REVIEW

Clinical potential of canagliflozin in cardiovascular risk reduction in patients with type 2 diabetes

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Abstract: Cardiovascular disease is the leading cause of morbidity and mortality among patients with diabetes mellitus, as well as the leading diabetes-associated health care cost. The prevalence and associated impact of cardiovascular disease among those with diabetes engenders the need to identify cardiovascular effects of antihyperglycemic agents. This review seeks to evaluate the impact of canagliflozin, a SGLT2 inhibitor, on cardiovascular risk factors and outcomes. The 14 published trials to-date exploring various cardiovascular risk factors and outcomes among patients receiving canagliflozin were identified and included within the review. Overall these studies demonstrate that among patients with type 2 diabetes mellitus, canagliflozin results in decreased systolic and diastolic blood pressure, lower body weight, and also exhibits reno-protective effects. These findings were similar when canagliflozin was compared to placebo or other antihyperglycemic agents and explored among subsets such as those with chronic kidney disease. In addition, findings from the three trials exploring cardio-vascular outcomes of canagliflozin included reduction in cardiovascular mortality and lower incidence of heart failure-associated hospitalizations. Results from studies including other SGLT2 inhibitors suggest that cardiovascular benefits are likely a class-effect found among current SGLT2 inhibitors. Continued research specific to canagliflozin is needed to clarify risks of adverse effects and determine optimal dosing requirements for canagliflozin in regard to cardiovascular risk reduction.

Keywords: antihyperglycemic, sodium-glucose co-transporter 2 inhibitors, cardiovascular disease, diabetes mellitus

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among individuals with diabetes mellitus (DM) and comprises the largest component of direct and indirect health care costs associated with DM.[1,2] The lifetime risk of the development of CVD among those with diabetes is heightened compared to the general population, ranging from 55% to 87% depending on gender and body mass index (BMI).[3] The prevalence of CVD and its potential fatality among this population engender a need to identify strategies and therapies that potentiate and reduce adverse CVD outcomes among those with DM.

A decade ago, the US Food and Drug Administration (FDA) set requirements to assess cardiovascular outcomes of novel antihyperglycemic therapies to address con-cerns of these therapies potentiating the risk of CVD among those with DM.[2] Since this requirement was put into place, a novel class of antihyperglycemic agents (AHAs),

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the SGLT2 inhibitors, has been developed. These agents are approved for the treatment of type 2 diabetes mellitus (T2DM), and have shown an estimated reduction in HbA1c by 0.5% to 1%.[4] Based on the mechanism of action, there is potential for SGLT2 inhibitors to positively affect some modifiable cardiovascular risk factors in addition to glucose control such as BMI, blood pressure (BP), dyslipidemia, and renal function.[5]

SGLT2 inhibitors block the main site of glucose reabsorption within the nephron, leading to greater urinary glucose excretion (UGE).[6,7] In patients without diabetes, glucose is filtered by renal glomeruli and reabsorbed in the proximal convoluted tubule. Six SGLTs actively assist in the reabsorption process, SGLT1 and SGLT2 being noted as the most important.[8] SGLT1 is present mainly in the small intestine, as well as the heart, liver, lung, and kidneys, while SGLT2 is located largely in the kidneys.[9,10] SGLT2 inhibitors prevent reabsorption of glucose in the proximal convoluted tubule, thereby facilitating glucose excretion in the urine. All SGLT2 inhibitors depend on blood glucose levels to exceed the decreased renal threshold for glucose to exert their mechanism of action, but there are pharmacologic differences between agents.[8] For example, each medication in this class has a different affinity for SGLT1 and SGLT2, though they are all selective for SGLT2. Canagliflozin has a selectivity ratio of approximately 160–410 for SGLT2 over SGLT1, dapagliflozin a ratio of 1,200 and empagliflozin 2,600.[11] Due to canagliflozin's lesser SGLT2 to SGLT1 selectivity, it is known to have effects on not only renal glucose reabsorption, but intestinal glucose absorption and metabolism as well. In a crossover study evaluating canagliflozin's effects on intestinal glucose absorption, canagliflozin reduced postprandial plasma glucose and insulin excursions by 35% and 43% ($P<0.001$ for both), as well as showing expected increases in UGE.[12] Thus, canagliflozin is potentially classifiable as a local and low-potency SGLT1 inhibitor as well as an SGLT2 inhibitor. The pharmacologic effects of the unique SGLT2 inhibitor, canagliflozin, warrant further exploration to garner greater understanding of all therapeutic effects of this agent. Evidence is emerging describing the clinical effects of SGLT2 inhibitors, including canagliflozin on CVD and risk factors that contribute to development of CVD.

