CARDIOVASCULAR OUTCOMES AND RISKS AFTER INITIATION OF A SODIUM GLUCOSE COTRANSPORTER 2 INHIBITOR: RESULTS FROM THE EASEL POPULATION-BASED COHORT STUDY

BACKGROUND: Clinical trials have shown cardiovascular benefits and potential risks from sodium glucose cotransporter 2 inhibitors (SGLT2i). Trials may have limited ability to address individual end points or safety concerns.

METHODS: We performed a population-based cohort study among patients with type 2 diabetes mellitus with established cardiovascular disease newly initiated on antihyperglycemic agents within the US Department of Defense Military Health System between April 1, 2013, and December 31, 2016. Incidence rates, hazard ratios (HRs), and 95% confidence intervals (CIs) for time to first composite end point of all-cause mortality and hospitalization for heart failure event, major adverse cardiovascular events (defined as all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke), and individual end points were evaluated using conditional Cox models comparing new SGLT2i users with other antihyperglycemic agents. The exploratory safety end point was below-knee lower extremity amputation. Intent-to-treat and on-treatment analyses were performed.

RESULTS: After propensity matching, 25,258 patients were followed for a median of 1.6 years. Compared with non-SGLT2i, initiation of SGLT2i was associated with a lower rate of all-cause mortality and hospitalization for heart failure (1.73 versus 3.01 events per 100 person-years; HR, 0.57; 95% CI, 0.50–0.65) and major adverse cardiovascular events (2.31 versus 3.45 events per 100 person-years; HR, 0.67; 95% CI, 0.60–0.75). SGLT2i initiation was also associated with an ≈2-fold higher risk of below-knee lower extremity amputation (0.17 versus 0.09 events per 100 person-years; HR, 1.99; 95% CI, 1.12–3.51). Because of the disproportionate canagliflozin exposure in the database, the majority of amputations were observed on canagliflozin. Results were consistent in the on-treatment analysis.

CONCLUSIONS: In this high-risk cohort, initiation of SGLT2i was associated with lower risk of all-cause mortality, hospitalization for heart failure, and major adverse cardiovascular events and higher risk of below-knee lower extremity amputation. Findings underscore the potential benefit and risks to be aware of when initiating SGLT2i. It remains unclear whether the below-knee lower extremity amputation risk extends across the class of medication, because the study was not powered to make comparisons among individual treatments.

Key Words: diabetes mellitus   diabetic therapy   heart failure   outcomes research   safety

Sources of Funding, see page 1459

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Clinical Perspective

What Is New?

- In this population-based cohort study of patients with type 2 diabetes mellitus and cardiovascular disease initiated on sodium glucose cotransporter 2 inhibitors (SGLT2i) or non-SGLT2i, initiation of SGLT2i was associated with a lower rate of all-cause mortality, hospitalization for heart failure, and major adverse cardiovascular events.
- SGLT2i initiation was also associated with an ≈2-fold higher risk of below-knee lower extremity amputation, similar to the risk observed with canagliflozin in the CANVAS Program (Canagliflozin Cardiovascular Assessment Study).

What Are the Clinical Implications?

- This study corroborated the results of clinical trials and other real-world studies in showing the comparative effectiveness of SGLT2i on cardiovascular outcomes for patients with type 2 diabetes mellitus and established cardiovascular disease.
- Although the study was not powered to address whether the risk of below-knee lower extremity amputation extends across the SGLT2i class, physicians and patients should monitor for potential risk factors for below-knee lower extremity amputation when initiating SGLT2i in high-risk patients.

Sodium glucose cotransporter 2 inhibitors (SGLT2i) are a new class of antihyperglycemic agents (AHAs) that function to concomitantly inhibit the reabsorption of glucose and sodium in the renal proximal convoluted tubule. These drugs result in glycosuria and natriuresis, which translates into an ≈0.7 to 1% reduction in circulating glycosemoglobin A1c, ≈5/2 mmHg blood pressure reduction, ≈2 to 3 kg loss in body weight, ≈30 to 40% reduction in albuminuria via a reduction in intraglomerular pressure, and other favorable metabolic effects. A number of cardiovascular (CV) outcome trials in patients with and without type 2 diabetes mellitus (T2DM) are ongoing to study the CV benefits and safety of these drugs compared with standard care.3–5 Two trials in patients with T2DM and high CV risk have recently reported reductions in major adverse cardiovascular events (MACE), specifically the composite of CV mortality, nonfatal myocardial infarction (MI), and nonfatal stroke, and particular benefit in reducing hospitalization for heart failure (HHF).6–8 It has been hypothesized that the benefit for HHF, which has been observed out of proportion to that of MACE, may in part be a result of plasma volume contraction and weight loss.3,10 Similarly, a lower risk of all-cause mortality (ACM) and HHF has been reported with the use of these medications in routine clinical practice. However, the use of an SGLT2i may result in potential harm, with reports of increased risk for genitourinary tract infections, diabetic ketoacidosis, acute kidney injury, fractures, and atraumatic below-knee lower extremity amputation (BKA).8,9,12–17 The latter complication is a less common but serious clinical manifestation of progressive disease with substantial associated morbidity, yet reliable data on this outcome are sparse.19 Given that trials may enroll a select patient population and be of limited size and duration to address individual efficacy end points and safety concerns,19 EASEL (Evidence for Cardiovascular Outcomes With Sodium Glucose Cotransporter 2 Inhibitors in the Real World), a population-based cohort study, was undertaken to evaluate whether new initiation of an SGLT2i is associated with a lower risk of CV events and increased risk of BKA compared with other AHAs in patients with T2DM and established CV disease (CVD).

METHODS

This was a retrospective, new user cohort study using the Department of Defense (DoD) Military Health System (MHS) data, which integrates all medical, clinical, pharmacy, and administrative data for every eligible MHS beneficiary across the United States.20 The DoD is composed of active or retired service members and their dependents, with ≈10 million patients actively receiving care. In accordance with transparency and openness promotion guidelines, the analytic methods and study materials will be stored at Health ResearchTx and made available to other researchers for purposes of reproducing the results or replicating the procedure.21 Given the patient intimacy of the data, study data may be made available on a case-by-case basis.

New Users Cohort Creation

The study included 2 comparator cohorts: new users of SGLT2i or new users of non-SGLT2i AHA on top of standard care therapy. The SGLT2i cohort included canagliflozin, empagliflozin, and dapagliflozin; the non-SGLT2i AHA cohort included dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, thiazolidinediones, sulfonylureas, insulin, and other AHAs (acarbose, bromocriptine, miglitol, nateglinide, and repaglinide). New users were defined as patients whose first exposure (index date) to 1 of the nonmetformin AHAs during the study period from April 1, 2013, to December 31, 2016, occurred ≥365 days after the start of observation in the database, with no prior exposure to any medication within the same AHA medication class in the prior 365 days. If a patient was a new user of both SGLT2i and non-SGLT2i AHAs, the patient would be classified as an SGLT2i new user, and the non-SGLT2i AHA would be considered a baseline or concomitant therapy. Eligible patients with T2DM were required to have ≥1 year of observation before the index date, with established CVD (including coronary artery disease, heart failure, cerebrovascular disease, and peripheral artery disease) (Table I in the online-only Data Supplement), and be ≥18 years of age. Patients with type 1 diabetes mellitus, secondary diabetes mellitus, and missing sex data before the index date were excluded from this study. Patients were followed from the index date until the first occurrence of any of...
the following: (1) outcome of interest, (2) death, (3) disenrollment from the DoD, or (4) last observation in the database.

To reduce confounding because of imbalance in study covariates, exposure propensity score (EPS) matching was used. A regularized logistic regression model was used to estimate the predicted probability of patients receiving SGLT2i therapy, and SGLT2i new users were EPS-matched to new users of non-SGLT2i AHAs in a 1:1 ratio. In creating a parsimonious model for EPS estimation, a systematic approach to variable selection was utilized. Approximately 1000 variables were considered for model inclusion, including patient demographics and characteristics, duration of diabetes mellitus, baseline comorbidities and medication use, comprehensive diagnoses and procedures mapped to respective Clinical Classifications Software categories, a calculated Charlson Comorbidity Index score, and various healthcare resource utilization measures. Baseline measures were assessed over 2 time periods, the full preindex period spanning back to April 1, 2008, and a 1-year preindex period, with the ability for all variables across both periods to be included in the final model.

