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ORIGINAL INVESTIGATIONS

SGLT-2 Inhibitors and Cardiovascular Risk

An Analysis of CVD-REAL

Matthew A. Cavender, MD, MPH,[a,b] Anna Norhammar, MD,[c] Kåre I. Birkeland, MD,[d] Marit Eika Jørgensen, MD,[e,f] John P. Wilding, MD,[g] Kamlesh Khunti, MD,[h] Alex Z. Fu, PhD,[i] Johan Bodegård, MD,[j] Betina T. Blak, PhD,[k] Eric Wittbrodt, PharmD, MPH,[l] Marcus Thuresson, PhD,[m] Peter Fenici, MD,[n] Niklas Hammar, PhD,[c,o] Mikhail Kosiborod, MD,[p] on behalf of the CVD-REAL Investigators and Study Group

ABSTRACT

BACKGROUND Prior studies found patients treated with sodium-glucose co-transporter-2 inhibitors (SGLT-2i) had lower rates of death and heart failure (HF). Whether the benefits of SGLT-2i vary based upon the presence of cardiovascular disease (CVD) is unknown.

OBJECTIVES This study sought to determine the association between initiation of SGLT-2i therapy and HF or death in patients with and without CVD.

METHODS The CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) study was a multinational, observational study in which adults with type 2 diabetes were identified. Patients prescribed an SGLT-2i or other glucose-lowering drugs (GLDs) were matched based on a propensity score for initiation of an SGLT-2i. Hazard ratios (HRs) for the risk of death, HF, and HF or death in patients with and without established CVD were estimated for each country and pooled.

RESULTS After propensity score matching, 153,078 patients were included in each group. At baseline, 13% had established CVD. Compared with therapy using other GLDs, initiation of an SGLT-2i was associated with lower risk of death in patients with and without CVD (HR: 0.56; 95% confidence interval [CI]: 0.44 to 0.70; and HR: 0.56; 95% CI: 0.50 to 0.63, respectively). There were also associations between SGLT-2i and lower risk of HF (HR: 0.72; 95% CI: 0.63 to 0.82; and HR: 0.61; 95% CI: 0.48 to 0.78, respectively) and the composite of HF or death (HR: 0.63; 95% CI: 0.57 to 0.70; and HR: 0.56; 95% CI: 0.50 to 0.62, respectively) observed in patients with and without established CVD.

CONCLUSIONS In this large, multinational, observational study, initiation of SGLT-2i was associated with lower risk of death and HF regardless of pre-existing CVD. Ongoing clinical trials will provide further evidence regarding the benefit of SGLT-2i in patients without established CVD. (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors [CVD-REAL]; NCT02993614) (J Am Coll Cardiol 2018;71:2497–506) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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From the [a]University of North Carolina, Chapel Hill, North Carolina; [b]Baim Institute of Clinical Research, Boston, Massachusetts; [c]Karolinska Institutet, Stockholm, Sweden; [d]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, and Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway; [e]Steno Diabetes Center, Copenhagen, Denmark; [f]National Institute of Public Health, University of Southern Denmark, Odense, Denmark; [g]Institute of Ageing and Chronic Disease,

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ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

GLD = glucose-lowering drug

HF = heart failure

SGLT-2i = sodium-glucose co-transporter-2 inhibitors

T2D = type 2 diabetes

Patients with type 2 diabetes (T2D) are at increased risk of cardiovascular disease (CVD), including heart failure (HF) and death (1,2). The EMPA-REG OUTCOME (EMPAgliflozin Removal of Excess of Glucose OUTCOME) trial was a randomized controlled trial of empagliflozin, a sodium-glucose co-transporter-2 inhibitor (SGLT-2i), in patients with T2D and established CVD. In that trial, empagliflozin reduced the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Furthermore, death and hospitalization for HF were also reduced with empagliflozin (3). Directionally similar results for cardiovascular death or HF were also seen in the CANVAS (CANagliflozin cardioVascular Assessment Study) program, which evaluated canagliflozin in 10,142 patients with T2D (4). The CANVAS program included patients with and without CVD at baseline; however, the majority of patients randomized into the program had established CVD (5). These results were overall similar to the association between SGLT-2i and major adverse cardiovascular events seen in registry-based data from Sweden, Denmark, and Norway (6).

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The CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) study, an observational study that included >300,000 propensity score-matched patients from 6 countries, found that initiation of SGLT-2i therapy was associated with a significantly lower risk of death and HF than other glucose-lowering drugs (GLDs) (7). However, whether these relationships differ in patients with T2D based on the presence of known CVD, particularly in the real-world setting, remains unclear. Thus, in this analysis of the CVD-REAL study, we sought to determine whether the associations among SGLT-2i, death, and HF varied depending on the presence or absence of CVD at the time of initiation of glucose-lowering therapy.

