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Comparative Effectiveness of Individual Sodium-Glucose Cotransporter 2 Inhibitors

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IMPORTANCE Evidence on cardiovascular benefits and safety of sodium-glucose cotransporter 2 (SGLT-2) inhibitors is mainly from placebo-controlled trials. Therefore, the comparative effectiveness and safety of individual SGLT-2 inhibitors remain unknown.

OBJECTIVE To compare the use of canagliflozin or dapagliflozin with empagliflozin for a composite outcome (myocardial infarction [MI] or stroke), heart failure hospitalization, MI, stroke, all-cause death, and safety outcomes, including diabetic ketoacidosis (DKA), lower-limb amputation, bone fracture, severe urinary tract infection (UTI), and genital infection and whether effects differed by dosage or cardiovascular disease (CVD) history.

DESIGN, SETTING, AND PARTICIPANTS This comparative effectiveness study using target trial emulation included adults with type 2 diabetes (T2D) using 3 US claims databases using data from August 2014 through June 2020. The study was conducted from August 2023 to July 2024, with a follow-up period of up to 8 years, and the analysis was completed in July 2024.

EXPOSURES First dispensing of canagliflozin, dapagliflozin, or empagliflozin without any use of SGLT-2 inhibitors during the prior 365 days.

MAIN OUTCOMES AND MEASURES Database-specific models were weighted using propensity score matching-weights to adjust for 129 confounders. Hazard ratios and 95% CIs for outcomes were estimated using weighted Cox proportional hazards models. HRs were pooled across databases using a fixed-effect meta-analysis.

RESULTS : Across the databases, 232 890 patients receiving canagliflozin, 129 881 patients receiving dapagliflozin, and 295 043 patients receiving empagliflozin were identified. Compared with empagliflozin initiators, those receiving canagliflozin or dapagliflozin were less likely to have diabetes-related conditions or a history of CVD at baseline. For MI/stroke risk, both canagliflozin (HR, 0.98; 95% CI, 0.91-1.05) and dapagliflozin (HR, 0.95; 95% CI, 0.89-1.03) were comparable to empagliflozin. For heart failure hospitalization, dapagliflozin initiators had a higher risk (HR, 1.19; 95% CI, 1.02-1.39), particularly at the low dose of 5 mg (HR, 1.30; 95% CI, 1.12-1.50). These findings were consistent across subgroups of CVD history. For safety events, compared with empagliflozin, canagliflozin initiators had a lower risk of genital infections (HR, 0.94; 95% CI, 0.91-0.97) but a higher risk of severe UTIs (HR, 1.13; 95% CI, 1.03-1.24), and dapagliflozin initiators had lower risks of genital infections (HR, 0.92; 95% CI, 0.89-0.95) and DKA (HR, 0.78; 95% CI, 0.68-0.90).

CONCLUSIONS AND RELEVANCE This study found that individual SGLT-2 inhibitors demonstrated comparable cardiovascular effectiveness at clinically effective doses, though low-dose dapagliflozin showed a reduced benefit for heart failure hospitalization compared with empagliflozin.

Supplemental content

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Sodium-glucose cotransporter 2 (SGLT-2) inhibitors, initially approved for managing hyperglycemia in type 2 diabetes (T2D),[1] have demonstrated cardiorenal benefits. These include a reduced risk of heart failure hospitalization in placebo-controlled cardiovascular outcomes trials in patients with T2D and varying risks for cardiovascular disease (CVD).[2-4] SGLT-2 inhibitors are now indicated to prevent cardiorenal events, irrespective of underlying T2D status.[5-12]

Placebo-controlled trials[2-4] of SGLT-2 inhibitors consistently showed benefits for heart failure hospitalization. However, the effect on other cardiovascular outcomes varies. Among patients with T2D and established or at high risk for CVD, canagliflozin and empagliflozin reduced the risk of a composite of major adverse cardiovascular events compared with placebo, whereas dapagliflozin did not. The efficacy against all-cause death and stroke also varied among different SGLT-2 inhibitors. Due to differences in baseline participant characteristics across these trials, direct comparison of trial results is challenging. In addition, the cardiovascular outcomes trial[4] of dapagliflozin did not evaluate the cardiovascular benefits of the initiation dose (5 mg) recommended for the management of hyperglycemia.[13] Moreover, there is limited evidence on the effectiveness of SGLT-2 inhibitors in people without CVD, the majority of individuals diagnosed with T2D,[14] who are underrepresented in trials. Finally, to our knowledge, no studies have compared individual SGLT-2 inhibitors for safety events, despite several safety signals specifically emerging for canagliflozin since 2015.[15,16]

To address these knowledge gaps, we emulated 2 target trials comparing cardiovascular and safety events in adults with T2D newly treated with canagliflozin or dapagliflozin vs empagliflozin in clinical practice.

Key Points

Question Do individual sodium-glucose cotransporter 2 (SGLT-2) inhibitors differ in their risks of cardiovascular and safety outcomes in individuals with type 2 diabetes?

Findings This comparative effectiveness study using a target trial emulation found that, compared with empagliflozin, canagliflozin and dapagliflozin at clinically effective doses demonstrated comparable cardiovascular effectiveness; however, low-dose dapagliflozin showed reduced effectiveness in preventing heart failure hospitalization. The safety profile of individual SGLT-2 inhibitors varied.

Meaning Although all 3 SGLT-2 inhibitors were equally effective in reducing cardiovascular risk, findings of this study supported the use of SGLT-2 inhibitors at doses recommended for cardiovascular benefits in individuals at higher risk of heart failure.

Methods

Data Sources

We used deidentified data derived from 3 large US health insurance claims databases: Optum's deidentified Clinformatics Data Mart Database (Clinformatics), MarketScan Research (MarketScan), and fee-for-service Medicare (Medicare). Clinformatics and MarketScan databases include individuals with employer-sponsored health insurance or a Medicare Advantage insurance plan across the US. The Medicare database includes beneficiaries aged 65 years or older, insured through a US federal health insurance program. In this study, we used data from fee-for-service Medicare beneficiaries with all parts A, B, and D. These databases contain individual-level, longitudinal information on demographics, health plan enrollment status, inpatient and outpatient diagnoses and procedures, and outpatient prescription dispensing. Individuals can be included in more than 1 database, provided they meet the eligibility criteria.

The data analysis was performed between August 2023 and July 2024. The study was approved by the Mass General Brigham institutional review board, and data use agreements were in place. Informed consent was waived because the study used deidentified secondary data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Study Design and Eligibility Criteria

We designed an observational study to emulate 2 target trials comparing individual SGLT-2 inhibitors for cardiovascular and safety events in individuals with T2D who were treated in clinical practice (**Table 1**).