This review seeks to explore the current evidence of cardiovascular risk reduction specifically for canagliflozin, the most widely prescribed oral SGLT2 inhibitor in the US.[13] The current diabetes care guideline from the American Diabetes Association recommends the addition of canagliflozin to lifestyle management and metformin among those with

T2DM and atherosclerotic CVD to reduce major adverse cardiovascular events (MACE).[1] It is crucial for health care professionals to consider the body of evidence regarding the cardiovascular effects of canagliflozin in order to optimize the care of individuals with T2DM.

Clinical trials and effects on specific cardiovascular risk factors

This review has identified 14 published studies to date that have explored various cardiovascular risk factors among patients receiving canagliflozin. Table 1 provides an overview of design, population characteristics, and endpoints of the clinical trials outlined in this review of canagliflozin. These various trials of patients with T2DM studied the effects of canagliflozin in comparison to placebo or other AHAs, such as sitagliptin, glimepiride, DPP4 inhibitors (DPP4-Is), GLP-1 receptor-agonists, and insulin. Key study endpoints included changes from baseline in HbA1c and modifiable cardiovascular risk factors including BP, body weight, and renal function. Further, several Phase 3 trials analyzed the effect of canagliflozin on the overall reduction of cardiovascular outcomes, including hospitalization for heart failure, acute myocardial infarction (MI), and nonfatal stroke.[14–16] These various cardiovascular risk factors and outcomes explored among patients receiving canagliflozin are summarized in Table 2.

Changes in BP

Hypertension is a major cardiovascular risk factor and common comorbidity of diabetes.[17] Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were evaluated in several clinical trials with results consistently showing a statistically significant reduction in both SBP and DBP with canagliflozin at doses of 100 mg or 300 mg compared with placebo. Minimal change in pulse rate was observed in canagliflozin 100 mg and 300 mg across all trials in relation to placebo.[7,17–20]

The canagliflozin cardiovascular assessment study (CANVAS) provided headway research on the efficacy and safety of canagliflozin before its FDA approval in 2009.[14] The CANVAS program, comprised of the CANVAS and CANVAS-R trials, revealed canagliflozin 100 mg and 300 mg to have a significant impact on the lowering of SBP and DBP compared to placebo.[14]

Additional research in trials such as the canagliflozin treatment and trial analysis-monotherapy (CANTATA-M) studied canagliflozin in patients with T2DM, but also included a sub-study of high-glycemic participants (HbA1c

Table 1 Study design and patient populations of studies evaluating canagliflozin and cardiovascular risk factors

