JAMA Cardiology | Original Investigation

Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes
A Meta-analysis

Darren K. McGuire, MD, MHSc; Weichung J. Shih, PhD; Francesco Cosentino, MD, PhD; Bernard Charbonnel, MD; David Z. I. Cherney, MD, PhD; Samuel Dagogo-Jack, MD, DSc; Richard Pratley, MD; Michelle Greenberg, BSc; Shuai Wang, PhD; Susan Huyck, DrPH; Ira Gantz, MD; Steven G. Terra, PharmD; Urszula Masiukiewicz, MD; Christopher P. Cannon, MD

IMPORTANCE Sodium-glucose cotransporter 2 (SGLT2) inhibitors favorably affect cardiovascular (CV) and kidney outcomes; however, the consistency of outcomes across the class remains uncertain.

OBJECTIVE To perform meta-analyses that assess the CV and kidney outcomes of all 4 available SGLT2 inhibitors in patients with type 2 diabetes.

DATA SOURCES A systematic literature search was conducted in PubMed from January 1, 2015, to January 31, 2020.

STUDY SELECTION One hundred forty-five records were initially identified; 137 were excluded because of study design or topic of interest. As a result, a total of 6 randomized, placebo-controlled CV and kidney outcomes trials of SGLT2 inhibitors in patients with type 2 diabetes were identified, with contributory data from 9 publications. All analyses were conducted on the total patient population of these trials.

DATA EXTRACTION AND SYNTHESIS Standardized data search and abstraction were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement. Data were analyzed using a fixed-effect model.

MAIN OUTCOMES AND MEASURES Outcomes included time to the first event of (1) the composite of major adverse CV events of myocardial infarction, stroke, or CV death, and each component, (2) the composite of hospitalization for heart failure (HHF) or CV death (HHF/CV death) and each component, and (3) kidney composite outcomes. For outcomes in the overall trial populations and in selected subgroups, hazard ratios (HRs) and 95% CIs were pooled and meta-analyzed across trials.

RESULTS Data from 6 trials comprised 46 969 unique patients with type 2 diabetes, including 31 116 (66.2%) with atherosclerotic CV disease. The mean (SD) age of all trial participants was 63.7 (7.9) years; 30 939 (65.9%) were men, and 36 849 (78.5%) were White. The median number of participants per trial was 8246 (range, 4401-17 160). Overall, SGLT2 inhibitors were associated with a reduced risk of major adverse CV events (HR, 0.90; 95% CI, 0.85-0.95; Q statistic, $P = .27$), HHF/CV death (HR, 0.78; 95% CI, 0.73-0.84; Q statistic, $P = .09$), and kidney outcomes (HR, 0.62; 95% CI, 0.56-0.70; Q statistic, $P = .09$), with no significant heterogeneity of associations with outcome. Associated risk reduction for HHF was consistent across the trials (HR, 0.68; 95% CI, 0.61-0.76; $I^2 = 0.0\%$), whereas significant heterogeneity of associations with outcome was observed for CV death (HR, 0.85; 95% CI, 0.78-0.93; Q statistic, $P = .02$; $I^2 = 64.3\%$). The presence or absence of atherosclerotic CV disease did not modify the association with outcomes for major adverse CV events (HR, 0.89; 95% CI, 0.84-0.95 and HR, 0.94; 95% CI, 0.83-1.07, respectively; $P = .63$ for interaction), with similar absence of associations with outcome modification by prevalent atherosclerotic CV disease for HHF/CV death ($P = .62$ for interaction), HHF ($P = .26$ for interaction), or kidney outcomes ($P = .73$ for interaction).

CONCLUSIONS AND RELEVANCE In this meta-analysis, SGLT2 inhibitors were associated with a reduced risk of major adverse CV events; in addition, results suggest significant heterogeneity in associations with CV death. The largest benefit across the class was for an associated reduction in risk for HHF and kidney outcomes, with benefits for HHF risk being the most consistent observation across the trials.

JAMA Cardiol. doi:10.1001/jamacardio.2020.4511
Published online October 7, 2020.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Darren K. McGuire, MD, MHSc, Division of Cardiology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75235 (darren.mcguire@utsouthwestern.edu).

Downloaded From: https://jamanetwork.com/ by Piergiorgio Gigliotti on 10/13/2020

Type 2 diabetes (T2D) is commonly complicated by atherosclerotic cardiovascular disease (ASCVD), heart failure, and chronic kidney disease.[1-4] The proven efficacy of the sodium-glucose cotransporter 2 (SGLT2) inhibitor class of medications has led to professional cardiology and endocrinology society consensus recommendations and guidelines[5-10] endorsing their use and supported by regulatory product labeling.

The objective of the present study is to update previous meta-analyses,[11-13] adding data from the sixth completed placebo-controlled cardiovascular (CV) and kidney clinical outcomes trial of an SGLT2 inhibitor in patients with T2D, the Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (VERTIS CV) trial.[14] The VERTIS CV trial assessed the effects of ertugliflozin vs placebo in patients with T2D and prevalent ASCVD.[15,16] Our study results represent the totality of CV outcomes trial data for the 4 SGLT2 inhibitors available in the United States and many other countries. These trials were conducted in accordance with regulatory guidance requiring CV outcomes assessment of drugs for T2D; furthermore, our study refined estimates of drug outcomes in patients with T2D and explored the heterogeneity of outcomes assessed by individual drugs in the overall class and within selected subgroups.

Key Points

Question Is the effectiveness of sodium-glucose cotransporter 2 (SGLT2) inhibitors on cardiovascular- and kidney-related outcomes similar across the class of medications overall and by the presence or absence of prevalent cardiovascular and chronic kidney disease?

Findings Results from a meta-analysis of 6 outcomes trials of 4 SGLT2 inhibitors suggest an associated reduction in risk of major adverse cardiovascular events and heterogeneity of cardiovascular death. The greatest magnitude of benefit was for reduction in risk for hospitalization for heart failure (HHF) and kidney disease progression, with estimates of HHF risk outcome the most consistent observation across the trials.

Meaning These findings suggest that SGLT2 inhibitors have some heterogeneity of associations with outcomes for cardiovascular death, with consistency of favorable HHF and kidney disease outcomes across the class.

Methods

Search Strategy and Selection Criteria

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[17] A systematic literature search of randomized, placebo-controlled CV and kidney outcomes trials of SGLT2 inhibitors in patients with T2D published from January 1, 2015, to January 31, 2020, was conducted in PubMed (eFigure 1 in the Supplement). One hundred forty-five records were initially identified; 137 were excluded because of study design or topic of interest. As a result, a total of 6 trials were identified, with contributory data from 9 publications. Trial eligibility was confirmed by 2 independent reviewers (M.G., S.W.); data extraction was performed by S.W. Study quality (performed by M.G., U.M., S.W.) was evaluated using the Cochrane Risk of Bias Tool[18] (eTable 1 in the Supplement).

