Stroke

CLINICAL AND POPULATION SCIENCES

Effect of SGLT2 Inhibitors on Stroke and Atrial Fibrillation in Diabetic Kidney Disease

Results From the CREDENCE Trial and Meta-Analysis

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BACKGROUND AND PURPOSE: Chronic kidney disease with reduced estimated glomerular filtration rate or elevated albuminuria increases risk for ischemic and hemorrhagic stroke. This study assessed the effects of sodium glucose cotransporter 2 inhibitors (SGLT2i) on stroke and atrial fibrillation/flutter (AF/AFL) from CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) and a meta-analysis of large cardiovascular outcome trials (CVOTs) of SGLT2i in type 2 diabetes mellitus.

METHODS: CREDENCE randomized 4401 participants with type 2 diabetes mellitus and chronic kidney disease to canagliflozin or placebo. Post hoc, we estimated effects on fatal or nonfatal stroke, stroke subtypes, and intermediate markers of stroke risk including AF/AFL. Stroke and AF/AFL data from 3 other completed large CVOTs and CREDENCE were pooled using random-effects meta-analysis.

RESULTS: In CREDENCE, 142 participants experienced a stroke during follow-up (10.9/1000 patient-years with canagliflozin, 14.2/1000 patient-years with placebo; hazard ratio [HR], 0.77 [95% CI, 0.55–1.08]). Effects by stroke subtypes were: ischemic (HR, 0.88 [95% CI, 0.61–1.28]; n=111), hemorrhagic (HR, 0.50 [95% CI, 0.19–1.32]; n=18), and undetermined (HR, 0.54 [95% CI, 0.20–1.46]; n=17). There was no clear effect on AF/AFL (HR, 0.76 [95% CI, 0.53–1.10]; n=115). The overall effects in the 4 CVOTs combined were: total stroke (HR_{pooled}, 0.96 [95% CI, 0.82–1.12]), ischemic stroke (HR_{pooled}, 1.01 [95% CI, 0.89–1.14]), hemorrhagic stroke (HR_{pooled}, 0.50 [95% CI, 0.30–0.83]), undetermined stroke (HR_{pooled}, 0.86 [95% CI, 0.49–1.51]), and AF/AFL (HR_{pooled}, 0.81 [95% CI, 0.71–0.93]). There was evidence that SGLT2i effects on total stroke varied by baseline estimated glomerular filtration rate (P=0.01), with protection in the lowest estimated glomerular filtration rate (<45 mL/min/1.73 m^2) subgroup (HR_{pooled}, 0.50 [95% CI, 0.31–0.79]).

CONCLUSIONS: Although we found no clear effect of SGLT2i on total stroke in CREDENCE or across trials combined, there was some evidence of benefit in preventing hemorrhagic stroke and AF/AFL, as well as total stroke for those with lowest estimated glomerular filtration rate. Future research should focus on confirming these data and exploring potential mechanisms.

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Key Words: atrial fibrillation ■ canagliflozin ■ glomerular filtration rate ■ hemorrhagic stroke ■ ischemic stroke

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For Sources of Funding and Disclosures, see page 1553.

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AFL	atrial flutter
CKD	chronic kidney disease
CREDENCE	Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation
CVOT	cardiovascular outcome trial
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
DECLARE-TIMI-58	Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58
eGFR	estimated glomerular filtration rate
EMPA-REG OUTCOME	Empagliflozin Cardiovascular Out come Event Trial in Type 2 Diabetes Mellitus Patients
HbA1c	glycated hemoglobin
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
LDL-C	low-density lipoprotein cholesterol
SGLT2i	sodium glucose cotransporter 2 inhibitor
T2DM	type 2 diabetes mellitus
UACR	urinary albumin:creatinine ratio

Chronic kidney disease (CKD) with reduced estimated glomerular filtration rate (eGFR) or elevated albuminuria is a risk factor for ischemic and hemorrhagic stroke.[1,2] Although the pathogenesis of stroke in patients with CKD has been widely investigated, stroke prevention in CKD remains an important problem due to the lack of effective interventions and specific guideline recommendations.[3–5] Sodium glucose cotransporter 2 inhibitors (SGLT2i) were developed as a new treatment for type 2 diabetes mellitus (T2DM) with a pharmacologic mechanism based upon inhibition of sodium and glucose reuptake in the proximal tubule resulting in enhanced glycosuria and natriuresis. A clear protective benefit of SGLT2i on cardiovascular events and kidney failure has now been defined in several large trials.[6–11] In a post hoc analysis from the CANVAS Program (Canagliflozin Cardiovascular Assessment Study), there was heterogeneity of the treatment effect on stroke by baseline eGFR, and a significant lowering in stroke risk was observed in participants with impaired kidney function.[12,13] Although it was not statistically significant in the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients),[14,15] a similar pattern of the effect of empagliflozin on stroke by baseline kidney function was observed, raising the possibility that the effect of SGLT2i on stroke may vary according to kidney function.

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In these analyses, we explored the effects of canagliflozin on stroke, stroke subtypes, and intermediate markers of stroke risk, including atrial fibrillation (AF) and atrial flutter (AFL), in participants with diabetic kidney disease from the CREDENCE trial (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation). Additionally, we meta-analyzed stroke outcomes from all large-scale, randomized, placebo-controlled, cardiovascular outcome trials (CVOTs) of SGLT2i in T2DM, given that no single trial was specifically designed and powered to detect treatment effects on stroke.

