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

Zien Zhou, MD; Meg J. Jardine, MBBS, PhD; Qiang Li, MBiostat; Brendon L. Neuen, MBBS (Hons), MSc; Christopher P. Cannon, MD; Dick de Zeeuw, MD, PhD; Robert Edwards, MPH; Adeera Levin, MD, FRCP; Kenneth W. Mahaffey, MD; Vlado Perkovic, MBBS, PhD; Bruce Neal, MB ChB, PhD; Richard I. Lindley, MD; CREDENCE Trial Investigators*

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 m2)] 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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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 m², 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 m². 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…
outcomes, whereas undetermined stroke represented a clinical
rhagic stroke were determined from the neuroimaging find-
ings, 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
and the Medical Dictionary of Regulatory Affairs preferred terms
were identified in the trial database of adverse events using
were masked to individual treatment allocations until the com-
pletion of the study. The protocol stipulated that study treat-
ment 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 inter-
vals 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 out-
comes 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 hemor-
rhagic stroke were determined from the neuroimaging find-
ings, 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 regres-
sion 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 par-
ticipant 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 avail-
able evidence, we performed an updated meta-analysis. We
followed the Preferred Reporting Items for Systemic Reviews
and Meta-Analyses statement18 except for protocol registra-
tion. Our recent systematic review and meta-analysis on the
effects of SGLT2i on cardiovascular events in patients with
T2DM10 identified 4 eligible trials: EMPA-REG OUTCOME,
DECLARE-TIMI-58 (Dapagliflozin Effect on Cardiovascular
Events—Thrombolysis in Myocardial Infarction 58), the CANVAS
Program, and CREDE. 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 attrib-
utable to heterogeneity beyond chance was estimated using the
I² statistic, with I² values of 25%, 50%, and 75% being
regarded as low, moderate, and high heterogeneity, respec-
tively. 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 m² and on hemorrhagic
stroke by baseline eGFR of ≥60, and <60 mL/min/1.73 m².
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 CREDE was approved by the ethics com-
mittees at each site. All participants provided written informed
consent.

RESULTS
Baseline Characteristics of CREDE
In CREDE, 4401 participants were followed for a
median follow-up of 2.6 years (Figure I in the Data Sup-
plement). 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 m². 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, ver-
sus 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 I). 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).

![Figure 1. Effects of canagliflozin on stroke in CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation).](image-url)

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                                           | 145.58 (1.02)†                                | 145.58 (1.02)†                                | −31% (−35% to −26%)§  |
| eGFR slope, mL/min/1.73 m²/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 (DECLARE-TIMI-58) years (DECLARE-TIMI-58). Among these, 1150 (3.0%) 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]; I²=36.5%, nonfatal stroke (HR pooled 0.97 [95% CI, 0.76–1.24]; I²=51.0%), fatal stroke (HR pooled 0.77 [95% CI, 0.50–1.17]; I²=0.0%), ischemic stroke (HR pooled 1.01 [95% CI, 0.89–1.14]; I²=0.0%), and undetermined stroke (HR pooled 0.86 [95% CI, 0.49–1.51]; I²=0.0%; Figure 3). A beneficial effect on hemorrhagic stroke was seen after pooling (HR pooled 0.50 [95% CI, 0.30–0.83]; I²=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 m² (HR pooled 0.50 [95% CI, 0.31–0.79]; I²=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]; I²=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
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. 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). Additionally, there is substantial uncertainty about the relative benefits and harms of anticoagulation in this group of patients. Although SGLT2i are not thought to have a direct effect on arrhythmias, their protection against heart failure and a possible benefit in myocardial dysfunction 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, 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]; \( P=0.23 \)) 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. A recent study reported an increased risk of hemorrhagic stroke in women with low LDL-C (<70 mg/dL) and triglyceride levels. 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 | \( P \) interaction* |
|----------------------------------|-----------------------------------------------|------------------|
| CANA                             | PBO                                     | HR (95% CI)     |
| All†                            | 115/4401                                  | 8.8             | 11.5 | 0.76 (0.53, 1.10) | 0.02 |
| History of AF/AFL                |                                          |                 |     |                   |
| 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                  |                                          |                 |     |                   |
| 60–<90 mL/min/1.73 m²            | 34/1809                                   | 6.4             | 8.1  | 0.80 (0.40, 1.57) | 0.94 |
| 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                            |                                          |                 |     |                   |
| ≤1000 mg/g                       | 55/2348                                   | 7.7             | 10.2 | 0.76 (0.45, 1.30) | 0.99 |
| >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.
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.
blood pressure–lowering effect of canagliflozin in the CREДЕНCE participants with lower screening eGFR might provide an explanation, but it was not seen in the CANVAS Program. The treatment effects of canagliflozin on AF were also consistent regardless of the screening eGFR in CREДЕНCE, 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. Our analysis did not show differential effects of canagliflozin on hematocrit across eGFR subgroups in the CANVAS Program or the CREДЕНCE trial.