METHODS

The CVD-REAL study (NCT02993614) design has previously been described in detail (7). For this particular analysis, we used observational data from medical records, medical claims, electronic health and death records, and national registers collected from 5 countries (United States, United Kingdom, Sweden, Norway, and Denmark) included in CVD-REAL. In the United States, MarketScan Claims and Encounters (Truven Health Analytics; IBM, Armonk, New York) and linked Medicare Supplemental and Coordination of Benefits databases were used, which included enrollment and demographic information, inpatient and outpatient medical, and outpatient pharmacy claims from >300 large, self-insured U.S. employers and >25 U.S. health plans. Mortality data were available from Truven Health Analytics (IBM) for a

University of Liverpool, Liverpool, United Kingdom; [h]Diabetes Research Centre, University of Leicester, Leicester, United Kingdom; [i]Georgetown University Medical Center, Washington, DC; [j]AstraZeneca, Oslo, Norway; [k]AstraZeneca, Luton, United Kingdom; [l]AstraZeneca, Wilmington, Delaware; [m]Statisticon AB, Uppsala, Sweden; [n]AstraZeneca, Cambridge, United Kingdom; [o]AstraZeneca, Gothenburg, Sweden; and the [p]Saint Luke's Mid America Heart Institute, Kansas City, Missouri, and University of Missouri-Kansas City, Kansas City, Missouri. Supported by AstraZeneca. Dr. Cavender has received personal fees from AstraZeneca, Janssen, Merck, Sanofi-Aventis, and Chiesi; and research support from Abbott Laboratories, AstraZeneca, GlaxoSmithKline, The Medicines Company, Merck, and Takeda. Dr. Norhammar has received personal fees from AstraZeneca; and honoraria for lectures and advisory board meetings from Novo Nordisk, Boehringer Ingelheim, and Eli Lilly. Dr. Birkeland has received grants through his institution from AstraZeneca; and has received honoraria for lectures and consulting from Novo Nordisk, Sanofi, Eli Lilly, Boehringer Ingelheim, and Merck Sharp & Dohme. Dr. Jørgensen holds shares in Novo Nordisk; was recently employed by Steno Diabetes Center A/S (owned by Novo Nordisk); and has received grants from AstraZeneca. Dr. Wilding has received lecture fees from Astellas, AstraZeneca, Boehringer Ingelheim, Janssen, Eli Lilly, Novo Nordisk, Orexigen, and Sanofi; has consulted for AstraZeneca, Boehringer Ingelheim, Janssen, Eli Lilly, and Orexigen; and has received grants through his institution from Takeda, Novo Nordisk, and AstraZeneca. Dr. Bodegård is employed by AstraZeneca. Dr. Fenici is employed by AstraZeneca. Dr. Khunti is a consultant and speaker for AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Eli Lilly, Merck Sharp & Dohme, Janssen, and Boehringer Ingelheim; has received research grants from AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Eli Lilly, Boehringer Ingelheim, Merck Sharp & Dohme, and Roche; is an advisory board member for AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Eli Lilly, Merck Sharp & Dohme, Janssen, and Boehringer Ingelheim; and is supported by the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care East Midlands. Dr. Fu has received grants from AstraZeneca and Merck Sharp & Dohme; and has received honoraria from Asclepius Analytics and Complete HEOR Services. Dr. Thuresson is an employee of Statisticon, for which AstraZeneca is a client. Dr. Kosiborod has received grants from AstraZeneca and Boehringer Ingelheim; is an advisory board member for AstraZeneca, Boehringer Ingelheim, Sanofi, Glytec, Novo Nordisk, Janssen, ZS Pharma, Eisai, and Merck Sharp & Dohme (Diabetes); and is a consultant for AstraZeneca, Sanofi, GlaxoSmithKline, Amgen, Janssen, Intarcia, Novo Nordisk, and ZS Pharma. Dr. Hammar is an employee of AstraZeneca. Dr. Blak is an employee of and holds shares in AstraZeneca. Dr. Wittbrodt is an employee of AstraZeneca.

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proportion of patients in which information from the Social Security Administration is integrated with the insurance enrollment and claims data and supplemented by claims for in-hospital deaths (8). Characteristics of U.S. patients with versus without linkage to Social Security Administration data were previously demonstrated to be similar, indicating data missing completely at random due to administrative reasons. In Denmark, Norway, and Sweden, national full-population registries were used that included all medications, hospitalizations, and cause of death. In the United Kingdom, the Clinical Practice Research Datalink (CPRD) was used, which includes primary care data from >670 general practices linked with hospitalization and mortality registries (9), and The Health Improvement Network (THIN) dataset, which includes data from >580 U.K. practices, with primary care data similar to those of CPRD (10). HF events were uncommon in the dataset from Germany (n = 11), and data regarding death were not available; therefore, we elected not to include data from Germany in this particular analysis from the CVD-REAL cohort.