The regularized logistic regression model was fit using a cyclic coordinate descending approach with L1 penalty (ie, least absolute shrinkage and selection operator [LASSO]) to avoid overfitting of the model. This process permits a large number of predictors within the model. Cross-validation was utilized to estimate optimal regularization hyperparameters. The number of unique baseline AHA medications was included in the EPS model to factor in differences in background AHA therapy. By design, the new use of other non-SGLT2i AHAs defined the control new-user exposure group and necessitated specific prescriptions of these drugs before the index date to not be included in the EPS estimation to avoid multicollinearity. Once the EPS scores were estimated, conventional greedy algorithms with nearest neighbor matching was used to create 2 balanced cohorts and minimize the absolute difference in EPS between the treatment cohorts. Maximum matching caliper of the EPS (on the logit scale) was 20% of the SD of the logit of the EPS. The final model used to estimate the EPS incorporated >850 variables.

**Statistical Analyses**

For descriptive statistics, frequencies and proportions were presented for categorical variables, whereas means and SDs were presented for continuous variables. Incidence rates were estimated using event counts and exposure follow-up time. Kaplan-Meier plots were generated to characterize the contour of risk over time for each outcome. Conditional Cox proportional hazards regression based on time to first event was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), comparing the treatment effect of SGLT2i against non-SGLT2i AHAs (reference group) in relation to each study end point. Outcomes data were analyzed both by intent-to-treat (ITT) and on-treatment, the latter of which included the outcomes of interest observed while exposed to the index therapy plus 7 days, to consider immediate biological effects. Because the results were generally consistent between both approaches, for the purpose of this reporting, we primarily focused on the ITT results, unless otherwise specified. Although the formal statistical analyses focused on the comparison of SGLT2i new users versus non-SGLT2i new users, additional descriptive data (eg, event rates) were summarized based on individual SGLT2i drugs (ie, canagliflozin, empagliflozin, and dapagliflozin) and non-SGLT2i therapeutic classes (ie, DPP-4, GLP-1, thiazolidinediones, sulfonyureas, insulin, and other AHAs).

As part of sensitivity analyses for efficacy end points, patients receiving insulin, sulfonyureas, and thiazolidinediones were removed (individually and collectively) from the non-SGLT2i cohort along with their SGLT2i matching pairs to further evaluate treatment effect, allowing the remaining matched cohort to be compared using the same conditional Cox proportional hazards model and determination of whether a specific AHA class contributed disproportionately to the results, as done previously. The study protocol also specified several subgroup analyses, including sex, age, recent insulin use (past 12 months), recent GLP-1 agonist use, history of heart failure, recent HHF (past 12 months), CVD type, renal disease by Charlson Comorbidity Index score, and
chronic renal disease. A post hoc sensitivity analysis excluding patients with dementia, a surrogate for frailty, was also explored. The study protocol was reviewed and approved by the DoD Institutional Review Board, and all analyses were performed by a research organization (Health ResearchTx, LLC) using SAS V9.4 (SAS Institute Inc).

RESULTS

Study Population

Overall, 111,576 new users of an AHA with T2DM and established CVD were identified during the study period, among which 13,757 were new users of an SGLT2i and 97,819 of a non-SGLT2i AHA. After EPS matching, 25,258 patients were ultimately matched and selected for comparison. Specifically, 12,629 (91.8% retention of the total 13,757 eligible) new users of an SGLT2i were matched 1:1 with 12,629 new users of a non-SGLT2i AHA. Among the SGLT2i therapies, 7,333 (58.1%) patients initiated canagliflozin, 3,341 (26.4%) empagliflozin, and 1,955 (15.5%) dapagliflozin.

Key clinical characteristics among new users of an AHA are presented in the Table before and after EPS matching. Before matching, compared with new users of non-SGLT2i AHAs, patients newly prescribed an SGLT2i therapy at baseline were younger, were more frequently white, had a longer duration of T2DM, and less frequently had a history of atrial fibrillation, heart failure, cardiomyopathy, MI, ischemic stroke, peripheral artery disease, chronic kidney disease, malignancy, and dementia. In addition, new users of an SGLT2i presented with higher rates of background treatment with all of the other AHAs and combination therapies with metformin.

After EPS matching, all baseline patient characteristics included in the EPS model were well balanced (standardized differences <0.1 for all baseline characteristics after propensity matching) (Figure I in the online-only Data Supplement). Among the matched cohort, the mean age was 65.8 (SD, 9.4) years, 44.1% were female, the mean duration of T2DM was 5.6 (SD, 2.0) years, and the mean duration of CVD was 4.4 (SD, 2.2) years. Approximately 14.1% of patients had a history of atrial fibrillation, 22.8% had a history of congestive heart failure, 10.7% had a history of ischemic stroke, and 16.6% had a history of MI. At baseline, among the matched cohort overall, 80.7% of patients were treated with metformin and 19.7% with insulin.

The median follow-up time was 1.6 years (interquartile range, 0.79–2.4) for the ITT cohort (1.7 and 1.5 years with SGLT2i and non-SGLT2i AHAs, respectively) and 0.67 years (interquartile range, 0.25–1.5) for the on-treatment cohort (0.72 and 0.63 years with SGLT2i and non-SGLT2i AHAs, respectively).

CV Outcomes

The primary composite outcome of ACM and HHF and secondary end points of MACE and individual components of these outcomes for patients in the ITT EPS-matched cohort are shown in Figure 1. The incidence rate of the primary outcome was 1.73 versus 3.01 per 100 person-years among new users of SGLT2i and non-SGLT2i AHAs, respectively (HR, 0.57; 95% CI, 0.50–0.65; P<0.0001) (Figure 1). Similarly, compared with non-SGLT2i AHAs, initiation of an SGLT2i was associated with a lower rate of ACM (1.29 versus 2.26 events per 100 person-years; HR, 0.57; 95% CI, 0.49–0.66; P<0.0001) and HHF (0.51 versus 0.90 events per 100 person-years; HR, 0.57; 95% CI, 0.45–0.73; P<0.0001). The treatment benefit associated with SGLT2i started early and persisted over the study period (Figure 2).

Within the ITT EPS-matched cohort, the rate of MACE (the composite of ACM, nonfatal MI, and nonfatal stroke) was also lower in patients newly initiated on an SGLT2i compared with a non-SGLT2i (2.31 versus 3.45 per 100 person-years; HR, 0.67; 95% CI, 0.60–0.75; P<0.0001). The rate of the individual end points of nonfatal MI (0.58 versus 0.71 per 100 person-years; HR, 0.81; 95% CI, 0.64–1.03; P=0.09) and nonfatal stroke (0.51 versus 0.60 per 100 person-years; HR, 0.85; 95% CI, 0.66–1.10; P=0.22) were not significantly different. When ACM, nonfatal heart failure, and atherothrombotic end points were considered in a single composite outcome, the rate of the composite of MACE and HHF was significantly lower among patients newly initiated on an SGLT2i compared with a non-SGLT2i (2.72 versus 4.11 per 100 person-years; HR, 0.66; 95% CI, 0.60–0.74; P<0.0001).

Overall, the association of treatment effects with the primary and secondary outcomes was qualitatively similar in the on-treatment analysis, albeit more amplified (Figure II in the online-only Data Supplement). Analysis of the primary outcome in the prespecified subgroups showed consistent results after initiation of an SGLT2i compared with another class of AHA across subgroups based on sex, age, insulin or GLP-1 agonist use within the prior 12 months, history of heart failure, CVD type, and renal disease (Figure III in the online-only Data Supplement). Results of sensitivity analyses that removed patients treated with insulin, sulfonylureas, and thiazolidinediones at baseline were consistent with the overall study results (Figure IV in the online-only Data Supplement). Results of the sensitivity analyses that removed patients with dementia at baseline were also consistent with the overall study results (HR, 0.58; 95% CI, 0.51–0.66).

