ORIGINAL RESEARCH

Sex Differences in Cardiovascular Effectiveness of Newer Glucose-Lowering Drugs Added to Metformin in Type 2 Diabetes Mellitus

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***Background*—**Randomized controlled trials showed that newer glucose-lowering agents are cardioprotective, but most participants were men. It is unknown whether benefits are similar in women.

***Methods and Results*—**Among adults with type 2 diabetes mellitus not controlled with metformin with no prior use of insulin, we assessed for sex differences in the cardiovascular effectiveness and safety of sodium-glucose-like transport-2 inhibitors (SGLT-2i), glucagon-like peptide-1 receptor agonists (GLP-1RA), dipeptidyl peptidase-4 inhibitors, initiated as second-line agents relative to sulfonylureas (reference-group). We studied type 2 diabetes mellitus American adults with newly dispensed sulfonylureas, SGLT-2i, GLP-1RA, or dipeptidyl peptidase-4 inhibitors (Marketscan-Database: 2011–2017). We used multivariable Cox proportional hazards models with time-varying exposure to compare time to first nonfatal cardiovascular event (myocardial infarction/unstable angina, stroke, and heart failure), and safety outcomes between drugs users, and tested for sex–drug interactions. Among 167 254 type 2 diabetes mellitus metformin users (46% women, median age 59 years, at low cardiovascular risk), during a median 4.5-year follow-up, cardiovascular events incidence was lower in women than men (14.7 versus 16.7 per 1000-person-year). Compared with sulfonylureas, hazard ratios (HRs) for cardiovascular events were lower with GLP-1RA (adjusted HR-women: 0.57, 95% CI: 0.48–0.68; aHR-men: 0.82, 0.71–0.95), dipeptidyl peptidase-4 inhibitors (aHR-women: 0.83, 0.77–0.89; aHR-men: 0.85, 0.79–0.91) and SGLT-2i (aHR-women: 0.58, 0.46–0.74; aHR-men: 0.69, 0.57–0.83). A sex-by-drug interaction was statistically significant only for GLP-1RA (P=0.002), suggesting greater cardiovascular effectiveness in women. Compared with sulfonylureas, risks of adverse events were similarly lower in both sexes for GLP-1RA (aHR-women: 0.81, 0.73–0.89; aHR-men: 0.80, 0.71–0.89), dipeptidyl peptidase-4 inhibitors (aHR-women: 0.82, 0.78–0.87; aHR-men: 0.83, 0.78–0.87) and SGLT-2i (aHR-women: 0.68, 0.59–0.78; aHR-men: 0.67, 0.59–0.78) (all sex–drug interactions for adverse events P>0.05).

***Conclusions*—**Newer glucose-lowering drugs were associated with lower risk of cardiovascular events than sulfonylureas, with greater effectiveness of GLP-1RA in women than men. Overall, they appeared safe, with a better safety profile for SGLT-2i than for GLP-1RA regardless of sex. **(*J Am Heart Assoc*. 2020;9:e012940. DOI: 10.1161/JAHA.119.012940.)**

Key Words: glucose-lowering agents • major cardiovascular events • population-based analysis • sex • type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a worldwide epidemic affecting both women and men.[1] Among adults with T2DM, cardiovascular disease (CVD) is the leading cause of mortality and morbidity, with double the risk in women compared with men.[2] Recent epidemiological data highlight potentially important sex differences in the cardiovascular consequences of T2DM.[3] Although in general women experience fewer cardiovascular events than men of the same age, diabetes mellitus reverses the "women's advantage" for atherosclerotic cardiovascular disease (ASCVD).[4,5] The unique metabolic environment in T2DM promotes endothelial dysfunction, increased oxidative stress, inflammation, and platelet activation/thrombosis, thus leading to the development of atherosclerosis.[6,7] Biological factors can

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Clinical Perspective

What Is New?

- This population-based analysis suggests that new glucose-lowering agents used with metformin are associated with a lower risk of major adverse cardiovascular events, as compared with sulfonylureas, and that this effect is more pronounced in women than men.
- Newer agents were also associated with a lower risk of adverse events with no clear sex interaction.

What Are the Clinical Implications?