Study	Design	Treatment	Population characteristics	Endpoints evaluated
CANVAS[14]	2 years, MC, DB, R, PCT	CAN 300 mg, 100 mg, or PBO daily	n=4,330 Mean age =63.5 years HbA1c =7%–10.5% Mean duration of T2DM =13.4 years >30 years of age with ASCVD history or >50 years of age with >2 CV risk factors	Primary: change in risk of CVD; safety and tolerability Secondary: change from baseline in beta-cell function, HbA1c, FPG, BW, BP, FPL, and side effects
CANVAS-R[25]	18 months, MC, DB, R, PCT	Initial: CAN 100 mg or PBO daily; Week 13 optional increase: CAN 300 mg or PBO daily	n=5,812 Mean age =64.0 years HbA1c =7%–10.5% Mean duration of T2DM =13.4 years eGFR >30 mL/min/1.72 m²	Primary: progression of albuminuria Secondary: composite outcome of hospitalization for HF or CV death
CANTATA-M[7]	26 weeks, DB, PCT	CAN 300 mg, 100 mg, or PBO daily	n=678 Mean age =52.4 years HbA1c =7%–10% or >10%–12% Mean duration of T2DM =4.6 years	Primary: change from baseline in HbA1c Secondary: achievement of HbA1c <7.0%; change from baseline in FPG, SBP, BW, HDL-C
Townsend et al[17]	6 weeks, MC, DB, R, PCT	CAN 300 mg, 100 mg, or PBO daily	n=171 Mean age =58.6 years HbA1c >7%–10% Mean duration of T2DM =9 years HTN = SBP >130 mmHg, DBP >70 mmHg	Primary: change from baseline in the mean 24-hour SBP Secondary: change from baseline in mean 24-hour DBP, daytime SBP and DBP, FPG, and BW
Wilding et al[25]	26 weeks, R, DB, PCT	CAN 300 mg, 100 mg, or PBO daily	n=469 Mean age =56.8 years HbA1c =7%–10.5% Mean duration of T2DM =9.6 years Receiving MET >1,500 mg per day for >8 weeks	Primary: change from baseline in HbA1c by week 26 Secondary: change from baseline in HbA1c by week 52; achievement of HbA1c <7.0%; change from baseline in FPG, BW, HDL-C, and TG
Yale et al[18]	52 weeks, R, DB, PCT	CAN 300 mg, 100 mg, or PBO once daily	n=272 Mean age =68.5 years HbA1c 7%–10.5% Mean duration of T2DM =16.3 years CKD Stage 3 eGFR 30–50 mL/min/1.73 m²	Primary: change from baseline in HbA1c by week 26 Secondary: achievement of HbA1c <7.0% by week 26; change from baseline in FPG, BP, BW, and FPL
Lavalle-Gonzalez et al[21]	26 week core study period with 26 weeks extension, R, DB, PBO, and active-controlled	CAN 300 mg, 100 mg, PBO, or SITA 100 mg once daily	n=1,284 Mean age =55.4 years HbA1c =7%–10.5% Mean duration of T2DM =6.9 years	Primary: change from baseline in HbA1c Secondary: achievement of proportion HbA1c <7.0%; change from baseline in FPG, SBP, BW, TG, and HDL-C
Schernthaner et al[22]	52 weeks, R, DB, active-controlled	CAN 300 mg or SITA 100 mg	n=756 Mean age =56.7 years HbA1c =7%–10.5% Receiving MET >1,500 mg per day for >8 weeks	Primary: change from baseline in HbA1c Secondary: achievement of HbA1c <7.0%; change from baseline in FPG, SBP, DBP, BW, TG, and HDL-C
Forst et al[23]	52 weeks, R, DB, PBO, and active-controlled trial	CAN 300 mg, 100 mg, PBO, or SITA 100 mg	n=342 Mean age =57.4 years HbA1c =7%–10.5% Mean duration of T2DM =10.5 years	Primary: change from baseline in HbA1c at week 26 Secondary: change from baseline in HbA1c at week 52; achievement of HbA1c <7.0%; change from baseline in FPG, SBP, beta-cell function; percent change in BW, HDL-C, and TG

(*Continued*)

Table 1 (*Continued*)

Study	Design	Treatment	Population characteristics	Endpoints evaluated
Rosenstock et al[24]	12 weeks, MC, R, DB, PBO, and active-controlled	CAN 50 mg, 100 mg, 200 mg, 300 mg once daily or 300 mg twice daily, PBO, or SITA 100 mg	n=451 Mean age =52.9 years HbA1c 7%–10.5% Mean duration of T2DM =6.0 years Receiving MET >1,500 mg per day for >8 weeks	Primary: change from baseline in HbA1c Secondary: achievement of HbA1c <7.0%; change from baseline in FPG, BW, overnight urinary glucose to creatinine ratio
Patorno et al[16]	Retrospective cohort	CAN 300 mg, 100 mg, or active control of DPP4 inhibitor, GLP-agonist, or sulfonylurea	n=224,999 Mean age =56.4 years Mean HbA1c =8.8%	Primary: hospitalization for HF; composite CV endpoint (hospitalization for acute MI, ischemic stroke, hemorrhagic stroke) Secondary: unstable angina, coronary revascularization, and individual components of CV events
CVD-REAL[15]	Retrospective cohort	SGLT2 inhibitor (canagliflozin, empagliflozin, or dapagliflozin) or other oral or injectable glucose lowering agent	n=262,339 (including 132,572 canagliflozin) Mean age =57.0 years T2DM	Primary: hospitalization for HF Secondary: all-cause mortality; composite of hospitalization for HF
CANDLE[49]	24 week, MC, R, DB, active controlled	CAN 100 mg, or GLIM 0.5 mg to 6 mg	n=250 HbA1c =7%–10.5% CHF: NYHA class I to III	Primary: percent change from baseline in NT-proBNP Secondary: changes from baseline in HbA1c, SBP, DBP, BW, QoL, echocardiogram, and renal function

Abbreviations: ASCVD, Atherosclerotic Cardiovascular Disease; BP, blood pressure; BW, body weight; CAN, canagliflozin; CHF, chronic heart failure; CKD, chronic kidney disease; CV, cardiovascular; DB, double blind; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; FPL, fasting plasma lipid; GLIM, glimepiride; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HTN, hypertension; MC, multi-center; MET, metformin; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PBO, placebo; PCT, placebo-controlled trial; QoL, quality of life; R, randomized; SBP, systolic blood pressure; SITA, sitagliptin; T2DM, type 2 diabetes mellitus; TG, triglyceride.