Cohort entry was defined as the date of the first prescription fill for an SGLT-2 inhibitor without prior use of any SGLT-2 inhibitor within the preceding 365 days and without concurrent exposure to multiple SGLT-2 inhibitors. Eligible individuals were adults aged 18 years or older (66 years or older in Medicare) at cohort entry. They had to have continuous health care insurance enrollment with complete medical and pharmacy benefits, and at least 1 diagnosis of T2D (inpatient or outpatient *International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes 250.x0 or 250. x2, or *Tenth Revision, Clinical Modification* [*ICD-10-CM*] code E11.xxx) within 1 year of cohort entry. We excluded individuals with missing information on age, sex, and region, as well as those with a history of type 1, secondary or gestational diabetes, organ transplant, end-stage kidney disease, bariatric surgery, or nursing home admission within 1 year of cohort entry.

Exposure Definition, Study Period, and Follow-Up

We focused on 3 SGLT-2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin), excluding ertugliflozin (approved by the US Food and Drug Administration [FDA] in December 2017) due to limited uptake by the end of the study period. Dosage was determined based on 2 approved strengths of the initial prescription for each drug: canagliflozin, 100 mg or 300 mg, dapagliflozin, 5 mg or 10 mg, and empagliflozin, 10 mg or 25 mg. The initial dispensed dose was considered as the ongoing doses because claims databases do not provide details on titration practice. We used an on-treatment exposure definition, extending the exposure effect window until 45 days after the expiration of the last prescription's supply.[17]

The cohort enrollment period spanned from August 1, 2014, when all 3 SGLT-2i were available in the US, to June 30, 2020, shortly after the May 5, 2020, label expansion of dapagliflozin to individuals with heart failure regardless of T2D.[18] This cutoff was chosen to mitigate the potential confounding by indication due to the expected decreasing use of canagliflozin,

Table 1. Target Trial Design Framework[a]

Component	Target trial	Emulated trial using clinical data
Eligibility	Inclusion criteria • Type 2 diabetes • Aged ≥18 y (>65 y in Medicare)	Inclusion criteria • Type 2 diabetes, identified by administrative claims diagnosis codes • Aged ≥18 y (>65 y in Medicare) • Continuous enrollment in US health insurance for at least 365 d with complete medical and pharmacy coverage, additionally applied to ensure the measurement of eligibility criteria and baseline covariates within the 365 d before cohort entry[b]
	Exclusion criteria • Prior use of any SGLT-2 inhibitors within 365 d of randomization • A history of type 1, gestational, or secondary diabetes • A history of organ transplant • A history of end-stage kidney disease • A history of bariatric surgery • A history of nursing home admission	Exclusion criteria • Prior use of any SGLT-2 inhibitors within 365 d of cohort entry • Following conditions, identified by administrative claims-based algorithms: • A history of type 1, gestational, or secondary diabetes • A history of organ transplant • A history of end-stage kidney disease • A history of bariatric surgery • A history of nursing home admission • Individuals with missing information on age, sex, and region were also excluded
Treatment strategies	Canagliflozin: low dose (100 mg) and high dose (300 mg); dapagliflozin: low dose (5 mg) and high dose (10 mg); empagliflozin: low dose (10 mg) and high dose (25 mg)	Canagliflozin: low dose (100 mg) and high dose (300 mg); dapagliflozin: low dose (5 mg) and high dose (10 mg); empagliflozin: low dose (10 mg) and high dose (25 mg)
Treatment assignment	Randomized nonblinded; Participants were 1:1:1:1 randomly assigned to: • Canagliflozin, low dose (100 mg) • Canagliflozin, high dose (300 mg) • Empagliflozin, low dose (10 mg) • Empagliflozin, high dose (25 mg)	Nonblinded and assumed to be randomized within time block, presence or absence of CVD, and levels of preexposure patient characteristics, including demographics, diabetes-related and other comorbidities, concomitant medications, and measures of health care utilization (eTable 3 in Supplement 1).
Follow-up start	At randomization	At the day after cohort entry
Follow-up end	First of outcome occurrence, death, loss to follow-up, administrative end of follow-up (end of study period), treatment discontinuation	First of outcome occurrence, death (for databases with all-cause death information), loss to follow-up, administrative end of follow-up (end of study period), treatment discontinuation
Outcomes	Primary outcomes • A composite of hospitalization for acute myocardial infarction or ischemic stroke • Heart failure hospitalization	Primary outcomes • A composite of hospitalization for acute myocardial infarction or ischemic stroke • Heart failure hospitalization
	Secondary outcomes • Hospitalization for acute myocardial infarction • Hospitalization for ischemic stroke • All-cause death	Secondary outcomes • Hospitalization for acute myocardial infarction • Hospitalization for ischemic stroke • All-cause death
	Safety outcomes • Diabetic ketoacidosis • Lower-limb amputations • Bone fractures • Severe urinary tract infections • Genital infections • Acute kidney injury • Severe hypoglycemia	Safety outcomes • Diabetic ketoacidosis • Lower-limb amputations • Bone fractures • Severe urinary tract infections • Genital infections • Acute kidney injury • Severe hypoglycemia
Causal contrast	Per-protocol effect (effect of receiving the treatment as stated in the protocol).	Observational analogue of per-protocol effect, ie, on-treatment effect.
Statistical analysis	Estimates of incidence rates, incidence rate differences, and hazard ratios comparing the treatment groups.	Adjustment of baseline confounding with propensity score matching weights followed by calculation of incidence rate differences and hazard ratios via Cox proportional hazards models.

Abbreviations: CVD, cardiovascular disease; SGLT-2, sodium-glucose cotransporter 2.

[a] The same target trial emulation framework applies to the dapagliflozin vs empagliflozin comparison. Outcomes were identified using validated *International Classification of Diseases, Ninth Revision, Clinical Modification* and *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-9/10-CM*) diagnosis and procedural codes (eTable 1 in Supplement 1). All-cause death was ascertained through four sources for Clinformatics: Centers for Medicare & Medicaid Services data, the Social Security Administration Death Master File, hospital discharge status indicating death, and death as a reason for insurance coverage discontinuation. For Medicare, all-cause death was ascertained through the vital status file. No information on all-cause death was available for MarketScan.

[b] Cohort entry was defined as the date of the first prescription fill for an SGLT-2i without prior use of any SGLT-2 inhibitor within the preceding 365 days and without concurrent exposure to multiple SGLT-2 inhibitor.

subsequent to the emergence of safety signals associated with its use, and the evolving channeling of dapagliflozin toward patients at risk of or with heart failure, subsequent to its label expansion in 2020.