Safety Outcome

As previously stated, patients with a prior BKA (n=6 in the SGLT2i cohort and n=3 in the non-SGLT2i co-
| Characteristic                                      | Before Matching | After Matching |
|----------------------------------------------------|-----------------|----------------|
|                                                    | Non-SGLT2i (n=97189) | SGLT2i (n=13757) | Non-SGLT2i (n=12629) | SGLT2i (n=12629) |
| Age, y†                                            | 69.6 (10.6)     | 65.5 (8.9)      | 65.9 (9.8)          | 65.8 (8.9)        |
| Sex, %                                             |                 |                |                   |                  |
| Male                                               | 56.2            | 56.4            | 55.1               | 56.7              |
| Female                                             | 43.8            | 43.6            | 44.9               | 43.3              |
| Race, %                                            |                 |                |                   |                  |
| White                                              | 26.8            | 36.9            | 33.6               | 36.7              |
| Black                                              | 6.0             | 5.6             | 6.3                | 5.6               |
| Asian or Pacific Islander                          | 1.7             | 1.7             | 1.7                | 1.7               |
| Other†                                             | 65.4            | 55.9            | 58.4               | 56.1              |
| T2DM duration, y†                                  | 5.0 (2.2)       | 5.7 (1.9)       | 5.7 (2.0)          | 5.6 (2.0)         |
| CV disease duration, y†                             | 4.3 (2.2)       | 4.4 (2.2)       | 4.4 (2.3)          | 4.4 (2.2)         |
| Charlson Comorbidity Index score                   | 6.0 (3.1)       | 5.0 (2.4)       | 5.0 (2.6)          | 5.0 (2.4)         |
| Comorbidities of interest, %                       |                 |                |                   |                  |
| Atrial fibrillation                                | 15.1            | 8.9             | 9.4                | 9.1               |
| AIDS/HIV                                           | 0.1             | 0.0             | 0.1                | 0.0               |
| Cardiomyopathy                                     | 6.5             | 4.0             | 4.2                | 4.1               |
| Cerebrovascular disease                            | 20.1            | 14.3            | 14.9               | 14.5              |
| Congestive heart failure                           | 19.2            | 10.2            | 10.6               | 10.6              |
| Chronic obstructive pulmonary disease              | 28.1            | 21.5            | 22.8               | 21.6              |
| Dementia                                           | 3.8             | 0.9             | 1.6                | 0.9               |
| Diabetes mellitus with chronic complication§       | 29.8            | 32.4            | 31.0               | 32.2              |
| Hemiplegia/paraplegia                             | 1.7             | 0.5             | 0.7                | 0.5               |
| Hepatic disease                                    | 7.3             | 8.2             | 7.7                | 8.0               |
| Hyperlipidemia                                     | 70.6            | 76.4            | 75.6               | 75.8              |
| Hypertension                                       | 86.0            | 86.6            | 85.8               | 86.5              |
| Ischemic stroke                                    | 6.9             | 3.5             | 4.0                | 3.6               |
| Malignancy                                         | 13.1            | 9.0             | 9.7                | 9.3               |
| Mild liver disease                                 | 7.2             | 8.1             | 7.7                | 8.0               |
| Moderate/severe liver disease                      | 0.7             | 0.4             | 0.5                | 0.4               |
| MI                                                 | 8.9             | 5.8             | 5.7                | 5.8               |
| Peptic ulcer disease                               | 1.5             | 1.0             | 1.0                | 1.0               |
| Peripheral vascular disease                        | 20.4            | 16.0            | 15.4               | 16.3              |
| Renal disease                                      | 21.9            | 10.7            | 12.3               | 11.1              |
| Rheumatic disease                                  | 3.7             | 2.7             | 2.9                | 2.6               |
| Metastatic solid tumor                             | 1.8             | 0.6             | 0.7                | 0.6               |
| Transient ischemic attack                          | 4.0             | 3.1             | 3.0                | 3.1               |
| Venous thromboembolism                             | 4.3             | 2.4             | 2.7                | 2.5               |
| Medications of interest, %                         |                 |                |                   |                  |
| ACE                                                | 40.4            | 41.8            | 41.3               | 41.6              |
| ARB                                                | 31.1            | 37.2            | 36.4               | 37.1              |
| ACE and/or ARB                                     | 67.9            | 75.1            | 74.2               | 74.7              |
| Antiarrhythmics                                    | 3.5             | 2.2             | 2.4                | 2.2               |
| β-Blockers                                         | 51.9            | 49.2            | 49.5               | 49.5              |
| Calcium channel blockers                           | 6.6             | 5.7             | 5.9                | 5.7               |

(Continued)
A total of 53 new BKA events were observed in the ITT cohort and 26 events in the on-treatment cohort. The rate of BKA was ≈2-fold higher in the ITT cohort, with 35 versus 18 events in patients after initiation of SGLT2i versus non-SGLT2i AHAs, respectively (0.17 versus 0.09 per 100 person-years; HR, 1.99; 95% CI, 1.12–3.51; \( P = 0.018 \)) (Figure 1). The risk was qualitatively similar in the on-treatment cohort, with 17 versus 9 events among new users of SGLT2i and non-SGLT2i AHAs, respectively (0.14 versus 0.07 per 100 person-years; HR, 2.01; 95% CI, 0.89–4.53; \( P = 0.0001 \)).

### Table. Continued

| Characteristic | Before Matching | After Matching |
|----------------|-----------------|---------------|
|                | Non-SGLT2i (n=97,819) | SGLT2i (n=13,757) |
|                | SGLT2i (n=12,629) | SGLT2i (n=12,629) |
| Digoxin        | 4.1 (2.8)       | 2.5 (2.8)     |
| Nonloop diuretics | 19.8 (18.7)         | 18.9 (18.8)       |
| Loop diuretics  | 23.3 (16.5)     | 17.0 (16.9)    |
| Statins or ezetimibe | 73.7 (82.4)         | 81.5 (82.0)       |
| NSAIDs         | 43.9 (46.6)     | 46.5 (46.5)    |
| Anticoagulants | 13.0 (9.4)      | 9.3 (9.6)      |
| Number of AHA medications* | 1.4 (1.2)       | 2.6 (1.4)     |
| **AHA therapies** |            |               |
| Insulin        | 6.7 (25.1)      | 16.6 (22.9)   |
| Metformin (any) | 62.8 (79.5)       | 83.0 (78.5)     |
| Sulfonylurea   | 24.1 (47.0)     | 44.4 (45.1)    |
| Thiolumidinediones | 6.0 (12.4)         | 12.6 (11.5)      |
| GLP-1 receptor agonists | 2.6 (22.0)         | 8.1 (19.5)       |
| DPP-4 inhibitors | 15.5 (59.2)         | 30.1 (58.4)      |
| Metformin plus 1+ AHAs | 28.9 (71.8)         | 59.2 (70.1)      |
| Other          | 1.2 (3.1)       | 2.8 (2.8)      |

Propensity matched using an EPS. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AHA, antihyperglycemic agent; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; EPS, exposure propensity score; GLP-1, glucagon-like peptide-1; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; SGLT2i, sodium glucose cotransporter 2 inhibitor; and T2DM, type 2 diabetes mellitus.

*Between-cohort standardized difference <0.1 for all covariates listed (Figure I in the online-only Data Supplement).
†Data are mean (SD).
‡Includes American Indian or Alaskan Native, other, and unknown/missing.
§As defined by CCI score.
\#Individual AHA therapies were not included in EPS matching and are presented for descriptive purposes. Therefore, standardized difference may not meet the <0.1 threshold after matching.

Figure 1. Risk of cardiovascular and mortality outcomes for patients in the propensity-matched ITT cohort by treatment status.

Propensity matched using an exposure propensity score. ACM indicates all-cause mortality; BKA, below-knee lower extremity amputation; CI, confidence interval; HHF, hospitalization for heart failure; ITT, intent to treat; MACE, major adverse cardiovascular event; and SGLT2i, sodium glucose cotransporter 2 inhibitor. *Patients with prior BKA (n=9) and their respective matches were removed from analyses.
P=0.09) (Figure II in the online-only Data Supplement). Results were consistent among all prespecified subgroups; however, the risk of BKA was not statistically significant given the limited sample size within any individual subgroup of interest (Figure V in the online-only Data Supplement).

