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Cardiovascular Events Associated With SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs

The CVD-REAL 2 Study

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ABSTRACT

BACKGROUND Randomized trials demonstrated a lower risk of cardiovascular (CV) events with sodium-glucose cotransporter-2 inhibitors (SGLT-2i) in patients with type 2 diabetes (T2D) at high CV risk. Prior real-world data suggested similar SGLT-2i effects in T2D patients with a broader risk profile, but these studies focused on heart failure and death and were limited to the United States and Europe.

OBJECTIVES The purpose of this study was to examine a broad range of CV outcomes in patients initiated on SGLT-2i versus other glucose-lowering drugs (oGLDs) across 6 countries in the Asia Pacific, the Middle East, and North American regions.

METHODS New users of SGLT-2i and oGLDs were identified via claims, medical records, and national registries in South Korea, Japan, Singapore, Israel, Australia, and Canada. Propensity scores for SGLT-2i initiation were developed in each country, with 1:1 matching. Hazard ratios (HRs) for death, hospitalization for heart failure (HHF), death or HHF, MI, and stroke were assessed by country and pooled using weighted meta-analysis.

RESULTS After propensity-matching, there were 235,064 episodes of treatment initiation in each group; ~27% had established CV disease. Patient characteristics were well-balanced between groups. Dapagliflozin, empagliflozin, ipragliflozin, canagliflozin, tofogliflozin, and luseogliflozin accounted for 75%, 9%, 8%, 4%, 3%, and 1% of exposure time in the SGLT-2i group, respectively. Use of SGLT-2i versus oGLDs was associated with a lower risk of death (HR: 0.51; 95% confidence interval [CI]: 0.37 to 0.70; $p < 0.001$), HHF (HR: 0.64; 95% CI: 0.50 to 0.82; $p = 0.001$), death or HHF (HR: 0.60; 95% CI: 0.47 to 0.76; $p < 0.001$), MI (HR: 0.81; 95% CI: 0.74 to 0.88; $p < 0.001$), and stroke (HR: 0.68; 95% CI: 0.55 to 0.84; $p < 0.001$). Results were directionally consistent across both countries and patient subgroups, including those with and without CV disease.

CONCLUSIONS In this large, international study of patients with T2D from the Asia Pacific, the Middle East, and North America, initiation of SGLT-2i was associated with a lower risk of CV events across a broad range of outcomes and patient characteristics. (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors [CVD-REAL]; NCT02993614)

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Cardiovascular disease (CVD) remains the leading cause of mortality and morbidity in patients with type 2 diabetes (T2D). The majority of patients with T2D worldwide reside outside of the United States and Europe, with the largest number in the Asia Pacific region, and many more in the Middle East (1–3). These regions are also experiencing the most rapid rise in the prevalence of T2D (1,2). There may be important differences in patient characteristics, treatment patterns, and the types of adverse CVD events experienced by patients in different regions of the world (e.g., stroke is much more common in Asia [4]). Yet, the outcomes of patients with T2D in general, and particularly in relation to novel drug treatments in regions outside of North America and Europe, including cardiovascular events, have not been well described. Recognizing this large gap in knowledge across Asia, the Asia-Pacific Cohort Studies Collaboration pooled retrospective studies from the region and confirmed that T2D was associated with a 2-fold increase in the risk of CVD and ~67% increase in the risk of all-cause death (ACD) among Asians, with even greater hazard ratios (HRs) in younger compared with older people (5).

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Recent cardiovascular trials have demonstrated a significant reduction in major adverse cardiovascular events, death, and hospitalizations for heart failure (HHF) with sodium-glucose cotransporter-2 inhibitors (SGLT-2i) in patients with T2D, most of whom had established CVD (6–8); however, only a minority of patients across these trials were recruited outside of the United States and Europe. Our prior large pharmacoepidemiological study—CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)—demonstrated that SGLT-2i are associated with similar cardiovascular effects across agents (suggesting a class effect), and in a much broader population of T2D, including those with a lower risk profile (9). However, those initial analyses focused on a limited number of outcomes (ACD and HHF), and only included patients from the United States and Europe.

Large, well-designed comparative effectiveness studies comparing cardiovascular outcomes with various T2D therapies have not been performed in the Asia Pacific and the Middle East. Specifically, given potential cardiovascular benefits of SGLT-2i, it is important to understand the effects associated with use of these agents in real-world clinical practice across various world regions, and across a broader range of cardiovascular outcomes. Accordingly, using well-established data sources, we evaluated the relationship between the initiation of SGLT-2i versus initiation of other glucose-lowering drugs (oGLDs) with a broad range of cardiovascular outcomes in over 400,000 patients from 3 major world regions: Asia Pacific (South Korea, Japan, Singapore, and Australia), Middle East (Israel), and North America (Canada).

ABBREVIATIONS AND ACRONYMS

ACD = all-cause death

ACEi = angiotensin converting enzyme inhibitor

ARB = angiotensin receptor blocker

CI = confidence interval

CVD = cardiovascular disease

HHF = hospitalization for heart failure

HR = hazard ratio

IR = incidence rate

MI = myocardial infarction

oGLD = other glucose-lowering drug

SGLT-2i = sodium-glucose cotransporter-2 inhibitors

T2D = type 2 diabetes

METHODS

DATA SOURCES. Deidentified health records across 6 countries (South Korea, Japan, Singapore, Israel, Australia, and Canada) were analyzed. In South Korea, information from the National Health Insurance

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Service was used. The National Health Insurance Service provides a centralized health insurance database that provides longitudinal data for 97% of the Korean population, with linkage to the National Death Registry (10,11).