Follow-up started the day after cohort entry and continued until the occurrence of a study outcome, death, treatment discontinuation, a switch to another SGLT-2 inhibitor, bariatric surgery, end of continuous health plan enrollment, or end of the study period, whichever occurred first.

Outcome Definitions

Primary outcomes were (1) a composite of hospitalization for acute MI or ischemic stroke (MI/stroke), and (2) heart failure hospitalization. We investigated MI/stroke and heart failure hospitalization as independent outcomes, as SGLT-2 inhibitors may affect them through distinct biological mechanisms. We did not assess major adverse cardiovascular events because the study databases lacked information on cardiovascular death. Secondary outcomes included individual occurrences of MI, stroke, and all-cause death. Safety outcomes comprised diabetic ketoacidosis (DKA), lower-limb amputation, bone fracture, severe urinary tract infection (UTI), genital infection, acute kidney injury, and severe hypoglycemia. Outcomes were identified using validated *ICD-9/10-CM* diagnosis and procedural codes (eTable 1 in Supplement 1). All-cause death was ascertained through 4 sources for

Clinformatics: Centers for Medicare & Medicaid Services data, the Social Security Administration Death Master File,[19] hospital discharge status indicating death, and death as a reason for insurance coverage discontinuation. For Medicare, all-cause death was ascertained through the vital status file.[20] No information on all-cause death was available for MarketScan.

Baseline Patient Characteristics

Potential confounders and predictors of outcomes were identified based on subject knowledge. These included demographics, lifestyle risk factors, markers of diabetes severity, diabetes-related and other comorbidities, use of glucose-lowering and other drugs, measures of health care utilization, proxies of socioeconomic status, and validated comorbidity[21] and frailty[22] indices (eTable 2 in Supplement 1), measured within 1 year before or on cohort entry. Race and ethnicity were included as a potential confounder and were defined as documented in the Medicare and Clinformatics databases. MarketScan does not include information on race. Laboratory test results were available for Clinformatics and MarketScan databases.

Pre Hoc Examination

We assessed temporal trends in SGLT-2 inhibitor use and baseline patient characteristics from August 2014 to December 2022 to inform confounding adjustment in the main analysis (eFigure 1 in Supplement 1).

Statistical Analysis

We evaluated cardiovascular and safety events for 2 drug comparisons, ie, canagliflozin vs empagliflozin and dapagliflozin vs empagliflozin, separately. Direct comparison between canagliflozin and dapagliflozin was not pursued because inference could be drawn indirectly from the other 2 comparisons. For each drug comparison, 4 levels of exposure (low and high doses of both drugs) were used to ensure similar distributions of baseline patient characteristics across individual drugs and different doses.

We controlled for potential confounding using propensity score (PS) matching weights.[23] The pre hoc examination of SGLT-2 inhibitor use trends and initiator characteristics (eFigure 1, eTable 3 in Supplement 1) revealed considerable changes in the use of the 3 SGLT-2 inhibitors over time, with a notable increase in heart failure prevalence specifically for dapagliflozin. To account for potential bias from these prescribing trends and history of CVD, we stratified each database into 4 strata based on the calendar year of cohort entry (T1: August 2014-December 2016; T2: January 2017-June 2020) and the presence or absence of CVD.[24] CVD history was defined as a diagnosis of conditions including MI, stable or unstable angina, ischemic stroke, transient ischemic attack, other ischemic heart diseases, coronary atherosclerosis, coronary procedure, congestive heart failure, and atherosclerotic peripheral vascular disease, identified within 365 days before or on cohort entry. PSs were estimated for each database and stratum of calendar time and CVD history using multinomial logistic regression conditional on all prespecified baseline covariates. Among the 4 levels of exposure, low-dose empagliflozin served as the reference because it was the most frequently used SGLT-2 inhibitor in our databases, both during the overall study period and in recent years.

The study cohort was weighted using matching weights, calculated by dividing the minimum propensity scores by the propensity score for the assigned treatment.[23] Covariate balance was assessed before and after weighting by standardized differences, separately for low and high doses in each drug comparison, eg, low-dose canagliflozin vs low-dose empagliflozin. Values less than 0.1 were considered acceptable for controlling confounding in treatment effect associations.[25,26] Although laboratory test results were not included in the PS models due to missing data, we evaluated their balance after weighting to check for potential residual confounding. We used the missing-indicator method to handle missing race data in Clinformatics, assuming that the missingness was conditionally independent of the outcomes.[27]

Within each database, we calculated unweighted and weighted number of events, incidence rates (IRs), and incidence rate differences (IRDs) per 1000 person-years (PYs) with 95% CIs. Hazard ratios (HRs) were estimated using weighted Cox proportional hazards models with robust variance estimators for low-dose and high-dose comparisons separately, ie, HR (low vs low) and HR (high vs high). We pooled the HRs across 3 databases for each dose comparison using a fixed-effect meta-analysis.[28] For the overall comparison of any dose vs any dose (HR [any vs any]), we pooled HRs from 2 dose comparisons and 3 databases, ie, 6 HRs total, using the same method. We report these pooled HR (any vs any) for all outcomes and the pooled HR (low vs low) and HR (high vs high) for the primary and secondary outcomes.

Secondary and Sensitivity Analyses

We conducted stratified analyses to evaluate differences in the primary and the secondary outcomes by history of CVD and dosage of the initial prescription, using a χ^2 test for homogeneity.[29]

Several sensitivity analyses were performed on the primary outcomes to assess the robustness of our findings (see Supplement 1 for rationales). First, we applied a modified on-treatment exposure definition without censoring on switch to another SGLT-2 inhibitor. Second, we performed an intention-to-treat analysis, by carrying forward the initial exposure for 365 days without considering treatment discontinuation or initiation of a comparator drug.[30] Third, we restricted the analysis to individuals treated with metformin and not receiving insulin at baseline. Last, we conducted stratified analyses for the first (August 2014-December 2016) and second (January 2017-June 2020) study periods.[31]

All analyses were performed using R statistical software (version 4.3.0; R Foundation),[32] with analytic files generated using the Aetion Evidence Platform (version 4.48).[33] No adjustments were applied for multiple testing.[34] We focused on the magnitude and precision of the effect estimates, and the consistency of findings across main and sensitivity analyses, rather than categorizing *P* values as statistically significant and nonsignificant.[35]

Table 2. Selected Baseline Characteristics of Initiators of Individual Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors Postmatching Weights, Pooled Across 3 Databases