Patient Population

All analyses were primarily conducted on the total patient population of each of the 6 trials identified: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)[19]; the CANVAS Program, consisting of 2 trials: the Canagliflozin Cardiovascular Assessment Study (CANVAS) and A Study of the Effects of Canagliflozin (JNJ-28431754) on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus (CANVAS-R)[20]; the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58)[21]; Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE)[22]; and VERTIS CV.[16] Secondary analyses were performed to assess heterogeneity of associations with outcomes of interest according to prespecified baseline characteristics including (1) ASCVD or multiple ASCVD risk factors; (2) history of heart failure; (3) estimated glomerular filtration rate (eGFR); (4) glycated hemoglobin (HbA_{1c}); and (5) albuminuria (eTable 2 in the Supplement). For all outcomes, sensitivity analyses were performed omitting the data from CREDENCE, which was primarily a kidney outcomes trial.

Outcomes

The primary outcome in all trials except CREDENCE was the time to first major adverse cardiovascular event (MACE) of myocardial infarction, stroke, or CV death. The primary outcome in CREDENCE was a composite kidney disease outcome with MACE as a prioritized secondary outcome. For the present meta-analysis, the primary outcome was time to first MACE, with secondary outcomes including time to first event for each component of MACE, the composite of hospitalization for heart failure (HHF) or CV death and each component outcome, all-cause mortality, and a composite of kidney outcomes. The composition of the principal kidney composite outcomes varied across trials (eAppendix 1 in the Supplement) and included in various permutations worsening eGFR or creatinine, end-stage kidney disease with or without requirement for kidney replacement therapy or transplant, kidney death, or CV death. In CREDENCE,[22] the kidney composite was the primary outcome. In DECLARE-TIMI 58 and VERTIS CV, analyses of kidney composite outcomes were prespecified in the primary analysis hierarchy.[15,16,23,24] In EMPA-REG OUTCOME and the CANVAS program trials, analysis of the kidney composite outcome was prespecified as exploratory.[20,25,26]

Statistical Analysis

A fixed-effect meta-analysis approach was used, with heterogeneity assessed using the Cochran Q test statistic and Higgins and Thompson I^2.[27,28] Heterogeneity was considered to be low, moderate, or high if I^2 was less than 25%, 25% to 75%,

Downloaded From: https://jamanetwork.com/ by Piergiorgio Gigliotti on 10/13/2020

or greater than 75%, respectively. The hazard ratio (HR) and its 100 × (1 - α)% CI was extracted from the publications of each individual study and converted to log(HR) and its SE before the meta-analysis. The meta-analysis was directly implemented on the natural log HR scale, with results exponentiated and reported on the original HR scale. For analyses of heterogeneity of association between treatment and outcomes among subgroups, a random-effects meta-regression approach using restricted maximum likelihood with Hartung and Knapp adjustment was used to obtain the *F* test statistic and *P* value of the interaction term for each subgroup.[29] The R package, metafor, version 3.6.2 (R Foundation) was used for all analyses and for forest plot generation. Statistical analyses were conducted from April 13, 2020, to April 27, 2020. Two-sided *P* values <.05 were considered significant.

Results

A total of 6 placebo-controlled clinical outcomes trials (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, CREDENCE, VERTIS CV) of 4 SGLT2 inhibitors in patients with T2D were identified, with cohort characteristics summarized in the **Table**, extracting data for the present analyses from the primary trial reports[16,19-22] as well as from a number of published secondary analyses.[13,24,30-32] Data from 46 969 patients were included for analyses, including 31 116 (66.2%) with prevalent ASCVD. The mean (SD) age of all trial participants was 63.7 (7.9) years; 30 939 (65.9%) were men, 16 030 (34.1%) were women, and 36 849 (78.5%) were White. The median number of participants per trial was 8246 (range, 4401-17 160). The search and selection process is summarized in eFigure 1 in the Supplement.

Across the 6 trials, median follow-up ranged from 2.4 to 4.2 years, T2D duration ranged from 11.8 to 15.8 years, and average baseline HbA_{1c} ranged from 8.1% to 8.3% (Table). The proportion of patients with prevalent ASCVD ranged from 40.6% in DECLARE-TIMI 58 to 100% in EMPA-REG OUTCOME and VERTIS CV. The proportion of patients with baseline eGFR less than 60 mL/min/1.73 m^2 ranged from 7.4% in DECLARE-TIMI 58 to 59.8% in CREDENCE. History of heart failure ranged from 10.0% in DECLARE-TIMI 58 to 23.7% in VERTIS CV (Table).

Overall, 4931 patients experienced a MACE, with 4024 (81.6%) of the MACE outcomes occurring in the subset of patients with prevalent ASCVD. Analyses of associations between SGLT2 inhibitors and outcomes on the hazard for MACE overall and by ASCVD status at baseline are presented in **Figure 1**. Overall, SGLT2 inhibitors significantly reduced the hazard for MACE (HR, 0.90; 95% CI, 0.85-0.95; Q statistic, *P* = .27); the presence or absence of ASCVD did not modify the treatment outcome on MACE (HR, 0.89; 95% CI, 0.84-0.95 and HR, 0.94; 95% CI, 0.83-1.07; *P* = .63 for interaction). Similar findings were observed in additional prespecified subgroup analyses by baseline HbA_{1c}, albuminuria, eGFR, and history of heart failure (eFigure 2 in the Supplement).

Overall, 2031 CV death events occurred, including 1680 (82.7%) of CV deaths in the subset of patients with prevalent ASCVD. Associations of SGLT2 inhibitors on the hazard for CV death overall and by ASCVD status are presented in **Figure 2**. Overall, the SGLT2 inhibitors significantly reduced the hazard for CV death (HR, 0.85; 95% CI, 0.78-0.93), with moderate heterogeneity observed across the trials (Q statistic, *P* = .02; I^2 = 64.3%), with no interaction of outcome observed for those with vs without ASCVD (HR, 0.83; 95% CI, 0.76-0.92 and HR, 0.95; 95% CI, 0.77-1.17, respectively; *P* = .41 for interaction). Similar findings were observed in additional prespecified subgroup analyses by baseline HbA_{1c}, albuminuria, eGFR, and history of heart failure (eFigure 3 in the Supplement). In analyses of all-cause mortality occurring in 3339 patients, SGLT2 inhibitors were associated with a reduced risk overall, with moderate heterogeneity of outcome (HR, 0.87; 95% CI, 0.81-0.93; Q statistic *P* = .06; I^2 = 56.5%), with no significant interaction by ASCVD status (*P* = .64 for interaction; eFigure 4 in the Supplement).

Overall, 3154 HHF/CV death composite events occurred, including 2560 (81.2%) of these events occurring in the subset of patients with prevalent ASCVD. Associations between SGLT2 inhibitors and outcomes on the hazard for HHF/CV death overall and analyses by prevalent ASCVD are presented in eFigure 5A and 5B in the Supplement. Overall, SGLT2 inhibitors were associated with a significant reduction in the hazard for HHF/CV death (HR, 0.78; 95% CI, 0.73-0.84), with moderate heterogeneity of associations with outcomes across trials (Q statistic *P* = .09; I^2 = 50.6%). There was no interaction of outcome observed for those with vs without ASCVD (HR, 0.77; 95% CI, 0.72-0.84 and HR, 0.81; 95% CI, 0.69-0.95, respectively; *P* = .62 for interaction). Similarly, no modification of treatment outcome was observed for HHF/CV death in prespecified analyses by baseline eGFR categories or history of heart failure (eFigure 5C and 5D in the Supplement).