In Japan, we used the Medical Data Vision Co., Ltd., a hospital-based database containing administrative claims and laboratory data, linked to the Diagnostic Procedure Combination (flat-fee payment system) inpatient hospital payment system, covering over 10 million patients across the country, corresponding to about 20% of the total population in Japan. Demographic characteristics including the age and sex distributions of these patients are known to be very similar to those of national statistics in Japan (12–14).

In Singapore, we used the SingHealth Diabetes Registry, a comprehensive clinical registry covering the largest public health care group in the nation and including both inpatient and outpatient data, with approximately 193,000 unique individuals (15). It is linked to other data sources (e.g., financial) via the SingHealth Electronic Health Intelligence System. Patient information is also mapped to outcome data available from the Singapore Cardiac Data Bank (16), a national registry collecting epidemiological and clinical information on CVDs and procedures (17). It is a rich source of national data, with 80% of hospital care delivered in public institutions. The data are used for a number of quality reporting purposes and research.

In Israel, the Maccabi Health Management Organization is the second largest health management organization, and includes complete medical data for over 100,000 patients with T2D (18). This comprehensive registry covers primary and secondary care, and both inpatient and outpatient settings, laboratory tests, and dispensed medications. It has been developed and validated to monitor major chronic diseases, including diabetes and cardiovascular outcomes (18–20).

In Australia, the National Diabetes Services Scheme includes 80% to 90% of all people with diabetes (21). The National Diabetes Services Scheme has been linked to the Pharmaceutical Benefits Scheme database and to the National Death Index to provide information on medication use and vital status, respectively. The linkages were performed by the Australian Institute of Health and Welfare using probabilistic matching techniques, as described elsewhere (22).

In Canada, the Manitoba Centre for Health Policy's Population Health Research Data Repository is a comprehensive collection of administrative, registry, survey, and other data primarily relating to residents of Manitoba. The Drug Program Information Network database is an electronic, online, point-of-sale prescription drug database that connects Manitoba Health and pharmacies in Manitoba (a representative province in Canada) (23). Information about pharmaceutical dispensations, prescriptions identified as potential drug utilization problems, nonadjudicated prescriptions, ancillary programs, and nondrug products is captured in real time for all Manitoba residents, regardless of insurance coverage or final payer. The Drug Program Information Network database can be linked to other administrative health databases, including the Manitoba Health Services Commission database, Vital Statistics databases, and the Canadian Institute for Health Information–Discharge Abstract Database via a unique personal health identification number that exists for each resident of Manitoba. Together, these administrative health databases capture all prescription medications, hospitalizations, and physician claims for more than 98% of residents (24).

PATIENT COHORT. All incident episodes of either an SGLT-2i or oGLD initiation among patients with T2D (defined by the standard diagnosis codes [Online Table 1], except in Australia where this was based on physician or diabetes nurse educator clinical diagnosis of T2D), were identified from each country starting from the date of first prescription or pharmacy dispensation of an SGLT-2i in each respective country (start date ranged from December 2013 in Australia to April 2015 in Israel). Treatment initiation episodes were defined as prescription/filling of a prescription (as initial or add-on therapy) for any SGLT-2i (canagliflozin, dapagliflozin, empagliflozin, in all countries; ipragliflozin in South Korea and Japan; and tofogliflozin and luseogliflozin in Japan) or oGLD (includes oral or injectable drug classes), including fixed-dose combinations, with no issued prescriptions of that medicine class during the preceding year. Additional inclusion criteria were age ≥18 years at the time of the first new user episode, and >1-year data history in the database. Patients with type 1 or gestational diabetes were excluded. Patients were followed from index date (initiation of either SGLT-2i or oGLD) until end of the index treatment (on-treatment analysis only), migration/leaving the practice/database, last date of data collection, outcome date, or censoring date (ranging from June 2016 in Australia to November 2017 in Singapore).

OUTCOMES. The outcomes included ACD, which was available in all countries, as well as HHF, composite of ACD or HHF, myocardial infarction (MI), and

stroke, which were available in all countries except Australia. Outcomes were defined as primary discharge diagnosis codes (Online Table 2). Of note, in Japan and Singapore, for the outcome of ACD, only information on deaths occurring in-hospital were available. However, in-hospital deaths represent the majority of fatal events in those countries (25,26).

STATISTICAL ANALYSIS. The baseline characteristics were analyzed using descriptive statistics. Categorical variables were described by frequencies and percentages, and continuous variables using mean ± SD. For continuous variables such as age, the overall mean across all databases was a summary estimate of country-specific means, weighted according to the number of patients in each respective country. The percentage of individual agents and their respective contributions to the overall SGLT-2i exposure time for SGLT-2i, and the percentage of individual index drug classes for the oGLD group, were summarized by country and overall.

For the primary analysis, we pursued an approach in which all episodes of SGLT-2i and oGLD initiation were eligible to be included. Consequently, each patient might have contributed more than 1 episode of new glucose-lowering medication initiation, for different drug classes (e.g., SGLT-2i as well as various classes of oGLDs) and at different time points. Since this leads to dependence between episodes within a patient, this dependence was accounted for in the statistical analyses using robust variance estimator, which is used for clustered observations (in this case, with more than 1 drug initiation episode being potentially clustered within the same patient), and is a way of statistically adjusting the confidence intervals (CIs) to take this into account (27). Such an approach was considered most optimal because many patients might have had initiation of both SGLT-2i and oGLD during the study period; it maximizes the ability to find a best match for the SGLT-2i and oGLD treatment initiation episodes, while appropriately ascribing the SGLT-2i exposure time to the SGLT-2i group and oGLD exposure time to the oGLD group for each patient.

A nonparsimonious propensity score for initiating an SGLT-2i was developed (separately within each country) and for each individual episode of a new treatment initiation. All available variables in each country that may have affected treatment assignment or outcomes were included in the propensity score (and are listed in Online Table 3; of note, in Australia, baseline comorbidity information was not available). Based on propensity scores, episodes of SGLT-2i initiation were matched 1:1 with episodes of oGLD initiation. The propensity matching was assessed by evaluating standardized differences of patient characteristics post-match. A significant imbalance was considered to be present if a >10% standardized difference was present between the 2 groups after propensity matching.