The main limitation of the CREДЕНCE 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 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 CREDiT 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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Affiliations

The George Institute for Global Health, UNSW Sydney, Australia (Z.Z., M.J.J., O.L., B.L.N., VP, BN). Department of Radiology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, China (Z.Z.). Concord Repatriation General Hospital, Sydney, Australia (M.J.J.). Cardiovascular Division, Brigham and Women’s Hospital and Baim Institute for Clinical Research, Boston, MA (C.P.C.). Department of Clinical Pharmacy and Pharmacology, University of Groningen, Groningen University Medical Center Groningen, the Netherlands (D.J.Z.). Janssen Research & Development, LLC, Parlin, NJ (REJ). Division of Nephrology, University of British Columbia, Vancouver, BC, Canada (A.L.). Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, CA (K.W.M.). Royal North Shore Hospital, Sydney, Australia (VP). Charles Perkins Centre, University of Sydney, Australia (BN). Imperial College London, London, United Kingdom (BN). Westmead Applied Research Centre, University of Sydney, Sydney, Australia (R.L.L.). The George Institute for Global Health, Sydney, Australia (R.L.L.).

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Disclosures

Dr Zhou reports a Scientia PhD Scholarship from the University of New South Wales, Sydney. Dr Jardine is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship; is responsible for research projects that have received unrestricted funding from Amgen, Baxter, CSL, Eli Lilly, Gambio, and Merck Sharp & Dohme; has served on steering committees for trials sponsored by CSL and Janssen; serves on a steering committee for an investigator-initiated trial with funding support from Dimerix; has served on advisory boards by sponsored by Akebia, AstraZeneca, Baxter, Boehringer Ingelheim, Merck Sharp & Dohme, and Vifor; and has spoken at scientific meetings sponsored by Janssen, Amgen, Roche, and Vifor, with any consultancy, honoraria, or travel support paid to her institution. O. Li reports being a full-time employee of the George Institute for Global Health. B.L. Neuen reports receiving research support from the Australian National Health and Medical Research Council Postgraduate Scholarship. He has received travel fees from Janssen and consultation fees from Bayer, with all honoraria paid to his institution. Dr Cannon has received research grants from Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Janssen, Merck, Novo Nordisk, and Pfizer and consulting fees from Aegerion, Alnylam, Amarin, Amgen, Applied Therapeutics, Ascenda, Boehringer Ingelheim, Bristol Myers Squibb, Corvidia, Eli Lilly, HLS Therapeutics, Innoven, Janssen, Kowa, Merck, Pfizer, Rhooshan, and Sanofi. Dr de Zeeuw reports serving on advisory boards or as a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mitsubishi Tanabe, and Travere Pharmaceuticals; serving on steering committees or as a speaker for AbbVie and Janssen; and serving on data safety and monitoring committees for Bayer, with all honoraria paid to his institution. R. Edwards is a full-time employee of Janssen Research and Development. Dr Levin serves as a scientific advisor to Boehringer Ingelheim, AstraZeneca, and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and is on the data and safety monitoring board for NIDDK, Kidney Precision Medicine, University of Washington Kidney Research Institute Scientific Advisory Committee, as well as being funded by Canadian Institute of Health Research (CIHR) and Kidney Foundation of Canada. She has received fees for time as CREDiT (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) National Coordinator from Janssen, directed to her academic team. Dr Mahaffey has received research support from Afferent, Amgen, Apple, Inc, AstraZeneca, Cardiva Medical, Inc, Daiichi Sankyo, Ferring, Google (Verily), Johnson & Johnson, Luitpold, Medtronic, Merck, National Institutes of Health (NIH), Novartis, Sanofi, St. Jude, and Tenax; and has served as a consultant (speaker fees for continuing medical education events only) for Abbott, Allynx, Anthos, AstraZeneca, Baim Institute, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Elsevier, GlaxoSmithKline, Intermountain Health, Johnson & Johnson, MedErgy, Medscape, Mitsubishi Tanabe, Mount Sinai, Mundipharma, Myokardia, NIH, Novartis, Novo Nordisk, Portola, Ratiometer, Regeneron, SmartMedics, Springer Publishing, Theravance, and University of California, San Francisco. Dr Perkovic reports receiving research support from the Australian National Health and Medical Research Council (Senior Research Fellowship and Program Grant); serving on steering committees for AbbVie, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Novartis, and Pfizer; and serving on advisory boards or speaking at scientific meetings for AbbVie, Astellas, AstraZeneca, Bayer, Baxter, Bristol Myers Squibb, Boehringer Ingelheim, Dimerex, Eli Lilly, Gilad, GlaxoSmithKline, Janssen, Merck, Metavant, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pfizer, PharmaLink, Relypsia, Retrophin, Roche, Sanofi, Servier, Tricida, UptioDate, and Vitae. Dr Neil is supported by an Australian National Health and Medical Research Council Principal Research Fellowship; holds a research grant for this study from Janssen; and has held research grants for other large-scale cardiovascular outcome trials from Roche, Servier, and Merck Schering Plough; and his institution has received consultancy, honoraria, or travel support for contributions he has made to advisory boards or the continuing medical education programs of Abbott, Beijing National Salt Corporation, Janssen, Mitsubishi Tanabe Pharma Corporation, Novartis, Nutek, Peking University, Pfizer, Roche, and Servier. Dr Lindley reports research support from the National Health and Medical Research Council of Australia and was a paid adjudicator for the CANVAS Program and CREDiT trials.

Supplemental Materials

Expanded Materials & Methods

Online Table I

Online Figures I–VI

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