METHODS

Data Availability

Data from the CREDENCE trial will be made available in the public domain via the Yale University Open Data Access Project (http://yoda.yale.edu/) once the product and relevant indication studied have been approved by regulators in the United States and European Union and the study has been completed for 18 months.

Program Design

The study design, participant characteristics, and main results of CREDENCE have been published.[9,16] In brief, CREDENCE was a randomized, double-blind, placebo-controlled, multicenter (690 centers in 34 countries) clinical trial that assessed the effect of canagliflozin on clinically important renal, cardiovascular, and safety outcomes in people with T2DM and CKD on background standard of care. The trial was closed early following a planned interim analysis that demonstrated clear evidence of benefit, and the final patient follow-up was performed in October 2018, with the database locked in November 2018.[9]

Participants

Participants in CREDENCE were those with glycated hemoglobin (HbA1c) 6.5% to 12.0%, ≥30 years of age, eGFR 30 to <90 mL/min/1.73 m^2 urinary albumin:creatinine ratio (UACR) >300 to 5000 mg/g, and being treated with a stable maximum labeled or tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for ≥4 weeks before randomization. By design, ≈60% of participants had a screening eGFR of 30- <60 mL/min/1.73 m^2. Key exclusion criteria were nondiabetic kidney disease, type 1 diabetes, and prior treatment of kidney disease with immunosuppression or a history of renal replacement therapy.

Randomization, Treatment, and Follow-Up

After a 2- to 10-week screening period (including a 2-week, single-blind, placebo run-in period), participants were randomly assigned in a 1:1 ratio to oral canagliflozin 100 mg daily or matching placebo. Randomization utilized permuted blocks with stratification by eGFR categories (30–<45, 45–<60, and 60–<90 mL/min/1.73 m^2]). Participants and all study staff were masked to individual treatment allocations until the completion of the study. The protocol stipulated that study treatment be continued until the commencement of dialysis, receipt of a kidney transplant, occurrence of diabetic ketoacidosis, pregnancy, receipt of disallowed therapy, or study conclusion. Use of other background therapy for glycemic management, prevention of stroke, and other renal or cardiovascular end points was according to best practice and local guidelines.

After randomization, face-to-face follow-up visits were scheduled at 3, 13, and 26 weeks, followed by alternating telephone contacts and face-to-face visits at 3-month intervals thereafter. An additional telephone visit was arranged 30 days after study drug discontinuation. Every follow-up included inquiry about primary and secondary outcome events and serious adverse events. Participants who prematurely discontinued study treatment continued scheduled follow-up wherever possible, with extensive efforts made to obtain full outcome data.

Outcomes

The primary outcome for these analyses was fatal or nonfatal stroke combined. Secondary outcomes included fatal stroke, nonfatal stroke, and different stroke subtypes (ischemic, hemorrhagic, or undetermined). An Endpoint Adjudication Committee adjudicated all renal and cardiovascular outcomes in CREDENCE, with stroke events adjudicated by experienced stroke physicians (Data Supplement). Stroke was defined using the 2013 American Heart Association/American Stroke Association criteria.[17] Ischemic and hemorrhagic stroke were determined from the neuroimaging findings, whereas undetermined stroke represented a clinical stroke without confirmation of pathologic stroke type. Possible intermediate markers of stroke risk were analyzed, including systolic blood pressure, diastolic blood pressure, body weight, HbA1c, cholesterol, triglycerides, hematocrit, UACR, eGFR, and site-reported adverse events related to AF or AFL, which were identified in the trial database of adverse events using the Medical Dictionary of Regulatory Affairs preferred terms of "atrial fibrillation" or "atrial flutter."

Statistical Analysis for CREDENCE

We used the full dataset with an intention-to-treat approach to compare all participants assigned to canagliflozin with those assigned to placebo. Analyses were based on the occurrence of the first event under investigation for dichotomous outcomes. Annualized incidence rates (participants with an event per 1000 patient-years of follow-up) were calculated in addition to hazard ratios (HRs) and 95% CIs determined from Cox regression models, with treatment as the explanatory variable and stratification according to screening eGFR strata. Cumulative event curves were plotted to show the evolution of stroke risk over time. We tested the homogeneity of treatment effects across subgroups defined by screening eGFR strata, baseline UACR levels (>1000 or ≤1000 mg/g), and other baseline participant characteristics after including interaction terms. Effects of canagliflozin on continuous intermediate markers of stroke risk were analyzed using the mixed-effects model for repeated measures in the on-treatment participants (unless otherwise noted), with an unstructured covariance and adjusting for the baseline value, treatment, screening eGFR strata, and trial visit.

Meta-Analysis

To explore our results in the context of the totality of the available evidence, we performed an updated meta-analysis. We followed the Preferred Reporting Items for Systemic Reviews and Meta-Analyses statement[18] except for protocol registration. Our recent systematic review and meta-analysis on the effects of SGLT2i on cardiovascular events in patients with T2DM[10] identified 4 eligible trials: EMPA-REG OUTCOME, DECLARE-TIMI-58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58), the CANVAS Program, and CREDENCE. We updated the literature search in Medline and Embase (from January 2019 to April 2020) and assessed the eligibility using the same search strategy, study selection criteria, and method for risk of bias assessment. Study-level data on total stroke, nonfatal stroke, fatal stroke, stroke subtypes, and AF or AFL were extracted from eligible trials and pooled. Summary HRs with 95% CIs were obtained using the DerSimonian and Laird random-effects model.[19] The percentage of variability across the pooled estimates attributable to heterogeneity beyond chance was estimated using the I^2 statistic, with I^2 values of 25%, 50%, and 75% being regarded as low, moderate, and high heterogeneity, respectively. We also explored the pooled treatment effects on total stroke and ischemic stroke by baseline eGFR of ≥90, 60 to <90, 45 to <60, and <45 mL/min/1.73 m^2 and on hemorrhagic stroke by baseline eGFR of ≥60, and <60 mL/min/1.73 m^2. Random-effects meta-regression was performed to test linear trend across ordered eGFR categories. SAS Enterprise Guide version 7.1 and Stata version 12.0 were used.