Incidence rates for all outcomes were assessed by treatment group. Only the first occurrence of each outcome was included, and the crude incidence rate (IR) in each group was calculated as the number of incident events divided by the total number of person-years at risk. Time to first event for the SGLT-2i and oGLD groups was compared using Cox proportional hazards models and presented as HR and 95% CI for each outcome separately by country. If there was an episode of SGLT-2i initiation, and at a later time point there was an episode of oGLD initiation for the same patient (or vice versa), any outcome event occurring after the initiation of oGLD would be accounted for in both treatment groups. To account for within-subject dependence for multiple episodes of treatment initiation within a study period, we used a robust variance estimator in the Cox models, as mentioned in the previous text (27). The primary analysis used an intention-to-treat approach, in which patients were followed from the start of an index treatment until either occurrence of the first outcome event or the censoring date (whichever is earlier), regardless of whether the index treatment was discontinued.

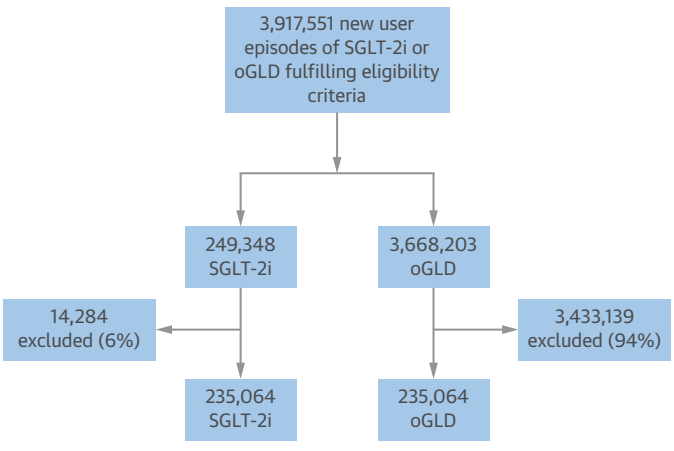
The HRs (95% CIs) for each of the endpoints from each individual country were then pooled together for an overall weighted summary (28), in which random-effects models with inverse variance weighting for each country were implemented (29). Forest plots displaying the country-specific HRs (95% CIs) along with the pooled overall HR (95% CI) were produced. Analyses for all outcomes were then repeated across multiple patient subgroups to examine whether the associations of SGLT-2i and oGLD with cardiovascular outcomes differed based on patient demographics or clinical and treatment characteristics. These pre-specified subgroup analyses were adjusted for multiple covariates, including age; sex; frailty; history of heart failure, MI, and atrial fibrillation; hypertension (if available); obesity/body mass index (if available); duration of diabetes (if available); and use of angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs), β-blockers, Ca+-channel blockers, statins, loop diuretics, and thiazide diuretics.

To test the stability of the findings, we performed several sensitivity analyses. First, the data for the primary analysis were additionally adjusted for multiple covariates on top of the propensity-score

matching (as stated in the previous text). Second, the analyses for each outcome were repeated using an on-treatment approach, in which follow-up was censored at discontinuation of the index treatment. Third, to further evaluate the robustness of the patient selection approach, we performed an additional analysis in which patients were assigned to the SGLT-2i or oGLD group based only on the first episode of new glucose-lowering treatment initiation during the study period (i.e., a patient for whom the first new prescription after the study start date was an SGLT-2i was assigned to the SGLT-2i group, and a patient for whom the first new prescription was oGLD, to the oGLD group). Thus, none of the patients in this sensitivity analysis had any prior oGLD initiation (before initiation of index agent) during the study inclusion period. Of note, the beginning of the study inclusion period was defined as the date on which the first SGLT-2i was introduced in each respective country (and thus differed across the countries). In this "first new-user" analysis, only 1 episode (rather than multiple episodes) of treatment initiation was counted for each patient; specifically, the first episode of glucose-lowering treatment initiation during the study inclusion period. Following patient selection, development of a propensity score for initiating SGLT-2i and 1:1 propensity-matching was performed in the same way as described for the primary analysis. Fourth, because only in-hospital deaths were evaluated in Japan and Singapore, the analyses for ACD were repeated after excluding the data from Japan and Singapore. Finally, because information on baseline comorbidities was not available (and thus not included in the propensity model) in Australia, we repeated the analyses for ACD after excluding the data from Australia.

Due to the deidentified nature of patient records, informed consent was not obtained. Analyses of deidentified data were conducted in accordance with local laws and regulations, and received approvals from respective scientific/ethics/data protection committees. The study was conducted according to the pre-defined study protocol. Country-specific analyses were conducted by independent academic/statistical groups. The meta-analyses were conducted by Statisticon and were validated by independent academic statisticians at St. Luke's Mid America Heart Institute.

FIGURE 1 Flow Chart for All Countries Combined



oGLD = other glucose-lowering drugs; SGLT-2i = sodium-glucose co-transporter-2 inhibitors.

RESULTS

STUDY POPULATION. A total of 3,917,551 new SGLT-2i or oGLD initiation episodes from 2,581,980 individual patients were identified, of which 249,348 were SGLT-2i and 3,668,203 were oGLD (**Figure 1**). Prior to propensity-matching, patients initiated on SGLT-2i were younger and had lower rates of chronic kidney disease, similar rates of cardiovascular comorbidities, and higher rates of microvascular complications. The use of statins, ACEis, ARBs, and β-blockers was greater, and the use of loop diuretics was lower in patients initiated on SGLT-2i versus oGLD. Patients initiated on SGLT-2i versus oGLD were more likely to be on other types of glucose-lowering medications at baseline prior to matching (Online Table 4).