Results According to Individual Treatment

Descriptive event rates for the primary and secondary outcomes and BKA events by the individual SGLT2 therapies and other AHA treatment classes in the ITT
DISCUSSION

EASEL was a population-based study of patients enrolled in 1 of the largest public health insurance claims programs in the United States, designed to examine the clinical effectiveness and safety of SGLT2i in patients with T2DM and established CVD in routine clinical practice. Compared with patients initiated on other AHAs, we observed a 33 to 43% lower rate of ACM, HHF, and MACE among patients with T2DM with established CVD who were newly treated with an SGLT2i. We also found a modestly lower risk of the individual CV end points of nonfatal MI and nonfatal stroke, findings that did not reach statistical significance. The lower risk of HHF with SGLT2i therapy seen in this study was consistent with findings reported in the EMPA-REG OUTCOME and CANVAS Program trials and the CVD-REAL study of empagliflozin, canagliflozin, and SGLT2i therapy, in general, respectively.6,8,11 EASEL is also the first population-based study to demonstrate a lower risk of MACE in patients with T2DM with established CVD initiated on SGLT2i therapy, which is qualitatively similar to what was seen in the EMPA-REG OUTCOME and CANVAS Program trials.6,8

This is also the first observational study to our knowledge to identify a significantly higher risk of BKA associated with SGLT2i initiation in routine clinical practice, although cases were infrequent. The higher risk of BKA associated with SGLT2i therapy in this study of high-risk patients with established CVD was similar to that reported in the CANVAS Program of canagliflozin, although the rate of BKA was lower in both the SGLT2i and non-SGLT2i cohorts.8 A higher incidence of BKA was not seen among the infrequent events reported in the EMPA-REG OUTCOME trial of empagliflozin, but there are limited data on BKA events within this class of medication overall.13,27 In the current study, most exposure to SGLT2i therapies, and thus most BKA events, occurred in new users of canagliflozin. However, because of the limited number of prescriptions of other SGLT2i drugs to date, formal statistical comparisons are currently not precise for evaluating the effectiveness or risk between individual SGLT2i therapies, even with appropriate adjustments for confounding.

and on-treatment cohorts are presented in Tables III–V in the online-only Data Supplement. After exclusion of patients with a prior BKA, the crude incidence rates for BKA among the individual SGLT2i therapies were 0.19, 0.09, and 0.12 per 100 person-years for canagliflozin, dapagliflozin, and empagliflozin, respectively, in the ITT cohort and 0.15, 0.10, and 0.16 per 100 person-years, respectively, in the on-treatment cohort (Table V in the online-only Data Supplement). The respective crude incidence rates of each subcohort’s paired patients initiating a non-SGLT2i AHA are also provided.

The approach of the ITT and on-treatment analyses resulted in fairly consistent results, although with an attenuation of the effect sizes for CV benefit within the ITT analysis. This observation, in part, may be a result of the 0.96-year median difference between exposure time (on-treatment) and overall follow-up time (ITT) because of premature discontinuation of SGLT2i therapy. Further, it supports the notion that, because these agents’ cardiometabolic and hemodynamic effects are time-dependent, expected CV benefits are sensitive to prompt attenuation on discontinuation. Similar to the results from the current study, an early CV benefit with SGLT2 inhibition was suggested by the early separation of the Kaplan-Meier curves for HHF and CV death seen with empagliflozin in the EMPA-REG OUTCOME trial and with canagliflozin in the CANVAS Program.6,8 Despite general consistency in the findings across the studies, residual bias associated with observational studies cannot be completely ruled out. Our baseline data showed that patients initiated on SGLT2i therapy tended to have a higher frequency of use of other AHAs at baseline as compared with the non-SGLT2i cohort, which may suggest difficulties with glycemic control and a more advanced stage of T2DM for patients initiated on SGLT2i therapy. Nevertheless, results for the primary effectiveness and safety outcomes were consistent across a number of prespecified subgroups, including patients with and without recent use of insulin or GLP-1 agonists, as well as among females and males, older and younger patients, and patients with or without established heart failure, peripheral artery disease, or renal disease.

The crude data for the CV benefits appeared to be consistent across the individual drugs within the class of currently approved SGLT2i. There were, however, few amputation events among empagliflozin, dapagliflozin, and canagliflozin alone to derive individual risk estimates for formal statistical comparison. Although there was a numeric imbalance in amputations observed among patients treated with canagliflozin compared with their propensity-matched cohort treated with non-SGLT2i AHAs, the propensity model was developed based on available clinical characteristics across the entire study cohort. Thus, although each patient may have a matched pair based on the propensity score, at the individual treatment level, the matched cohorts may not be equally balanced on all major confounding factors, particularly in relation to BKA. Moreover, the extremely small numbers of events observed in the matched pairs of individual treatment-level patients preclude any meaningful statistical evaluation or clinical conclusion. Longer follow-up and exposure time as well as additional sources of data will likely provide more precise estimates for intra- and interdrug comparisons. In addition, further research in this field
is urgently needed to clarify the mechanism of action and identify which patients are most susceptible to amputation risk.

This study has a number of strengths. First, with a contemporary and diverse cohort of >111,000 newly treated patients with T2DM and established CVD, we were able to establish comparable treatment cohorts and had robust statistical precision to investigate efficacy end points (a combined total of >700 on-treatment and 1400 ITT events) and explore safety hypotheses. Moreover, the database used for this study is generally representative of many demographic and clinical characteristics of the US population. Furthermore, we utilized a strategy of establishing a base cohort from which to distinguish new AHA initiation from prevalent users, reduce the risk of left truncation, and optimize the detection of key baseline characteristics, including duration of diabetes mellitus. This approach also improved the efficiency and optimization of the propensity score-matching algorithm. Finally, the DoD MHS has extensive drug coverage and more longitudinal data than most comparable health insurance claims data available to investigate this new class of AHAs in routine practice.

There are, however, limitations to our study, which underscore that our results should be interpreted with caution and require independent replication. First, the MHS database lacked sufficient determinants of the cause of death, and we were therefore limited to assessing ACM rather than CV death. However, >50% of the cause of death in this high-risk cohort with T2DM was expected to be from CV causes.\(^6,8,28\) Second, given the dynamic nature of T2DM pharmacotherapy, our analysis may be susceptible to unmeasured confounding and residual bias. To reduce this risk, differences in baseline clinical and demographic characteristics were adjusted for by the use of a highly efficient propensity score-matching algorithm. Residual imbalance in specific classes of baseline AHA medication use, however, although minimal, was seen and expected after EPS matching. This is because the new use of specific classes of non-SGLT2i AHAs defined the control group’s new-user exposure status (as opposed to a clinical trial that compared new use of SGLT2i therapy versus new use of placebo). This study design reduces selection bias but necessitated specific prescriptions of these drugs before the index date to not be included in the EPS estimation to avoid multicollinearity. Instead, to account for potential differences in background AHA therapy, the number of unique baseline AHA medications was factored into the EPS model, and this was well balanced after matching. Moreover, except for SGLT2i therapy, other AHA therapies (either as baseline or new use) were comparable between the 2 treatment groups. Therefore, any residual imbalance at baseline in classes of baseline AHA medication use would not be expected to significantly impact our results. Nevertheless, our estimates of CV risk reduction appear to be exaggerated compared with the findings reported in large outcome trials despite similar rates of drug discontinuation.\(^6,8\) This observed difference underscores that caution is due for any direct comparison of the results between clinical trials and observational studies. Unmeasured confounding cannot be totally ruled out, and therefore additional research might be warranted for further evaluation. Third, we relied on pharmaceutical dispensing records to infer medication use. However, misclassification of the exposure would suggest that any results we observed were biased toward the null.

In conclusion, the role of pharmacoepidemiologic studies goes beyond an ability to validate whether clinical trial results are reproducible in a generalizable patient population. Observational studies are also critical in filling a knowledge gap to inform about the real-world effectiveness of new therapies and potentially serious adverse events not readily detected in clinical trials. Our findings in a cohort with T2DM and established CVD support those recently seen in 2 large CV outcome trials—that initiation of SGLT2i is associated with a lower risk of mortality, HHF, and MACE. However, the use of SGLT2i was also associated with an ≈2-fold higher risk of BKA, a serious adverse event seen in a similar magnitude within the CANVAS Program of canagliflozin. Although these observations require replication in other settings, our findings underscore the potential CV benefit and a rare but serious risk that physicians and patients should monitor for when initiating this class of medication.