Standard Protocol Approvals, Registrations, and Patient Consents

The protocol for CREDENCE was approved by the ethics committees at each site. All participants provided written informed consent.

RESULTS

Baseline Characteristics of CREDENCE

In CREDENCE, 4401 participants were followed for a median follow-up of 2.6 years (Figure I in the Data Supplement). Mean age was 63 years, 34% were women, mean duration of diabetes was 15.8 years, 50% had a history of cardiovascular disease, and 16% had prior stroke. Mean baseline values were HbA1c 8.3%, systolic blood pressure 140 mm Hg, diastolic blood pressure 78 mm Hg, and eGFR 56.2 mL/min/1.73 m^2. Median baseline UACR was 927 mg/g. There were 142 (3.2%) individuals who experienced 157 stroke events during follow-up (129 had 1 event, 11 had 2 events, and 2 had 3 events). Participants with stroke during follow-up, versus nonstroke participants, had higher classical stroke risk factors of baseline HbA1c levels, prior hypertension, AF or AFL, retinopathy, and cardiovascular or atherosclerotic vascular disease. They were also more likely to take a beta-blocker or antithrombotic drug at baseline (Table I in the Data Supplement).

Effects of Canagliflozin on Stroke in CREDENCE

Participants receiving canagliflozin versus placebo had fewer, but nonsignificant, fatal, or nonfatal strokes during follow-up (10.9/1000 patient-years versus 14.2/1000 patient-years) with a corresponding HR of 0.77 (95% CI, 0.55–1.08; Figure I and Figure II in the Data Supplement). Most stroke events were nonfatal (119 participants) and ischemic (111 participants). Point estimates of effect were consistently below unity for nonfatal stroke (n=119; HR, 0.80 [95% CI, 0.56–1.15]), fatal stroke (n=24; HR, 0.72 [95% CI, 0.32–1.63]), ischemic stroke (n=111; HR, 0.88 [95% CI, 0.61–1.28]), hemorrhagic stroke (n=18; HR, 0.50 [95% CI, 0.19–1.32]), and undetermined stroke (n=17; HR, 0.54 [95% CI, 0.20–1.46]), but none of these individual results were statistically significant. Effects of treatment on fatal or nonfatal stroke were similar across screening eGFR strata (*P* interaction=0.16) and baseline UACR of >1000 versus ≤1000 mg/g (*P* interaction=0.64; Figure 1). There was also no evidence of heterogeneity of treatment effects for other participant subgroups (all *P* interaction >0.31; Figure III in the Data Supplement).

Effects on Possible Intermediate Markers of Stroke Risk in CREDENCE

There were favorable effects of canagliflozin on systolic blood pressure, diastolic blood pressure, body weight, HbA1c, high-density lipoprotein cholesterol (HDL-C), UACR, and eGFR (Table). Small increases were observed for hematocrit and total cholesterol with null effects on low-density lipoprotein cholesterol (LDL-C), triglycerides, and the ratio of LDL-C to HDL-C.

During the trial, 127 AF and 12 AFL adverse events in 115 participants were reported by site investigators. There was no clear effect of canagliflozin on the incidence of AF or AFL (n=115; HR, 0.76 [95% CI, 0.53–1.10]; *P*=0.15). Effects were consistent across screening eGFR strata (*P* interaction=0.94) or baseline UACR levels (*P* interaction=0.99), but there was evidence of differential effects across the subsets of participants with and without history of AF or AFL at baseline (*P* interaction=0.02; Figure 2).

	Participants with an event (n/N)	Participants with an event per 1000 patient-years: CANA	PBO	HR (95% CI)	*P* interaction*
Fatal or nonfatal stroke	142/4401	10.9	14.2	0.77 (0.55, 1.08)	
Nonfatal	119/4401	9.3	11.7	0.80 (0.56, 1.15)	
Fatal	24/4401	1.7	2.4	0.72 (0.32, 1.63)	
Ischemic	111/4401	9.1	10.5	0.88 (0.61, 1.28)	
Hemorrhagic	18/4401	1.0	2.1	0.50 (0.19, 1.32)	
Undetermined	17/4401	1.0	1.9	0.54 (0.20, 1.46)	
Fatal or nonfatal stroke by screening eGFR					
60-<90 mL/min/1.73 m^2	56/1809	11.6	12.5	0.94 (0.56, 1.60)	0.16
45-<60 mL/min/1.73 m^2	42/1279	12.6	12.8	0.99 (0.54, 1.81)	
30-<45 mL/min/1.73 m^2	44/1313	8.3	18.0	0.46 (0.24, 0.87)	
Fatal or nonfatal stroke by baseline UACR					
≤1000 mg/g	72/2348	10.6	12.9	0.83 (0.52, 1.32)	0.64
>1000 mg/g	70/2053	11.3	15.8	0.72 (0.45, 1.16)	

