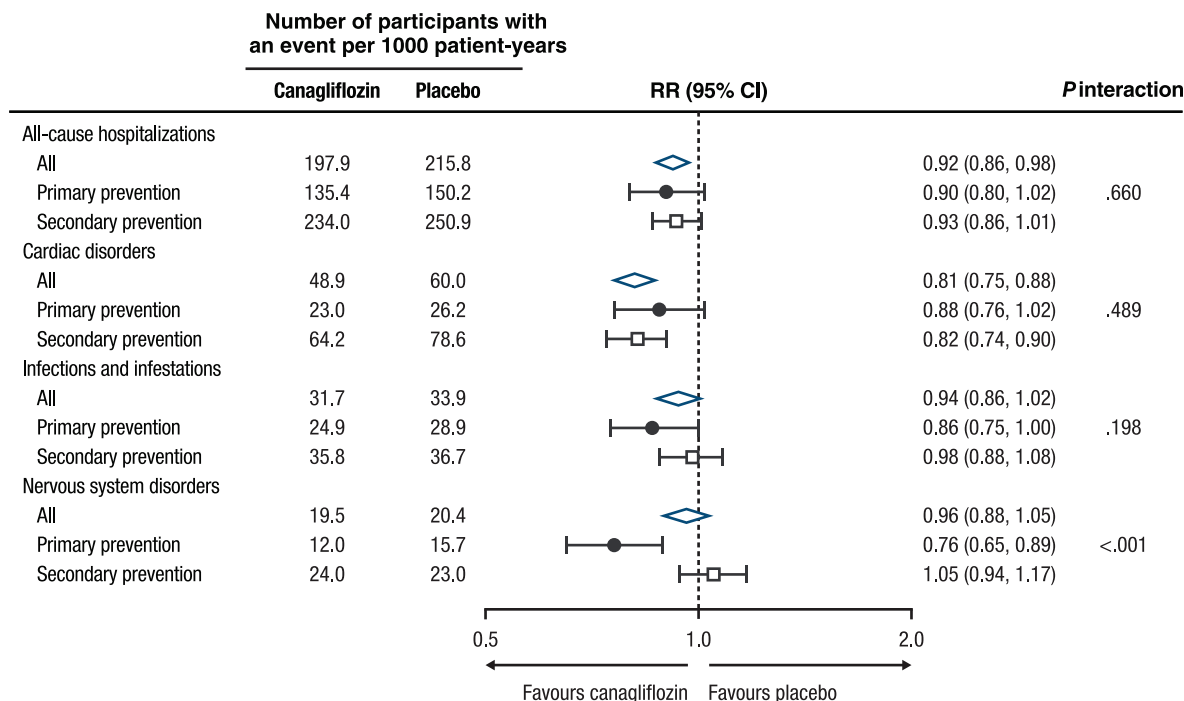


FIGURE 3 Rates of total hospitalizations in the CANVAS programme. RRs and 95% CIs were estimated using negative binomial models for the rate of total (first and all recurrent) all-cause hospitalizations and the three most common reasons for hospitalization, stratified by primary versus secondary prevention cohorts. CANVAS, CANagliflozin cardioVascular Assessment Study; CI, confidence interval; RR, rate ratio

[HR 1.01; 95% CI 0.82, 1.24]). First hospitalization analyses are shown in Figure S3.

A supplemental analysis was performed showing that participants who were hospitalized had higher mortality than those who were not hospitalized (Table S3).

4 | DISCUSSION

In this secondary analysis of the CANVAS programme, more than one-third of the participants were hospitalized during the study, and those who were hospitalized had significantly different baseline characteristics compared with those who were not. Participants who were hospitalized were more probable to be older, be male, have microvascular complications, and have a history of cardiovascular disease. Hospitalizations were more common in the secondary prevention group than in the primary prevention group. The most common reasons for hospitalization were cardiac disorders, infections and infestations, and nervous system disorders. We showed that canagliflozin, compared with placebo, significantly reduced the rate of total ACH, and for total hospitalizations as a result of cardiac disorders, but did not increase total hospitalizations because of infections and infestations. Because of the differing randomization categories and follow-up durations between the CANVAS and CANVAS-R trials, we used an unbiased estimate of the drug effect on the hospitalization outcomes based on event rates rather than proportions with events. Further, if annualized incidence rates for total (first plus

recurrent events) are used, then power to compare the effect of canagliflozin and placebo is maximized and the assessment of total hospitalization burden is achieved. The importance of assessing total ACH is illustrated by our finding that, while time to first ACH was not significant between the canagliflozin and placebo groups, the total ACH was reduced by canagliflozin.