**ARTICLE INFORMATION**

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Cardiovascular Outcomes and Risks After Initiation of a Sodium Glucose Cotransporter 2 Inhibitor: Results From the EASEL Population-Based Cohort Study (Evidence for Cardiovascular Outcomes With Sodium Glucose Cotransporter 2 Inhibitors in the Real World)

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### Supplemental Table I. Inclusion and Exclusion Criteria Diagnosis Codes

| Concept code | Concept name                                                                 | Vocabulary |
|--------------|------------------------------------------------------------------------------|------------|
| **Inclusion Criteria** |                                                                              |            |
| **Type 2 diabetes** |                                                                              |            |
| 250.x0       | Diabetes, type II or unspecified type, not stated as uncontrolled              | ICD-9      |
| 250.x2       | Diabetes, type II or unspecified type, uncontrolled                           | ICD-9      |
| E11.x        | Type 2 diabetes mellitus                                                      | ICD-10     |
| **Cerebrovascular disease** |                                                                              |            |
| 430          | Subarachnoid hemorrhage                                                       | ICD-9      |
| 431          | Intracerebral hemorrhage                                                      | ICD-9      |
| 432.x        | Other and unspecified intracranial hemorrhage                                | ICD-9      |
| 433.x        | Occlusion and stenosis of precerebral arteries                               | ICD-9      |
| 434.x        | Occlusion of cerebral arteries                                                | ICD-9      |
| 435.x        | Transient cerebral ischemia                                                   | ICD-9      |
| 436          | Acute, but ill-defined, cerebrovascular disease                              | ICD-9      |
| 437.x        | Other and ill-defined cerebrovascular disease                                | ICD-9      |
| 438.x        | Late effects of cerebrovascular disease                                       | ICD-9      |
| I60.x-I69.x  | Cerebrovascular diseases                                                      | ICD-10     |
| G45.x        | Transient cerebral ischemic attacks and related syndromes                     | ICD-10     |
| **Coronary artery disease** |                                                                              |            |
| 410.x-414.x  | Ischemic heart disease                                                        | ICD-9      |
| I20.x        | Angia pectoris                                                                | ICD-10     |
| I21.x        | ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction      | ICD-10     |
| I22.x        | Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction | ICD-10     |
| I23.x        | Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28 day period) | ICD-10     |
| I24.0        | Acute coronary thrombosis not resulting in myocardial infarction              | ICD-10     |
| I25.x        | Chronic ischemic heart disease                                                | ICD-10     |
Heart failure

428.x Heart failure ICD-9
150.x Heart failure ICD-10

Peripheral artery disease

440.2x Atherosclerosis of native arteries of the extremities ICD-9
443.81 Peripheral angiopathy in diseases classified elsewhere ICD-9
443.89 Other specified peripheral vascular diseases ICD-9
443.9 Peripheral vascular disease, unspecified ICD-9
447.1 Stricture of artery ICD-9
447.2 Rupture of artery ICD-9
447.6 Arteritis, unspecified ICD-9
447.8 Other specified disorders of arteries and arterioles ICD-9
447.9 Unspecified disorders of arteries and arterioles ICD-9
459.2 Compression of vein ICD-9
459.3x Chronic venous hypertension (idiopathic) ICD-9
459.8x Other specified diseases of the circulatory system ICD-9
459.9 Unspecified circulatory system disorder ICD-9
170.2x Atherosclerosis of native arteries of the extremities ICD-10
173.89 Other specified peripheral vascular diseases ICD-10
173.9 Peripheral vascular disease, unspecified ICD-10
177.1 Stricture of artery ICD-10
177.2 Rupture of artery ICD-10
177.6 Arteritis, unspecified ICD-10
177.8 Other specified disorders of arteries and arterioles ICD-10
177.9 Disorders of arteries and arterioles, unspecified ICD-10
179.8 Other disorders of arteries, arterioles and capillaries in diseases classified elsewhere ICD-10
187.1 Compression of vein ICD-10
187.3x Chronic venous hypertension (idiopathic) ICD-10
199.8 Other disorder of the circulatory system ICD-10
199.9 Unspecified disorder of the circulatory system ICD-10
| Concept code | Concept name                                      | Vocabulary |
|-------------|--------------------------------------------------|------------|
| **Exclusion Criteria** |                                                  |            |
| **Type 1 diabetes** |                                                  |            |
| 250.x1      | Diabetes, type I [juvenile type], not stated as uncontrolled | ICD-9      |
| 250.x3      | Diabetes, type I [juvenile type], uncontrolled    | ICD-9      |
| E10.x       | Type 1 diabetes mellitus                         | ICD-10     |
| **Secondary diabetes** |                                                |            |
| 249.x       | Secondary diabetes mellitus                      | ICD-9      |
| E08.x       | Diabetes mellitus due to underlying condition    | ICD-10     |
| E09.x       | Drug or chemical induced diabetes mellitus       | ICD-10     |
| E13.x       | Other specified diabetes mellitus                | ICD-10     |

Abbreviations: ICD-9, *International Classification of Disease, Ninth Revision*; ICD-10, *International Classification of Disease, Tenth Revision*. 
| Concept code | Concept name | Vocabulary |
|--------------|--------------|------------|
| HHF          |              |            |
| 428.x        | Heart failure| ICD-9      |
| 150.x        | Heart failure| ICD-10     |
| Stroke       |              |            |
| 433.x1       | Occlusion and stenosis of precerebral arteries- carotid artery | ICD-9 |
| 434.x1       | Occlusion of cerebral arteries- cerebral embolism | ICD-9 |
| 436          | Acute but ill-defined cerebrovascular disease | ICD-9 |
| I63.x        | Cerebral infarction | ICD-10 |
| I67.8x       | Other specified cerebrovascular disease | ICD-10 |
| 430          | Subarachnoid hemorrhage | ICD-9 |
| 431          | Intracerebral hemorrhage | ICD-9 |
| I60.x        | Nontraumatic subarachnoid hemorrhage | ICD-10 |
| I61.x        | Nontraumatic intracerebral hemorrhage | ICD-10 |
| MI           |              |            |
| 410.x        | Acute myocardial infarction | ICD-9 |
| 121.x        | ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction | ICD-10 |
| BKA          |              |            |
| 27880        | Amputation, leg, through tibia and fibula | CPT-4 |
| 27881        | Amputation, leg, through tibia and fibula; with immediate fitting technique including application of first cast | CPT-4 |
| 27882        | Amputation, leg, through tibia and fibula; open, circular (guillotine) | CPT-4 |
| 27886        | Amputation, leg, through tibia and fibula; re-amputation | CPT-4 |
| 27888        | Amputation, ankle, through malleoli of tibia and fibula (eg, Syme, Pirogoff type procedures), with plastic closure and resection of nerves | CPT-4 |
| 28800        | Amputation, foot; midtarsal (eg, Chopart type procedure) | CPT-4 |
| 28805        | Amputation, foot; transmetatarsal | CPT-4 |
| 28810        | Amputation, metatarsal, with toe, single | CPT-4 |
| 28820        | Amputation, toe; metatarsophalangeal joint | CPT-4 |
| 28825        | Amputation, toe; interphalangeal joint | CPT-4 |
| 84.11        | Amputation of toe | ICD-9 |
| 84.12        | Amputation through foot | ICD-9 |
| 84.13        | Disarticulation of ankle | ICD-9 |
| 84.14        | Amputation of ankle through malleoli of tibia and fibula | ICD-9 |
| 84.15        | Other amputation below knee | ICD-9 |
| 84.16        | Disarticulation of knee | ICD-9 |