Adult patients with T2D who had at least 1 year of historical data available for analysis were eligible for inclusion in the study. Patients known to have type 1 or gestational diabetes were excluded. Patients who were newly initiated on either an SGLT-2i (canagliflozin, dapagliflozin, or empagliflozin) or other GLDs and did not have prescriptions for that particular medication class within the prior year were identified. Baseline characteristics of the patients prior to the match have been published previously (7). A nonparsimonious propensity score using variables that might have affected treatment assignment or outcomes was developed separately within each country to predict the likelihood a patient would be prescribed SGLT-2i (11–13). Candidate variables used in the development of the propensity score have been listed (Online Table 1). Patients in the 2 treatment groups were matched 1:1 based on propensity scores. For the matching in the United States and United Kingdom, nearest neighbor caliper width of 0.25 multiplied by the SD of the propensity score distribution was used (11), whereas an automated balance-optimization method using function matching software (R software: R Core Team, Vienna, Austria) and a caliper of 0.2 were used for matching in Sweden, Norway, and Denmark. Standardized differences of post-matched patient characteristics were used to assess the adequacy of propensity score matching, where >10% standardized difference between the 2 groups after propensity score matching was considered a non-negligible imbalance (12).

All analyses were performed using the intention-to-treat principle in which patients were followed from the time their therapy began (start date of the SGLT-2i or other GLD ranged from November 2012 in the United Kingdom to July 2013 in Sweden) until they had a cardiovascular event or were censored at the end of follow-up (ranged from September 2015 in the United States to November 2016 in Sweden). An on-treatment analysis was also performed as a sensitivity analysis in which patients were followed from the index date until they either completed therapy with that particular drug, or died, or were censored at end of follow-up. Patients were stratified based upon the presence or absence of known CVD at the time when glucose-lowering therapy was initiated. Patients were considered to have CVD if they had a prior history of acute myocardial infarction, unstable angina, stroke, HF, transient ischemic attack, coronary revascularization, or occlusive peripheral artery disease.

The primary endpoints of interest were time to death, HF, and composite endpoint of HF or death. Hazard ratios (HRs) for each endpoint were estimated for each country and then pooled using a random effects model with inverse variance weighting for each country to generate a pooled HR and 95% confidence interval (CI) (14). HRs were adjusted for age, sex, frailty (defined as ≥1 hospital stay of ≥3 days within 1 year prior to the index date; defined in the United Kingdom as ≥1 hospital stay within 1 year prior to the index date), history of myocardial infarction, history of atrial fibrillation, history of HF, hypertension, obesity/body mass index, duration of GLD treatment or diabetes, use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers, β-blocker or α-blocker, calcium-channel blocker, loop diuretic, aldosterone antagonist, or thiazide diuretic.

Analyses of de-identified data were conducted in accordance with local laws and regulations and received approvals from respective scientific/ethics/data protection committees.

RESULTS

After propensity score matching, 306,156 patients were included in the analysis (153,078 patients in each treatment group). Baseline characteristics were balanced between treatment groups in patients with and without established CVD (**Table 1**). Most patients in the propensity score-matched cohort did not have established CVD; only 12.8% had a history of CVD, and 3.0% had a history of HF.

In the SGLT-2i group, of the total on-treatment exposure time, 53.2% of patients received canagliflozin, 41.4% received dapagliflozin, and 5.4%