Diabetes has been long known to be associated with increased rates of hospitalizations.¹⁵ In this study, 34% of the participants contributed to 7115 hospitalizations over a mean follow-up time of 3.6 years, consistent with prior studies showing that diabetes is also associated with higher rates of rehospitalization.^{1,16} Reducing the complications from diabetes that result in hospitalizations is a high priority, not only from a patient care perspective, but also from an economics standpoint, where the costs are rising both for the healthcare system and the individual patient.¹⁷ The inclusion of recurrent hospitalizations, rather than just the first, allows a more in-depth understanding of the totality of the hospitalization morbidity, and to the degree to which canagliflozin may mitigate this undesirable outcome. A similar analytical approach based on total events has also been performed for the DECLARE-TIMI 58 trial, which showed that dapagliflozin, compared with placebo, decreased the incidence of atrial fibrillation and atrial flutter.¹⁸ Our findings are consistent with a secondary analysis of the EMPA-REG OUTCOME trial, which also showed that empagliflozin, compared with placebo, significantly reduced the total ACH in participants with diabetes.¹⁹ In the current study, the overall reduction of total ACH by SGLT2 inhibitors was driven by the reductions in hospitalizations because of cardiac

disorders, which were the main cause of hospitalizations. Proportional reductions in cardiac hospitalizations were similar in the primary and secondary prevention cohorts, but the much higher event rates in the latter suggest that it is the secondary prevention cohort that may have the most to benefit.²⁰

The effects of canagliflozin on the rate of hospitalizations from other causes are consistent with the safety profile of SGLT2 inhibitors in general. Increased rates of infection are a predominant concern for patients with diabetes and especially for those taking SGLT2 inhibitors, given their glycosuria effects. Infections and infestations, a MedDRA system organ level category that included fungal infections, were the second most common cause for hospitalizations, consisting of 15% of all hospitalization events in the CANVAS programme. Prior cardiovascular outcome trials found significantly higher rates of genital infections in patients taking SGLT2 inhibitors and, in 2015, the US Food and Drug Administration released a warning for serious urinary tract infections.^{3-5,21} However, although our study was not powered to determine treatment effects for hospitalizations because of infections or specific types of infections, no increase in total hospitalizations attributable to infections or infestations was observed with canagliflozin compared with placebo. A recent large cohort analysis of commercial claim databases also showed no increased risk for severe urinary tract infections or outpatient urinary tract infections in patients taking canagliflozin compared with those taking other second-line antidiabetic medications.²² The authors acknowledge that, while hospitalizations are an integral part of the safety profile of a medication, there may be important adverse events that do not lead to hospitalization. For instance, canagliflozin increased the incidence of osmotic diuresis and volume depletion, although it did not increase the incidence of acute kidney injury, hypoglycaemia, or diabetic ketoacidosis.⁴

The most common reason for hospitalization in the CANVAS programme were cardiac disorders. When stratified by cohort, cardiac disorders was the second most common reason for hospitalization in the primary prevention cohort but was the most common reason in the secondary prevention cohort, which probably reflects the inclusion criteria of the cohorts. In this study, canagliflozin led to a reduction in both the rate of a first hospitalization and the rate of total hospitalizations because of cardiac disorders. Our study is consistent with a prespecified analysis of the CANVAS programme, which showed that canagliflozin reduced a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.¹³ The reduction in hospitalizations because of cardiac disorders may also have been driven by a reduction in HF hospitalizations, particularly in the secondary prevention cohort, where 17.6% had HF at baseline versus 8.2% in the primary prevention cohort.¹³ Furthermore, canagliflozin also led to a profound reduction in hospitalizations because of respiratory, thoracic, and mediastinal disorders, a MedDRA system organ class that may have captured some HF hospitalizations that presented initially as a respiratory symptom (Figure S1). This effect of SGLT2 inhibitors in reducing HF hospitalizations has been further substantiated in randomized controlled trials of dapagliflozin and empagliflozin in patients with HF with reduced ejection fraction,