Following propensity matching, a total of 470,128 new SGLT-2i or oGLD initiation episodes from 447,106 individual patients were identified, of which 235,064 were in each treatment group (**Figure 1**). Baseline characteristics were well-balanced between groups post-match, overall and by country (**Table 1**), with standardized differences for all variables ≤3% (**Table 1**, Online Figure 1). Mean age was 57 years, 45% were women, and ~27% had established CVD. Overall, ~65% of patients received statins, ~62% antihypertensive medications, ~54% ACEis/ARBs, and ~74% metformin.

The distribution of specific SGLT-2i compounds within the SGLT-2i group and classes of index medications in the oGLD group are shown in Online Tables 5 and 6, respectively. In terms of total exposure time, dapagliflozin contributed 75% followed by empagliflozin with 9%, with other SGLT-2i ranging from 1% to 8% (**Table 2**).

SGLT-2i AND ACD. For the primary analysis, mean follow-up time was 374 days for the SGLT-2i group and 392 days for the oGLD group. Mean follow-up time by treatment group for individual countries and overall is shown in Online Table 7. Over 493,380 person-years of follow-up, there were 5,216 events, of which 1,930 occurred in the SGLT-2i group (IR 0.80 per 100 person-years) and 3,286 in the oGLD group (IR 1.30 per 100 person-years; event rate by treatment group in Online Table 8). Initiation of SGLT-2i versus oGLD was associated with a lower risk of ACD (ITT unadjusted approach; pooled HR: 0.51; 95% CI: 0.37 to 0.70; $p < 0.001$) (**Figure 2A**). HRs consistently favored SGLT-2i versus oGLD in each country. Similar results were observed in the ITT-adjusted and on-treatment analyses (Online Figure 2A, Online Figure 3A). In the sensitivity analysis using "first new-user design," the magnitude of the association between SGLT-2i initiation and lower risk of ACD was attenuated; nevertheless, point estimates continued to strongly favor SGLT-2i versus oGLD, and remained highly statistically significant (Online Figures 4A and 4F). The results also remained consistent in the sensitivity analyses excluding the data from Japan and Singapore (Online Figure 5) and in a separate sensitivity analysis excluding the data from Australia (Online Figure 6).

SGLT-2i AND HHF. Over 441,357 person-years of follow-up, there were 5,997 events, of which 2,646 occurred in the SGLT-2i group (IR 1.23 per 100 person-years) and 3,351 in the oGLD group (IR 1.48 per 100 person-years; event rate by treatment group in Online Table 8). Initiation of SGLT-2i versus oGLD was associated with a lower risk of HHF (ITT, unadjusted approach; pooled HR: 0.64; 95% CI: 0.50 to 0.82; $p = 0.001$) (**Figure 2B**). HRs consistently favored SGLT-2i versus oGLD in each country. Similar results were observed in the ITT, adjusted and on-treatment analyses (Online Figures 2B and 3B). In the sensitivity analysis using "first new-user design," the magnitude of the association between SGLT-2i initiation and lower risk of HHF was attenuated; nevertheless, point estimates continued to strongly favor SGLT-2i versus oGLD, and remained highly statistically significant (Online Figures 4B and 4F).

SGLT-2i AND COMPOSITE OUTCOME OF HHF OR DEATH. Over 441,357 person-years of follow-up, there were 9,788 events, of which 4,118 occurred in the SGLT-2i group (IR 1.91 per 100 person-years) and 5,670 in the oGLD group (IR 2.51 per 100 person-years; event rate by treatment group in Online Table 8). Initiation of SGLT-2i versus oGLD was associated with a lower risk of HHF or death (ITT, unadjusted approach; pooled HR: 0.60; 95% CI: 0.47 to 0.76; $p < 0.001$) (**Figure 2C**). HRs consistently favored SGLT-2i versus oGLD in each country. Similar results were observed in the ITT, adjusted and on-treatment analyses (Online Figures 2C and 3C). In the sensitivity analysis using "first new-user design," the magnitude of the association between SGLT-2i initiation and lower risk of HHF or death was attenuated; nevertheless, point estimates continued to strongly favor SGLT-2i versus oGLD, and remained highly statistically significant (Online Figures 4C and 4F).

TABLE 1 Baseline Characteristics for All 6 Countries Combined (Post-Match)

	SGLT-2i (n = 235,064)	oGLD (n = 235,064)	Standardized Difference (%)
Age, yrs (SD)	56.7 (12.0)	56.7 (12.9)	0.4
Women	105,843 (45.0)	106,863 (45.5)	0.9
CV history	59,222 (26.8)	56,576 (25.6)	2.7
Myocardial infarction	7,624 (3.4)	7,479 (3.4)	0.4
Unstable angina	12,480 (5.6)	12,235 (5.5)	0.5
Heart failure	15,151 (6.8)	14,741 (6.7)	0.7
Atrial fibrillation	6,026 (2.7)	5,843 (2.6)	0.5
Stroke	20,983 (9.5)	20,153 (9.1)	1.3
PAD	2,446 (1.1)	2,384 (1.1)	0.3
Microvascular disease	116,370 (52.6)	114,630 (51.8)	1.6
CKD	4,211 (1.9)	4,021 (1.8)	0.6
Frailty (yes)*	14,758 (6.7)	14,912 (6.7)	0.3
Metformin	173,783 (73.9)	175,266 (74.6)	1.4
Sulphonylurea	121,209 (51.6)	119,466 (50.8)	1.5
DPP-4 inhibitors	130,674 (55.6)	128,096 (54.5)	2.2
Thiazolidinedione	30,503 (13.0)	29,573 (12.6)	1.2
GLP-1 receptor agonist	6,163 (2.6)	6,022 (2.6)	0.4
Insulin	46,486 (19.8)	44,480 (18.9)	2.2
Antihypertensive therapy	147,166 (62.6)	145,014 (61.7)	1.9
Loop diuretics	16,451 (7.0)	16,100 (6.8)	0.6
Low-ceiling diuretics	17,608 (7.5)	17,173 (7.3)	0.7
ACE inhibitors	20,199 (8.6)	20,062 (8.5)	0.2
ARBs	109,620 (46.6)	109,347 (46.5)	0.2
Statin therapy	153,694 (65.4)	153,466 (65.3)	0.2
Beta-blockers	44,786 (19.1)	43,947 (18.7)	0.9
Aldosterone antagonists	6,719 (2.9)	6,548 (2.8)	0.4
Index year			
2013	741 (1.5)	660 (1.3)	1.4
2014	31,639 (14.0)	32,009 (14.2)	0.5
2015	71,405 (32.3)	71,485 (32.3)	0.1
2016	116,940 (52.8)	115,997 (52.4)	0.9
2017	14,339 (27.0)	14,913 (28.1)	2.4