Baseline characteristic	No. (%)									
	Canagliflozin vs empagliflozin						Dapagliflozin vs empagliflozin			
	Low dose			High dose			Low dose		High dose		
	Canagliflozin (n = 38 821)	Empagliflozin (n = 38 698)	SMD	Canagliflozin (n = 38 815)	Empagliflozin (n = 38 736)	SMD	Dapagliflozin (n = 44 287)	Empagliflozin (n = 44 175)	SMD	Dapagliflozin (n = 44 433)	Empagliflozin (n = 44 170)	SMD
Demographics[a]												
Age, mean (SD), y	61.21 (9.11)	61.24 (9.09)	0	61.21 (9.10)	61.25 (9.11)	0	60.93 (8.10)	60.96 (8.13)	0	60.92 (8.11)	60.96 (8.13)	0
Female sex	16 849 (43.4)	16 805 (43.4)	0	16 776 (43.2)	16 726 (43.2)	0	19 887 (44.9)	19 932 (45.1)	0	19 892 (44.8)	19 812 (44.9)	0
Male sex	21 972 (56.6)	21 893 (56.6)	0	22 039 (56.8)	22 010 (56.8)	0	24 400 (55.1)	24 243 (54.9)	0	24 541 (55.2)	24 358 (55.1)	0
Life-style risk factors												
Smoking	6218 (16.0)	6181 (16.0)	0	6205 (16.0)	6170 (15.9)	0	6942 (15.7)	6926 (15.7)	0	6939 (15.6)	6908 (15.6)	0
Obese (BMI 30-39.9)	6313 (16.3)	6308 (16.3)	0	6303 (16.2)	6313 (16.3)	0	7497 (16.9)	7457 (16.9)	0	7477 (16.8)	7463 (16.9)	0
Morbid obese (BMI ≥40)	5543 (14.3)	5526 (14.3)	0	5509 (14.2)	5475 (14.1)	0	6339 (14.3)	6347 (14.4)	0	6359 (14.3)	6303 (14.3)	0
Risk scores												
Combined comorbidity score, mean (SD)	1.02 (1.77)	1.02 (1.76)	0	1.02 (1.79)	1.01 (1.75)	0.01	1.04 (1.78)	1.04 (1.77)	0	1.03 (1.80)	1.04 (1.78)	0.01
Frailty score, empirical version, mean (SD)	0.16 (0.04)	0.16 (0.04)	0	0.16 (0.04)	0.16 (0.04)	0	0.16 (0.04)	0.16 (0.05)	0	0.16 (0.05)	0.16 (0.05)	0
Comorbidities												
Diabetic nephropathy	4026 (10.4)	4092 (10.6)	0.01	4041 (10.4)	4055 (10.5)	0	4493 (10.1)	4496 (10.2)	0	4486 (10.1)	4512 (10.2)	0
Diabetic neuropathy	7580 (19.5)	7604 (19.6)	0	7578 (19.5)	7611 (19.6)	0	8315 (18.8)	8347 (18.9)	0	8378 (18.9)	8344 (18.9)	0
Diabetic retinopathy	3339 (8.6)	3377 (8.7)	0	3370 (8.7)	3386 (8.7)	0	3929 (8.9)	3938 (8.9)	0	3944 (8.9)	3951 (8.9)	0
Diabetic foot or lower-limb amputations	773 (2.0)	771 (2.0)	0	766 (2.0)	767 (2.0)	0	952 (2.1)	969 (2.2)	0.01	968 (2.2)	962 (2.2)	0
Hypoglycemia	3600 (9.3)	3606 (9.3)	0	3583 (9.2)	3624 (9.4)	0.01	4114 (9.3)	4071 (9.2)	0	4090 (9.2)	4094 (9.3)	0
Hyperglycemia or HONK	17 932 (46.2)	17 914 (46.3)	0	17 924 (46.2)	17 867 (46.1)	0	20 792 (46.9)	20 795 (47.1)	0	20 869 (47.0)	20 780 (47.0)	0
Acute myocardial infarction	518 (1.3)	514 (1.3)	0	516 (1.3)	521 (1.3)	0	642 (1.4)	646 (1.5)	0.01	646 (1.5)	656 (1.5)	0
Congestive heart failure	2267 (5.8)	2265 (5.9)	0	2259 (5.8)	2241 (5.8)	0	3095 (7.0)	3155 (7.1)	0	3138 (7.1)	3142 (7.1)	0
ASCVD[b]	2690 (6.9)	2691 (7.0)	0	2683 (6.9)	2662 (6.9)	0	3340 (7.5)	3306 (7.5)	0	3290 (7.4)	3310 (7.5)	0
PAD and generalized/unspecified atherosclerosis	2611 (6.7)	2591 (6.7)	0	2570 (6.6)	2595 (6.7)	0	3294 (7.4)	3344 (7.6)	0.01	3345 (7.5)	3334 (7.5)	0
Acute kidney injury	729 (1.9)	748 (1.9)	0	746 (1.9)	747 (1.9)	0	1005 (2.3)	1028 (2.3)	0	1018 (2.3)	1011 (2.3)	0
CKD stage 3-4	1941 (5.0)	1995 (5.2)	0.01	1978 (5.1)	1990 (5.1)	0	2399 (5.4)	2416 (5.5)	0	2399 (5.4)	2423 (5.5)	0
COPD	2929 (7.5)	2885 (7.5)	0	2901 (7.5)	2872 (7.4)	0	3302 (7.5)	3305 (7.5)	0	3300 (7.4)	3266 (7.4)	0
Obstructive sleep apnea	6659 (17.2)	6643 (17.2)	0	6681 (17.2)	6668 (17.2)	0	7600 (17.2)	7575 (17.1)	0	7614 (17.1)	7562 (17.1)	0
MASH/MASLD	2316 (6.0)	2312 (6.0)	0	2314 (6.0)	2291 (5.9)	0	2703 (6.1)	2734 (6.2)	0	2735 (6.2)	2699 (6.1)	0
Osteoarthritis	7686 (19.8)	7660 (19.8)	0	7657 (19.7)	7654 (19.8)	0	8955 (20.2)	8952 (20.3)	0	8950 (20.1)	8937 (20.2)	0
Osteoporosis or fractures	1873 (4.8)	1855 (4.8)	0	1850 (4.8)	1853 (4.8)	0	2336 (5.3)	2330 (5.3)	0	2325 (5.2)	2321 (5.3)	0
Urinary tract infections	3958 (10.2)	3915 (10.1)	0	3921 (10.1)	3921 (10.1)	0	4824 (10.9)	4860 (11.0)	0	4857 (10.9)	4813 (10.9)	0
Genital infections	1493 (3.8)	1472 (3.8)	0	1479 (3.8)	1486 (3.8)	0	1641 (3.7)	1640 (3.7)	0	1653 (3.7)	1615 (3.7)	0
Cancer	2069 (5.3)	2046 (5.3)	0	2050 (5.3)	2040 (5.3)	0	2293 (5.2)	2261 (5.1)	0	2270 (5.1)	2250 (5.1)	0