Abbreviations: HHF, hospitalization for heart failure; MI, myocardial infarction; BKA, below-knee lower extremity amputation; CPT-4, *Current Procedural Terminology, 4th Edition*; ICD-9, *International Classification of Disease, Ninth Revision*; ICD-10, *International Classification of Disease, Tenth Revision*. 
Supplemental Table III. Number and Rate of Cardiovascular Outcomes and Mortality by Treatment in the Propensity-Matched ITT Cohort*

| Outcome | Canagliflozin (n = 7,333) | Dapagliflozin (n = 1,955) | Empagliflozin (n = 3,341) | DPP-4 inhibitor (n = 3,806) | GLP-1 receptor agonist (n = 2,083) | TZD (n = 766) | SU (n = 2,747) | Insulin (n = 3,057) | Other (n = 310) |
|---------|--------------------------|---------------------------|---------------------------|-----------------------------|----------------------------------|---------------|---------------|------------------|----------------|
| Composite of ACM and HHF, n | 275 | 49 | 39 | 149 | 74 | 42 | 121 | 231 | 16 |
| Follow-up, y | 14,997.6 | 3,465.7 | 2,563.3 | 5,717.4 | 3,650.1 | 1,271.4 | 4,086.2 | 5,689.3 | 581.3 |
| Incidence rate per 100 person-years | 1.83 | 1.41 | 1.52 | 2.61 | 2.03 | 3.30 | 2.96 | 4.06 | 2.75 |
| ACM, n | 214 | 30 | 28 | 107 | 51 | 32 | 91 | 184 | 13 |
| Follow-up, y | 15,073.0 | 3,483.6 | 2,571.7 | 5,768.5 | 3,683.7 | 1,283.0 | 4,125.3 | 5,764.8 | 587.6 |
| Incidence rate per 100 person-years | 1.42 | 0.86 | 1.09 | 1.85 | 1.38 | 2.49 | 2.21 | 3.19 | 2.21 |
| HHF, n | 77 | 20 | 11 | 52 | 30 | 11 | 33 | 62 | 4 |
| Follow-up, y | 14,997.6 | 3,465.7 | 2,563.3 | 5,717.4 | 3,650.1 | 1,271.4 | 4,086.2 | 5,689.3 | 581.3 |
| Incidence rate per 100 person-years | 0.51 | 0.58 | 0.43 | 0.91 | 0.82 | 0.87 | 0.81 | 1.09 | 0.69 |
| MACE, n | 363 | 71 | 49 | 165 | 89 | 53 | 137 | 260 | 16 |
| Follow-up, y | 14,886.3 | 3,440.0 | 2,559.3 | 5,699.8 | 3,639.2 | 1,256.4 | 4,077.5 | 5,649.3 | 584.6 |
| Incidence rate per 100 person-years | 2.44 | 2.06 | 1.91 | 2.89 | 2.45 | 4.22 | 3.36 | 4.60 | 2.74 |
| Nonfatal stroke, n | 79 | 18 | 11 | 31 | 22 | 10 | 25 | 36 | 2 |
| Follow-up, y | 14,985.2 | 3,466.8 | 2,566.8 | 5,739.8 | 3,663.2 | 1,273.6 | 4,106.3 | 5,714.1 | 585.9 |
| Incidence rate per 100 person-years | 0.53 | 0.52 | 0.43 | 0.54 | 0.60 | 0.79 | 0.61 | 0.63 | 0.34 |
| Nonfatal MI, n | 85 | 24 | 12 | 36 | 20 | 15 | 30 | 48 | 1 |
| Follow-up, y | 14,974.1 | 3,456.7 | 2,564.3 | 5,728.6 | 3,659.7 | 1,264.6 | 4,096.0 | 5,698.3 | 586.3 |
| Incidence rate per 100 person-years | 0.57 | 0.69 | 0.47 | 0.63 | 0.55 | 1.19 | 0.73 | 0.84 | 0.17 |
| Composite of MACE and HHF, n | 419 | 88 | 60 | 198 | 111 | 61 | 161 | 303 | 19 |
| Follow-up, y | 14,832.3 | 3,423.3 | 2,552.2 | 5,662.5 | 3,608.3 | 1,249.3 | 4,049.3 | 5,604.0 | 579.3 |
|-------------|----------|----------|----------|----------|----------|----------|----------|----------|--------|
| Incidence rate per 100 person-years | 2.82 | 2.57 | 2.35 | 3.50 | 3.08 | 4.88 | 3.98 | 5.41 | 3.28 |

Propensity matched using an exposure propensity score. Abbreviations: BKA, below-knee lower extremity amputation; ITT, intent-to-treat; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; TZD, thiazolidinedione; SU, sulfonylurea; ACM, all-cause mortality; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction. *Patients within the non-SGLT2i cohort were able to simultaneously initiate medications across multiple non-SGLT2i medication classes; therefore, a single patient could contribute to >1 non-SGLT2i medication class cohort.
Supplemental Table IV. Number and Rate of Cardiovascular Outcomes and Mortality by Treatment in the Propensity-Matched On-Treatment Cohort

| Outcome                                      | Canagliflozin (n = 7,333) | Dapagliflozin (n = 1,955) | Empagliflozin (n = 3,341) | DPP-4 inhibitor (n = 3,806) | GLP-1 receptor agonist (n = 2,083) | TZD (n = 766) | SU (n = 2,747) | Insulin (n = 3,057) | Other (n = 310) |
|----------------------------------------------|---------------------------|---------------------------|---------------------------|-----------------------------|-----------------------------------|---------------|---------------|-------------------|-----------------|
| Composite of ACM and HHF, n                  | 89                        | 22                        | 21                        | 95                          | 31                                | 16            | 61            | 121               | 7               |
| Follow-up, y                                 | 8,218.4                   | 2,016.7                   | 1,896.8                   | 3,664.5                     | 2,042.4                           | 735.4         | 2,318.7       | 3,359.2           | 223.0           |
| Incidence rate per 100 person-years          | 1.08                      | 1.09                      | 1.11                      | 2.59                        | 1.52                              | 2.18          | 2.63          | 3.60              | 3.14            |
| ACM, n                                       | 72                        | 13                        | 14                        | 64                          | 16                                | 12            | 45            | 92                | 4               |
| Follow-up, y                                 | 8,228.1                   | 2,022.2                   | 1,899.9                   | 3,688.2                     | 2,048.4                           | 735.6         | 2,333.6       | 3,380.7           | 223.4           |
| Incidence rate per 100 person-years          | 0.88                      | 0.64                      | 0.74                      | 1.74                        | 0.78                              | 1.63          | 1.93          | 2.72              | 1.79            |
| HHF, n                                        | 20                        | 9                         | 7                         | 36                          | 16                                | 4             | 17            | 34                | 3               |
| Follow-up, y                                 | 8,168.3                   | 2,003.2                   | 1,892.9                   | 3,651.2                     | 2,033.3                           | 729.2         | 2,310.3       | 3,326.7           | 222.8           |
| Incidence rate per 100 person-years          | 1.76                      | 1.75                      | 1.53                      | 2.68                        | 1.92                              | 3.57          | 3.12          | 4.18              | 2.69            |
| MACE, n                                      | 144                       | 35                        | 29                        | 98                          | 39                                | 26            | 72            | 139               | 6               |
| Follow-up, y                                 | 8,198.2                   | 2,016.3                   | 1,896.9                   | 3,673.1                     | 2,040.4                           | 732.9         | 2,325.9       | 3,355.8           | 222.8           |
| Incidence rate per 100 person-years          | 1.76                      | 1.75                      | 1.53                      | 2.68                        | 1.92                              | 3.57          | 3.12          | 4.18              | 2.69            |
| Nonfatal stroke, n                           | 39                        | 6                         | 7                         | 19                          | 14                                | 6             | 10            | 24                | 2               |
| Follow-up, y                                 | 8,198.2                   | 2,016.3                   | 1,895.9                   | 3,666.3                     | 2,041.3                           | 731.9         | 2,318.1       | 3,351.7           | 223.4           |
| Incidence rate per 100 person-years          | 0.48                      | 0.30                      | 0.37                      | 0.52                        | 0.69                              | 0.82          | 0.43          | 0.72              | 0.90            |
| Nonfatal MI, n                               | 35                        | 16                        | 9                         | 22                          | 10                                | 9             | 22            | 25                | 0               |
| Follow-up, y                                 | 8,198.1                   | 2,009.1                   | 1,895.9                   | 3,666.3                     | 2,041.3                           | 731.9         | 2,318.1       | 3,351.7           | 223.4           |
| Incidence rate per 100 person-years          | 0.43                      | 0.80                      | 0.47                      | 0.60                        | 0.49                              | 1.23          | 0.95          | 0.75              | –               |
| Composite of MACE and HHF, n                 | 161                       | 44                        | 36                        | 125                         | 54                                | 30            | 85            | 165               | 9               |
| Follow-up, y                                 | 8,158.6                   | 1,997.6                   | 1,889.8                   | 3,630.1                     | 2,027.4                           | 729.0         | 2,298.1       | 3,306.6           | 222.3           |
| Incidence rate per 100 person-years          | 1.97                      | 2.20                      | 1.90                      | 3.44                        | 2.66                              | 4.12          | 3.70          | 4.99              | 4.05            |
Propensity matched using an exposure propensity score. Abbreviations: BKA, below-knee lower extremity amputation; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; TZD, thiazolidinedione; SU, sulfonylurea; ACM, all-cause mortality; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction. *Patients within the non-SGLT2i cohort were able to simultaneously initiate medications across multiple non-SGLT2i medication classes; therefore, a single patient could contribute to >1 non-SGLT2i medication class cohort.
Supplemental Table V. Number and Rate of BKA Outcomes by SGLT2i Medication and Non-SGLT2i Matches in the Propensity-Matched Cohort*