Values are n (%) unless otherwise stated. *Frailty, hospitalized for >3 consecutive days the last year (31–35).

ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; CKD = chronic kidney disease; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; oGLD = other glucose-lowering drugs; PAD = peripheral artery disease; SD = standard deviation; SGLT-2i = sodium-glucose co-transporter-2 inhibitors.

TABLE 2 Composition of SGLT-2i in Terms of Total Exposure Time

	South Korea	Japan	Singapore	Israel	Canada	Australia	Total
SGLT-2i	168,322	33,890	1,363	9,736	8,032	13,721	235,064
Dapagliflozin	91.3	26.1	68.5	50.9	52.0	80.8	74.7
Empagliflozin	4.3	13.6	17.9	49.1	7.7	0.0	9.0
Canagliflozin	0.0	10.6	13.7	0.0	40.2	19.2	4.4
Ipragliflozin	4.4	29.8	0.0	0.0	0.0	0.0	8.3
Luseogliflozin	0.0	6.3	0.0	0.0	0.0	0.0	1.1
Tofogliflozin	0.0	13.7	0.0	0.0	0.0	0.0	2.5

Values are %.
SGLT-2i = sodium-glucose co-transporter-2 inhibitors.

SGLT-2i AND MI. Over 443,307 person-years of follow-up, there were 2,249 events, of which 973 occurred in the SGLT-2i group (IR 0.45 per 100 person-years) and 1,276 in the oGLD group (IR 0.56 per 100 person-years; event rate by treatment group in Online Table 8). Initiation of SGLT-2i versus oGLD was associated with a lower risk of MI (ITT, unadjusted approach; pooled HR: 0.81; 95% CI: 0.74 to 0.88; $p < 0.001$) (**Figure 2D**). HRs consistently favored SGLT-2i versus oGLD in each country. Similar results were observed in the ITT, adjusted and on-treatment analyses (Online Figures 2D and 3D). In the sensitivity analysis using "first new-user design," the magnitude of the association between SGLT-2i initiation and lower risk of MI was similar to the primary analysis, and point estimates continued to favor SGLT-2i versus oGLD and remained highly statistically significant (Online Figures 4D and 4F).

SGLT-2i AND STROKE. Over 440,346 person-years of follow-up, there were 6,439 events, of which 2,791 occurred in the SGLT-2i group (IR 1.30 per 100 person-years) and 3,648 in the oGLD group (IR 1.62 per 100 person-years; event rate by treatment group in Online Table 8). Initiation of SGLT-2i versus oGLD was associated with a lower risk of stroke (ITT, unadjusted approach; pooled HR: 0.68; 95% CI: 0.55 to 0.84; $p < 0.001$) (**Figure 2E**). HRs consistently favored SGLT-2i versus oGLD in each country. Similar results were observed in the ITT, adjusted and on-treatment analyses (Online Figures 2E and 3E). In the sensitivity analysis using "first new-user design," the magnitude of the association between SGLT-2i initiation and lower risk of stroke was attenuated; nevertheless, point estimates continued to favor SGLT-2i versus oGLD and remained highly statistically significant (Online Figures 4E and 4F).

The summary of the associations between initiation of SGLT-2i versus oGLD across the countries pooled for all outcomes is presented in **Figure 2F**.