(continued)

Table 2. Selected Baseline Characteristics of Initiators of Individual Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors Postmatching Weights, Pooled Across 3 Databases (continued)

Baseline characteristic	No. (%)										
	Canagliflozin vs empagliflozin						Dapagliflozin vs empagliflozin				
	Low dose			High dose			Low dose			High dose		
	Canagliflozin (n = 38 821)	Empagliflozin (n = 38 698)	SMD	Canagliflozin (n = 38 815)	Empagliflozin (n = 38 736)	SMD	Dapagliflozin (n = 44 287)	Empagliflozin (n = 44 175)	SMD	Dapagliflozin (n = 44 433)	Empagliflozin (n = 44 170)	SMD
Physician specialties[c]												
Cardiologist visit	1681 (4.3)	1689 (4.4)	0	1687 (4.3)	1686 (4.4)	0	2347 (5.3)	2372 (5.4)	0	2373 (5.3)	2387 (5.4)	0
Endocrinologist visit	4064 (10.5)	4111 (10.6)	0	4126 (10.6)	4158 (10.7)	0	4415 (10.0)	4413 (10.0)	0	4501 (10.1)	4507 (10.2)	0
Internist visit	20 174 (52.0)	20 189 (52.2)	0	20 195 (52.0)	20 153 (52.0)	0	23 060 (52.1)	22 974 (52.0)	0	23 049 (51.9)	22 985 (52.0)	0
Health care utilization												
Any recent hospitalizations[d]	403 (1.0)	403 (1.0)	0	400 (1.0)	406 (1.0)	0	520 (1.2)	519 (1.2)	0	517 (1.2)	508 (1.2)	0
No. of ED visits, mean (SD)	0.41 (1.51)	0.42 (1.59)	0.01	0.41 (1.54)	0.42 (1.52)	0.01	0.53 (1.83)	0.54 (2.11)	0.01	0.53 (1.89)	0.53 (1.89)	0
No. of office visits, mean (SD)	11.01 (9.07)	11.02 (9.04)	0	11.01 (9.07)	10.99 (9.12)	0	11.11 (9.02)	11.16 (9.13)	0.01	11.12 (9.19)	11.11 (9.17)	0
No. of HbA_{1c} test orders, mean (SD)	2.40 (1.25)	2.40 (1.23)	0	2.39 (1.26)	2.39 (1.25)	0	2.40 (1.24)	2.40 (1.22)	0	2.40 (1.24)	2.40 (1.24)	0
Glucose-lowering drug use												
Concomitant initiation or current use												
Metformin	7943 (20.5)	7758 (20.0)	0.01	7829 (20.2)	7910 (20.4)	0	7752 (17.5)	7526 (17.0)	0.01	7688 (17.3)	7734 (17.5)	0.01
Second-generation SU	1464 (3.8)	1497 (3.9)	0.01	1498 (3.9)	1457 (3.8)	0.01	1554 (3.5)	1541 (3.5)	0	1537 (3.5)	1531 (3.5)	0
DPP-4i	2554 (6.6)	2548 (6.6)	0	2538 (6.5)	2420 (6.2)	0.01	2104 (4.8)	2181 (4.9)	0	2241 (5.0)	2064 (4.7)	0.01
GLP-1 RA	993 (2.6)	1038 (2.7)	0.01	1041 (2.7)	1014 (2.6)	0.01	1308 (3.0)	1350 (3.1)	0.01	1351 (3.0)	1321 (3.0)	0
Insulin	1045 (2.7)	1083 (2.8)	0.01	1081 (2.8)	1067 (2.8)	0	1213 (2.7)	1216 (2.8)	0.01	1201 (2.7)	1202 (2.7)	0
Other concomitant medications												
ACE inhibitors and ARBs	28 495 (73.4)	28 424 (73.5)	0	28 472 (73.4)	28 439 (73.4)	0	32 345 (73.0)	32 272 (73.1)	0	32 474 (73.1)	32 295 (73.1)	0
β-Blockers	12 664 (32.6)	12 625 (32.6)	0	12 627 (32.5)	12 617 (32.6)	0	14 724 (33.2)	14 724 (33.3)	0	14 742 (33.2)	14 688 (33.3)	0
Calcium channel blockers	9940 (25.6)	9940 (25.7)	0	9960 (25.7)	9963 (25.7)	0	11 536 (26.0)	11 476 (26.0)	0	11 561 (26.0)	11 517 (26.1)	0
Loop diuretics	3840 (9.9)	3835 (9.9)	0	3830 (9.9)	3809 (9.8)	0	4730 (10.7)	4753 (10.8)	0	4717 (10.6)	4726 (10.7)	0
Thiazide and thiazide-like diuretics	4760 (12.3)	4772 (12.3)	0	4779 (12.3)	4758 (12.3)	0	5546 (12.5)	5516 (12.5)	0	5544 (12.5)	5515 (12.5)	0
Anticoagulants (oral)	2254 (5.8)	2239 (5.8)	0	2257 (5.8)	2256 (5.8)	0	2726 (6.2)	2747 (6.2)	0	2712 (6.1)	2713 (6.1)	0
Antiplatelet agents	3434 (8.8)	3402 (8.8)	0	3400 (8.8)	3403 (8.8)	0	4126 (9.3)	4110 (9.3)	0	4132 (9.3)	4109 (9.3)	0
Statins	27 613 (71.1)	27 550 (71.2)	0	27 609 (71.1)	27 607 (71.3)	0	31 531 (71.2)	31 475 (71.3)	0	31 700 (71.3)	31 499 (71.3)	0
Corticosteroids (oral)	6588 (17.0)	6568 (17.0)	0	6557 (16.9)	6513 (16.8)	0	7906 (17.9)	7919 (17.9)	0	7900 (17.8)	7802 (17.7)	0
Antiosteoporosis agents	943 (2.4)	938 (2.4)	0	932 (2.4)	932 (2.4)	0	1162 (2.6)	1167 (2.6)	0	1160 (2.6)	1161 (2.6)	0
Opioids	12 279 (31.6)	12 184 (31.5)	0	12 228 (31.5)	12 148 (31.4)	0	13 510 (30.5)	13 422 (30.4)	0	13 496 (30.4)	13 366 (30.3)	0
Antidepressants	10 210 (26.3)	10 174 (26.3)	0	10 177 (26.2)	10 173 (26.3)	0	11 688 (26.4)	11 682 (26.4)	0	11 703 (26.3)	11 624 (26.3)	0

Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin 2 receptor blockers; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; ED, emergency department; GLP-1 RA, glucagon-like peptide-1 agonists; HbA_{1c}, hemoglobin A1c; HONK, hyperosmolar hyperglycemic nonketotic syndrome; MASH/MASLD, metabolic dysfunction-associated steatohepatitis/metabolic dysfunction-associated steatotic liver disease; PAD, peripheral artery disease; SMD, standardized mean difference; SU, sulfonylurea.