Overall, 1430 HHF events occurred, including 1151 (80.5%) in the subset of patients with prevalent ASCVD. Associations between SGLT2 inhibitors and outcomes on the hazard for HHF overall and by ASCVD status are presented in **Figure 3**. The SGLT2 inhibitors were associated with a significant reduction in the hazard for HHF (HR, 0.68; 95% CI, 0.61-0.76), with consistency of effectiveness across the trials (Q statistic *P* = .85; I^2 = 0.0%), and similarly in those with vs without prevalent ASCVD (HR, 0.70; 95% CI, 0.62-0.78 and HR, 0.63; 95% CI, 0.50-0.80, respectively; *P* = .26 for interaction).

Overall, 1426 kidney composite outcome events occurred. Outcomes of SGLT2 inhibitors on the hazard for progression of kidney disease overall and by ASCVD status are presented in **Figure 4**. Overall, the SGLT2 inhibitors were associated with a significant reduction in the hazard for progression of kidney disease (HR, 0.62; 95% CI, 0.56-0.70) with moderate heterogeneity across the trials (Q statistic *P* = .09; I^2 = 49.7%). There was no interaction of outcome on progression of kidney disease observed for those with vs without ASCVD (HR, 0.64; 95% CI, 0.56-0.72 and HR, 0.60; 95% CI, 0.50-0.73, respectively; *P* = .73 for interaction). Similarly, no interaction of effectiveness was observed for outcomes of SGLT2 inhibitors on the kidney composite outcome in prespecified analyses by baseline albuminuria or history of heart failure (eFigure 6 in the Supplement).

Downloaded From: https://jamanetwork.com/ by Piergiorgio Gigliotti on 10/13/2020

Table. Baseline Characteristics From Included Cardiovascular and Kidney Outcomes Trials With SGLT2 Inhibitors[a]

Characteristic	No. (%)[b]				
	EMPA-REG outcome[19] (n = 7020)	CANVAS program[20] (n = 10 142)	DECLARE-TIMI 58[21] (n = 17 160)	CREDENCE[22] (n = 4401)	VERTIS CV[16] (n = 8246)
SGLT2 inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin
Duration of follow-up, median, y	3.1	2.4	4.2	2.6	3.0
Patient characteristics					
Men	5016 (71.5)	6509 (64.2)	10 738 (62.6)	2907 (66.1)	5769 (70.0)
Women	2004 (28.5)	3633 (35.8)	6422 (37.4)	1494 (33.9)	2477 (30.0)
Age, mean (SD), y	63.1 (8.6)	63.3 (8.3)	63.9 (6.8)	63.0 (9.2)	64.4 (8.1)
Race/ethnicity					
White	5081 (72.4)	7944 (78.3)	13 653 (79.6)	2931 (66.6)	7240 (87.8)
Asian	1517 (21.6)	1284 (12.7)	2303 (13.4)	877 (19.9)	498 (6.0)
Black or African American	357 (5.1)	336 (3.3)	603 (3.5)	224 (5.1)	235 (2.8)
Other/missing	65 (0.9)	578 (5.7)	601 (3.5)	369 (8.4)	273 (3.3)
Diabetes characteristics					
HbA_{1c}, mean (SD), %	8.1 (0.8)	8.2 (0.9)	8.3 (1.2)	8.3 (1.3)	8.2 (1.0)
Diabetes duration, mean (SD), y	57 > 10[c]	13.5 (7.8)	11.8 (7.8)	15.8 (8.6)	13.0 (8.3)
Cardiovascular characteristics					
Established cardiovascular disease	7020 (100)	6656 (65.6)	6974 (40.6)	2220 (50.4)	8246 (100)
History of heart failure	706 (10.1)	1461 (14.4)	1724 (10.0)	652 (14.8)	1958 (23.7)
Renal characteristics					
Reduced kidney function[d]	1819 (25.9)	2039 (20.1)	1265 (7.4)	2631 (59.8)	1807 (21.9)
Urine ACR ≥300 mg/g	769 (11.0)	760 (7.6)	1169 (6.8)	3874 (88.0)	755 (9.2)
Cardiovascular medications					
ACEI or ARB blockade	5666 (80.7)	8116 (80.0)	13 950 (81.3)	4395 (99.9)	6686 (81.1)
β-Blocker	4554 (64.9)	5421 (53.5)	9030 (52.6)	1770 (40.2)	5692 (69.0)
Statin/ezetimibe	5403 (77.0)	7599 (74.9)	12 868 (75.0)	3036 (69.0)	6790 (82.3)
Antihyperglycemic medications					
Insulin	3387 (48.2)	5095 (50.2)	7013 (40.9)	2884 (65.5)	3900 (47.3)
Metformin	5193 (74.0)	7825 (77.2)	14 068 (82.0)	2545 (57.8)	6292 (76.3)
Sulfonylurea	3006 (42.8)	4361 (43.0)	7322 (42.7)	1268 (28.8)	3390 (41.1)
DPP-4 inhibitor	796 (11.3)	1261 (12.4)	2888 (16.8)	751 (17.1)	911 (11.0)
GLP-1 receptor agonist	196 (2.8)	407 (4.0)	750 (4.4)	183 (4.2)	278 (3.4)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ACR, albumin/creatinine ratio; ARB, angiotensin receptor blocker; CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; DECLARE-TIMI 58, Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; DPP-4, dipeptidyl peptidase-4; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; GLP-1, glucagon-like peptide-1; HbA_{1c}, hemoglobin A_{1c}; SGLT2, sodium-glucose cotransporter 2; VERTIS CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

[a] Adapted from Arnott et al, 2020.[12]

[b] Values written as No. (%) unless otherwise specified.

[c] Approximately 57% more than 10 years.

[d] Estimated glomerular filtration rate <60 mL/min per 1.73 m^2 based on the Modification of Diet in Renal Disease equation in EMPA-REG OUTCOME, the CANVAS Program, and VERTIS CV, and the Chronic Kidney Disease Epidemiology Collaboration equation in DECLARE-TIMI 58 and CREDENCE.

Results of additional analyses overall and by predefined subgroups for myocardial infarction and stroke are presented in eFigures 7 and 8 in the Supplement. The results of the sensitivity analyses that excluded CREDENCE are presented in eFigures 9 to 16 in the Supplement. For completeness, trial level summaries of adverse events of special interest including severe diabetic ketoacidosis, bone fractures, amputations, genital mycotic infections, and acute kidney injury events are presented in eTable 3 in the Supplement; however, broad differences across trials in definitions, ascertainment, and reporting of such events preclude meaningful meta-analyses.