TABLE 1 Baseline Characteristics

	Cardiovascular Disease at Baseline			No Cardiovascular Disease at Baseline		
	SGLT-2i (n = 19,529)	Other GLD (n = 19,764)	Standardized Difference, %	SGLT-2i (n = 133,549)	Other GLD (n = 133,314)	Standardized Difference, %
Age, yrs	62.7 ± 9.7	63.5 ± 10.4	8.3	56.0 ± 9.8	56.0 ± 10.5	0.6
Women	7,018 (35.9)	7,234 (36.6)	1.1	60,783 (45.5)	60,924 (45.7)	0.3
Duration of diabetes, yrs	8.7 ± 4.4	9.1 ± 4.5	9.2	7.6 ± 4.3	7.7 ± 4.4	4.3
History of CV disease*	19,529 (100.0)	19,764 (100.0)	NA	0 (0.0)	0 (0.0)	NA
AMI	3,651 (18.7)	3,733 (18.9)	0.4	0 (0.0)	0 (0.0)	NA
Unstable angina	2,477 (12.7)	2,513 (12.7)	0.1	0 (0.0)	0 (0.0)	NA
Heart failure	4,635 (23.7)	4,677 (23.7)	0.1	0 (0.0)	0 (0.0)	NA
Atrial fibrillation	2,721 (13.9)	2,854 (14.4)	1.2	2,835 (2.1)	2,765 (2.1)	0.3
Stroke	5,878 (30.1)	5,924 (30.0)	0.2	0 (0.0)	0 (0.0)	NA
PAD	4,924 (25.2)	4,920 (24.9)	0.6	0 (0.0)	0 (0.0)	NA
Microvascular disease	8,671 (44.4)	8,566 (43.3)	1.7	32,825 (24.6)	32,901 (24.7)	0.2
CKD	978 (5.0)	909 (4.6)	1.6	2,746 (2.1)	2,976 (2.2)	1.0
Frailty	5,130 (26.3)	5,413 (27.4)	2.1	7,015 (5.3)	7,102 (5.3)	0.3
Baseline glucose-lowering therapies						
Metformin	14,690 (75.2)	15,740 (79.6)	8.5	105,778 (79.2)	106,647 (80.0)	1.6
Sulfonylurea	7,414 (38.0)	7,830 (39.6)	2.8	51,843 (38.8)	51,819 (38.9)	0.1
DPP-4i	6,214 (31.8)	6,423 (32.5)	1.2	44,728 (33.5)	43,184 (32.4)	1.9
Thiazolidinedione	1,305 (6.7)	1,295 (6.6)	0.4	12,336 (9.2)	11,670 (8.8)	1.4
GLP-1 RA	4,259 (21.8)	3,867 (19.6)	4.5	26,864 (20.1)	23,000 (17.3)	5.9
Insulin	7,695 (39.4)	7,645 (38.7)	1.2	37,163 (27.8)	36,748 (27.6)	0.5
Cardiovascular therapies						
Antihypertensive therapy†	17,955 (91.9)	18,288 (92.5)	1.8	104,806 (78.5)	104,332 (78.3)	0.4
Loop diuretics	5,099 (26.1)	5,268 (26.7)	1.0	9,105 (6.8)	8,966 (6.7)	0.3
Thiazides	4,656 (23.8)	4,714 (23.9)	0.0	37,385 (28.0)	37,383 (28.0)	0.1
β-blockers	10,059 (51.5)	10,136 (51.3)	0.4	29,043 (21.7)	29,120 (21.8)	0.2
Calcium-channel blockers	6,396 (32.8)	6,635 (33.6)	1.4	29,525 (22.1)	29,445 (22.1)	0.0
Aldosterone antagonists	1,642 (8.4)	1,796 (9.1)	2.0	2,759 (2.1)	2,638 (2.0)	0.5
ACE inhibitors	9,119 (46.7)	9,351 (47.3)	1.0	57,258 (42.9)	57,352 (43.0)	0.2
ARBs	7,462 (38.2)	7,667 (38.8)	1.0	40,978 (30.7)	40,547 (30.4)	0.5
Statin therapy	15,852 (81.2)	16,211 (82.0)	1.8	87,560 (65.6)	87,355 (65.5)	0.1
Index year						
2012	1 (0.0)	43 (0.5)	9.6	19 (0.1)	153 (0.6)	8.3
2013	2,760 (14.1)	3,006 (15.2)	2.5	18,369 (13.8)	22,554 (16.9)	7.3
2014	8,106 (41.5)	7,084 (35.8)	9.5	62,605 (46.9)	51,476 (38.6)	13.6
2015	7,982 (40.9)	9,045 (45.8)	8.1	50,478 (37.8)	56,900 (42.7)	8.2
2016	680 (8.2)	586 (6.9)	3.9	2,078 (7.5)	2,231 (8.1)	1.8

Values are mean ± SD or n (%), unless otherwise stated. *Myocardial infarction, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization, or occlusive peripheral artery disease. †Includes ACE inhibitors, ARBs, calcium-channel blockers, β-blockers, and thiazides.

AMI = acute myocardial infarction; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; DPP-4i = dipeptidyl peptidase-4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; GLD = glucose-lowering drug; PAD = peripheral artery disease; SGLT-2i = sodium-glucose cotransporter-2 inhibitor.

received empagliflozin. There was a significant amount of geographical variation with regard to the specific SGLT-2i used. Canagliflozin was used predominantly (75.9%) in the United States, and dapagliflozin was used predominantly (92.2%) in European countries ($p < 0.001$). Empagliflozin was used infrequently in both the United States and in Europe. In patients who began receiving other GLDs, the most common classes were insulin (33.7%), dipeptidyl peptidase-4 inhibitors (17.3%), sulfonylureas (17.1%), glucagon-like peptide-1 receptor agonists (13.8%), and metformin (11.4%).

The mean follow-up time ranged from 313 to 387 days in patients treated with SGLT-2i and from 299 to 383 days in patients treated with other GLDs. There were 1,871 deaths and 1,586 HF events included in the analysis. In patients with established CVD, the death rate was 2.7 per 100 person-years, and the HF rate was 2.7 per 100 patient-years; whereas in patients without established CVD, the death rate was 0.7 per 100 person-years, and the HF rate was 0.2 per 100 patient-years (**Figure 1**).

Patients treated with SGLT-2i, including those with and without established CVD, had lower absolute

rates of HF, death, and HF or death than patients taking other GLDs (**Figure 2,** Online Table 2). Compared to other GLDs, the use of SGLT-2i was associated with lower risk of death in both patients with and without CVD (1.8 vs. 3.6 events per 100 patient-years, respectively; HR: 0.56; 95% CI: 0.44 to 0.70; and 0.5 vs. 0.9 events per 100 patient-years, respectively; HR: 0.56; 95% CI: 0.50 to 0.63). There was no significant geographical heterogeneity in this association among patients with or without CVD ($p = 0.06$ and $p = 0.56$, respectively). Compared with other GLDs, SGLT-2i were also associated with lower risk of HF in both subgroups (2.3 vs. 3.2 events per 100 patient-years, respectively; HR: 0.72; 95% CI: 0.63 to 0.82; and 0.1 vs. 0.2 events per 100 patient-years, respectively; HR: 0.61; 95% CI: 0.48 to 0.78) (**Central Illustration**). When we evaluated these endpoints as a composite, the overall relationship persisted, and use of SGLT-2i, compared with other GLDs, was associated with lower risk of the composite endpoint of death or HF in patients with and without CVD (4.0 vs. 6.7 events per 100 patient years, respectively; HR: 0.63; 95% CI: 0.57 to 0.70; and 0.6 vs. 1.1 events per 100 patient years, respectively; HR: 0.56; 95% CI: 0.50 to 0.62) (**Figure 3**). Similar findings were seen when limiting the analyses to a cohort that was on-treatment (Online Figures 1 and 2). As a further sensitivity analysis using data from Sweden and Norway, separate propensity scores were developed specifically in the cohorts with and without established cardiovascular disease, and the results were consistent with the overall findings (Online Table 3, Online Figures 3 and 4).