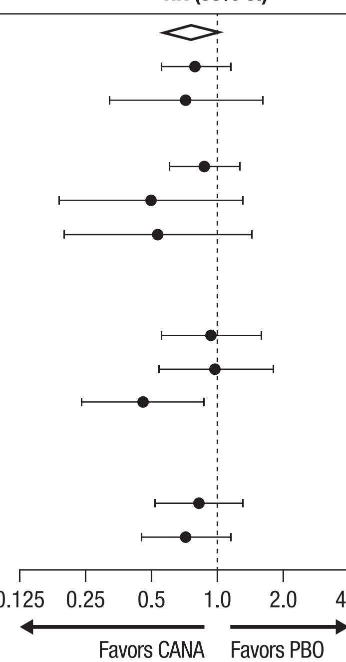

Figure 1. Effects of canagliflozin on stroke in CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation).

CANA indicates canagliflozin; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PBO, placebo; and UACR, urinary albumin:creatinine ratio. **P* value for interaction across subgroups.

Table. Effects of Canagliflozin on Possible Intermediate Markers of Stroke Risk

	Least-squares mean change (±SE) over 182 wk after randomization*		Mean or relative treatment difference* (95% CI)
	CANA	PBO	
SBP, mm Hg	−2.82 (0.22)	0.48 (0.23)	−3.30 (−3.87 to −2.73)
DBP, mm Hg	−1.37 (0.13)	−0.42 (0.13)	−0.95 (−1.28 to −0.61)
Body weight, kg	−1.13 (0.07)	−0.33 (0.07)	−0.80 (−0.92 to −0.69)
HbA1c, %	−0.42 (0.02)	−0.16 (0.02)	−0.25 (−0.31 to −0.20)
HDL cholesterol, mmol/L	0.01 (<0.01)	−0.01 (<0.01)	0.02 (0.01 to 0.03)
LDL cholesterol, mmol/L	0.05 (0.02)	0.01 (0.02)	0.04 (−0.01 to 0.09)
Ratio of LDL to HDL, %	2.58 (1.82)	3.55 (1.86)	−0.97 (−5.82 to 3.89)
Triglycerides, mmol/L	0.11 (0.03)	0.10 (0.03)	0.01 (−0.07 to 0.09)
Total cholesterol, mmol/L	0.12 (0.02)	0.05 (0.02)	0.07 (0.01 to 0.13)
Hematocrit, %	1.61 (0.08)	−0.92 (0.08)	2.52 (2.32 to 2.73)
Geometric UACR,† mg/g	541.58 (1.02)‡	781.07 (1.02)‡	−31% (−35% to −26%)§
eGFR slope,‖ mL/min/1.73 m^2/y	−3.19 (0.15)	−4.71 (0.15)	1.52 (1.11 to 1.93)

CANA indicates canagliflozin; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PBO, placebo; SBP, systolic blood pressure; and UACR, urinary albumin:creatinine ratio.

*Analyzed in the on-treatment participants with both baseline and ≥1 postbaseline measurement using the mixed-effects model for repeated measures, with an unstructured covariance and adjusting for the baseline value, trial group, category of screening eGFR, and trial visit (except geometric UACR and eGFR slope).

†Analyzed in the intention-to-treat participants with log-transformed UACR.

‡Geometric mean (±SE) estimation using the mixed-effects model for repeated measures, with an unstructured covariance and adjusting for logarithm of baseline value, trial group, and trial visit.

§Percentage reduction of the geometric mean of UACR in CANA relative to PBO.

‖The mean eGFR slope at wk 130 after randomization was calculated as a weighted combination of the 2-slope model with a knot at wk 3 (acute slope from baseline to wk 3, chronic slope from wk 3 to end of treatment), including the fixed effects of trial group, baseline eGFR, category of screening eGFR, continuous time, and time spline (1 knot at wk 3), with 2-way interactions of trial group by time; trial group by time spline; category of screening eGFR by time; category of screening eGFR by time spline; and the random effects of intercept, time, and time spline.

Meta-Analysis of SGLT2i Effects

The update of the literature search yielded 343 potentially eligible articles or conference abstracts, of which 26 articles were reviewed in full. One more trial (DAPA-HF [Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure][20]) was identified but was excluded due to lack of stroke outcome data. A total of 38 723 patients with T2DM from the 4 included trials (7020 in EMPA-REG OUTCOME, 17 160 in DECLARE-TIMI-58, 10 142 in the CANVAS Program, and 4401 in CREDENCE) were randomized to treatment with SGLT2i or placebo, with a median follow-up of 2.4 (CANVAS Program) to 4.2 years (DECLARE-TIMI-58). Among these, 1150 (3.0%) participants (233 [3.3%] in EMPA-REG OUTCOME, 466 [2.7%] in DECLARE-TIMI-58, 309 [3.0%] in the CANVAS Program, and 142 [3.2%] in CREDENCE) had a stroke event during the trial with an overall null effect of SGLT2i on total stroke (HR_{pooled}, 0.96 [95% CI, 0.82–1.12]; I^2=36.5%), nonfatal stroke (HR_{pooled}, 0.97 [95% CI, 0.76–1.24]; I^2=51.0%), fatal stroke (HR_{pooled}, 0.77 [95% CI, 0.50–1.17]; I^2=0.0%), ischemic stroke (HR_{pooled}, 1.01 [95% CI, 0.89–1.14]; I^2=0.0%), and undetermined stroke (HR_{pooled}, 0.86 [95% CI, 0.49–1.51]; I^2=0.0%; Figure 3). A beneficial effect on hemorrhagic stroke was seen after pooling (HR_{pooled}, 0.50 [95% CI, 0.30–0.83]; I^2=0.0%). There was significant heterogeneity of treatment effects on total stroke by baseline kidney function (*P*=0.01), with a pattern of protection among those with eGFR <45 mL/min/1.73 m^2 (HR_{pooled}, 0.50 [95% CI, 0.31–0.79]; I^2=0.0%) but not in those with higher eGFR (Figure 4). Differential treatment effects across baseline eGFR levels were not identified on either ischemic stroke (*P*=0.07) or hemorrhagic stroke (*P*=0.23) alone after pooling related data from the DECLARE-TIMI-58, CANVAS Program, and CREDENCE (Figures IV and V in the Data Supplement). AF or AFL data from DECLARE-TIMI-58, CANVAS Program, and CREDENCE were pooled with an overall beneficial effects of SGLT2i on AF or AFL (HR_{pooled}, 0.81 [95% CI, 0.71–0.93]; I^2=0.0%; Figure VI in the Data Supplement).