Table 2 Reported cardiovascular clinical endpoint data

Study	Canagliflozin dose	Number of patients receiving canagliflozin	Change in SBP from baseline, mmHg	Change in DBP from baseline, mmHg	Orthostatic hypotension, n (%)	Change in HR from baseline, beats per minute	Change in BW from baseline, kg
CANVAS program[14]	100 mg or 300 mg once daily	5,795	−3.93±0.40	−1.39+0.30	26.0/1,000 pt-yr	NR	−1.60+0.10
CANTATA-M[7]	100 mg daily	195	−3.3+0.8	−1.7+0.5	0	−1.6	−2.5
	300 mg daily	197	−5.0±0.8	−2.1+0.5	0	−0.4	−3.4
Townsend et al[17]	100 mg daily	57	−3.3±3.4	−1.9±2.1	2 (3.8)	−0.6	−1.3
	300 mg daily	57	−4.9±3.4	−2.9±2.1	4 (7.1)	−0.4	−1.7
Wilding et al[20]	100 mg daily	157	−4.9±1.0	−2.9±0.6	1 (0.6)	0.9	−1.1
	300 mg daily	156	−4.3±1.0	−2.3±0.6	6 (3.8)	−1.2	−1.7
Yale et al[18]	100 mg daily	90	−6.1±1.5	−2.6±0.9	0	−1.9	−1.2
	300 mg daily	89	−6.4±1.5	−3.5±0.9	1 (1.1)	−1.1	−1.4
Lavalle-Gonzalez et al[21]	100 mg daily	368	−3.5±0.6	−1.8±0.4	0	−1.3	−3.3±0.2
	300 mg daily	367	−4.7±0.6	−1.8±0.4	1 (0.3)	−1.9	−3.7±0.2
Schernthaner et al[22]	300 mg daily	377	−5.9±1.7	−2.7±1.1	0	NR	−2.3
Forst et al[23]	100 mg daily	113	−5.3±1.0	−3.3±0.7	9 (8.0)	−0.3	−2.6
	300 mg daily	114	−4.7±1.0	−3.5±0.7	5 (4.4)	−1.3	−3.7
Rosenstock et al[24]	50 mg daily	64	NR	NR	0	NR	−2.3
	100 mg daily	64	NR	NR	4 (6)	NR	−2.6
	200 mg daily	65	NR	NR	3 (5)	NR	−2.7
	300 mg daily	64	NR	NR	1 (2)	NR	−3.4
	330 mg twice daily	64	NR	NR	1 (2)	NR	−3.4

Abbreviations: BW, body weight; DBP, diastolic blood pressure; HR, heart rate; NR, not reported; pt-yr, patient-years; SBP, systolic blood pressure.

>10.0% and ≤12.0%) to further evaluate its safety and efficacy.[7] Canagliflozin 100 mg and 300 mg were associated with reductions in SBP and DBP in the study and the sub-study populations. Likewise, significant BP reductions were also found in a study specifically exploring the use of canagliflozin 100 mg and 300 mg in participants with T2DM and stage 3 chronic kidney disease (CKD).[18]

Other placebo-controlled trials of canagliflozin found similar BP effects. A trial evaluating BP effects at 6 weeks found significant decreases in BP among those subjects receiving canagliflozin.[17] Similarly, a pooled analysis discussed the effects of canagliflozin on BP compared to placebo.[19] The analysis supports the results of significant decrease in SBP with both canagliflozin 100 mg and 300 mg compared to placebo. However, the pooled analysis only found significant DBP reductions among subjects who received canagliflozin 300 mg, compared to 100 mg and placebo. In addition, the analysis revealed that the effect of canagliflozin on SBP and DBP resulted regardless of background antihypertensive therapeutics.

When studies explored canagliflozin in addition to or in comparison with other AHAs, the canagliflozin cohort experienced similar BP lowering effects.[20] When canagliflozin was evaluated as add-on therapy to metformin and a sulfonylurea, canagliflozin provided significant reductions in SBP and DBP compared to placebo.[20] Several clinical trials compared canagliflozin to sitagliptin 100 mg, a DPP-4 inhibitor, to assess efficacy and safety. Canagliflozin 100 mg and 300 mg were associated with significant reductions in SBP and DBP compared to sitagliptin 100 mg across all three published trials.[21–23] Additionally, minimal changes in pulse rate were observed between both doses of canagliflozin compared to sitagliptin.