irrespective of history of diabetes.^{7,8} Mechanisms proposed by which SGLT2 inhibitors reduce HF hospitalizations are reverse remodelling of the left ventricle and improvement in diastolic function.²³⁻²⁵ While it has also been proposed that SGLT2 inhibitors have anti-inflammatory effects and can reduce oxidative stress as part of the development of atherosclerosis, there is controversy as to whether SGLT2 inhibitors reduce atherosclerotic cardiovascular events.²⁶⁻²⁸ A pooled analysis of three large SGLT2 inhibitor cardiovascular outcome trials showed that, although SGLT2 inhibitors reduce the risk for non-fatal myocardial infarction, this effect did not extend to non-fatal strokes, suggesting that SGLT2 inhibitors' effects on cardiovascular outcomes result from its impact on HF hospitalizations rather than atherosclerotic cardiovascular events.²⁹ Further research with a longer follow-up would help in delineating the effects of SGLT2 inhibitors on atherosclerotic outcomes.

There are several strengths to this study. To our knowledge, this is the first study assessing and comparing the reasons for hospitalizations in a large cohort of patients taking an SGLT2 inhibitor. Prior studies have not delineated hospitalizations by more specific means, and serious adverse events previously reported for the CANVAS programme did not specify the proportion requiring hospitalizations. In addition, this study was performed on a contemporary cohort of participants, 75% of whom were prescribed a statin. Statins are recommended in patients with diabetes and a history of atherosclerotic cardiovascular disease or other risk factors, and uptake over the last decade has been increasing steadily.^{30,31} However, this study has several limitations. Aside from HF hospitalizations, analyses of reasons for hospitalization were not prespecified, and the trial was not designed with the statistical power to show differences in hospitalization for specific reasons. Furthermore, the reasons for hospitalization were reported by site investigators and were not adjudicated. The MedDRA hierarchy for determining categories of hospitalizations, although comprehensive and widely used, has limitations in the granularity of the information provided, especially at the system organ class level. Depending on classification schemes, trends in similar categories of reasons for hospitalizations may vary, particularly as they pertain to how infections are classified.³² Lastly, length of hospitalization was not available, and thus it is unclear whether the severity of hospitalizations for participants in the canagliflozin group was different from the placebo group.

In conclusion, in the CANVAS programme of patients with type 2 diabetes, the most common reasons for hospitalization were cardiac disorders, infections and infestations, and nervous system disorders. Canagliflozin, compared with placebo, reduced the rate of total ACH. Further research is needed to better characterize the hospitalizations and the mechanism of canagliflozin's impact on hospitalizations.

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CONFLICT OF INTEREST

KYF has nothing to disclose. JWJ has nothing to disclose. JI is a full-time employee of Janssen Scientific Affairs. DdZ has served on advisory boards and/or as a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma, and Mitsubishi Tanabe; has served on steering committees and/or as a speaker for AbbVie and Janssen; and has served on Data Safety and Monitoring Committees for Bayer. GRF has received research support from Novo Nordisk and has served on advisory boards and as a consultant for Janssen, Novo Nordisk, Boehringer Ingelheim, and Merck Sharp & Dohme. MP is a full-time employee of Janssen Scientific Affairs. DRM has received research support from Janssen; has served on advisory boards and as a consultant for Novo Nordisk, Novartis, Sanofi-Aventis, Janssen, and Servier; and has given lectures for Novo Nordisk, Servier, Sanofi-Aventis, Novartis, Janssen, Mitsubishi Tanabe, and Aché Laboratories.

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AUTHOR CONTRIBUTIONS

KYF made substantial contributions to conception and design, drafting the article or revising it critically for important intellectual

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PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14525>.

DATA AVAILABILITY STATEMENT

Data from the CANVAS Program are available in the public domain via the Yale University Open Data Access Project (YODA; <http://yoda.yale.edu>).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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