DISCUSSION

Neither the CREDENCE trial nor the meta-analysis of the 4 existing studies provided definite evidence that SGLT2i results in stroke prevention. Meta-analysis indicated a possibility that SGLT2i reduced the risk of hemorrhagic stroke and AF. There was some evidence that the effects of SGLT2i on stroke may vary by baseline kidney function with a possible benefit in those with

	Participants with an event (n/N)	Participants with an event per 1000 patient-years CANA	Participants with an event per 1000 patient-years PBO	HR (95% CI)	*P* interaction*
All†	115/4401	8.8	11.5	0.76 (0.53, 1.10)	
History of AF/AFL					0.02
Yes	14/273	29.8	11.3	2.87 (0.88, 9.36)	
No	101/4128	7.5	11.6	0.64 (0.43, 0.96)	
Screening eGFR					0.94
60-<90 mL/min/1.73 m²	34/1809	6.4	8.1	0.80 (0.40, 1.57)	
45-<60 mL/min/1.73 m²	34/1279	8.3	12.2	0.68 (0.35, 1.35)	
30-<45 mL/min/1.73 m²	47/1313	12.5	15.7	0.80 (0.45, 1.42)	
UACR					0.99
≤1000 mg/g	55/2348	7.7	10.2	0.76 (0.45, 1.30)	
>1000 mg/g	60/2053	10.1	13.1	0.76 (0.46, 1.27)	

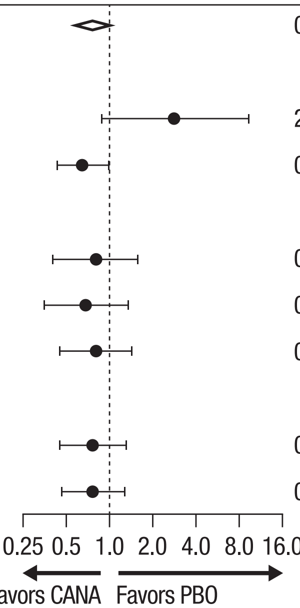

Figure 2. Effects of canagliflozin on the incidence of atrial fibrillation (AF) or atrial flutter (AFL) in CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation).

CANA indicates canagliflozin; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PBO, placebo; and UACR, urinary albumin:creatinine ratio. **P* value for interaction across subgroups. †Events of AF or AFL were identified from site investigator–reported adverse events.

significantly reduced eGFR. Data from ongoing trials in general patients with T2DM or in those with CKD should help to answer this question.

Strokes are more common in patients with CKD compared with the general population. Although stroke and CKD share common risk factors (aging, diabetes, hypertension, dyslipidemia, obesity, and smoking), CKD (defined as eGFR <60 mL/min/1.73 m²) is an independent risk factor for stroke.[21] Causes include increased blood viscosity and arterial wall stiffness mediated by multiple mechanisms (rennin-angiotensin-aldosterone system activation, platelet dysfunction, oxidative stress, inflammation, etc) and a high prevalence of AF (around 1 in 5 not receiving dialysis and 1 in 3 receiving dialysis).[22] Additionally, there is substantial uncertainty about the relative benefits and harms of anticoagulation in this group of patients.[22,23] Although SGLT2i are not thought to have a direct effect on arrhythmias, their protection against heart failure and a possible benefit in myocardial dysfunction[24,25] may indirectly reduce the risk of AF. A recent post hoc analysis from DECLARE-TIMI-58 indicated beneficial effects of dapagliflozin on the incidence of AF,[26] which should then lead to a lower risk of ischemic stroke. We did not see a significant reduction of AF risk by canagliflozin versus placebo in the CANVAS Program (n=209; HR, 0.84 [95% CI, 0.64–1.12]; *P*=0.23)[12] and CREDENCE (n=115; HR, 0.76 [95% CI, 0.53–1.10]; *P*=0.15), but there was some evidence of protection against AF by SGLT2i across the 3 studies combined.