- Among adults with type 2 diabetes mellitus not controlled with metformin, the selection of add-on glucose-lowering agents should be based not only on cardiovascular risk and comorbidities but also sex.
- Randomized controlled trials with glucose-lowering drugs should guarantee an adequate inclusion of women participants to assess the existence of any sex differences in efficacy and safety of drugs that can inform future clinical practice guidelines.

influence in a sex-specific manner the pathophysiology of T2DM-associated cardiovascular complications as well as the pharmacodynamics/kinetics of drugs commonly used in the treatment of individuals with T2DM.[6,7] Therefore, it is plausible that pharmacological strategies might have a different efficacy in men and women with T2DM. Indeed, a personalized approach in the management of CVD in women with T2DM has been suggested.[3,8]

The American and Canadian diabetes mellitus associations have recently released new guidelines for sodium-glucose cotransporter-2 inhibitors (SGLT-2i), glucagon-like peptide-1 receptor agonists (GLP-1RA), and dipeptidyl peptidase-4 inhibitors (DPP-4i) to be second-line agents in T2DM instead of sulfonylureas when required in addition to metformin (the typical first-line agent).[9] SGLT-2i or GLP-1RA are recommended as the preferred second-line agents for reducing major adverse cardiovascular events in T2DM individuals with established ASCVD.[9] The approach in T2DM adults without ASCVD is less clear and is mainly guided by the presence of comorbidities such as diabetic kidney disease or heart failure.[9] These recommendations are considered to be evidence-based and applicable to all, despite the underrepresentation of women in randomized controlled trials (RCTs).

The objective of this population-based analysis was to assess whether sex differences exist in the cardiovascular effectiveness and safety of SGLT-2i, GLP-1RA, and DPP-4i, compared with sulfonylureas, in T2DM individuals not controlled on metformin therapy alone.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because of the data use agreement with Truven Health. Any supplemental results not shown in the article are available from the corresponding author upon request.

Data Source

We used the Commercial Plans and Encounters Database of the Truven Health MarketScan Research Databases (2010–2017)[10] to construct a population-based cohort using T2DM adults treated with metformin who initiated second-line glucose-lowering drugs. This claims-based database contains integrated longitudinal data for individuals covered by employer-sponsored private health insurance from payers across the United States. Raw data obtained from payers are frequently reviewed for quality, standardized, and aggregated. A unique enrollee identifier links patient-level demographic and enrollment information to inpatient, outpatient, and emergency department medical claims, and outpatient pharmacy claims. Within the database, diagnoses and procedures are coded using the *International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth* (*ICD-9* and *ICD-10*) *Revisions* diagnostic and procedure codes, the Current Procedural Terminology, and the Diagnosis-Related Groups codes, whereas drugs are coded with the National Drug Code.[10]

Analyses of de-identified data were conducted in accordance with local laws and regulations and received approvals from the McGill University ethics review board.

Cohort Derivation

We constructed a user cohort of adult individuals, 18 years or older, initiating sulfonylureas, DPP-4i, SGLT-2i, or GLP-1RA between January 1, 2011 and December 31, 2017. We defined the first dispensation date as cohort entry and excluded individuals with prior use of any of these medications and with any use of insulin 1 year before cohort entry. The latter exclusion criteria were formulated to create a sample of individuals who were largely similar, aside from the type of oral glucose-lowering agent that was added. We further selected individuals with ongoing metformin use (with at least 1 prescription in 90 days before cohort entry) and with a diagnosis of T2DM. The latter was defined as individuals with at least 2 codes for T2DM (*ICD-9* codes 250.X0/250.X2 or *ICD-10* code E11), with a minimum of 3 months apart between diagnoses in outpatient/inpatient settings from 1 year before to 1 month after cohort entry. In

an attempt to optimize the specificity of our T2DM definition, we excluded individuals with diagnosis of type 1 diabetes mellitus (*ICD-9* codes 250.X1/250.X3 or *ICD-10* code E10) in the same period and a diagnosis of gestational diabetes mellitus (*ICD-9* code 648.8 or *ICD-10* code O24) within 9 months before cohort entry up to 6 months after. Additionally, we excluded individuals with a diagnosis of cystic fibrosis (*ICD-9*: 227 or *ICD-10*: E84) because this condition may be associated with insulin deficiency but does not represent typical T2DM.