In order to determine the possibility of unmeasured residual confounding despite propensity score matching, we evaluated a negative control. In the Marketscan (Truven Health Analytics; IBM) dataset from the United States, there were 219 occurrences of atrial fibrillation in the on-treatment analysis. There was no association between initiation of SGLT-2i and other GLDs and the onset of atrial fibrillation (HR: 0.96; 95% CI: 0.73 to 1.25).

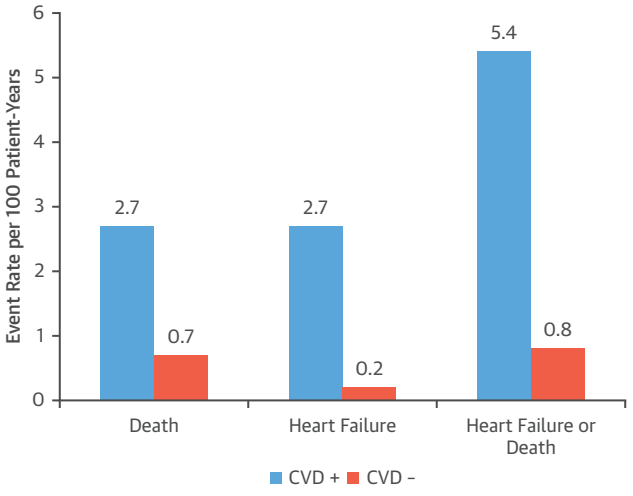
DISCUSSION

In this observational analysis of the CVD-REAL study, which included >300,000 patients from 5 countries, the following important findings are noted. First, most patients treated with SGLT-2i in clinical practice during the course of this study did not have an established history of CVD. Second, we found an association between the use of SGLT-2i and a lower risk of death and HF that was observed across the spectrum of risk including patients with and without established CVD. This association provides supports for the benefit of SGLT-2i, particularly with regard to HF, that were seen in 2 prior trials. As such, our findings suggest that the benefits seen in clinical trials may extend to patients treated with SGLT-2i as part of clinical practice (15). In this analysis, we present stratified data suggesting a similar association (from a relative risk standpoint) in patients with and without established CVD; thus, it is possible the benefits of SGLT-2i could extend to a broad population of patients with T2D. This is especially important given that patients with diabetes are typically risk stratified using only clinical variables and history, such as the presence of a prior cardiovascular event, although this may not be the best strategy to identify those patients who are at highest risk for future cardiovascular events (16,17).

The relative risk of the associations among SGLT-2i and HF and death seen in the CVD-REAL study were similar in patients with and without established CVD. However, the absolute event rates which we observed suggest that the number needed to treat (in a hypothetical randomized controlled trial) would likely be substantially greater in patients without established CVD than in those with CVD. Conversely, the number needed to treat would be expected to be lower in the subgroup with known CVD (18).

The association between SGLT-2i and outcomes seen in CVD-REAL was directionally consistent across the different countries included in the analysis.

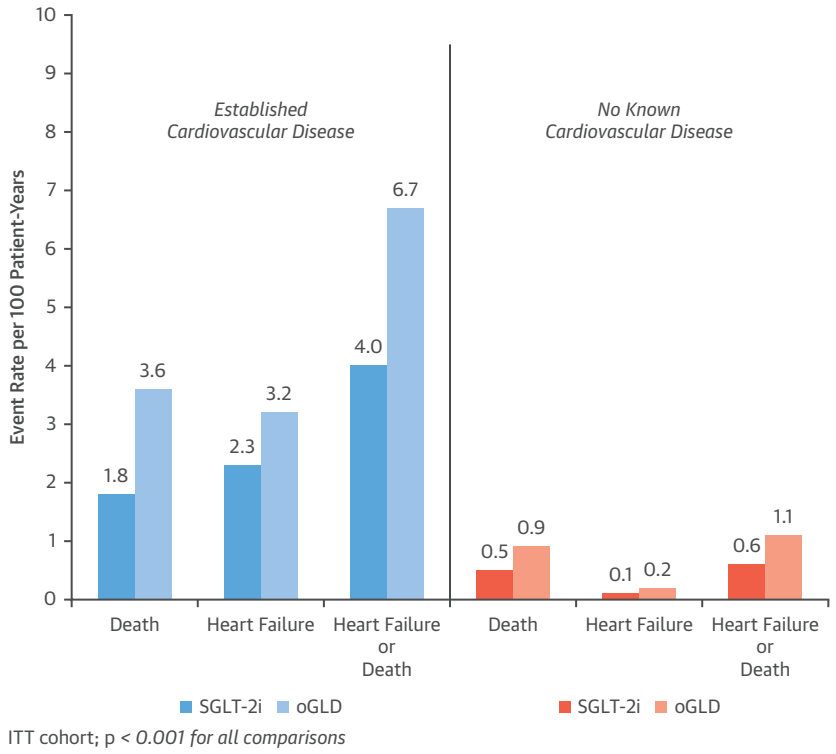
FIGURE 1 Event Rates Following Initiation of Glucose-Lowering Therapy in Patients With and Without Cardiovascular Disease



ITT cohort; p < *0.001 for all comparisons*

CVD = cardiovascular disease; ITT = intention-to-treat.