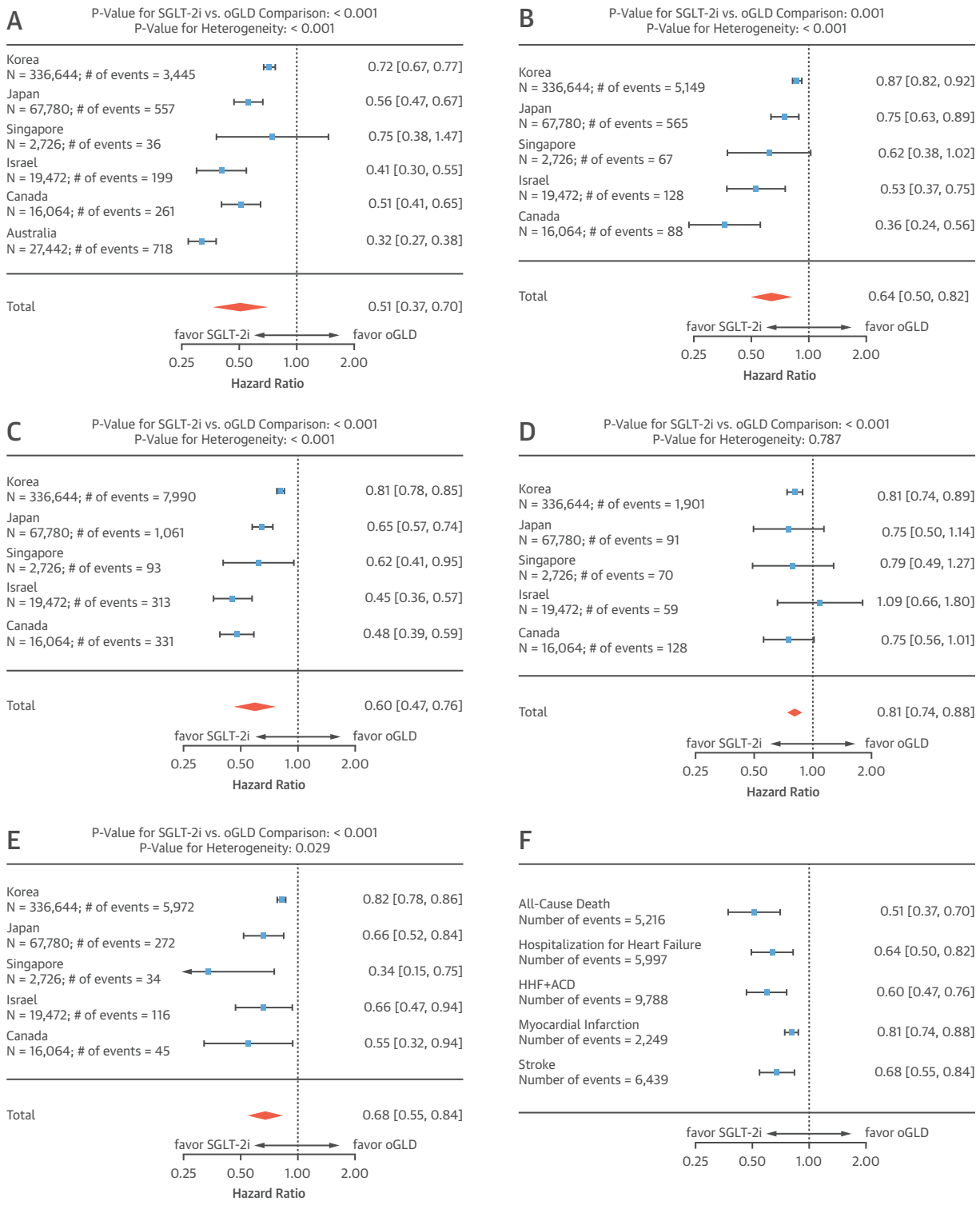
SUBGROUP ANALYSES. In all subgroup analyses, for all outcomes, no meaningful interactions emerged with patients' demographic, clinical, or treatment characteristics, suggesting that none of these variables appeared to be effect modifiers for the association between SGLT-2i and cardiovascular events (Online Figures 7 to 11). Although a small number of interactions were nominally significant, this should be interpreted with caution, as the results were based on very large numbers and were not adjusted for multiple comparisons.

Importantly, in patients with and without established CVD at baseline, SGLT-2i inhibitors were associated with significantly lower risks of death, HHF, death or HHF, MI, and stroke, with no statistically significant interactions across these 2 subgroups for any of the outcomes (**Figure 3**).

DISCUSSION

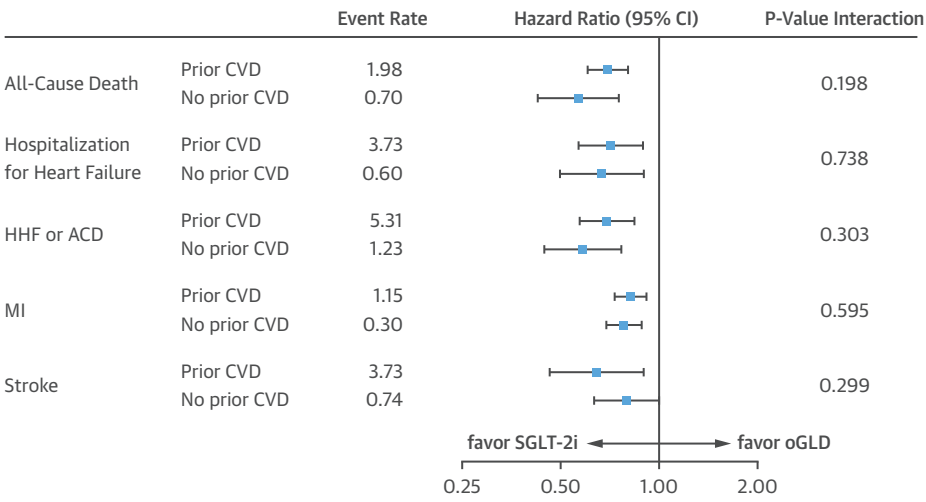
In this international study incorporating well-established data sources from clinical practice across 6 countries and 3 major world regions, with >400,000 patients and 490,000 patient-years of follow-up, we have demonstrated that initiation of SGLT-2i, compared with oGLD, is associated with significantly lower risk of ACD, heart failure events, MI, and stroke (**Central Illustration**). Although there were some differences in point estimates across countries for many outcomes, the directionality of associations was consistent—despite variable patient characteristics, health care settings, practice patterns, and specific SGLT-2i compounds used. These findings were stable in multiple sensitivity analyses. Importantly, the results were also consistent across various patient subgroups, including those with and without established CVD. These findings suggest that the cardiovascular benefits of SGLT-2i may extend both across various patient ethnic and racial backgrounds, as well as across the cardiovascular risk continuum, and likely represent a class effect.

FIGURE 2 **Cardiovascular Outcomes Associated With SGLT-2i Versus Other Glucose-Lowering Drugs**



Pooled hazard ratios (95% CI) for **(A)** all-cause death, **(B)** hospitalization for heart failure, **(C)** composite of all-cause death or hospitalization for heart failure, **(D)** myocardial infarction, **(E)** stroke, and **(F)** all 5 outcomes (intent-to-treat, unadjusted analysis). ACD = all-cause death; HHF = hospitalization for heart failure; other abbreviations as in Figure 1.