Discussion

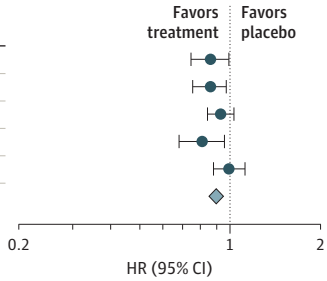
The present meta-analysis includes clinical outcomes data among patients with T2D for all 4 SGLT2 inhibitors in clinical use in the United States and many other countries. Compared with previous meta-analyses of cardiorenal outcomes of SGLT2 inhibitors,[12,13] similar search methods and statistical methodology were used in the present study. One difference in the present analyses includes the extraction of HR and 100 × (1 − α)% CI for all eligible trials, whereas previous meta-analyses lim-

Downloaded From: https://jamanetwork.com/ by Piergiorgio Gigliotti on 10/13/2020

Figure 1. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Major Adverse Cardiovascular Events—Composite of Myocardial Infarction, Stroke, or Cardiovascular Death

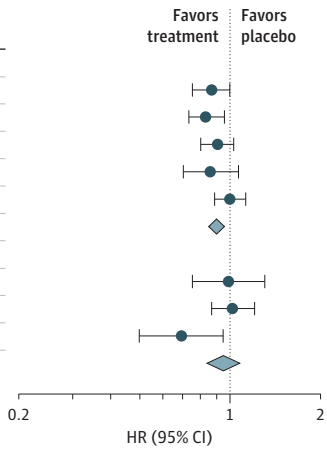
A Overall MACEs

	Treatment		Placebo			Favors treatment	Favors placebo	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)			
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)			15.72
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)			20.12
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)			32.02
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)			10.92
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)			21.23
Fixed-effects model (Q = 5.22; *df* = 4; *P* = .27; I^2 = 23.4%)					0.90 (0.85-0.95)			



B MACEs by ASCVD status

	Treatment		Placebo			Favors treatment	Favors placebo	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)			
Patients with ASCVD								
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)			19.19
CANVAS program	NA/3756	34.1	NA/2900	41.3	0.82 (0.72-0.95)			21.16
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)			24.90
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)			8.82
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)			25.93
Fixed-effects model (Q = 4.53; *df* = 4; *P* = .34; I^2 = 11.8%)					0.89 (0.84-0.95)			
Patients without ASCVD								
CANVAS program	NA/2039	15.8	NA/1447	15.5	0.98 (0.74-1.30)			21.70
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	1.01 (0.86-1.20)			62.07
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)			16.23
Fixed-effects model (Q = 4.59; *df* = 2; *P* = .10; I^2 = 56.5%)					0.94 (0.83-1.07)			



ASCVD indicates atherosclerotic cardiovascular disease; CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; DECLARE-TIMI 58, Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; MACEs, major adverse cardiovascular events; NA, not available; VERTIS CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

ited extraction to analyses reporting HR and 95% CI[13] or pooled different outcome metrics (eg, relative risk, odds ratio, HR) in the same analysis.[12] The present meta-analysis adds to those previously published not only by the inclusion of data from the VERTIS CV trial but also with the inclusion of additional subgroup analyses (eg, baseline albuminuria level, baseline HbA_{1c} level) where data were published for 2 or more trials.

The present results augment the growing evidence base that SGLT2 inhibitors in general are associated with favorable CV and kidney outcomes; in addition, the present study refines understanding of important differences in outcomes associated with drugs within the class. The trials completed to date assessing the CV safety and effectiveness of SGLT2 inhibitors in patients with T2D have predominantly focused on ASCVD-related outcomes. In this context, it is key to note that in the overall pooled estimate, the beneficial outcome of SGLT2 inhibitors on MACE is rather modest and is demonstrated within trials only for empagliflozin and canagliflozin. Likewise, only empagliflozin has demonstrated significant outcomes for CV death risk reduction,[19] with moderate heterogeneity across the class. Notably, the predominant CV outcome of the SGLT2 inhibitors is an associated reduction in HHF, highly consistent across the class achieving nominal significance in each of the trials, with similar consistency across the class for improving kidney outcomes, with ertugliflozin being the only SGLT2 inhibitor without this demonstrated benefit.

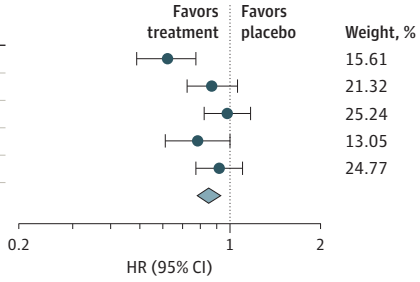
Observed heterogeneity across the class for selected outcomes, specifically for MACE, CV death, and composite kidney outcomes, requires further exploration. Whether this is due to differences in the populations studied and their risk profiles, differences in capture or definition of outcomes, or differences in the drugs requires further evaluation. Pharmacologically, ertugliflozin is most similar to empagliflozin with regard to selectivity for SGLT2, with dapagliflozin slightly less selective and canagliflozin the least selective of the 4 drugs,[33] yet only empagliflozin was associated with an improved risk for CV death, and ertugliflozin is the only SGLT2 inhibitor of the 4 studied that failed to reach statistical significance on the

Downloaded From: https://jamanetwork.com/ by Piergiorgio Gigliotti on 10/13/2020

Figure 2. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Cardiovascular Death

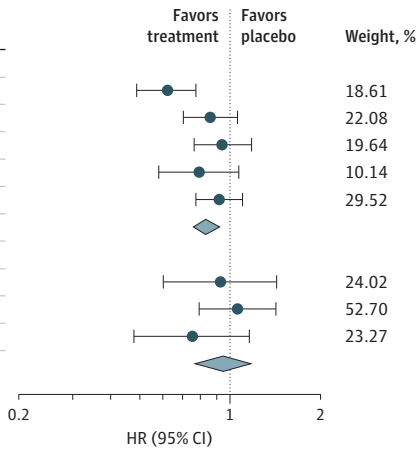
A Overall CV death

	Treatment		Placebo					
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo	Weight, %
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)			15.61
CANVAS program	NA/5795	11.6	NA/4347	12.8	0.87 (0.72-1.06)			21.32
DECLARE-TIMI 58	245/8582	7.0	249/8578	7.1	0.98 (0.82-1.17)			25.24
CREDENCE	110/2202	19.0	140/2199	24.4	0.78 (0.61-1.00)			13.05
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)			24.77
Fixed-effects model (Q = 11.22; *df* = 4; *P* = .02; I^2 = 64.3%)					0.85 (0.78-0.93)			



B CV death by ASCVD status

	Treatment		Placebo					
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo	Weight, %
Patients with ASCVD								
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)			18.61
CANVAS program	NA/3756	14.8	NA/2900	16.8	0.86 (0.70-1.06)			22.08
DECLARE-TIMI 58	153/3474	10.9	163/3500	11.6	0.94 (0.76-1.18)			19.64
CREDENCE	75/1113	25.7	93/1107	32.4	0.79 (0.58-1.07)			10.14
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)			29.52
Fixed-effects model (Q = 9.10; *df* = 4; *P* = .06; I^2 = 56.1%)					0.83 (0.76-0.92)			
Patients without ASCVD								
CANVAS program	NA/2039	6.5	NA/1447	6.2	0.93 (0.60-1.43)			24.02
DECLARE-TIMI 58	92/5108	4.4	86/5078	4.1	1.06 (0.79-1.42)			52.70
CREDENCE	35/1089	12.2	47/1092	16.4	0.75 (0.48-1.16)			23.27
Fixed-effects model (Q = 1.65; *df* = 2; *P* = .44; I^2 = 0.0%)					0.95 (0.77-1.17)			



ASCVD indicates atherosclerotic cardiovascular disease; CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; CV, cardiovascular; DECLARE-TIMI 58, Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; NA, not available; VERTIS CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

prespecified kidney composite end point, although analysis of eGFR change was associated with a significant improvement by ertugliflozin. The definition of events comprising the renal composite end point differed from that of the other CV and renal outcomes trials. These discordant observations do not seem attributable to differences in the doses studied, as pharmacodynamic outcomes on HbA_{1c}, blood pressure, and body weight were similar across the trials. This finding amplifies the possibility that CV and kidney benefits are due to mechanisms other than SGLT2. For example, off-target effects of SGLT2 inhibitors have been proposed, including the direct effect on the sodium-hydrogen exchanger 1 (NHE1) in the heart, NHE3 in the kidney, and NHE9 in inflammatory cells that could influence MACE, heart failure, and kidney outcomes.[34] In addition, effects of selected SGLT2 inhibitors on myocardial sodium, calcium, and potassium channels have been demonstrated in preclinical models,[35,36] raising the possibility of the drugs having effects on myocardial function and rhythm stability independent of SGLT2 engagement. Continued investigation into the potential clinical relevance of such observations and to what degree these effects differ between members of the class is of utmost importance.