FIGURE 2 Event Rates Following Initiation of Glucose-Lowering Therapy in Patients With and Without Cardiovascular Disease Stratified by Treatment With Sodium-Glucose Co-Transporter-2 Inhibitors or Other Glucose-Lowering Drugs



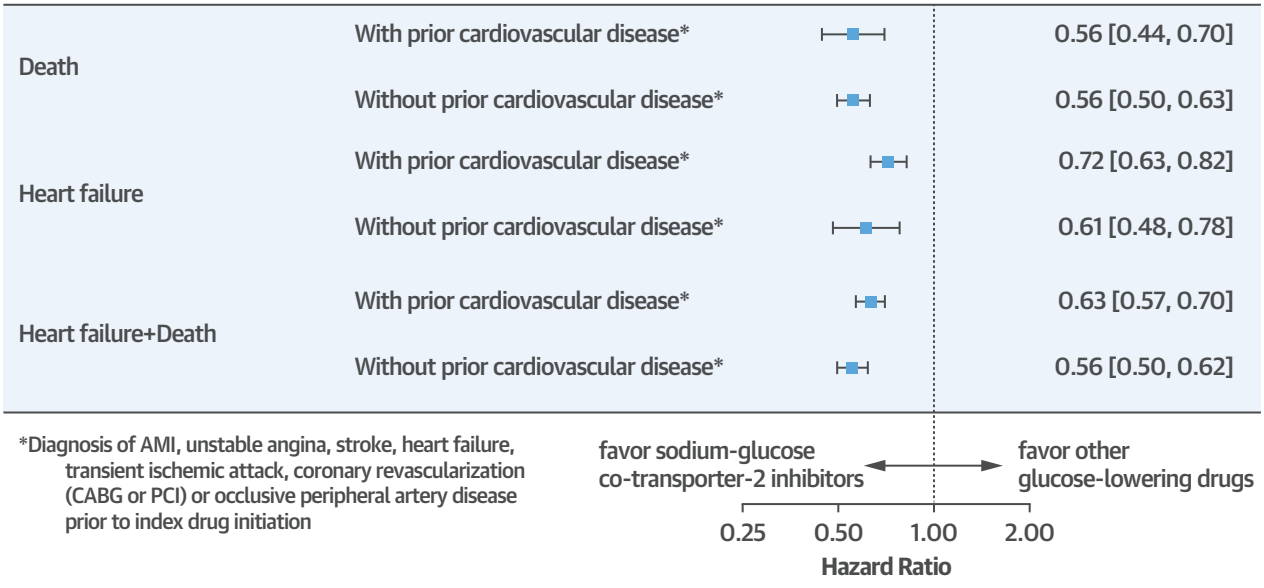
ITT = intention-to-treat; oGLD = other glucose-lowering drugs; SGLT-2i = sodium-glucose cotransporter-2 inhibitors.

Despite considerable variation in the specific SGLT-2i used in the United States and Europe, there was no geographic heterogeneity in the associations between initiation of SGLT-2i (versus other glucose-lowering agents) and events of HF and death (19–21). These findings provide indirect evidence for the possibility that SGLT-2 inhibition, regardless of the particular agent, is associated with lower risk of death or HF (22).

It is important to consider these findings in the context of randomized controlled trials of SGLT-2i. The EMPA-REG trial showed that treatment with empagliflozin in patients with established CVD significantly reduced major adverse cardiovascular events, defined as cardiovascular death, myocardial infarction, and stroke (3). Empagliflozin was also shown to reduce the risk of death (HR: 0.68) and hospitalization for HF (HR: 0.65). All patients randomized in the EMPA-REG trial had established CVD, providing strong evidence for cardiovascular benefit in this population; however, the effects of empagliflozin in patients without established CVD remain unknown.

The CANVAS program included results from 2 separate studies that had similar inclusion criteria and data collection processes. In the integrated analysis of the CANVAS program, most patients had known CVD, but approximately 30% of the combined population was at increased risk for cardiovascular events and no history of CVD. In those trials, patients with established CVD at baseline had a statistically significant reduction in the primary endpoint of time to cardiovascular death, myocardial infarction, or stroke, whereas there was no statistically significant reduction seen in the subgroup without established CVD (HR: 0.98; 95% CI: 0.74 to 1.30) (5). However, the CANVAS program was not powered for superiority of the primary endpoint of major adverse cardiac event(s) within each of these subgroups, and there was no statistical evidence of heterogeneity in the effect of canagliflozin by the presence of established CVD (p [heterogeneity] = 0.18). Furthermore, the effects of canagliflozin on death and HF were similar in the subgroups of patients with and without CVD (23). As such, these data, in conjunction with this

CENTRAL ILLUSTRATION **Sodium-Glucose Co-Transporter-2 Inhibitors in Patients With and Without Cardiovascular Disease**



Cavender, M.A. et al. J Am Coll Cardiol. 2018;71(22):2497–506.