[a] eTables 5-12 in Supplement 1 include the complete list of baseline patient characteristics before and after matching weights from both pooled and individual databases. Weighted populations were rounded to the nearest whole number.

[b] Defined as history of ischemic stroke, hemorrhagic stroke, atherosclerotic cerebrovascular disease, cerebrovascular procedure, or other cerebrovascular disease.

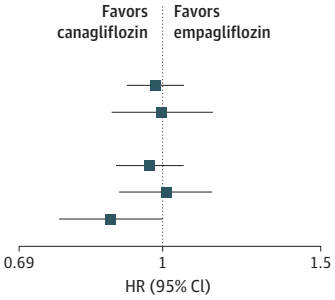
[c] Defined as specialist visits occurring within 14 days prior to cohort entry.

[d] Any hospitalizations within prior 30 days.

Figure 1. Hazard Ratios (HRs) for Cardiovascular Outcomes, Comparing Individual Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors, Weighted and Pooled Across 3 Databases

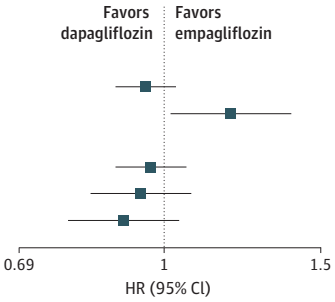
A Canagliflozin vs empagliflozin

Outcome	Events, No. (IR/1000 PY) Canagliflozin	Empagliflozin	HR (95% CI)
Primary			
MI or stroke	700 (9.2)	826 (9.2)	0.98 (0.91-1.05)
Heart failure	199 (1.9)	241 (1.8)	1.00 (0.88-1.14)
Secondary			
MI	455 (6.2)	551 (6.4)	0.96 (0.88-1.05)
Stroke	254 (3.0)	288 (2.7)	1.00 (0.89-1.13)
Mortality	215 (4.8)	300 (5.8)	0.87 (0.76-1.00)



B Dapagliflozin vs empagliflozin

Outcome	Events, No. (IR/1000 PY) Dapagliflozin	Empagliflozin	HR (95% CI)
Primary			
MI or stroke	820 (8.3)	895 (8.5)	0.95 (0.89-1.03)
Heart failure	347 (1.7)	314 (1.6)	1.19 (1.02-1.39)
Secondary			
MI	559 (6.0)	601 (6.1)	0.97 (0.88-1.06)
Stroke	274 (2.2)	305 (2.4)	0.94 (0.83-1.07)
Mortality	203 (5.2)	258 (6.0)	0.90 (0.78-1.04)



IR indicates incidence rate; MI, myocardial infarction; PY, person-years. Mortality is from all causes. No information on all-cause death was available for the MarketScan database. The number of events, incidence rates, and HRs were weighted using matching weights.

Results

Across the 3 databases, we identified 232 890 patients receiving canagliflozin, 129 881 patients receiving dapagliflozin, and 295 043 patients receiving empagliflozin (eTable 4 in Supplement 1). Selected postweighting baseline patient characteristics are presented in **Table 2**, with complete preweighted and postweighted characteristics in eTables 5 and 6 in Supplement 1. Before weighting, dapagliflozin initiators were younger compared with empagliflozin initiators (61 vs 64 years for the low-dose and 60 vs 62 years for the high-dose comparison), and both canagliflozin and dapagliflozin initiators were less likely to have diabetes-related conditions, CVD, or CKD, with comparable health care utilization. After weighting, baseline characteristics were well balanced across comparisons, with standardized differences all below 0.1, including laboratory test results. These patterns were consistent across all databases (eTables 7-12 in Supplement 1).

The mean (SD) follow-up times on treatment were (13.3) 11.7 months for canagliflozin, 11.6 (13.1) months for dapagliflozin, and 11.8 (12.1) months for empagliflozin. Most individuals were censored due to treatment discontinuation (63%), disenrollment (18%), or the end of the study period (11%; eTable 13 in Supplement 1).

After weighting (**Figure 1**; eTable 14 in Supplement 1 for IRDs and unweighted effect estimates), canagliflozin initiators showed similar risks for MI/stroke (HR [any vs any] = 0.98; 95% CI, 0.91-1.05) and heart failure hospitalization (HR [any vs any] = 1.00; 95% CI, 0.88-1.14) compared with empagliflozin. Dapagliflozin initiators showed a similar risk for MI/stroke (HR [any vs any] = 0.95; 95% CI, 0.89-1.03) but a higher risk for heart failure hospitalization (HR [any vs any] = 1.19; 95% CI, 1.02-1.39). Weighted Kaplan-Meier curves are in eFigure 2 in Supplement 1. No significant differences were noted in the effectiveness of individual SGLT-2 inhibitors on secondary outcomes, except that canagliflozin was associated with a numerically lower risk of all-cause death compared with empagliflozin (HR [any vs any] = 0.87; 95% CI, 0.76-1.00). These results were consistent across all 3 databases (eTable 14 in Supplement 1) and subgroups of CVD history (eFigure 3 in Supplement 1).

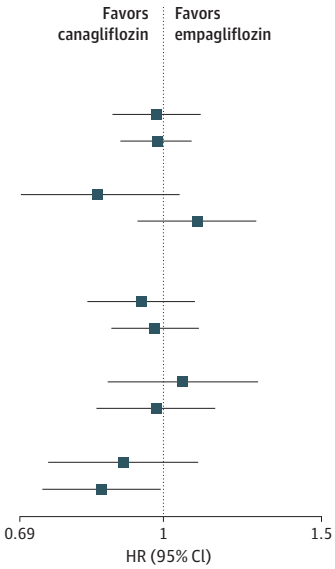
Dose-dependent analyses (**Figure 2**; eTables 15 and 16 in Supplement 1) showed that low-dose dapagliflozin was associated with a higher risk of heart failure hospitalization (HR [low vs low] = 1.30; 95% CI, 1.12-1.50), whereas high-dose dapagliflozin was not (HR [high vs high] = 1.06; 95% CI, 0.88-1.27). The results for the primary outcomes remained consistent across sensitivity analyses (eFigure 4 in Supplement 1), except in the intention-to-treat analysis where canagliflozin showed a higher risk of heart failure hospitalization compared with empagliflozin (HR [any vs any] = 1.15; 95% CI, 1.04-1.28).