We restricted our analyses to individuals with continued medical and pharmacy benefits for 12 months before cohort entry.

Definition of Exposure

We considered 4 time-dependent exposure groups based on current use of sulfonylurea, SGLT-2i, GLP-1RA, or DPP-4i. To this end, each adult's follow-up time was divided into consecutive time intervals, with a new interval starting whenever the glucose-lowering agent used was changed or discontinued for more than 30 days. For overlapping prescriptions of the same drug (or drugs within the same class), the individual was assumed to have had prescriptions refilled early and completed the first prescription before starting the second. When there was a gap of <30 days between 2 consecutive prescriptions of the same drug/drug class, it was assumed that the drug was taken continuously to account for any remaining stockpiled medications. When there was a gap of >30 days between prescriptions, it was assumed that the individual was not exposed to any drug.

Outcomes

The composite cardiovascular effectiveness outcome comprised the first nonfatal major cardiovascular events: acute myocardial infarction, unstable angina, heart failure, or stroke.[11–14] The safety outcome comprised a composite of hypoglycemic episodes, pancreatitis, urosepsis, lower limb amputation, genital yeast infection, and acute kidney injury.[15–18] Both cardiovascular effectiveness and safety outcomes were ascertained from hospitalization and emergency room visit records and defined using *ICD-9* and *ICD-10* codes (Table S1).

Potential Confounders

Baseline characteristics, assessed at the time of cohort entry, considered as potential confounders included the following: sex, age, year of cohort entry, drug used for prevention (ie, antihypertensives, statins, and aspirin), employment status (ie, full-time versus others), region of residence (ie, rural versus urban), comorbidities (based on 2 or more *ICD* codes for cerebrovascular disease, myocardial infarction, congestive heart failure, peripheral vascular disease, and renal disease), Charlson Comorbidity Index (value ≥1 versus 0), and indicators of healthcare use in the year before cohort entry (number of emergency department visits, number of hospitalizations, and number of physician visits) considered as markers of general health.

Statistical Analysis

Descriptive analyses compared baseline characteristics between men and women using medians and interquartile intervals for continuous variables, and frequency distributions for categorical variables. For each treatment group, we calculated crude incidence rates (IR), with 95% CI, for the composite CVD event and safety outcomes, separately for each to sex. We also estimated the IR for each event separately.

Main analyses relied on time-to-event methods. Cohort entry (time 0) corresponded to the date of the start of the first prescription for either drug of interest. Individuals were followed until the date of the outcome of interest, loss of medical and pharmacy coverage, death (obtained from hospital discharge data), or end of the study data (December 31, 2017).

Unadjusted Kaplan-Meier curves estimated separately for men and women were plotted to compare the incidence of CVD events and the composite safety outcome across groups of subjects who initiated treatment with each of the 4 glucose-lowering agent groups. Differences between drug groups were compared using the log-rank test.

For each outcome, multivariable Cox proportional hazards models[19] were used to estimate adjusted hazard ratios (HRs), with 95% CIs, with sulfonylureas as the reference. The main exposure variables were time-varying indicators of current use of SGLT-2i, GLP-1RA, and DPP-4i, with sulfonylureas as the reference category. Models were adjusted for all potential confounders listed in the "Confounders" section above. We used an additional time-varying variable to indicate switching during the follow-up to a different class of glucose-lowering agent. In addition, all multivariable models included a binary time-varying covariate indicating the subject was currently exposed to the corresponding glucose-lowering agent. This variable was necessary to discriminate between current use of the reference drug class (sulfonylureas) versus not being exposed to any of the drugs of interest.[20] For each outcome, 2 different multivariable Cox models were used. The first model included only the main effect of sex, in addition to other potential confounders and, thus, estimated the common drug effects for women and men, in terms of adjusted HRs associated with current use of a specific drug class, relative to the reference group of sulfonylurea users. The second model

included, in addition, a series of 2-way interactions between each of the nonreference drug classes and sex. The statistical significance of each of the drug-by-sex interaction was tested using model-based Wald test, at 2-tailed α=0.05, to assess whether the potential risk reduction associated with use of a given glucose-lowering agent relative to sulfonylureas did differ between women and men. In the case of a statistically significant interaction, the results of the model with interaction were used to reconstruct the separate adjusted HRs for women and men.[21]