Body weight reductions

Obesity and sedentary lifestyle contribute to the progression of T2DM and increase the risk of CVD. Therefore, the first step in T2DM management is often weight loss, which is associated with lower insulin resistance, improved glycemic control, and decreased risk of comorbidity development.[7] Canagliflozin 100 mg and 300 mg consistently resulted in significant reduction in body weight across all currently published trials.

In the placebo-controlled trials, canagliflozin 100 mg and 300 mg resulted in significant body weight reductions compared to placebo ($P<0.001$).[7,14,19,20] The CANTATA-M trial found weight loss to be rapid through week 6 with progressive decline through week 26.[7] The short-term weight loss caused

by canagliflozin was supported by the 6-week ambulatory BP monitoring trial, with significant weight loss seen in the canagliflozin treatment groups.[17] In the trials that used sitagliptin 100 mg as an active control, canagliflozin was associated with significant body weight reductions compared to sitagliptin ($P<0.001$).[21–23] One 52-week trial reported weight loss from canagliflozin to have occurred more rapidly through week 6, with a slow decrease to an apparent plateau at week 34.[21] In a 12-week dose-range study, canagliflozin resulted in significant weight loss in all studied regimens compared to placebo and sitagliptin 100 mg ($P<0.001$).[24]

Changes in renal function

Renal function decline is a frequent complication of T2DM and is closely associated with an increased risk in CVD.[18] The assessment of renal function is measured through parameters such as estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), and urine albumin levels. Modification of these parameters directly impacts the development of renal disease and cardiovascular risk.[25] Trials exploring the effect of canagliflozin on renal function have resulted in prolonged maintenance of eGFR and regression of albuminuria.[20,25]

The CANVAS-R trial was the lead study assessing the effects of canagliflozin on renal function. This trial demonstrated canagliflozin's reno-protective properties, through changes in albuminuria and eGFR.[25] In this study, canagliflozin caused significant reduction in the risk of progression of albuminuria and more frequent regression of albuminuria compared to placebo. CANVAS-R participants were analyzed in subgroups based on eGFR set at ≥90, >90–60, >60–45, and <45 mL/min/1.73 m².[25] An initial decline in eGFR was observed in canagliflozin vs placebo at week 13 of treatment.[25] The eGFR subgroups experienced placebo-subtracted least squares (LS) mean changes of −1.89, –2.33, –2.85, and –2.75, respectively.[25] However, after week 13 canagliflozin was associated with an upward trend in eGFR toward baseline and significant slowing of annual decline in kidney function in T2DM patients (LS mean changes of 1.47, 1.09, 1.05, and 1.35 with respect to eGFR subgroups).

Among patients with stage 3 CKD, those taking canagliflozin 100 mg and 300 mg had a lower amount of albuminuria progression vs placebo (5.1, 8.3, and 11.8%, respectively).[18] In addition, the trial measured eGFR, BUN, and urine albumin/creatinine ratio to assess renal function in canagliflozin relative to placebo. Canagliflozin 100 mg and 300 mg resulted in an initial decrease in eGFR that was largest at week 3, then trended back toward baseline over the 26-week treatment period (LS mean percent changes –4.6

and −5.6%, respectively). Canagliflozin 100 mg and 300 mg were associated with an increased BUN vs placebo (LS mean changes 7.2% and 7.6%, respectively). There was a greater decrease in urine albumin/creatinine ratio seen with canagliflozin 100 mg and 300 mg compared to placebo (LS mean changes of −22.4% and −13.4%, respectively).

In addition, SGLT2 inhibitors are considered to confer reno-protective effects through an increase in hematocrit. The rise in hematocrit is thought to be caused by recovery from diabetes-induced tubulointerstitial injury within the nephrons and subsequent increased production of erythropoietin.[26] Among patients receiving canagliflozin specifically, a mean rise in hemoglobin concentrations from baselines was found to be 0.47 mg/dL and 0.51 mg/dL among patients on 100 mg and 300 mg doses respectively.[27]

Further research and ongoing studies, including the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial,[28] will help to better characterize the clinical kidney outcomes of canagliflozin in patients with T2DM.