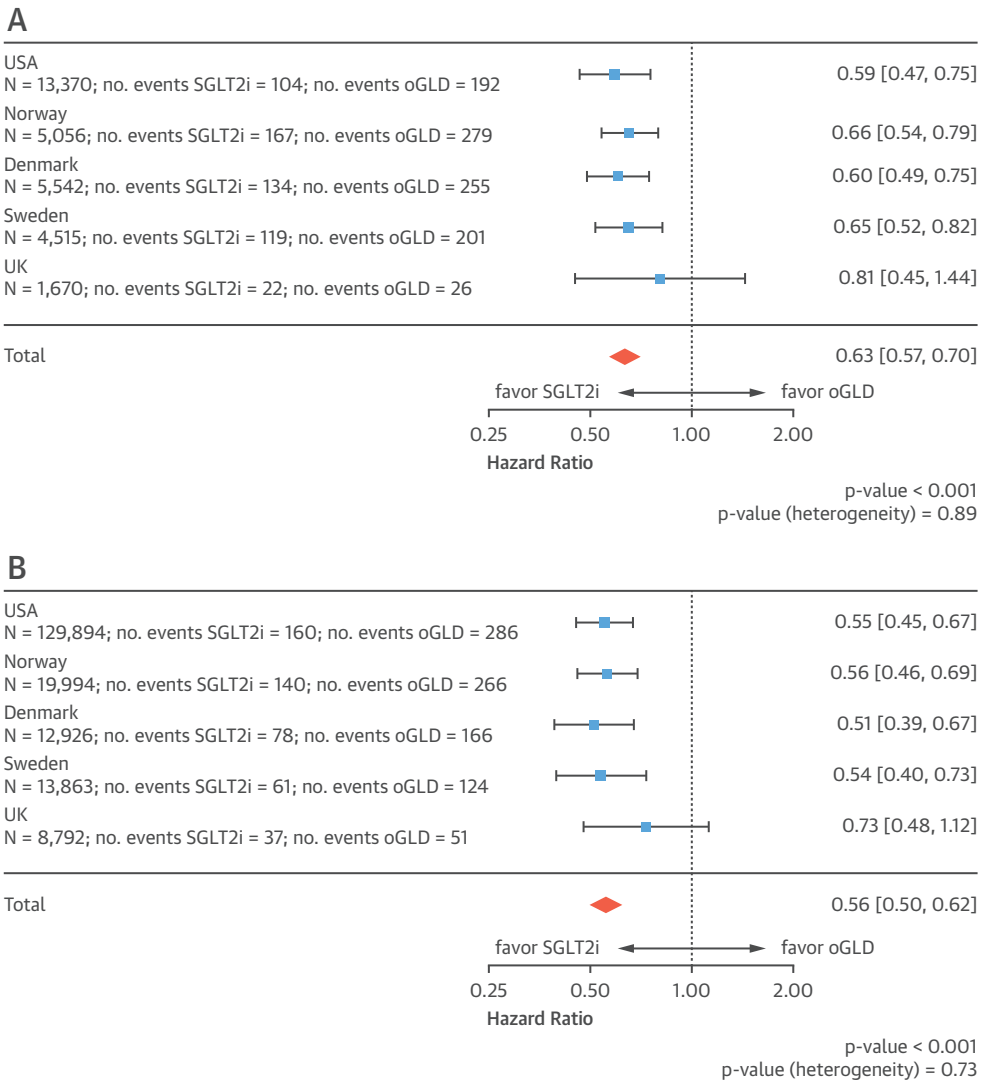
Pooled adjusted hazard ratios from meta-analyses for death, heart failure, and heart failure or death in patients with and without cardiovascular disease at initiation of the index drug in the intention-to-treat cohort. AMI = acute myocardial infarction; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

observational data, support the hypothesis that the presence of established CVD is not an effect modifier for the efficacy of SGLT-2i with regard to HF and death, and provide cardiovascular benefit in patients without established CVD (24).

The DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events) trial is currently ongoing and is testing the efficacy of dapagliflozin in patients with either established CVD or with risk factors for CVD (25). The co-primary efficacy endpoint of this trial is cardiovascular death or HF, similar to the endpoints evaluated in our CVD-REAL study. Most patients randomized in DECLARE-TIMI 58 do not have established CVD (26). Thus, that trial will provide important additional data regarding the effectiveness of SGLT-2i in patients without established CVD (27). Nevertheless, it is important to consider that patients without CVD included in randomized trials still represent a higher risk cohort, due to inclusion criteria requiring presence of CV risk factors, than those without CVD in the CVD-REAL study. It is unlikely, therefore, that the type of "primary prevention" patients we evaluated in this analysis would ever be included in a future clinical trial, and large population-based studies such as CVD-REAL may represent the only opportunity to better understand potential cardiovascular effects associated with SGLT-2i in this group.