The benefits on risk for HHF and related outcomes apply broadly to the class, independent of baseline ASCVD and prior heart failure and across the spectrum of baseline eGFR. These observations provide strong support for contemporary guidelines and medical society recommendations supporting the use of SGLT2 inhibitors, regardless of glucose control, for patients with T2D with prevalent ASCVD and with or at high risk of heart failure.[5-7,9,10] This guidance prioritizes the use of SGLT2 inhibitors with proven efficacy (empagliflozin or canagliflozin for MACE; empagliflozin, canagliflozin, or dapagliflozin for kidney outcomes; all 4 drugs for heart failure), independent of glucose control considerations, in patients with T2D with or at high risk for CV and kidney complications.

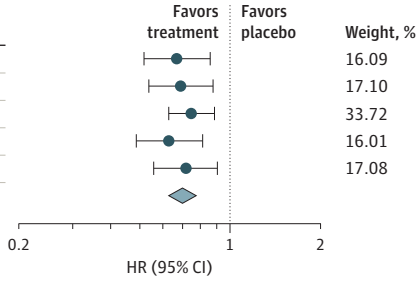
Although the mechanisms underpinning the CV and kidney outcomes of SGLT2 inhibitors remain uncertain, it is clear that the benefits are not attributable to glucose control per se. For example, there was no association between baseline or achieved glucose and CV or kidney outcomes in the EMPA-REG

Downloaded From: https://jamanetwork.com/ by Piergiorgio Gigliotti on 10/13/2020

Figure 3. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Hospitalization for Heart Failure

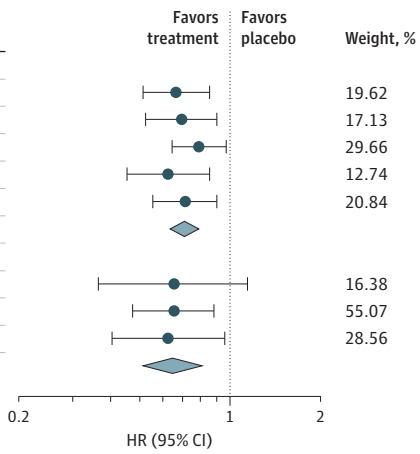
A Overall HHF

	Treatment		Placebo					
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo	Weight, %
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)			16.09
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)			17.10
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)			33.72
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)			16.01
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)			17.08
Fixed-effects model (Q = 1.39; *df* = 4; *P* = .85; I^2 = 0.0%)					0.68 (0.61-0.76)			



B HHF by ASCVD status

	Treatment		Placebo					
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo	Weight, %
Patients with ASCVD								
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)			19.62
CANVAS program	NA/3756	7.3	NA/2900	11.3	0.68 (0.51-0.90)			17.13
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	0.78 (0.63-0.97)			29.66
CREDENCE	59/1113	20.6	92/1107	33.2	0.61 (0.44-0.85)			12.74
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)			20.84
Fixed-effects model (Q = 1.97; *df* = 4; *P* = .74; I^2 = 0.0%)					0.70 (0.62-0.78)			
Patients without ASCVD								
CANVAS program	NA/2039	2.6	NA/1447	4.2	0.64 (0.35-1.15)			16.38
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	0.64 (0.46-0.88)			55.07
CREDENCE	30/1089	10.6	49/1092	17.5	0.61 (0.39-0.96)			28.56
Fixed-effects model (Q = 0.03; *df* = 2; *P* = .99; I^2 = 0.0%)					0.63 (0.50-0.80)			



ASCVD indicates atherosclerotic cardiovascular disease; CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; DECLARE-TIMI 58, Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HHF, hospitalization for heart failure; NA, not available; VERTIS CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

OUTCOME trial supported by only modest association between HbA_{1c} and outcomes in mediation analyses from that trial.[37-39] Similarly, in CREDENCE, whereas the between-group contrast in HbA_{1c} was the smallest of reported trials as expected with lower eGFR by the glucose-lowering mechanism of action, the magnitude of benefits for MACE and for HHF were numerically the largest across the trials. Although not specifically analyzed in the DAPA-HF (Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction) trial of dapagliflozin vs placebo, a patient population that included patients with or without diabetes, benefits on CV death, HHF, and their composite were no different in those with or without diabetes, providing additional evidence discounting the role of the glucose-modifying effects of the SGLT2 inhibitors accounting for their benefit in CV disease. Outcomes trials are under way to assess the use of empagliflozin and dapagliflozin for CV and kidney disease in extended patient populations independent of diabetes status in patients with heart failure with reduced and preserved[40-42] ejection fraction and chronic kidney disease of diverse diabetic and nondiabetic kidney disease etiologies.[43,44] The first of these 2 latter trials, DAPA-CKD trial of dapagliflozin vs placebo, was stopped early for efficacy outcome, with results presented at the 2020 European Society of Cardiology Scientific Sessions but not yet published.[45]

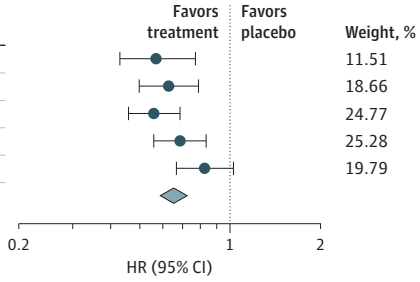
When initially approved for clinical use, SGLT2 inhibitors had product-labeled cautions or contraindications for use in patients with reduced eGFR, based exclusively on the attenuation of glycemic efficacy as eGFR wanes and without specific safety concerns that typically underpin eGFR-based prescriptions. However, with the demonstration of CV and kidney benefits across the spectrum of kidney function in patients enrolled in trials to date, an eGFR as low as 30 mL/min/1.73 m^2 in EMPA-REG OUTCOME, the CANVAS trials, VERTIS CV, and CREDENCE, liberalization of these restrictions is now justified. For example, based on the results from CREDENCE,[22] canagliflozin has a product-labeled indication to reduce the incidence and progression of kidney disease, approved for initiation down to an eGFR of 30 mL/min/1.73 m^2, with use allowed to continue in patients taking canagliflozin until initiation of dialysis. Similarly, society recommendations and