Changes in cardiovascular outcomes

Patients with T2DM and an elevated risk for CVD are more likely to experience nonfatal MI, nonfatal stroke, and death from cardiovascular causes.[14] Several published studies specifically evaluated cardiovascular outcomes as their primary endpoints, and similarly concluded that canagliflozin significantly reduces the risk of cardiovascular event occurrence.[14,15,29]

In the CANVAS program, canagliflozin resulted in a significant decrease in composite death from cardiovascular causes (nonfatal MI and nonfatal stroke) compared to placebo (P<0.001).[14] This study tested canagliflozin vs placebo in two cohorts of T2DM patients. The primary prevention cohort included patients ≥50 years old with ≥2 cardiovascular event risk factors but no previous cardiovascular event, while the secondary prevention cohort included patients ≥30 years old with a previous cardiovascular event. One third of patients were included in the primary prevention cohort while 66% of patients met inclusion for the secondary prevention cohort. Patients within the primary prevention cohort were 1 year younger (63 vs 64 years old), included 1.4 times as many female patients, and had diabetes for 1 year longer (14 vs 13 years) than the secondary prevention cohort.[14] The composite primary endpoint included nonfatal MI, nonfatal stroke, or cardiovascular death, and occurred at a higher rate in the secondary prevention group than the primary prevention group (36.9 vs 15.7/1,000 patient-years, P<0.001). In the overall study population including both primary and secondary

prevention groups, the primary endpoint was reduced with canagliflozin (26.9 vs 31.5/1,000 patient-years, P<0.001 for non-inferiority).[14] Furthermore, canagliflozin 100 mg and 300 mg resulted in a decreased hospitalization for heart failure compared to placebo consistently across both primary and secondary prevention cohorts, with overall 16 fewer patients compared to placebo experiencing heart failure hospitalization events in 1,000 patients over 5 years.[29]

The CVD-REAL study that included canagliflozin and other SGLT2 inhibitors found a lower risk of hospitalization for heart failure among patients taking SGLT2 inhibitors compared to patients taking other oral or injectable glucose lowering agents (P<0.001).[15] In addition, SGLT2 inhibitors were associated with significantly lower risk of all-cause death compared to other AHAs (P<0.001). Of the patients included in this study who were taking an SGLT2 inhibitor, 53% were taking canagliflozin, 42% were taking dapagliflozin, and 5% were taking empagliflozin.[15]

An additional study comparing canagliflozin to other AHAs was conducted retrospectively and found patients taking canagliflozin had a decreased risk of hospitalization for heart failure compared to those taking DPP4-Is, GLP-1 receptor agonists, and sulfonylureas (91 vs 124 events per 1,000 patient years, with respect to canagliflozin and the competitor AHA).[16]

In consideration of SGLT2's effects on cardiovascular outcomes such as heart failure hospitalization rates, it is also important to evaluate the underlying effect of these agents on vascular function and cardiac function. It is known that hyperglycemia-related arterial stiffness can contribute to new-onset or worsening hypertension.[30] Empagliflozin has been found to decrease markers of arterial stiffness (SBP, pulse) in young patients with type 1 DM and T2DM.[30,31] Similarly, canagliflozin has also elicited beneficial decreases on these markers of arterial stiffness vs placebo in patients with T2DM in multiple studies.[32–34]

Changes in cardiac function studied among those receiving SGLT2 inhibitors reveal favorable outcomes. One systematic analysis of echocardiogram results of patients with T2DM taking empagliflozin showed a significant reduction in left ventricular mass index and improved diastolic function, suggesting the ability of SGLT2 inhibitors to reverse cardiovascular remodeling and improve diastolic function among patients with T2DM and CVD.[35] This positive effect on cardiac function was further assessed in a murine study with empagliflozin and a human study with canagliflozin, where similar effects on improvement in left ventricular diastolic function were seen.[36,37] Patients receiving canagliflozin

who had substantial improvements in HbA1c demonstrated the most apparent improvements in cardiac function.[37] In addition, another recent study of canagliflozin among patients with T2DM found a delay in the rise of cardiac biomarkers associated with an increased risk of cardiovascular events when elevated. The cardiac biomarkers with delayed rise among patients receiving canagliflozin included: N-terminal pro-B-type natriuretic peptide, high-sensitivity troponin I, sST2, and Gal-3.[38] Together the effect of canagliflozin and other SGLT2 inhibitors on vascular and cardiac function have the potential to delay the onset of heart failure or prevent it altogether among patients with T2DM.[37]

Safety and tolerability

Several studies on canagliflozin explored the agent's safety and tolerability related to cardiovascular-specific endpoints and consistently found the agent to be well-tolerated with a modestly higher incidence of pre-specified adverse events (AEs) compared to placebo. Such pre-specified AEs included: urinary tract infections, genital mycotic infections, hypoglycemia, and events related to osmotic diuresis.

Safety evaluations related to cardiovascular endpoints included the collection of intravascular volume depletion-related and osmotic diuresis-related events. The AEs associated with osmotic diuresis included pollakiuria (urine frequency) and polyuria (urine volume). The AEs that comprised intravascular volume depletion included postural dizziness and orthostatic hypotension.