For safety outcomes, compared with empagliflozin at any dose, initiators of both canagliflozin (57.2 events/1000 PY) and dapagliflozin (54.9 events/1000 PY) at any dose had a modestly lower risk for genital infections (HR_{cana} = 0.94; 95% CI, 0.91-0.97; HR_{dapa} = 0.92; 95% CI, 0.89-0.95). Canagliflozin was associated with a higher risk for severe UTIs (HR_{cana} = 1.13; 95% CI, 1.03-1.24), whereas dapagliflozin was associated with a lower risk for DKA (HR_{dapa} = 0.78; 95% CI, 0.68-0.90; **Figure 3**; eTable 14 in Supplement 1).

Figure 2. Dose-Dependent Effects on Cardiovascular Outcomes and Mortality, Comparing Individual Sodium-Glucose Cotransporter 2 Inhibitors, Weighted and Pooled Across 3 Databases

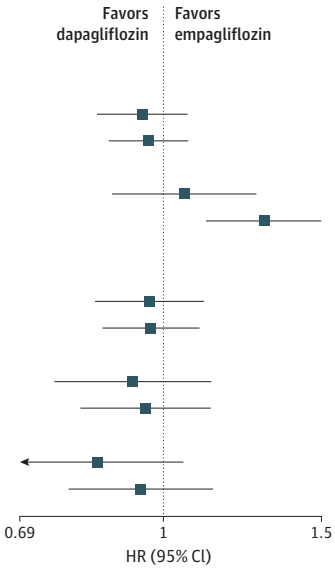
A Canagliflozin vs empagliflozin

Outcome	Events, No. (IR/1000 PY) Canagliflozin	Empagliflozin	HR (95% CI)
Primary			
MI/stroke			
High	359 (9.4)	416 (9.3)	0.98 (0.88-1.10)
Low	340 (9.1)	410 (9.1)	0.98 (0.89-1.07)
Heart failure			
High	95 (1.7)	129 (1.9)	0.84 (0.68-1.04)
Low	104 (2.1)	112 (1. 7)	1.09 (0.94-1.27)
Secondary			
MI/stroke			
High	232 (6.2)	280 (6.5)	0.94 (0.82-1.08)
Low	223 (6.2)	271 (6.3)	0.98 (0.87-1.09)
Stroke			
High	132 (3.2)	142 (2.7)	1.05 (0.86-1.27)
Low	122 (2.9)	146 (2.7)	0.98 (0.84-1.14)
Mortality			
High	119 (5.4)	159 (6.2)	0.90 (0.74-1.09)
Low	97 (4.4)	142 (5.4)	0.85 (0. 73-0.99)



B Dapagliflozin vs empagliflozin

Outcome	Events, No. (IR/1000 PY) Dapagliflozin	Empagliflozin	HR (95% CI)
Primary			
MI/stroke			
High	422 (8.7)	464 (8.8)	0.95 (0.84-1.06)
Low	397 (8.0)	431 (8.2)	0.96 (0.87-1.06)
Heart failure			
High	163 (1.5)	165 (1.6)	1.06 (0.88-1.27)
Low	184 (1.8)	149 (1.7)	1.30 (1.12-1.50)
Secondary			
MI/stroke			
High	294 (6.5)	315 (6.3)	0.96 (0.84-1.11)
Low	265 (5.6)	286 (5.8)	0.97 (0.86-1.10)
Stroke			
High	136 (2.0)	155 (2.4)	0.92 (0.76-1.13)
Low	138 (2.4)	150 (2.4)	0.96 (0.81-1.13)
Mortality			
High	102 (5.4)	137 (6.3)	0.84 (0.67-1.05)
Low	101 (5.2)	121 (5.7)	0.94 (0.78-1.14)



HR indicates hazard ratio; IR, incidence rate; MI, myocardial infarction; PY, person-years. Doses were determined based on the strength of the active ingredients on the initial filled prescription. Two doses have been approved for each SGLT-2 inhibitor: canagliflozin (100 mg and 300 mg), dapagliflozin (5 mg and 10 mg), and empagliflozin (10 mg and 25 mg). *P* values for homogeneity tests were all >.05.

Discussion

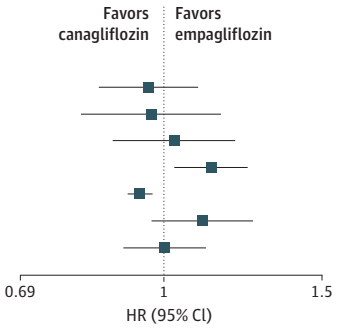
In this large multidatabase cohort study of adults with T2D, we observed comparable benefits in reducing the risk of MI/stroke across individual SGLT-2 inhibitors and the risk of heart failure hospitalization between canagliflozin and empagliflozin. However, low-dose dapagliflozin (5 mg) showed a higher risk of heart failure hospitalization compared with empagliflozin. Although there were differences in the risk of specific safety outcomes—such as a lower risk of genital infection for canagliflozin and dapagliflozin initiators compared with empagliflozin, a higher risk of severe UTI with canagliflozin, and a lower risk of DKA with dapagliflozin—the overall risk for safety events, including bone fracture and lower-limb amputation, was similar across the 3 SGLT-2 inhibitors.[36,37]

Across all placebo-controlled cardiovascular outcomes trials in individuals with T2D, SGLT-2 inhibitors reduced the risk of MI, showed variable efficacy on stroke, and lowered the risk of heart failure hospitalization, indicating a class effect.[2-4] Notably, dapagliflozin was only investigated at a high dose of 10 mg in the cardiovascular outcomes trial,[4] whereas both low and high doses were evaluated for canagliflozin and empagliflozin, with similar HRs for cardiovascular outcomes across doses.[2,3] Therefore,

Figure 3. Hazard Ratios (HRs) for Safety Outcomes, Comparing Individual Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors, Weighted and Pooled Across 3 Databases

