Effects of SGLT2 inhibitors on stroke in type 2 diabetes according to baseline kidney function

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INTRODUCTION

- No clear effect of SGLT2i on stroke in recent large trials.[1-4]
- Results from the CANVAS Program indicated heterogeneity of treatment effect on stroke by baseline eGFR levels and a significant lowering of stroke risk with canagliflozin versus placebo was seen in participants with impaired kidney function.[5]
- Similar pattern observed in the EMPA-REG OUTCOME[6] and CREDENCE trial raised the possibility that the effect of SGLT2i on stroke may vary by level of kidney function.

OBJECTIVE

- Extract stroke data from the EMPA-REG OUTCOME, DECLARE-TIMI 58, CAVNAS Program, and CREDENCE trials to define more completely the effects of SGLT2i on stroke according to baseline kidney function.

METHODS

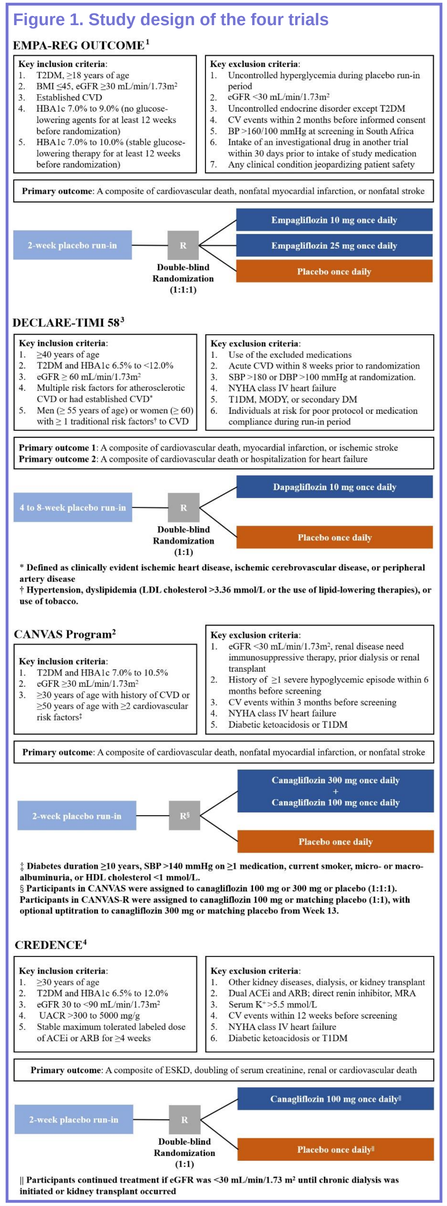
Study Design and Participants

- Key features of the study design, including inclusion criteria, exclusion criteria and the primary outcome of the four trials are described in **Figure 1**

Outcome

- The primary outcome for these analyses was fatal or nonfatal stroke.
- Secondary outcomes were fatal or nonfatal stroke by subgroups according to baseline eGFR of ≥90, 60-<90, 45-<60, and <45 mL/min/1.73m^2.

Figure 1. Study design of the four trials



Statistical Analysis

- Pooled HRs with 95% CIs were obtained using the random-effects model.
- The percentage of variability across the pooled estimates attributable to heterogeneity beyond chance was estimated using the I^2 statistic.
- Homogeneity of pooled treatment effects across eGFR subgroups was tested by random-effects meta-regression.
- P-value (2 sided) <0.05 was deemed significant. Stata (version 12.0) was used.

RESULTS

Participants

- A total of 38,723 participants were randomized to treatment with SGLT2i or placebo, with median follow-up of 3.1 (EMPA-REG OUTCOME), 4.2 (DECLARE-TIMI 58), 2.4 (CAVNAS Program), 2.6 years (CREDENCE). (**Table**)

Effects on Stroke by Kidney Function

- 1150 (3.0%) participants (233 [3.3%] in EMPA-REG OUTCOME, 466 [2.7%] in DECLARE-TIMI 58, 309 [3.0%] in CANVAS Program, 142 [3.2%] in CREDENCE) had stroke during follow-up.
- Overall, null effect of SGLT2i on stroke (pooled HR 0.96, 95% CI 0.82-1.12, I^2=36.5%)
- Significant heterogeneity (P=0.01) of effects by baseline kidney function after pooling, with a pattern of protection amongst those with reduced kidney function (pooled HR 0.50, 95% CI 0.31-0.79, I^2=0.0% for those with eGFR <45 mL/min/1.73m^2) but not those with preserved kidney function (pooled HR 1.24, 95% CI 0.98-1.57, I^2=0.0% for those with eGFR ≥90 mL/min/1.73m^2) (**Figure 2**).