In placebo-controlled studies, the incidence of AEs related to intravascular volume reduction was low and similar in canagliflozin and placebo.[7,14,17,19,20] In the sitagliptin-controlled studies, incidence of postural dizziness and hypotension were low across all groups. In the 52-week extension study, canagliflozin 100 mg had higher incidence of intravascular volume reduction AEs compared to canagliflozin 300 mg and placebo/sitagliptin.[21–23] The events of postural dizziness and hypotension that did occur with canagliflozin were reported as mild or moderate in intensity and few led to discontinuation of canagliflozin.[7,20]

Reported similarly across all placebo-controlled trials, the treatment with canagliflozin 100 mg and 300 mg was associated with an increased incidence of osmotic diuresis-related AEs compared to placebo.[7,14,17,19,20] In the Phase 3 studies that compared canagliflozin to sitagliptin, canagliflozin resulted in a higher incidence of osmotic diuresis AEs.[21–23] The majority of reported osmotic diuresis-related events occurred within the initial weeks of treatment. All events

were reported as mild to moderate in intensity and few led to discontinuation.[19,21–23]

Additional noteworthy AEs associated with canagliflozin include increased risk of bone fractures, amputation, and changes in lab values compared to placebo.[14] The CANVAS program reported a higher rate of lower extremity amputation with canagliflozin 100 mg and 300 mg vs placebo.[14] Several trials reported that canagliflozin caused an increase in hemoglobin and hematocrit, whereas sitagliptin and placebo caused a decrease in both values.[7,18–23]

Discussion/clinical considerations

The class of SGLT2 inhibitors has sparked considerable interest as a potential therapeutic option for T2DM. In addition to providing a modest glycemic benefit, some SGLT2 inhibitors have also demonstrated efficacy in reduction of several cardiovascular risk factors such as BP and body weight. While many traditional therapies for T2DM result in weight gain or are weight neutral, the added benefit of weight loss with SGLT2 inhibitors is clinically important. Canagliflozin in particular, when compared with other SGLT2 inhibitors, resulted in the greatest reduction in body weight in one meta-analysis.[39] Canagliflozin has also demonstrated consistent improvement in several individual cardiovascular risk factors such as BP, body weight, and renal function across multiple published studies.

Many earlier studies evaluated these individual cardiovascular risk factors only as secondary or exploratory endpoints rather than primary areas of focus. These studies were not designed or powered to fully determine the clinical impact of canagliflozin on BP or the result of this impact on overall morbidity and mortality. Recent larger-scale studies have been designed to evaluate if properties like the antihypertensive benefits observed in canagliflozin and other SGLT2 inhibitors translate into clinically significant cardiovascular benefit, as the impact of these modifications on cardiovascular risk factors may not necessarily translate into reduction of overall cardiovascular risk.

Empagliflozin was the first SGLT2 inhibitor to show improved cardiovascular outcomes, including reduction in death from cardiovascular causes via the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose) study.[40] While this study demonstrated benefit of empagliflozin in cardiovascular outcomes with high-risk patients, questions persisted regarding whether the overall cardiovascular benefits seen with empagliflozin were agent-

or class specific. Composite results from the CANVAS program suggest a broader class effect in cardiovascular benefit with SGLT2 inhibitors. While the sample size of CANVAS was smaller and included a patient population with lower incidence of established CVD than that of EMPA-REG OUTCOME, a reduction in death from CV causes, nonfatal MI, and nonfatal stroke was still demonstrated. The recently completed DECLARE-TIMI 58 trial evaluating dapagliflozin compared with placebo in patients with T2DM and high CVD risk found dapagliflozin to be non-inferior for major cardiovascular AEs and demonstrated a statistically significant reduction in the composite endpoint that includes heart failure hospitalization or cardiovascular death.[41] Future studies may provide further evidence to the class- vs agent-specific cardiovascular benefits of SGLT2 inhibitors. Other studies are also evaluating the role of SGLT2 inhibitors specifically in kidney disease, including CREDENCE (canagliflozin) and DAPA-CKD (dapagliflozin). It should be noted that while these cardiovascular and renal endpoint trials are informative, they are not designed to provide any direct comparisons among individual SGLT2 agents, and data should be considered in the context of the individual patient and the inherent variability of patient response to a particular drug.