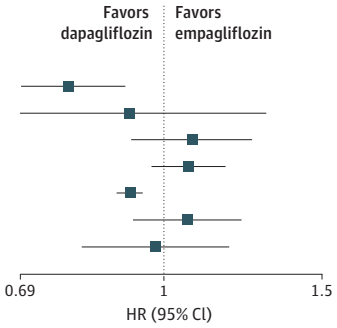
A Canagliflozin vs empagliflozin

Outcome	Events, No. (IR/1000 PY) Canagliflozin	Empagliflozin	HR (95% CI)
Safety			
DKA	225 (3.2)	266 (3.2)	0.96 (0.85-1.09)
LLA	157 (2.2)	187 (2.2)	0.97 (0.81-1.16)
Bone fractures	258 (3.3)	306 (3.4)	1.03 (0.88-1.20)
Severe UTI	405 (3.7)	410 (3.4)	1.13 (1.03-1.24)
Genital infections	3818 (57.2)	4469 (57.2)	0.94 (0.91-0.97)
AKI	211 (1.9)	217 (2.0)	1.10 (0.97-1.26)
Severe hypoglycemia	299 (2.8)	346 (2.8)	1.00 (0.90-1.11)



B Dapagliflozin vs empagliflozin

Outcome	Events, No. (IR/1000 PY) Dapagliflozin	Empagliflozin	HR (95% CI)
Safety			
DKA	222 (2.6)	293 (3.3)	0. 78 (0.68-0.90)
LLA	186 (1.7)	207 (2.2)	0.92 (0.65-1.30)
Bone fractures	330 (3.0)	330 (3.1)	1.07 (0.92-1.25)
Severe UTI	513 (3.0)	507 (3.1)	1.06 (0.97-1.17)
Genital infections	4517 (54.9)	5088 (60.0)	0.92 (0.89-0.95)
AKI	239 (1.5)	241 (1.6)	1.06 (0.92-1.22)
Severe hypoglycemia	436 (2.2)	444 (2.8)	0.98 (0.81-1.18)



AKI indicates acute kidney injury; DKA, diabetic ketoacidosis; IR, incidence rate; LLA, lower-limb amputation; PY, person-years; UTI, urinary tract infection. Mortality is from all causes. No information on all-cause death was available for the MarketScan database. The number of events, incidence rates, and HRs were weighted using matching weights.

low doses of canagliflozin and empagliflozin are recommended for glycemic control and reducing CVD risk, whereas 5 mg of dapagliflozin is recommended for glycemic control and 10 mg is recommended for CVD risk reduction.[38] Our study showed that, compared with empagliflozin initiators, both canagliflozin and dapagliflozin initiators were associated with similar risks for MI/stroke, but dapagliflozin initiators, especially at the low 5-mg dose, were associated with an increased risk of heart failure hospitalization. These findings reinforce the use of dapagliflozin, 10 mg, or other SGLT-2 inhibitors when the therapeutic goal is to reduce the risk of heart failure.

Genital infections are a known adverse event of SGLT-2 inhibitors. Our results showed a small decrease in risk for canagliflozin (6%) and dapagliflozin (8%) compared with empagliflozin, although the frequent occurrence of these infections warrants attention. This might be attributed to the high specificity of empagliflozin[39] for the SGLT-2 receptor, leading to greater urinary glucose excretion and a more conducive environment for microbial growth. Our results align with a previous observational study[40] comparing canagliflozin and empagliflozin, despite its small study population and imprecise estimates. In addition, we observed a higher risk of severe UTIs with canagliflozin and a lower risk of DKA with dapagliflozin compared with empagliflozin. Although the association between SGLT-2 inhibitors and the risk of UTIs is debated, our results suggest possible separate mechanisms.[41] The broader inhibition profile of canagliflozin, including SGLT-1 receptors, might affect the gut microbiome or other physiological processes, affecting the risk of UTIs.[42,43] The lower affinity of dapagliflozin for SGLT-2 receptors may explain its lower risk of DKA compared with empagliflozin.[44,45] Despite these differences, the overall safety profile was similar across the 3 SGLT-2 inhibitors.

A meta-analysis of randomized clinical trials on SGLT-2 inhibitors showed consistent results with ours regarding all-cause mortality, heart failure hospitalization, and safety outcomes.[46] Any discrepancies might arise from variations in study populations, evaluated dosages, or outcome definitions, as seen in differing findings between this meta-analysis and another examining a distinct set of SGLT-2 inhibitor trials.[47] A US observational study[48] comparing dapagliflozin to empagliflozin in patients with heart failure produced results consistent with our findings on all-cause mortality. However, although our study showed a higher risk of heart failure hospitalization with dapagliflozin compared with empagliflozin, 2 non-US observational studies using Danish registries[49] and Japanese claims data[50] found no differences in this risk. These discrepancies might be attributable to differences in prescribed dosages between the US and other countries, outcome definitions, and analytical approaches, such as intention-to-treat vs on-treatment analyses.

Limitations

This study has limitations. First, there is potential for residual confounding by unmeasured variables, such as duration and severity of diabetes and CVD. To mitigate this, we ensured comparability across SGLT-2 inhibitors by (1) limiting the analysis to a single drug class to reduce confounding by indication bias[51]; (2) exclud-

ing recent databased on our pre hoc examination; and (3) stratifying by baseline CVD and the calendar time of cohort entry, without using year of enrollment as an independent variable to prevent the inclusion of potential instruments in the propensity score models. Second, the study databases lacked information on cardiovascular death, and all-cause death data was complete only for Medicare. Third, the intention-to-treat analysis showed a higher risk of heart failure hospitalization for canagliflozin compared to empagliflozin. This finding is unlikely due to switch to another SGLT-2 inhibitor because the findings from a sensitivity analysis with a modified on-treatment exposure definition were consistent with the primary analysis; additional studies would clarify this. Fourth, we used a fixed effect meta-analysis to pool estimates across 3 databases, assuming the true effect size is the same across all studies, which may not hold due to the differences in underlying populations. Last, misclassification of dose information is possible because claims databases do not accurately capture dose changes, such as titration or pill splitting. For example, individuals splitting pills based on physician recommendations or to reduce financial burden could result in high-dose groups taking lower doses, potentially diluting effect estimates, particularly for dapagliflozin. In addition, up-titration may be more common among dapagliflozin users because the low dose is recommended only for glycemic control, not CVD risk reduction, unlike empagliflozin.

Conclusions

In this comparative effectiveness study of adults with T2D, individual SGLT-2 inhibitors showed comparable cardiovascular effectiveness at doses recommended for cardiovascular benefits. The initiation of low-dose dapagliflozin was associated with attenuated benefits in reducing the risk of heart failure hospitalization compared with empagliflozin. Despite similar overall risks for safety events, the varying safety profiles of the 3 SGLT-2 inhibitors necessitate careful consideration of their specific risks and benefits. Notably, the frequent occurrence of genital infections warrants attention, particularly in susceptible populations like older adults.

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Concept and design: Shin, Patorno.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Shin.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Shin, DiCesare, Alix, Glynn.
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Supervision: Everett, Patorno.

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