Table. Baseline characteristics of participants in the four trials

	EMPA-REG OUTCOME (N=7020)	DECLARE-TIMI 58 (N=17160)	CANVAS Program (N=10142)	CRE-DENCE (N=4401)
Age, y, mean	63.1	64.0	63.3	63.0
Male, %	71.5	62.6	64.2	66.1
Race, %				
White	72.4	79.6	78.3	66.6
Asian	21.6	13.4	12.7	19.9
Black	5.1	3.5	3.3	5.1
Other or missing	0.9	3.5	5.7	8.4
Current smoker, %	NR	NR	17.8	14.5
Hypertension, %	NR	NR	90.0	96.8
DM duration, y, mean	NR	11.0	13.5	15.8
CVD, %	99.2	40.6	65.6	50.4
Heart failure, %	10.1	10.0	14.4	14.8
Myocardial infarction, %	46.6	NR	29.1	10.0
Cerebrovascular disease, %	23.3*	7.6	19.3	15.9
PVD, %	20.8	6.0	20.8	23.8
Amputation, %	NR	NR	2.3	5.3
SBP, mmHg, mean	135.5	135.0	136.6	140.0
DBP, mmHg, mean	76.7	NR	77.7	78.3
BMI, kg/m^2, mean	30.6	32.1	32.0	31.3
HBA1c, %, mean	8.1	8.3	8.2	8.3
eGFR, mL/min/1.73 m^2				
Mean	74.1	85.3	76.5	56.2
≥90, %	21.9	24.4	47.6	0.0†
60-<90, %	52.2	55.5	45.1	41.1†
45-<60, %	17.8	14.6	7.4	29.1†
<45, %	8.1	5.5	0.0	29.8†
Missing, %	<0.1	<0.1	<0.1	0.0†
Microalbuminuria, %	28.7	NR	22.6	11.3
Macroalbuminuria, %	11.0	7.0	7.6	88.0

*History of stroke †Based on screening (rather than baseline) eGFR

SUMMARY

- In T2DM patients, the effects of SGLT2i on stroke may vary by level of kidney function.
- There is a strong rationale for further studies specifically powered to investigate the effects of SGLT2i on stroke risk amongst patients with significantly impaired kidney function.
- Meanwhile, potential mechanisms warrant further investigation.

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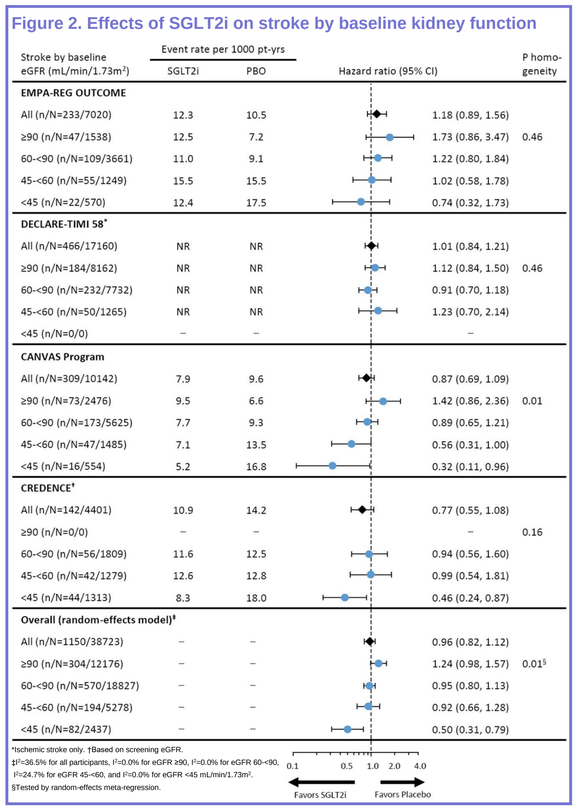
Figure 2. Effects of SGLT2i on stroke by baseline kidney function



*Ischemic stroke only. †Based on screening eGFR.
‡I^2=36.5% for all participants, I^2=0.0% for eGFR ≥90, I^2=0.0% for eGFR 60-<90, I^2=24.7% for eGFR 45-<60, and I^2=0.0% for eGFR <45 mL/min/1.73m^2.
§Tested by random-effects meta-regression.

ABBREVIATIONS

ACEi, angiotensin-converting enzyme inhibitor; **ARB**, angiotensin receptor blocker; **BMI**, body mass index; **BP**, blood pressure; **CANVAS**, Canagliflozin Cardiovascular Assessment Study; **CI**, confidence interval; **CREDENCE**, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; **CV**, cardiovascular; **CVD**, cardiovascular disease; **DECLARE-TIMI 58**, The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; **DBP**, diastolic blood pressure; **DM**, diabetes mellitus; **eGFR**, estimated glomerular filtration rate; **EMPA-REG OUTCOME**, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; **HBA1c**, glycated hemoglobin; **HDL**, high-density lipoprotein; **HR**, hazard ratio; **LDL**, low-density lipoprotein; **MI**, myocardial infarction; **MODY**, maturity onset diabetes of the young; **MRA**, mineralocorticoid receptor antagonist; **NR**, not reported; **NYHA**, New York Heart Association; **PBO**, placebo; **pt-yrs**, patient-years; **PVD**, peripheral vascular disease; **SGLT2i**, sodium glucose co-transporter 2 inhibitor; **T1DM**, type 1 diabetes mellitus; **T2DM**, type 2 diabetes mellitus; **R**, randomization; **SBP**, systolic blood pressure; **UACR**, urine albumin to creatine ratio.

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DISCLOSURES

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