| Analytic Approach | Canagliflozin matched cohort | Dapagliflozin matched cohort | Empagliflozin matched cohort |
|------------------|-----------------------------|-----------------------------|----------------------------|
|                  | Canagliflozin (n=7,333)     | Dapagliflozin (n=1,955)     | Empagliflozin (n=3,341)     |
|                  | Non-SGLT2i                  | Non-SGLT2i                  | Non-SGLT2i                  |
| Intent-to-treat†, n | 29                          | 9                           | 3                           |
| Follow-up, y     | 15,045.7                    | 12,247.0                    | 3,478.2                     |
| Incidence rate per 100 person-years | 0.19                        | 0.07                        | 0.09                        |
| On-treatment†, n | 12                          | 4                           | 2                           |
| Follow-up, y     | 8,217.9                     | 7,122.9                     | 2,020.3                     |
| Incidence rate per 100 person-years | 0.15                        | 0.06                        | 0.10                        |

Propensity matched using an exposure propensity score. Abbreviations: BKA, below-knee lower extremity amputation; SGLT2i, sodium glucose co-transporter 2 inhibitor. *The propensity model was developed based on available clinical characteristics of the entire study cohort. While each patient may have his/her own matched pair (based on propensity score), the specific sub-cohorts (e.g., canagliflozin vs. matched set; dapagliflozin vs. matched set, and empagliflozin vs. matched set) may not be equally balanced on all major confounding factors, particularly in relation to BKA. †Patients with prior BKA (n = 9) and their respective match were removed from analyses.
SUPPLEMENTAL FIGURES AND FIGURE LEGENDS

Supplemental Figure I. Covariate balance of (A) selected and (B) total baseline characteristics.

A.
Abbreviations: ED, emergency department; SD, standardized difference; CV, cardiovascular; CVD, cardiovascular disease; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drug.
Supplemental Figure II. Risk of cardiovascular and mortality outcomes for patients in the propensity-matched on-treatment cohort by treatment status.

|                     | Non-SGLT2i (N = 12,629) | SGLT2i (N = 12,629) | Hazard ratio (95% CI) | P value |
|---------------------|-------------------------|---------------------|-----------------------|---------|
|                     | Incidence rate per 100 patient-years | Incidence rate per 100 patient-years |                      |         |
| Composite of ACM and HHF | 2.69                    | 1.09                | 0.41 (0.33–0.50)      | <0.0001 |
| ACM                 | 1.88                    | 0.81                | 0.44 (0.35–0.55)      | <0.0001 |
| HHF                 | 0.89                    | 0.30                | 0.33 (0.23–0.44)      | <0.0001 |
| MACE                | 3.09                    | 1.72                | 0.56 (0.47–0.66)      | <0.0001 |
| Nonfatal stroke     | 0.61                    | 0.43                | 0.70 (0.49–0.99)      | 0.0438  |
| Nonfatal myocardial infarction | 0.71               | 0.50                | 0.69 (0.50–0.96)      | 0.0292  |
| Composite of MACE and HHF | 3.83                    | 2.00                | 0.52 (0.45–0.61)      | <0.0001 |
| BKA*                | 0.07                    | 0.14                | 2.01 (0.89–4.53)      | 0.0949  |

Propensity matched using an exposure propensity score. Abbreviations: SGLT2i, sodium glucose co-transporter 2 inhibitor; CI, confidence interval; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular event; BKA, below-knee lower extremity amputation. *Patients with prior BKA (n = 9) and their respective match were removed from analyses.
Supplemental Figure III. Risk of the primary outcome in the propensity-matched ITT cohort stratified by treatment status and baseline subgroups.

| Subgroup                                           | Non-SGLT2i n/N | SGLT2i n/N | Hazard ratio (95% CI) | P value |
|----------------------------------------------------|----------------|------------|-----------------------|---------|
| Sex                                                |                |            |                       |         |
| Female                                             | 231/5670       | 139/5474   | 0.62 (0.50–0.76)      | 0.3368  |
| Male                                               | 395/6959       | 224/7155   | 0.54 (0.46–0.64)      |         |
| Age                                                |                |            |                       |         |
| <65 y                                              | 130/5272       | 71/5292    | 0.58 (0.43–0.77)      | 0.0997  |
| ≥65 y                                              | 496/7357       | 292/7337   | 0.56 (0.49–0.65)      |         |
| Insulin usage, prior 12 months                     |                |            |                       |         |
| Yes                                                | 131/2093       | 106/2887   | 0.61 (0.47–0.79)      | 0.5036  |
| No                                                 | 495/10,536     | 257/9742   | 0.55 (0.47–0.64)      |         |
| GLP-1 usage, prior 12 months                       |                |            |                       |         |
| Yes                                                | 53/1026        | 52/2467    | 0.49 (0.33–0.72)      | 0.2439  |
| No                                                 | 573/11,603     | 311/10,162 | 0.61 (0.53–0.70)      |         |
| HF, any criterion                                  |                |            |                       |         |
| Yes                                                | 265/2548       | 181/2495   | 0.68 (0.56–0.82)      | 0.0201  |
| No                                                 | 361/10,081     | 182/10,134 | 0.50 (0.42–0.59)      |         |
| HHF, prior 12 months                               |                |            |                       |         |
| Yes                                                | 68/320         | 50/278     | 0.75 (0.52–1.08)      | 0.1558  |
| No                                                 | 558/12,309     | 313/12,351 | 0.55 (0.48–0.64)      |         |
| PAD                                                |                |            |                       |         |
| Yes                                                | 158/1946       | 88/1991    | 0.52 (0.40–0.68)      | 0.5408  |
| No                                                 | 468/10,683     | 275/10,638 | 0.59 (0.51–0.68)      |         |
| CV risk factors                                    |                |            |                       |         |
| 1                                                   | 266/7386       | 143/7422   | 0.54 (0.44–0.66)      | 0.3714  |
| 2-3                                                | 360/5243       | 220/5207   | 0.60 (0.51–0.71)      |         |
| Renal disease, CCI component                       |                |            |                       |         |
| Yes                                                | 152/1552       | 95/1401    | 0.68 (0.53–0.88)      | 0.1752  |
| No                                                 | 474/11,077     | 268/11,228 | 0.55 (0.47–0.64)      |         |
| Chronic renal disease                              |                |            |                       |         |
| Yes                                                | 155/1565       | 97/1418    | 0.68 (0.52–0.87)      | 0.1748  |
| No                                                 | 471/11,064     | 266/11,211 | 0.55 (0.47–0.64)      |         |