Although there were few events, the meta-analysis showed a significant reduction in hemorrhagic stroke with no heterogeneity across the EMPA-REG OUTCOME, CANVAS Program, and CREDENCE trials, suggesting a potential benefit of SGLT2i on hemorrhagic events. Blood pressure lowering, which can be achieved with SGLT2i, leads to greater reduction for hemorrhagic stroke compared with other stroke subtypes.[27] A recent study reported an increased risk of hemorrhagic stroke in women with low LDL-C (<70 mg/dL) and triglyceride levels.[28] Although a significant increase of LDL-C and triglyceride by SGLT2i (that may contribute to the prevention of hemorrhagic stroke in those with low baseline LDL-C) was seen in the CANVAS Program, it was not confirmed in the CREDENCE and EMPA-REG OUTCOME trials. Further confirmation is needed to determine whether different SGLT2i have comparable treatment effects on hemorrhagic stroke and if any variation in their effects between ischemic and hemorrhagic stroke or across ischemic stroke subtypes are attributed to different underlying cause.

The mechanism by which kidney function modifies the effects of SGLT2i on stroke risk is unclear. In terms of possible mediators of the heterogeneity, the greater

	Participants with an event (n/N)	Participants with an event per 1000 patient-years (absolute event rate, %) SGLT2i	PBO	HR (95% CI)	Risk ratio (95% CI)
Total stroke					
EMPA-REG OUTCOME (EMPA)	233/7020	12.3 (3.5)	10.5 (3.0)	1.18 (0.89, 1.56)	1.18 (0.90, 1.56)
DECLARE-TIMI 58 (DAPA)*	466/17,160	6.9 (2.7)	6.8 (2.7)	1.01 (0.84, 1.21)	1.02 (0.85, 1.22)
CANVAS Program (CANA)	309/10,142	7.9 (3.0)	9.6 (3.1)	0.87 (0.69, 1.09)	0.99 (0.80, 1.24)
CREDENCE (CANA)	142/4401	10.9 (2.8)	14.2 (3.6)	0.77 (0.55, 1.08)	0.77 (0.56, 1.07)
Pooled (random-effects)	1150/38,723	(3.0)	(2.9)	0.96 (0.82, 1.12)	1.00 (0.87, 1.14)
Heterogeneity				I^2 = 36.5%, *P* = 0.19	I^2 = 21.5%, *P* = 0.28
Nonfatal stroke					
EMPA-REG OUTCOME (EMPA)	210/7020	NR (3.2)	NR (2.6)	1.24 (0.92, 1.67)	1.24 (0.93, 1.67)
DECLARE-TIMI 58 (DAPA)	NR	NR	NR	NR	–
CANVAS Program (CANA)	274/10,142	7.1 (2.7)	8.4 (2.7)	0.90 (0.71, 1.15)	1.02 (0.81, 1.29)
CREDENCE (CANA)	119/4401	9.3 (2.4)	11.7 (3.0)	0.80 (0.56, 1.15)	0.80 (0.56, 1.15)
Pooled (random-effects)	603/21,563	(2.8)	(2.7)	0.97 (0.76, 1.24)	1.02 (0.82, 1.28)
Heterogeneity				I^2 = 51.0%, *P* = 0.13	I^2 = 42.4%, *P* = 0.18
Fatal stroke					
EMPA-REG OUTCOME (EMPA)	27/7020	NR (0.3)	NR (0.5)	0.72 (0.33, 1.55)	0.72 (0.34, 1.56)
DECLARE-TIMI 58 (DAPA)	NR	NR	NR	NR	–
CANVAS Program (CANA)	39/10,142	1.0 (0.4)	1.2 (0.4)	0.84 (0.44, 1.59)	0.97 (0.52, 1.83)
CREDENCE (CANA)	24/4401	1.7 (0.5)	2.4 (0.6)	0.72 (0.32, 1.63)	0.71 (0.32, 1.60)
Pooled (random-effects)	90/21,563	(0.4)	(0.5)	0.77 (0.50, 1.17)	0.82 (0.54, 1.24)
Heterogeneity				I^2 = 0.0%, *P* = 0.94	I^2 = 0.0%, *P* = 0.78
Ischemic stroke					
EMPA-REG OUTCOME (EMPA)	213/7020	NR (3.2)	NR (2.7)	1.19 (0.89, 1.58)†	1.19 (0.89, 1.58)
DECLARE-TIMI 58 (DAPA)	466/17,160	6.9 (2.7)	6.8 (2.7)	1.01 (0.84, 1.21)	1.02 (0.85, 1.22)
CANVAS Program (CANA)	253/10,142	6.7 (2.6)	7.5 (2.4)	0.95 (0.72, 1.22)	1.07 (0.84, 1.38)
CREDENCE (CANA)	111/4401	9.1 (2.4)	10.5 (2.7)	0.88 (0.61, 1.28)	0.88 (0.61, 1.27)
Pooled (random-effects)	1043/38,723	(2.8)	(2.6)	1.01 (0.89, 1.14)	1.04 (0.92, 1.18)
Heterogeneity				I^2 = 0.0%, *P* = 0.57	I^2 = 0.0%, *P* = 0.64
Hemorrhagic stroke					
EMPA-REG OUTCOME (EMPA)	16/7020	NR (0.2)	NR (0.3)	0.64 (0.24, 1.72)†	0.64 (0.24, 1.72)
DECLARE-TIMI 58 (DAPA)	NR	NR	NR	NR	–
CANVAS Program (CANA)	30/10,142	0.5 (0.2)	1.3 (0.4)	0.43 (0.20, 0.89)	0.50 (0.24, 1.04)
CREDENCE (CANA)	18/4401	1.0 (0.3)	2.1 (0.5)	0.50 (0.19, 1.32)	0.50 (0.19, 1.33)
Pooled (random-effects)	64/21,563	(0.2)	(0.4)	0.50 (0.30, 0.83)	0.53 (0.32, 0.88)
Heterogeneity				I^2 = 0.0%, *P* = 0.82	I^2 = 0.0%, *P* = 0.92
Undetermined stroke					
EMPA-REG OUTCOME (EMPA)	7/7020	NR (0.1)	NR (0.1)	1.24 (0.24, 6.41)†	1.24 (0.24, 6.41)
DECLARE-TIMI 58 (DAPA)	NR	NR	NR	NR	–
CANVAS Program (CANA)	29/10,142	0.8 (0.3)	0.8 (0.3)	1.04 (0.48, 2.22)	1.23 (0.58, 2.60)
CREDENCE (CANA)	17/4401	1.0 (0.3)	1.9 (0.5)	0.54 (0.20, 1.46)	0.54 (0.20, 1.47)
Pooled (random-effects)	53/21,563	(0.2)	(0.3)	0.86 (0.49, 1.51)	0.95 (0.54, 1.66)
Heterogeneity				I^2 = 0.0%, *P* = 0.53	I^2 = 0.0%, *P* = 0.42