The following additional analyses were performed: (1) we tested for the presence of any sex differences in the cardiovascular effectiveness and safety of sulfonylureas (reference group), by adapting the methods described above to also test sex-by-sulfonylureas interactions, separately for CVD events and safety outcomes; (2) we performed the same analyses using an extended composite outcome with the addition of transient ischemic attack, coronary artery bypass graft, and percutaneous coronary intervention.

All analyses were performed using SAS version 9.4 (SAS Institute Inc).

Results

A total of 167 254 adults with T2DM (46% women, median age 59 years) filled at least 1 prescription for any of the medications of interest and met our cohort entry criteria (Figure 1). At baseline, the most commonly used second-line agent was sulfonylurea in both men and women (Table 1). Compared with men, women were more often prescribed GLP-1RA and less often prescribed DPP-4i as a second-line agent, while the proportion of women and men treated with SGLT-2i was similar (Table 1). Overall, the prevalence of risk factors and comorbidities in this population was relatively low, albeit women were slightly less likely to have comorbidities such as prior myocardial infarction, congestive heart failure, peripheral vascular disease, and renal disease. Use of antihypertensive drugs and statins was also less frequent among women than men (Table 1).

During a median follow-up 4.5 [2.1–6.3] years, 4742 women experienced a major cardiovascular event (IR=14.7 per 1000 person-year [PY], 95% CI 14.3–15.1) whereas among men, 6354 major adverse cardiovascular events occurred (IR=16.7 per 1000 PY, 95% CI 16.3–17.2) (Table 2). Major cardiovascular events were less frequent in women than in men, across all drug groups (Table 2), as illustrated by Kaplan-Meier curves (Figure 2) and the overall log-rank test (P<0.001). The higher incidence of the composite CVD outcome in men was mostly driven by myocardial infarction and procedures related to ischemic heart disease including percutaneous coronary intervention and coronary artery bypass graft (Table 2).

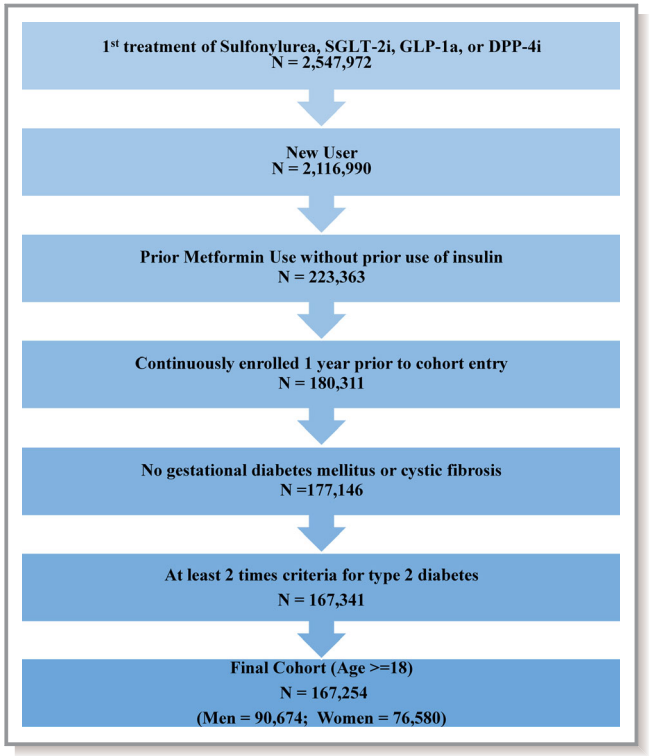

Figure 1. Derivation of the sample. DPP-4i indicates dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; SGLT-2i, sodium-glucose-like transport-2 inhibitors.