FIGURE 3 Outcomes in Subgroups of Patients With and Without Established Cardiovascular Disease at Baseline for All 5 Outcomes (Intent-to-Treat, Adjusted Analysis)

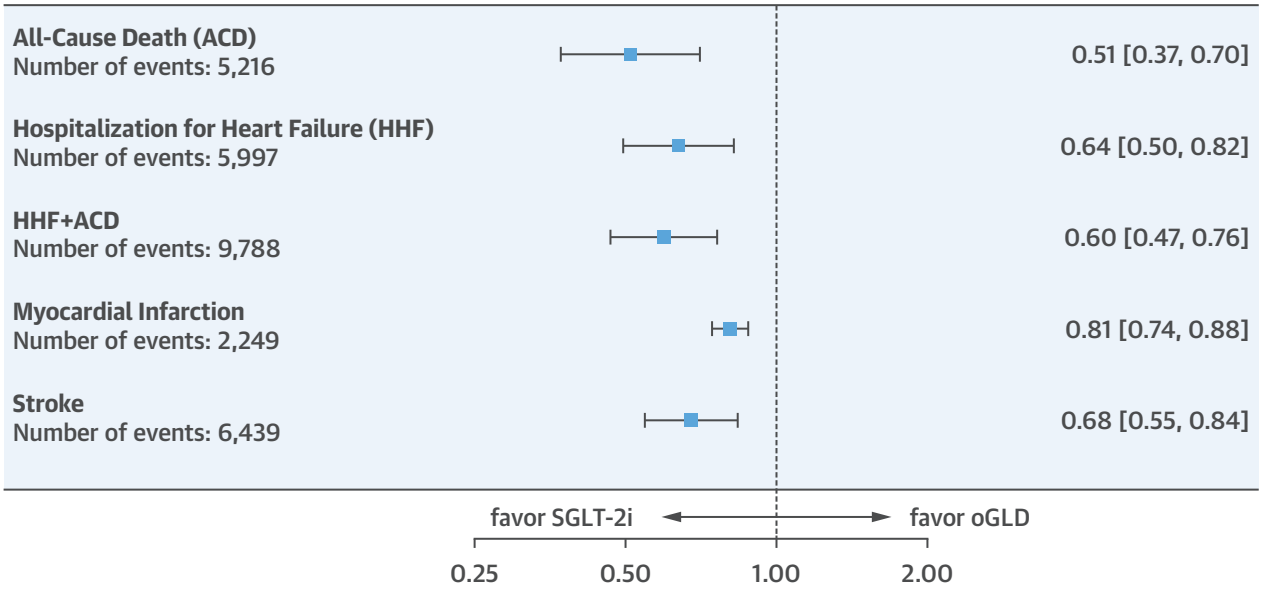


Hazard ratio (95% confidence interval [CI]) for ACD: prior CVD: 0.70 (95% CI: 0.60 to 0.80), no prior CVD: 0.57 (95% CI: 0.43 to 0.75). ACD = all-cause death; CVD = cardiovascular disease; HHF = hospitalization for heart failure; MI = myocardial infarction; other abbreviations as in Figure 2.

Our data should be considered as complementary to the other large cardiovascular outcomes trials of SGLT-2i, including EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) and the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program (6–8). Comparisons of effect sizes between observational studies (such as CVD-REAL 2) and clinical trials (such as EMPA-REG OUTCOME and the CANVAS Program) can be challenging due to the marked differences in the study design and data ascertainment methods, as well as the number and definitions of events and comparators (placebo vs. oGLD). In particular, the comparison of the event rates between the cardiovascular outcomes trials (CVOTs) and CVD-REAL/CVD-REAL 2 is challenging given that in EMPA-REG OUTCOME nearly all participants had established cardiovascular events, and in the CANVAS Program the majority of the participants had established CVD (with 28% of the CANVAS Program population being in the "primary prevention" cohort). In contrast, in CVD-REAL 2, performed in a population that more closely mirrors the utilization of SGLT-2i in clinical practice, SGLT-2i were being used in a broad, low-risk population, where the majority of patients (~74%) did not have established CVD. Moreover, there are substantial differences in the number of events accrued; specifically, despite having a shorter follow-up duration and including lower-risk patients in CVD-REAL 2 (as compared with EMPA-REG OUTCOME or CANVAS), the number of ACDs, for example, was considerably larger in our study (due to a much larger sample size) than in either of the reported CVOTs (5,216 events in CVD-REAL 2 vs. 463 events in EMPA-REG OUTCOME and 681 events in the CANVAS Program).

Within the context of these limitations in comparing the results of various studies, it should be noted that for the outcome of ACD, the overall event rates were comparable in patients with and without established CVD between CVD-REAL 2 and the CVOTs. The observed magnitude of the effect in terms of lower risk of ACD associated with SGLT-2i versus oGLD in the subgroup of patients with established CVD is quite similar between the CVD-REAL 2 study (HR: 0.70; 95% CI: 0.60 to 0.80) and EMPA-REG OUTCOME, and somewhat more pronounced compared with the CANVAS Program, although the directionality of the effects are similar; the results are generally comparable, with overlap in 95% CI. Although the magnitude of the effect in terms of lower risk of ACD associated with SGLT-2i versus oGLD was somewhat more pronounced in the CVD-REAL 2 study in patients without established CVD, as compared with the CANVAS primary prevention cohort, the directionality of the effects was again similar, and the results generally comparable, with overlap in 95% CI.

CENTRAL ILLUSTRATION **Lower Cardiovascular Risk Associated With SGLT-2 Inhibitors**



Kosiborod, M. et al. J Am Coll Cardiol. 2018;71(23):2628–39.