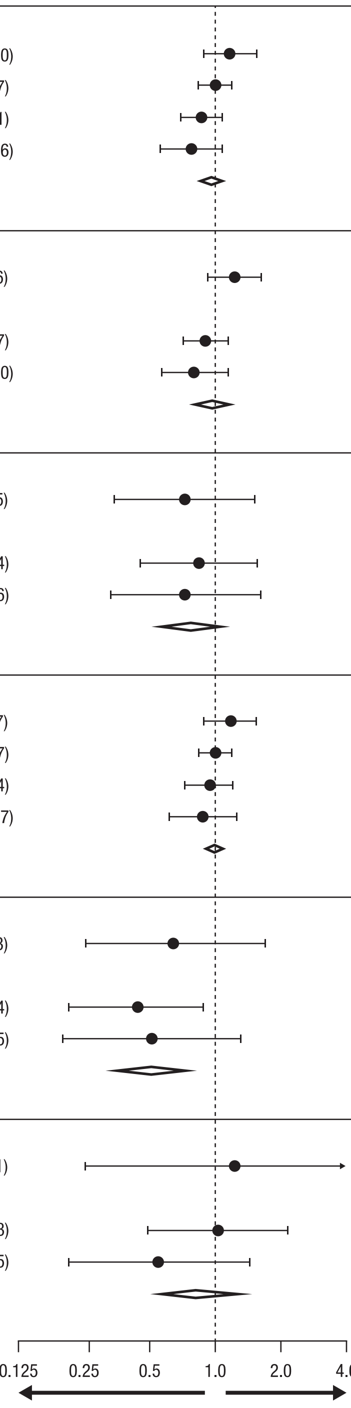

Figure 3. Meta-analysis of the treatment effects of sodium glucose cotransporter 2 inhibitors (SGLT2i) on stroke and stroke subtypes.

CANA indicates canagliflozin; CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; DAPA, dapagliflozin; DECLARE-TIMI-58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA, empagliflozin; EMPA-REG OUTCOME, EMPA Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR, hazard ratio; NR, not reported; and PBO, placebo. *Data on ischemic stroke. †Hazard ratio was estimated by risk ratio.

	Participants with an event (n/N)	Participants with an event per 1000 patient-years: SGLT2i	Participants with an event per 1000 patient-years: PBO	HR (95% CI)	*P* homogeneity
EMPA-REG OUTCOME (EMPA vs PBO)					
All	233/7020	12.3	10.5	1.18 (0.89, 1.56)	
eGFR ≥90 mL/min/1.73 m²	47/1538	12.5	7.2	1.73 (0.86, 3.47)	0.46
eGFR 60-<90 mL/min/1.73 m²	109/3661	11.0	9.1	1.22 (0.80, 1.84)	
eGFR 45-<60 mL/min/1.73 m²	55/1249	15.5	15.5	1.02 (0.58, 1.78)	
eGFR <45 mL/min/1.73 m²	22/570	12.4	17.5	0.74 (0.32, 1.73)	
DECLARE-TIMI 58 (DAPA vs PBO)*					
All	466/17,160	6.9	6.8	1.01 (0.84, 1.21)	
eGFR ≥90 mL/min/1.73 m²	184/8162	NR	NR	1.12 (0.84, 1.50)	0.46
eGFR 60-<90 mL/min/1.73 m²	232/7732	NR	NR	0.91 (0.70, 1.18)	
eGFR 45-<60 mL/min/1.73 m²	50/1265	NR	NR	1.23 (0.70, 2.14)	
eGFR <45 mL/min/1.73 m²	0/0	–	–	–	
CANVAS Program (CANA vs PBO)					
All	309/10,142	7.9	9.6	0.87 (0.69, 1.09)	
eGFR ≥90 mL/min/1.73 m²	73/2476	9.5	6.6	1.42 (0.86, 2.36)	0.01
eGFR 60-<90 mL/min/1.73 m²	173/5625	7.7	9.3	0.89 (0.65, 1.21)	
eGFR 45-<60 mL/min/1.73 m²	47/1485	7.1	13.5	0.56 (0.31, 1.00)	
eGFR <45 mL/min/1.73 m²	16/554	5.2	16.8	0.32 (0.11, 0.96)	
CREDENCE (CANA vs PBO)†					
All	142/4401	10.9	14.2	0.77 (0.55, 1.08)	
eGFR ≥90 mL/min/1.73 m²	0/0	–	–	–	0.16
eGFR 60-<90 mL/min/1.73 m²	56/1809	11.6	12.5	0.94 (0.56, 1.60)	
eGFR 45-<60 mL/min/1.73 m²	42/1279	12.6	12.8	0.99 (0.54, 1.81)	
eGFR <45 mL/min/1.73 m²	44/1313	8.3	18.0	0.46 (0.24, 0.87)	
Overall (random-effects model)‡					
All	1150/38,723	–	–	0.96 (0.82, 1.12)	
eGFR ≥90 mL/min/1.73 m²	304/12,176	–	–	1.24 (0.98, 1.57)	0.01§
eGFR 60-<90 mL/min/1.73 m²	570/18,827	–	–	0.95 (0.80, 1.13)	
eGFR 45-<60 mL/min/1.73 m²	194/5278	–	–	0.92 (0.66, 1.28)	
eGFR <45 mL/min/1.73 m²	82/2437	–	–	0.50 (0.31, 0.79)	