STUDY LIMITATIONS. Our findings should be considered in the context of several potential limitations. First, due to the observational nature of these analyses, the possibility of residual, unmeasured confounding cannot be eliminated, despite the use of a robust (nonparsimonious) propensity score matching and additional statistical adjustments. While the fact that there was no evidence of association between SGLT-2i and a negative control provides support for the robustness of the association between SGLT-2i and lower rates of HF and death, this does not completely eliminate the possibility of residual confounding. In this analysis, we used a propensity score developed within each country for the overall cohort based on the data and variables collected within that specific country, outcomes were then evaluated in the subgroups of patients with and without established CVD. Subgroup-specific propensity scores in patients with and without established CVD were not developed to prevent

FIGURE 3 Adjusted Hazard Ratios for Heart Failure or Death



Adjusted hazard ratios for heart failure or death in patients **(A)** with established cardiovascular disease and **(B)** without established cardiovascular disease at initiation of the index drug in the ITT cohort. Abbreviations are as in **Figures 1 and 2**.

introducing instability into the point estimates, which could occur if one were to develop propensity scores that were both country- and subgroup-specific. However, when such subgroup-specific scores were developed in Sweden and Norway, the results were highly consistent. Several ongoing clinical trials in patients with T2D and a range of CVD risk are presently testing the effects of SGLT-2i on cardiovascular events and will provide considerable insight into these potential benefits, including efficacy in important subgroups (DECLARE [NCT01730534] and VERTIS [Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease; NCT01986881] trials) (25,28). Second, although the current study included many patient-years of follow-up, use of SGLT-2i in clinical practice is limited; thus, additional follow-up would be useful to better understand whether the effects associated with SGLT-2i are sustained over time. Third, we were unable to assess for adverse effects including the risk of amputation as seen in a recent randomized clinical trial with an SGLT-2i. Finally, mortality may not be completely captured in the Truven Health Analytics (IBM) dataset due to changes in the acquisition of data in the death master file, which is one source of mortality data in

the United States. However, this would not be expected to affect the overall associations between SGLT-2i and death, as any missing mortality data would occur completely at random, due to administrative reasons (8). This is supported by the finding of similar associations between SGLT-2i use and death across the different geographic areas.

CONCLUSIONS

In this observational analysis of the CVD-REAL study, most patients treated with SGLT-2i in clinical practice across 5 countries do not have established CVD. Patients with and without established CVD are at lower associated risk of both death and HF after initiation of SGLT-2i therapy compared to therapy with other GLDs. Although long-term follow-up data from observational studies such as CVD-REAL and ongoing randomized clinical trials are needed to fully understand whether the effects of SGLT-2i are sustained over time, these findings suggest that the cardiovascular benefits of SGLT-2i may not be specific to a single compound, and may extend to a broader population of patients with T2D than previously considered. Data from ongoing randomized clinical trials will provide further evidence regarding the cardiovascular benefits of different SGLT-2i, including in patients without established CVD.

ACKNOWLEDGMENTS Data from Norway were obtained from the Norwegian Cause of Death Registry, the Norwegian Patient Registry, and the Norwegian Prescription Registry. The interpretation and reporting of these data were the sole responsibilities of the authors, and no endorsement by the Norwegian patient register was intended nor should be inferred. This study is based in part on data from the Clinical Practice Research Datalink (CPRD) obtained under license from the U.K. Medicines and Healthcare Products Regulatory Agency. Data were provided by patients and collected by the National Health Service as part of patient care and support. This CPRD study also used data from the Office for National Statistics and Hospital Episode Statistics (with permission from the Health and Social Care Information Centre). The study was approved by the Independent Scientific Advisory Committee of the CPRD (protocol 16_064RAR). The Health Improvement Network data from the U.K. were also used, and the independent Scientific Review Committee approved the study (protocol 16THIN027A1). The interpretation and conclusions contained in this study are those of the authors alone. Editorial support was provided by Nicola Truss, PhD, inScience Communications, Springer Healthcare, and funded by AstraZeneca.

ADDRESS FOR CORRESPONDENCE: Dr. Matthew A. Cavender, University of North Carolina at Chapel Hill, Burnett-Womack Building, 160 Dental Circle, CB 7075, Chapel Hill, North Carolina 27599. E-mail: matt.cavender@unc.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a large multinational population of patients with T2D from Europe and North America, treatment with SGLT-2i was associated with lower rates of death and HF regardless of the presence of established cardiovascular disease. These data suggest that the benefit from SGLT-2i could extend across the continuum of cardiovascular risk.

TRANSLATIONAL OUTLOOK: Further studies are needed to clarify the mechanisms by which SGLT-2i reduce cardiovascular events.

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KEY WORDS cardiovascular disease, CVD-REAL, heart failure, sodium-glucose co-transporter-2 inhibitors

APPENDIX For a complete list of the CVD-REAL Investigators and Study Group as well as supplemental tables and figures, please see the online version of this paper.