Pooled hazard ratios for the outcomes of all-cause death, hospitalization for heart failure, composite of all-cause death or hospitalization for heart failure, myocardial infarction, and stroke. ACD = all-cause death; HHF = hospitalization for heart failure; oGLD = other glucose-lowering drugs; SGLT-2i = sodium-glucose co-transporter-2 inhibitors.

Furthermore, the associations with SGLT-2i observed in regard to heart failure events in our study were generally similar to those observed in clinical trials, despite a broader patient population with a lower risk profile. For the outcomes of MI, our results were also directionally consistent with those observed in both EMPA-REG and the CANVAS Program, and for the outcome of stroke, our data were directionally consistent with the CANVAS Program (6,7). In this regard, it is important to point out that due to the predominantly Asian patient population in our study, the number of stroke events was high (in fact, stroke was the most common cardiovascular event). Potential limitations of observational data notwithstanding, these findings are clinically important. Specifically, the association between SGLT-2i and lower risk of stroke in our study should offer additional reassurance with regard to the effects of SGLT-2i on atherothrombotic events. It is also important to note that the overall event rates in our study were fairly low, as would be expected in a population where >70% of patients did not have established CVD. However, we were able to collect a substantial number of events for all outcomes due to the large number of patients. Since studying such a low-risk population in a randomized clinical trial may not be feasible, investigations such as CVD-REAL may provide the only available data of SGLT-2i effects for very low-risk patients. Generally, therapies that "work" in higher-risk patients would also be expected to "work" in lower-risk patients, albeit with important differences in absolute risk reductions and numbers needed to treat. Further information on this will come from the currently ongoing DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events-Thrombolysis In Myocardial Infarction 58) clinical trial (NCT01730534), which includes a broad population of patients with T2D (the majority without established CVD).

Furthermore, the findings were directionally consistent across countries, despite differences in type of SGLT-2i used (e.g., 6 SGLT-2i compounds used in Japan), suggesting a class effect. Importantly, these results expand on the data from the original CVD-REAL report by extending the observations across a much more geographically and ethnically diverse patient population, in particular including populations from the Asia Pacific and Middle East regions. If further confirmed by the ongoing

DECLARE-TIMI 58 clinical trial, these findings would collectively have substantial implications for clinical practice, especially as it applies to SGLT-2i use in lower-risk patients.

STUDY LIMITATIONS. The results of our study should be considered in the context of several potential limitations. First, due to the observational nature of the study, and despite robust statistical techniques, including propensity-matching and multiple sensitivity analyses, a possibility of residual, unmeasured confounding cannot be excluded. Specifically, certain patient and physician factors may not be adequately captured even in well-structured and established datasets. However, all countries included in CVD-REAL 2 offer universal health coverage; it is, therefore, unlikely that economic factors had a large role in selection of patients for initiation of SGLT-2i versus oGLD. Second, the issue of potential "immortal time" bias had previously been raised with regard to large pharmacoepidemiological analyses such as ours (30). However, the methods we employed (matching episodes of new glucose-lowering agent initiation, and sensitivity analysis that examined only "first new-users") substantially reduced the possibility of such bias. In this regard, the magnitude of the association between SGLT-2i and lower risk across all cardiovascular outcomes was more pronounced in our primary analysis, and was somewhat attenuated in the most conservative sensitivity analysis (first new-user design)—however, even in this case, all point estimates still strongly favored SGLT-2i versus oGLD. Therefore, the clinical interpretation of the results would be similar, regardless of the methodological approach that was used. Third, we only had available mortality data from inpatient settings in Japan and Singapore; however, most fatal events in these countries occur in the hospital (25,26), and the results were directionally similar in other countries, where capture of the mortality data was more comprehensive. Fourth, we did not have comorbidity information in Australia, and were thus unable to include this information in the propensity score in that country. However, extensive comorbidity information was included in all other countries, with results in all countries being directionally consistent. In addition, the sensitivity analyses of ACD excluding the data from Japan and Singapore, and separately excluding the data from Australia, yielded consistent results. Fifth, we focused on cardiovascular outcomes only, and did not examine safety. Finally, despite a large number of patient-years of follow-up, our average follow-up time was relatively limited, as SGLT-2i use in real-world practice is still relatively recent; longer-term follow-up will be needed to evaluate if effects are sustained over time.

CONCLUSIONS

In a large, international study spanning 6 countries and 3 major world regions, evaluating a broad population of patients with T2D from clinical practice, we found that initiation of SGLT-2i as compared with oGLD was associated with a significantly lower risk of cardiovascular outcomes, including death, heart failure, and atherothrombotic events. Collectively, our results suggest that the cardiovascular benefits of SGLT-2i may be applicable to a considerably broader patient population than previously considered. If further confirmed by the ongoing DECLARE-TIMI 58 trial, which is investigating the efficacy and safety of dapagliflozin in a broad population of patients with T2D, these findings could have substantial implications for clinical practice.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In over 400,000 patients with type 2 diabetes mellitus in the Asia Pacific, the Middle East, and North America, initiation of SGLT-2i versus other glucose-lowering agents was associated with lower rates of death, heart failure, MI, and stroke, irrespective of patient characteristics or presence of established CVD. These observations suggest that the cardiovascular benefits associated with SGLT-2i may extend across a broader range of patients, as defined by ethnic and racial background, and degree of cardiovascular risk.

TRANSLATIONAL OUTLOOK: Further studies are necessary to elucidate the mechanisms by which SGLT-2i may reduce death, heart failure, and possibly atherothrombotic events in patients with diabetes.

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KEY WORDS death, diabetes mellitus, heart failure, observational studies, sodium glucose cotransporter-2 inhibitors, SGLT-2 inhibitor

APPENDIX For a list of the CVD-REAL 2 Investigator and Study Group as well as supplemental tables and figures, please see the online version of this paper.