In adjusted multivariate analyses of the comparative cardiovascular effectiveness, the risk of major cardiovascular events was significantly lower for current users of all glucose-lowering agents compared with sulfonylurea users: SGLT-2i (adjusted HR: 0.64, 95% CI: 0.55–0.75), GLP-1RA (adjusted HR: 0.70, 95% CI: 0.62–0.78), and DPP-4i (adjusted HR: 0.85, 95% CI: 0.80–0.89). Analysis indicated that current exposure to sulfonylureas had similar effects in men and women (P=0.38).

In the multivariate model that considered potential effect modification by sex, 2-way drug-by-sex interaction was statistically significant (P=0.001 for GLP-1RA) (Figure 3), indicating that the cardiovascular effectiveness of these newer agents, relative to sulfonylureas, was different for women and men. Indeed, after adjusting for potential confounders and taking into account drug-by-sex interactions, we noticed stronger risk reductions in women than in men: women currently treated with GLP-1RA (aHR: 0.57, 95% CI: 0.48–0.68), DPP-4i (aHR: 0.83, 95% CI: 0.77–0.89), and SGLT-2i (aHR: 0.58, 95% CI: 0.46–0.74) were all at significantly lower risk of the primary composite outcome than women currently exposed to sulfonylureas. In contrast, for men, the corresponding risk reductions with newer agents relative to sulfonylureas were smaller: GLP-1RA (aHR: 0.82, 95% CI: 0.71–0.95), DPP-4i (aHR: 0.85, 95% CI: 0.79–0.91) and SGLT-2i (aHR: 0.69, 95% CI: 0.57–0.83) (Figure 3).

Table 1. Baseline Characteristics of Type 2 Diabetes Mellitus Patients Using Metformin According to Sex

	Men (n=90 674)	Women (n=76 580)
First agent used at baseline as second-line agent		
SU	50 110 (55.3)	38 995 (51.0)*
DPP-4i	28 299 (31.2)	23 379 (30.5)*
GLP-1RA	5942 (6.6)	8755 (11.4)*
SGLT-2i	6323 (6.9)	5451 (7.1)
Age (y) at cohort entry, median [IQR]	59 [51–67]	59 [51–68]
Age (y) at cohort entry by first agent used, median [IQR]		
SU	62 [53–72]	61 [52–70]
DPP-4i	58 [51–65]	58 [50–64]
GLP-1RA	53 [46–60]	54 [47–62]
SGLT-2i	54 [48–60]	54 [47–60]
Year of cohort entry		
2011	31 410 (34.6)	26 912 (35.1)
2012	13 576 (15.0)	11 446 (14.9)
2013	9473 (10.4)	7728 (10.1)
2014	10 029 (11.1)	8153 (10.6)
2015	8587 (9.5)	7402 (9.7)
2016	8870 (9.8)	7627 (10.0)
2017	8729 (9.6)	7312 (9.6)
Full-time employment	36 545 (40.3)	29 277 (38.2)*
Urban residency	72 013 (81.7)	60 700 (81.7)
Charlson comorbidity index (≥1)	23 995 (26.5)	22 386 (29.2)*
ASCVD		
Cerebrovascular disease	5924 (6.5)	4921 (6.4)
Myocardial infarction	2599 (2.9)	1139 (1.5)*
Peripheral vascular disease	4272 (4.7)	2748 (3.56)*
Congestive heart failure	4054 (4.5)	2917 (3.8)*
Any renal disease	3581 (3.9)	2818 (3.7)*
Any liver disease	332 (0.6)	300 (0.6)
Medications		
Antihypertensive	72 455 (79.9)	60 568 (79.1)*
Aspirin	677 (0.7)	493 (0.6)*
Statins	60 019 (66.2)	46 738 (61.0)*
Emergency room visits (≥1) 1 y before cohort entry	18 772 (20.7)	19 608 (25.6)*
Hospitalizations visits (≥1) 1 y before cohort entry	9482 (10.5)	8191 (10.7)
Physician visits (≥1) 1 y before cohort entry	87 885 (96.9)	74 690 (97.5)*

Data are presented as numbers of patients (%) unless otherwise specified. ASCVD indicates atherosclerotic cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; IQR, interquartile range; SGLT-2i, sodium-glucose like transport-2 inhibitors; SU, sulfonylureas.
*P<0.05.