Downloaded From: https://jamanetwork.com/ by Piergiorgio Gigliotti on 10/13/2020

Figure 4. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Kidney-Related Outcomes

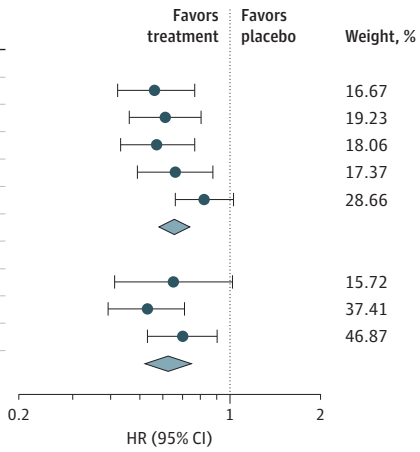
A Overall kidney outcomes

	Treatment		Placebo					
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo	Weight, %
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)			11.51
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)			18.66
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)			24.77
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)			25.28
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)			19.79
Fixed-effects model (Q = 7.96; *df* = 4; *P* = .09; I^2 = 49.7%)					0.62 (0.56-0.70)			



B Kidney outcomes by ASCVD status

	Treatment		Placebo					
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo	Weight, %
Patients with ASCVD								
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)			16.67
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)			19.23
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)			18.06
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)			17.37
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)			28.66
Fixed-effects model (Q = 6.09; *df* = 4; *P* = .19; I^2 = 34.4%)					0.64 (0.56-0.72)			
Patients without ASCVD								
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)			15.72
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)			37.41
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)			46.87
Fixed-effects model (Q = 1.86; *df* = 2; *P* = .40; I^2 = 0.0%)					0.60 (0.50-0.73)			



ASCVD indicates atherosclerotic cardiovascular disease; CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; DECLARE-TIMI 58, Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; NA, not available; VERTIS CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

guidelines endorse the use of all SGLT2 inhibitors for patients with an eGFR of 30 mL/min/1.73 m^2 or higher, independent of glucose considerations and based wholly on the CV and kidney benefits as supported by the present meta-analyses.[5,10]

The safety profile of the SGLT2 inhibitors is firmly established, and the addition of the VERTIS CV data did not materially alter risk considerations for any specific adverse event. The most common adverse effect is mycotic genital infections,[16,19-22] typically mild and most often treated with over-the-counter therapies. With regard to diabetic ketoacidosis, unlike the situation in patients with type 1 diabetes treated with SGLT2 inhibitors, where the relative risk and absolute risk increment for diabetic ketoacidosis is much greater,[46] the present summary of reports from outcomes trials of patients with T2D demonstrates a much lower incidence and a much more modest incremental absolute risk for diabetic ketoacidosis. Risk mitigation strategies for SGLT2 inhibitor-associated diabetic ketoacidosis focusing largely on type 1 diabetes have been published by international authorities in the field, and probably can also be applied to patients with T2D.[46] Specifically, patients are advised to not take the medication on days with diminished oral intake and, when feeling generally unwell, to monitor ketones with either urine dipsticks or point-of-care blood monitoring of beta-hydroxybutyrate.[46,47] With regard to amputation risk, there is significant variability across the trials, with a significant increase only observed in the CANVAS program with canagliflozin. Of note, in the CANVAS program and in EMPA-REG OUTCOME, amputation events were captured through adverse event reporting without dedicated prospective event capture and source document collection, except during the final few months of the CANVAS program when systematic data capture for amputations was implemented. All subsequent trials have prospectively captured amputation events as an adverse event of special interest with no evident incremental risk noted, including in the CREDENCE trial of canagliflozin.[22] In CREDENCE, investigators were instructed to examine participants' feet at every study visit, and the investigational product was withheld during incident diabetic foot complications. Therefore, it remains unclear whether the amputation risk observed with

Downloaded From: https://jamanetwork.com/ by Piergiorgio Gigliotti on 10/13/2020

canagliflozin in the CANVAS trials was a spurious finding or attributable to different populations studied, or whether avoidance in the setting of diabetic foot complications mitigated the associated risk.

Limitations

A number of limitations are acknowledged. Differences in eligibility criteria, cohort characteristics, and trial duration may have affected the meta-analysis. For example, in the combined data set, the majority of patients had prevalent ASCVD, advanced kidney disease, or both, so further data might help elucidate the outcomes of this class in primary prevention populations. Although the CV outcomes were very similarly defined across the trials, there were notable differences in the components comprising the composite renal outcomes. Each of these limitations may introduce bias into the analyses, and such results should be interpreted accordingly. At the review level, although incomplete retrieval of primary trial reports is unlikely given the scope of such clinical outcomes trials and their high-profile reporting, the possibility exists of incomplete retrieval of reports and results from secondary analyses and outcomes, which may introduce further bias into these results.

Conclusions

Study results suggest that the SGLT2 inhibitor class of medications favorably affects risk for CV outcomes in patients with T2D with noted heterogeneity of outcomes between specific members of the class. Furthermore, results suggest that empagliflozin is associated with reduced risk for CV death, canagliflozin with reduced risk for MACE and for the incidence and progression of kidney disease, and dapagliflozin with reduced risk for HHF; each indication is reflected in the product labeling. Beyond product labeling, across the class, there are robust and consistent associations with reduction in risk for HHF, independent of baseline ASCVD status or kidney function. These data support contemporary society recommendations to prioritize the use of SGLT2 inhibitors with demonstrated outcomes, independent of glucose control considerations, in patients with T2D with or at high risk for CV and kidney complications. The heterogeneity of the associations with outcomes of different SGLT2 inhibitors on CV death among patients with T2D and ASCVD requires further study.

ARTICLE INFORMATION

Accepted for Publication: July 30, 2020.

Published Online: October 7, 2020. doi:10.1001/jamacardio.2020.4511

Open Access: This is an open access article distributed under the terms of the CC-BY-NC-ND License. © 2020 McGuire DK et al. *JAMA Cardiology*.

Author Affiliations: Department of Internal Medicine, University of Texas Southwestern Medical Center, and Parkland Health and Hospital System, Dallas (McGuire); Rutgers School of Public Health, Rutgers Biomedical and Health Sciences, Piscataway, New Jersey (Shih); Rutgers Cancer Institute of New Jersey, New Brunswick (Shih); Unit of Cardiology, Karolinska Institute and Karolinska University Hospital Solna, Stockholm, Sweden (Cosentino); Department of Endocrinology, University of Nantes, Nantes, France (Charbonnel); Division of Nephrology, Department of Medicine, University Health Network, University of Toronto, Toronto, Ontario, Canada (Cherney); Department of Medicine, University of Tennessee Health Science Center, Memphis (Dagogo-Jack); AdventHealth Translational Research Institute, Orlando, Florida (Pratley); Pfizer Inc, Groton, Connecticut (Greenberg, Wang, Masiukiewicz); Merck & Co Inc, Kenilworth, New Jersey (Huyck, Gantz); Pfizer Inc, Andover, Massachusetts (Terra); Cardiovascular Division, Brigham and Women's Hospital, Baim Institute for Clinical Research, Harvard Medical School, Boston, Massachusetts (Cannon).