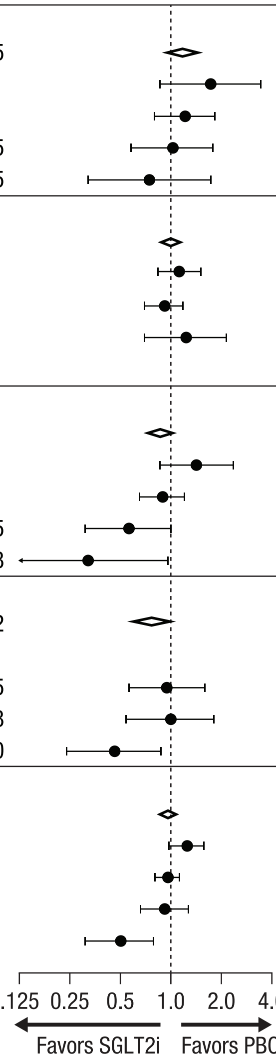

Figure 4. Effects of sodium glucose cotransporter 2 inhibitors (SGLT2i) on stroke according to baseline kidney function. CANA, canagliflozin; CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; DAPA, dapagliflozin; DECLARE-TIMI-58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; eGFR, estimated glomerular filtration rate; EMPA, empagliflozin; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR, hazard ratio; NR, not reported; and PBO, placebo; *Ischemic stroke only. †Based on screening (rather than baseline) eGFR. ‡The heterogeneity of meta-analysis is I^2=36.5% (P=0.19) for all participants, I^2=0.0% (P=0.44) for eGFR ≥90 mL/min/1.73 m² I^2=0.0% (P=0.65) for eGFR 60–<90 mL/min/1.73 m² I^2=24.7% (P=0.26) for eGFR 45–<60 mL/min/1.73 m² and I^2=0.0% (P=0.46) for eGFR <45 mL/(min·1.73 m²). §Tested by random-effects meta-regression with the hypothesis of no linear trend across ordered eGFR categories (eGFR ≥90, 60–<90, 45–<60, and <45 mL/min/1.73 m²).

blood pressure–lowering effect of canagliflozin in the CREDENCE participants with lower screening eGFR might provide an explanation,[29] but it was not seen in the CANVAS Program.[13] The treatment effects of canagliflozin on AF were also consistent regardless of the screening eGFR in CREDENCE, similar to the result of DECLARE-TIMI-58. An elevation of blood viscosity with SGLT2i treatment, as reflected by a rise in hematocrit, has raised concerns about possible adverse effects of SGLT2i on stroke. However, the between-group difference was small in every study observed that has reported data.[30] Our analysis did not show differential effects of canagliflozin on hematocrit across eGFR subgroups in the CANVAS Program or the CREDENCE trial.

The main limitation of the CREDENCE stroke analysis is the lack of statistical power for stroke events, part of the secondary composite outcome of major adverse cardiovascular events (cardiovascular death, myocardial infarction, or stroke) in the original trial. The early closure of the trial reduced stroke events further. To enhance statistical power, we undertook a study-level meta-analysis by including stroke data from other large-scale CVOTs of SGLT2i in patients with T2DM, and these analyses suggest no protective effect of SGLT2i against overall stroke. Prior exclusion of those with CKD from CVOTs[31] and the absence of dedicated randomized trials designed to test stroke risk in patients with CKD mean that most evidence on stroke prevention in CKD is extrapolated from trials in people with normal kidney function or from observational studies. This has resulted in low-level guideline recommendations, and thus these results may provide additional useful information. Our data also provide rationale for further investigation of the effects of SGLT2i on stroke or stroke subtypes risk among patients with significantly impaired kidney function, either through overviews including additional data from ongoing trials, as they become available, or through dedicated new studies.

CONCLUSIONS

In conclusion, neither the CREDENCE trial nor the meta-analysis of the 4 existing studies provided definite evidence of stroke prevention by SGLT2i. There may be differential effects of SGLT2i on stroke risk according to the level of kidney function and possible benefit in those with significantly reduced kidney function or benefit for hemorrhagic stroke and AF, which warrant further investigation.

ARTICLE INFORMATION

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Supplemental Materials

Expanded Materials & Methods
Online Table I
Online Figures I–VI

APPENDIX

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