One notable difference in class effects between canagliflozin and other SGLT2 inhibitors has been in the safety profile. The canagliflozin group had an increased risk of amputation and fracture noted in the CANVAS trial that was not seen in EMPA-REG, with the highest absolute risk for amputation occurring in patients with peripheral vascular disease and prior amputation. The approximately two-fold increase in risk of amputation among patients receiving canagliflozin in CANVAS was unexpected, though there is not currently evidence to suggest a fully causal relationship between amputation risk and canagliflozin.[42] However, in a pharmacovigilance analysis using the FDA's Adverse Event Reporting System, Fandini et al reported that canagliflozin was found to have a higher incidence of any amputation among patients with DM (0.32%) compared to empagliflozin (0.09%) and dapagliflozin (0%).[43] There are a few possible mechanisms whereby amputation risk could have been increased in the CANVAS program, though the true mechanism remains unknown. The overall amputation rate in patients with T2DM has declined over the last few decades, but diabetic foot disease (DFD) remains prevalent, increasing risk of lower-extremity amputation in itself.[43,44] In the CANVAS program, a history of DFD and prior amputation were both risk factors for amputation.[42] In a CANVAS sub-group analysis, there was a greater reduction of MACE

in patients with a history of amputation than those without. This reduction in MACE occurred early in CANVAS, while amputation occurred more frequently in the late phase. This finding has led some researchers to postulate that perhaps a decrease in MACE could have been related to an increase in amputation risk. Despite these findings, a recent retrospective cohort study found no increased risk of lower extremity amputation for canagliflozin compared to other SGLT2 inhibitors and other AHAs.[45] This finding could indicate the CANVAS program's increased risk of amputation was related to other factors, such as non-adherence or other adverse effects. Compared to the empagliflozin group in the EMPA-REG OUTCOME trial, the canagliflozin group in the CANVAS program had an increased incidence of volume depletion-related AEs, which could have contributed to circulatory failure and perhaps increased the risk of amputation.[42] Also, adherence to study drugs was lower in the CANVAS program (29%)[14] compared with the EMPA-REG OUTCOME trial (25%).[40] The lower adherence could have increased the incidence of amputation among canagliflozin patients, as discontinuation of the SGLT2 inhibitor could have led to further progression in peripheral arteriosclerosis.[42] While a higher risk for amputation with canagliflozin may be inferred from this data, it should be noted that data on amputations were not specifically collected for EMPA-REG or other previous studies on other SGLT2 inhibitors. Therefore, further studies evaluating this risk as a class- or agent-specific effect should be conducted in order to determine the true clinical significance. In the meantime, clinicians should exercise caution in initiating canagliflozin in patients at risk of fractures or amputations.

Lastly, further research should evaluate the potential dose-response relationship between canagliflozin and its cardiovascular benefits. While one earlier meta-analysis did not find a significant difference in BP lowering effects between the different SGLT2 inhibitors, the authors did note the presence of a significant association between increasing doses of canagliflozin and decreasing SBP.[39] This dose response relationship may also correspond to overall cardiovascular benefits. Future studies are needed to discern if there is a target dose of canagliflozin that is necessary to achieve the full impact of cardiovascular risk reduction.

On the horizon of oral anti-diabetic agents is the investigational SGLT2 inhibitor, sotagliflozin, for which the New Drug Application was accepted by the FDA in May of 2018. Sotagliflozin is a dual inhibitor of SGLT1 and SGLT2 that could be approved for use in patients with type 1 diabetes in combination with insulin to improve clinical outcomes and

overall glycemic control.[45] In the Tandem 1 and 2 trials, sotagliflozin 200 mg and 400 mg reduced HbA1c with optimized insulin use compared to placebo. The most recent Tandem 3 trial testing sotagliflozin vs placebo showed a greater proportion of type 1 DM patients achieving an HbA1c <7% in the sotagliflozin group compared to placebo.[46] Tandem 3 also achieved statistical significance in secondary endpoints including favorable changes in HbA1c from baseline, SBP, mean daily bolus insulin dose, and body weight.[47] If approved, sotagliflozin would be the first oral therapy approved in the US to be used alongside insulin. Canagliflozin also has activity at SGLT1, and while small studies have not proven the use of canagliflozin in patients with type 1 DM, further studies may demonstrate the benefit of its use in this patient population.[48]

Conclusion

Canagliflozin has consistently demonstrated, through published clinical trials, a reduction in cardiovascular risk factors such as BP, body weight, and renal function. These results suggest a class-benefit of SGLT2 inhibitors rather than agent-specific effects. Further research is needed to clarify risks of canagliflozin related to fractures and amputations, and determine optimal dosing requirements for canagliflozin in regard to cardiovascular risk reduction.

Disclosure

The authors report no conflicts of interest in this work.

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