Author Contributions: Dr McGuire had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: McGuire, Shih, Cosentino, Charbonnel, Cherney, Dagogo-Jack, Greenberg, Wang, Huyck, Gantz, Terra, Masiukiewicz, Cannon.
Acquisition, analysis, or interpretation of data: McGuire, Shih, Cosentino, Charbonnel, Cherney, Pratley, Greenberg, Wang, Huyck, Gantz, Terra, Masiukiewicz, Cannon.
Drafting of the manuscript: McGuire, Shih, Cosentino, Charbonnel, Greenberg, Wang, Huyck, Gantz, Terra, Masiukiewicz.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Shih, Wang.
Obtained funding: Cannon.
Administrative, technical, or material support: Cherney, Cannon.
Supervision: McGuire, Masiukiewicz, Cannon.
Nephrology expertise: Cherney.
Facilitating review and concurrence of written text: Gantz.

Conflict of Interest Disclosures: Dr McGuire reported receiving honoraria for clinical trial leadership from AstraZeneca, Boehringer Ingelheim, Eisai, Esperion, GlaxoSmithKline, Janssen, Lexicon, Merck, Novo Nordisk, and Sanofi, and consultancy fees from Afimmune, Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Lilly, Merck, Pfizer, Novo Nordisk, Metavant, and Sanofi outside the submitted work. Dr McGuire reported receiving personal fees and nonfinancial support from Merck and nonfinancial support from Pfizer outside the submitted work. Dr Cannon reported receiving grants and personal fees from Merck and Pfizer during the conduct of the study; grants from Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Janssen, Merck, and Pfizer; and personal fees from Aegerion, Alnylam, Amarin, Amgen, Applied Therapeutics, Ascendia, Boehringer Ingelheim, Bristol Myers Squibb, Corvidia, Eli Lilly, HLS Therapeutics, Innovent, Janssen, Kowa, Merck, Pfizer, Rhoshan, and Sanofi outside the submitted work. Dr Cosentino reported receiving fees from Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Merck Sharp & Dohme, Novo Nordisk, and Pfizer; research grants from Swedish Research Council, Swedish Heart & Lung Foundation, and the King Gustav V and Queen Victoria Foundation; nonfinancial support from Merck Sharp & Dohme and Pfizer; and personal fees from Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Merck Sharp & Dohme, Novo Nordisk, and Pfizer outside the submitted work. Dr Charbonnel reported receiving personal fees from Merck, Pfizer, AstraZeneca, Sanofi, Novo Nordisk, MundiPharma, and Lilly and fees from AstraZeneca, Boehringer Ingelheim, Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi, and Takeda during the conduct of the study. Dr Cherney reported receiving personal fees from Boehringer Ingelheim-Eli Lilly, Merck, AstraZeneca, Sanofi, Mitsubishi-Tanabe, AbbVie, Janssen, Bayer, Prometic, Bristol Myers Squibb, and Novo Nordisk; and operating grants from Boehringer Ingelheim-Eli Lilly, Merck, Janssen, Sanofi, AstraZeneca, and Novo Nordisk outside the submitted work. Dr Dagogo-Jack reported leading clinical trials for AstraZeneca, Boehringer Ingelheim, and Novo Nordisk; consulting fees from AstraZeneca, Boehringer Ingelheim, Janssen, Merck, and Sanofi; and equity interests in Jana Care Inc and Aerami outside the submitted work. Dr Pratley reported receiving research grants, consulting, or speaker fees (directed to AdventHealth) from Hanmi Pharmaceutical Co Ltd, Janssen, Merck, Novo Nordisk, Pfizer, Poxel SA, Sanofi, Scohia Pharma, and Sun Pharmaceutical Industries; publication support from Merck; speaker and consulting fees from AstraZeneca; consulting fees from GlaxoSmithKline, Glytec, and Janssen; grants from Lexicon Pharmaceuticals; and grants and consulting fees from Ligand Pharmaceuticals, Lilly, Sanofi, and Merck outside the submitted work. All payments for Dr Pratley's services were made directly to AdventHealth, a nonprofit organization. Dr Shih reported serving as consultant to the scientific advisory committee of Merck. Drs Gantz and Huyck reported being employees of Merck & Co, Inc, Kenilworth, New Jersey, and own stock in the company. Ms Greenberg and Drs Wang, Terra, and Masiukiewicz reported being employees and shareholders of Pfizer. No other disclosures were reported.

Downloaded From: https://jamanetwork.com/ by Piergiorgio Gigliotti on 10/13/2020

Funding/Support: This study was supported by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, New Jersey, in collaboration with Pfizer Inc, New York, New York.

Role of the Funder/Sponsor: In their role as authors, employees of Pfizer Inc, New York, New York, and Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, New Jersey, were involved in protocol development and the analysis plan, the interpretation of data, preparation, review and approval of the manuscript and the decision to submit for publication, along with their coauthors. The study sponsors approved the manuscript from an intellectual property perspective.

Meeting Presentation: This work was presented in part at the 80th Scientific Sessions of the American Diabetes Association; June 12-16, 2020. This meeting was held online owing to the COVID-19 pandemic.

Additional Contributions: Editorial support was provided by Diane Hoffman, PhD, of Engage Scientific Solutions and was funded by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, New Jersey, in collaboration with Pfizer Inc, New York, New York. The support consisted solely of formatting for submission; no contribution was made to content.

REFERENCES

1. Rawshani A, Rawshani A, Franzén S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;376(15):1407-1418. doi:10.1056/NEJMoa1608664

2. Rawshani A, Rawshani A, Franzén S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2018;379(7):633-644. doi:10.1056/NEJMoa1800256

3. Ofstad AP, Atar D, Gullestad L, Langslet G, Johansen OE. The heart failure burden of type 2 diabetes mellitus-a review of pathophysiology and interventions. *Heart Fail Rev*. 2018;23(3):303-323. doi:10.1007/s10741-018-9685-0

4. Standl E, Schnell O, McGuire DK. Heart failure considerations of antihyperglycemic medications for type 2 diabetes. *Circ Res*. 2016;118(11):1830-1843. doi:10.1161/CIRCRESAHA.116.306924

5. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43(suppl 1):S98-S110. doi:10.2337/dc20-S009

6. Das SR, Everett BM, Birtcher KK, et al. 2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology task force on expert consensus decision pathways. *J Am Coll Cardiol*. 2018;72(24):3200-3223. doi:10.1016/j.jacc.2018.09.020

7. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2019;140(11):e596-e646. doi:10.1161/CIR.0000000000000678

8. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2020 executive summary. *Endocr Pract*. 2020;26(1):107-139. doi:10.4158/CS-2019-0472

9. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2020;43(2):487-493. doi:10.2337/dci19-0066

10. Cosentino F, Grant PJ, Aboyans V, et al; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;41(2):255-323. doi:10.1093/eurheartj/ehz486

11. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. *Circulation*. 2019;139(17):2022-2031. doi:10.1161/CIRCULATIONAHA.118.038868

12. Arnott C, Li Q, Kang A, et al. Sodium-glucose cotransporter 2 inhibition for the prevention of cardiovascular events in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *J Am Heart Assoc*. 2020;9(3):e014908. doi:10.1161/JAHA.119.014908

13. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393(10166):31-39. doi:10.1016/S0140-6736(18)32590-X