Propensity matched using an exposure propensity score. Abbreviations: ITT, intent-to-treat; SGLT2i, sodium glucose co-transporter 2 inhibitor; CI, confidence interval; GLP-1, glucagon-like peptide-1; HF, heart failure; HHF, hospitalization for HF; PAD, peripheral artery disease; CV, cardiovascular; CCI, Charlson co-morbidity index.
Supplemental Figure IV. Sensitivity analyses of the propensity-matched ITT cohort.*

| Outcomes per model | Non-SGLT2i Events (n) | SGLT2i Events (n) | Hazard ratio (95% CI) | P value |
|--------------------|-----------------------|-------------------|-----------------------|---------|
| ACM or HHF         |                       |                   |                       |         |
| Primary            | 626                   | 363               | 0.57 (0.50–0.65)       | <0.0001 |
| No insulin         | 395                   | 289               | 0.69 (0.59–0.80)       | <0.0001 |
| No TZD             | 584                   | 339               | 0.57 (0.50–0.65)       | <0.0001 |
| No SU              | 505                   | 250               | 0.51 (0.44–0.59)       | <0.0001 |
| No insulin/TZD/SU  | 234                   | 153               | 0.63 (0.52–0.77)       | <0.0001 |
| ACM                |                       |                   |                       |         |
| Primary            | 475                   | 272               | 0.57 (0.49–0.66)       | <0.0001 |
| No insulin         | 291                   | 223               | 0.72 (0.61–0.86)       | 0.0003  |
| No TZD             | 443                   | 253               | 0.57 (0.49–0.66)       | <0.0001 |
| No SU              | 384                   | 185               | 0.50 (0.42–0.59)       | <0.0001 |
| No insulin/TZD/SU  | 169                   | 118               | 0.68 (0.54–0.86)       | 0.0011  |
| HIF                |                       |                   |                       |         |
| Primary            | 188                   | 108               | 0.57 (0.45–0.73)       | <0.0001 |
| No insulin         | 126                   | 78                | 0.58 (0.44–0.77)       | 0.0002  |
| No TZD             | 177                   | 101               | 0.57 (0.45–0.73)       | <0.0001 |
| No SU              | 155                   | 78                | 0.53 (0.40–0.69)       | <0.0001 |
| No insulin/TZD/SU  | 83                    | 41                | 0.48 (0.33–0.70)       | 0.0001  |
| MACE               |                       |                   |                       |         |
| Primary            | 714                   | 483               | 0.67 (0.59–0.75)       | <0.0001 |
| No insulin         | 454                   | 392               | 0.82 (0.71–0.94)       | 0.0035  |
| No TZD             | 661                   | 453               | 0.68 (0.59–0.78)       | <0.0001 |
| No SU              | 577                   | 336               | 0.59 (0.52–0.68)       | <0.0001 |
| No insulin/TZD/SU  | 266                   | 216               | 0.79 (0.69–0.95)       | 0.0100  |
| Nonfatal stroke    |                       |                   |                       |         |
| Primary            | 125                   | 108               | 0.85 (0.66–1.10)       | 0.2190  |
| No insulin         | 99                    | 90                | 0.95 (0.71–1.29)       | 0.7559  |
| No TZD             | 115                   | 103               | 0.88 (0.67–1.15)       | 0.3476  |
| No SU              | 100                   | 79                | 0.80 (0.60–1.08)       | 0.1433  |
| No insulin/TZD/SU  | 54                    | 56                | 1.01 (0.90–1.16)       | 0.9703  |
| Nonfatal MI        |                       |                   |                       |         |
| Primary            | 148                   | 121               | 0.81 (0.64–1.03)       | 0.0888  |
| No insulin         | 109                   | 94                | 0.89 (0.67–1.18)       | 0.4279  |
| No TZD             | 133                   | 112               | 0.84 (0.65–1.08)       | 0.1672  |
| No SU              | 118                   | 84                | 0.72 (0.55–0.96)       | 0.0250  |
| No insulin/TZD/SU  | 56                    | 48                | 0.83 (0.57–1.23)       | 0.3596  |
| MACE or HHF        |                       |                   |                       |         |
| Primary            | 845                   | 567               | 0.66 (0.60–0.74)       | <0.0001 |
| No insulin         | 542                   | 451               | 0.78 (0.69–0.89)       | 0.0001  |
| No TZD             | 784                   | 534               | 0.67 (0.59–0.75)       | <0.0001 |
| No SU              | 684                   | 397               | 0.59 (0.52–0.67)       | <0.0001 |
| No insulin/TZD/SU  | 322                   | 249               | 0.75 (0.63–0.88)       | 0.0006  |
| BKA†               |                       |                   |                       |         |
| Primary            | 18                    | 35                | 1.99 (1.12–3.51)       | 0.0183  |
| No insulin         | 9                     | 27                | 2.87 (1.34–6.14)       | 0.0065  |
| No TZD             | 17                    | 34                | 2.05 (1.14–3.67)       | 0.0161  |
| No SU              | 15                    | 29                | 2.01 (1.08–3.75)       | 0.0283  |
| No insulin/TZD/SU  | 2                     | 20                | 3.83 (1.43–10.28)      | 0.0076  |

Propensity matched using an exposure propensity score. Abbreviations: SGLT2i, sodium glucose co-transporter 2 inhibitor; CI, confidence interval; ACM, all-cause mortality; HHF, hospitalization for heart failure; TZD, thiazolidinedione; SU, sulfonylurea; MACE, major adverse cardiovascular event; MI, myocardial infarction; BKA, below-knee lower extremity amputation. *Cohort size: primary = 25,258; no
insulin = 19,144; no TZD = 23,726; no SU = 19,764; no insulin/TZD/SU = 12,182. The cohort sizes for the BKA analysis were slightly smaller because patients with prior amputations were excluded from analysis. †Patients with prior BKA (n = 9) and their respective match were excluded from analysis.
Supplemental Figure V. Risk of BKA in the propensity-matched ITT cohort stratified by treatment status and baseline subgroups.

| Subgroup                              | Non-SGLT2i n/N | SGLT2i n/N | Hazard ratio (95% CI) | P value |
|---------------------------------------|----------------|------------|-----------------------|---------|
| **Sex**                               |                |            |                       |         |
| Female                                | 7/5666         | 9/5469     | 1.33 (0.50–3.57)      | 0.3817  |
| Male                                  | 11/6954        | 26/7151    | 2.38 (1.17–4.82)      |         |
| **Age**                               |                |            |                       | 0.5485  |
| <65 y                                 | 4/5269         | 10/5289    | 2.44 (0.77–7.78)      |         |
| ≥65 y                                 | 14/7351        | 25/7331    | 1.81 (0.94–3.48)      |         |
| **Insulin usage, prior 12 months**    |                |            |                       | 0.2217  |
| Yes                                   | 3/2089         | 14/2882    | 3.77 (1.10–12.93)     |         |
| No                                    | 15/10,531      | 21/9738    | 1.52 (0.78–2.96)      |         |
| **GLP-1 usage, prior 12 months**      |                |            |                       | 0.0707  |
| Yes                                   | 4/1024         | 5/2465     | 0.76 (0.20–2.89)      |         |
| No                                    | 14/11,596      | 30/10,155  | 2.41 (1.27–4.56)      |         |
| **HF, any criterion**                 |                |            |                       | 0.4866  |
| Yes                                   | 6/2547         | 15/2493    | 2.51 (0.96–6.60)      |         |
| No                                    | 12/10,073      | 20/10,127  | 1.73 (0.85–3.51)      |         |
| **HHF, prior 12 months**              |                |            |                       | 0.3473  |
| Yes                                   | 1/320          | 5/277      | 5.11 (0.59–44.53)     |         |
| No                                    | 17/12,300      | 30/12,343  | 1.81 (0.99–3.28)      |         |
| **PAD**                               |                |            |                       | 0.5271  |
| Yes                                   | 7/1944         | 17/1986    | 2.44 (1.01–5.91)      |         |
| No                                    | 11/10,682      | 18/10,637  | 1.68 (0.79–3.55)      |         |
| **CV risk factors**                   |                |            |                       | 0.7544  |
| 1                                     | 7/7379         | 12/7418    | 1.75 (0.69–4.45)      |         |
| 2-3                                   | 11/5241        | 23/5202    | 2.13 (1.04–4.38)      |         |
| **Renal disease, CCI component**      |                |            |                       | 0.6239  |
| Yes                                   | 5/1549         | 7/1400     | 1.52 (0.49–4.65)      |         |
| No                                    | 13/11,071      | 28/11,220  | 2.20 (1.13–4.27)      |         |
| **Chronic renal disease**             |                |            |                       | 0.3587  |
| Yes                                   | 6/1562         | 7/1417     | 1.25 (0.43–3.64)      |         |
| No                                    | 12/11,058      | 28/11,203  | 2.39 (1.21–4.72)      |         |

Propensity matched using an exposure propensity score. Abbreviations: BKA, below-knee lower extremity amputation; ITT, intent-to-treat; SGLT2i, sodium glucose co-transporter 2 inhibitor; CI, confidence interval; GLP-1, glucagon-like peptide-1; HF, heart failure; HHF, hospitalization for HF; PAD, peripheral artery disease; CV, cardiovascular; CCI, CCI, Charlson co-morbidity index.