14. Cardiovascular outcomes following ertugliflozin treatment in type 2 diabetes mellitus participants with vascular disease, the VERTIS CV study (MK-8835-004). Clinicaltrials.gov identifier: NCT01986881. Updated April 27, 2020. Accessed August 31, 2020. https://clinicaltrials.gov/ct2/show/NCT01986881

15. Cannon CP, McGuire DK, Pratley R, et al; VERTIS-CV Investigators. Design and baseline characteristics of the eValuation of ERTugliflozin efficacy and Safety CardioVascular outcomes trial (VERTIS-CV). *Am Heart J*. 2018;206:11-23. doi:10.1016/j.ahj.2018.08.016

16. Cannon CP, Pratley R, Dagogo-Jack S, et al; VERTIS CV Investigators. Ertugliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. Published online September 23, 2020. doi:10.1056/NEJMoa2004967

17. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. doi:10.1136/bmj.b2535

18. Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi:10.1136/bmj.d5928

19. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720

20. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. doi:10.1056/NEJMoa1611925

21. Wiviott SD, Raz I, Bonaca MP, et al; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357. doi:10.1056/NEJMoa1812389

22. Perkovic V, Jardine MJ, Neal B, et al; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. doi:10.1056/NEJMoa1811744

23. Wiviott SD, Raz I, Bonaca MP, et al. The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial. *Am Heart J*. 2018;200:83-89. doi:10.1016/j.ahj.2018.01.012

24. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol*. 2019;7(8):606-617. doi:10.1016/S2213-8587(19)30180-9

25. Wanner C, Inzucchi SE, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375(4):323-334. doi:10.1056/NEJMoa1515920

26. Wanner C, Lachin JM, Inzucchi SE, et al; EMPA-REG OUTCOME Investigators. Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. *Circulation*. 2018;137(2):119-129. doi:10.1161/CIRCULATIONAHA.117.028268

27. Cochran WG. The comparison of percentages in matched samples. *Biometrika*. 1950;37(3-4):256-266. doi:10.1093/biomet/37.3-4.256

28. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186

29. Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. *Stat Med*. 2001;20(24):3875-3889. doi:10.1002/sim.1009

30. Furtado RHM, Bonaca MP, Raz I, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes mellitus and previous myocardial infarction. *Circulation*. 2019;139(22):2516-2527. doi:10.1161/CIRCULATIONAHA.119.039996

31. Neuen BL, Ohkuma T, Neal B, et al. Effect of canagliflozin on renal and cardiovascular outcomes across different levels of albuminuria: data from the CANVAS program. *J Am Soc Nephrol*. 2019;30(11):2229-2242. doi:10.1681/ASN.2019010064

32. Mahaffey KW, Jardine MJ, Bompoint S, et al. Canagliflozin and cardiovascular and renal outcomes in type 2 diabetes mellitus and chronic kidney disease in primary and secondary cardiovascular prevention groups. *Circulation*. 2019;140(9):739-750. doi:10.1161/CIRCULATIONAHA.119.042007

33. Mascitti V, Maurer TS, Robinson RP, et al. Discovery of a clinical candidate from the structurally unique dioxa-bicyclo[3.2.1]octane class of sodium-dependent glucose cotransporter 2

Downloaded From: https://jamanetwork.com/ by Piergiorgio Gigliotti on 10/13/2020

inhibitors. *J Med Chem*. 2011;54(8):2952-2960. doi:10.1021/jm200049r

34. Packer M. Reconceptualization of the molecular mechanism by which sodium-glucose cotransporter 2 inhibitors reduce the risk of heart failure events. *Circulation*. 2019;140(6):443-445. doi:10.1161/CIRCULATIONAHA.119.040909

35. Arow M, Waldman M, Yadin D, et al. Sodium-glucose cotransporter 2 inhibitor dapagliflozin attenuates diabetic cardiomyopathy. *Cardiovasc Diabetol*. 2020;19(1):7. doi:10.1186/s12933-019-0980-4

36. Uthman L, Baartscheer A, Schumacher CA, et al. Direct cardiac actions of sodium glucose cotransporter 2 inhibitors target pathogenic mechanisms underlying heart failure in diabetic patients. *Front Physiol*. 2018;9:1575. doi:10.3389/fphys.2018.01575

37. Cooper ME, Inzucchi SE, Zinman B, et al. Glucose control and the effect of empagliflozin on kidney outcomes in type 2 diabetes: an analysis from the EMPA-REG OUTCOME trial. *Am J Kidney Dis*. 2019;74(5):713-715. doi:10.1053/j.ajkd.2019.03.432

38. Inzucchi SE, Zinman B, Fitchett D, et al. How does empagliflozin reduce cardiovascular mortality? insights from a mediation analysis of the EMPA-REG OUTCOME trial. *Diabetes Care*. 2018;41(2):356-363. doi:10.2337/dc17-1096

39. Inzucchi SE, Fitchett D, Jurišić-Eržen D, et al; EMPA-REG OUTCOME® Investigators. Are the cardiovascular and kidney benefits of empagliflozin influenced by baseline glucose-lowering therapy? *Diabetes Obes Metab*. 2020;22(4):631-639. doi:10.1111/dom.13938

40. Empagliflozin outcome trial in patients with chronic heart failure with reduced ejection fraction (EMPEROR-reduced). Clinicaltrials.gov identifier: NCT03057977. Updated August 11, 2020. Accessed August 31, 2020. https://clinicaltrials.gov/ct2/show/NCT03057977

41. Empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction (EMPEROR-Preserved). Clinicaltrials.gov identifier: NCT03057951. Updated August 11, 2020. Accessed August 31, 2020. https://clinicaltrials.gov/ct2/show/NCT03057951

42. Dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction heart failure (DELIVER). Clinicaltrials.gov identifier: NCT03619213. Updated August 6, 2020. Accessed August 31, 2020. https://clinicaltrials.gov/ct2/show/NCT03619213

43. A study to evaluate the effect of dapagliflozin on renal outcomes and cardiovascular mortality in patients with chronic kidney disease (DAPA-CKD). Clinicaltrials.gov identifier: NCT03036150. Updated August 20, 2020. Accessed August 31, 2020. https://clinicaltrials.gov/ct2/show/NCT03036150

44. EMPA-KIDNEY. (the study of heart and kidney protection with empagliflozin). Clinicaltrials.gov identifier: NCT03594110. Updated August 24, 2020. Accessed August 31, 2020. https://www.clinicaltrials.gov/ct2/show/NCT03594110

45. Heerspink HJL, Stefansson BV, Chertow GM, et al. Dapagliflozin in patients with chronic kidney disease: DAPA-CKD. Paper presented at the European Society of Cardiology 2020 Congress: The Digital Experience; August 30, 2020. Virtual.

46. Danne T, Garg S, Peters AL, et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium-glucose cotransporter (SGLT) inhibitors. *Diabetes Care*. 2019;42(6):1147-1154. doi:10.2337/dc18-2316

47. Cherney DZ, Udell JA. Use of sodium glucose cotransporter 2 inhibitors in the hands of cardiologists: with great power comes great responsibility. *Circulation*. 2016;134(24):1915-1917. doi:10.1161/CIRCULATIONAHA.116.024764

Downloaded From: https://jamanetwork.com/ by Piergiorgio Gigliotti on 10/13/2020