Similar findings were also obtained when the composite outcome also included transient ischemic attack, percutaneous coronary intervention, and coronary artery bypass graft. The 2-way drug-by-sex interactions were statistically significant (P=0.001) only for GLP-1RA. Specifically, after adjusting for potential confounders and taking into account drug-by-sex interactions, women currently treated with GLP-1RA (aHR: 0.59, 95% CI: 0.50–0.70), DPP-4i (aHR: 0.82, 95% CI: 0.76–0.88), and SGLT-2i (aHR: 0.57, 95% CI: 0.45–0.72) were all at significantly lower risk of the extended composite outcome including cardiac procedures and transient ischemic attack, compared with women currently exposed to sulfonylureas. For men, the corresponding risk reductions with newer agents were GLP-1RA (aHR: 0.84, 95% CI: 0.74–0.97), DPP-4i (aHR: 0.87, 95% CI: 0.82–0.93), and SGLT-2i (aHR: 0.67, 95% CI: 0.56–0.80).

During a median follow-up of 4.2 [1.9–6.2] years, 10 110 adverse events occurred in women (IR=31.2 per 1000 PY, 95% CI: 30.6–31.9) and 9471 (IR=27.7 per 1000 PY, 95% CI: 27.1–28.2) in men. Across all drug classes, women experienced significantly higher incidence of adverse events than men (Table 3 and Figure 4; P<0.001 for the log-rank test, Figure 4). Compared with men, the most common adverse event in women was urosepsis (18.3 per 1000 PY, versus 13.1 per 1000 PY in men) and genital yeast infection (3.1 per 1000 PY versus 2.2 in men) (Table 3). Acute renal failure (11.8 per 1000 PY in men versus 9.9 per 1000 PY in women) and lower limb amputation (0.9 per 1000 PY in men versus 0.6 per 1000 PY in women) were more common in men compared with women (Table 3). When looking at safety according to treatment group at the cohort entry, the incidence of composite safety outcome in women was 36.5, 26.0, 22.9, and 17.6 per 1000 PY for sulfonylureas, DPP-4i, GLP-1RA, and SGLT-2i respectively, whereas in men it was 32.1, 21.7, 21.7, and 15.6 per 1000 PY. Severe hypoglycemic episodes, urosepsis, and acute kidney injury occurred most commonly in users of sulfonylureas. However, compared with sulfonylurea, women users of SGLT-2i experienced more genital infections (Table 3).

In multivariate safety time-dependent analyses, after adjusting for potential confounders, the risks of adverse events were significantly lower in GLP-1RA (aHR: 0.80, 95% CI: 0.74–0.86), DPP-4i (aHR: 0.83, 95% CI: 0.79–0.86), and SGLT-2i (aHR: 0.67, 95% CI: 0.61–0.75) users compared with sulfonylureas; however, all interactions with sex were not statistically significant (Figure 5). Of note, SGLT-2i were significantly safer than GLP-1RA (aHR: 0.84, 95% CI: 0.75–0.95).

Discussion

This retrospective cohort study suggests that newer glucose-lowering drugs initiated as second-line agents with metformin

Table 2. Cardiovascular Effectiveness Outcomes According to Sex and Glucose-Lowering Agent Prescribed at the Cohort Entry

	Men Overall (n=90 674)	Women Overall (n=76 580)	Men SU (n=50 110)	Women SU (n=38 995)	Men DPP-4i (n=28 299)	Women DPP-4i (n=23 379)	Men GLP-1RA (n=5942)	Women GLP-1RA (n=8755)	Men SGLT-2i (n=6323)	Women SGLT-2i (n=5451)
Major cardiovascular event*										
No. of events	6354	4742	4452	3335	1544	1132	257	213	101	62
Incidence per 1000 PY	16.7 (16.3–17.2)	14.7 (14.3–15.1)	19.6 (18.9–20.1)	18.4 (17.8–19.0)	13.9 (12.4–13.7)	11.4 (10.8–12.2)	11.9 (10.5–13.4)	6.6 (5.8–7.6)	8.5 (6.9–10.3)	5.7 (4.4–7.4)
Myocardial infarction										
No. of events	1472	703	999	492	367	167	71	31	35	13
Incidence per 1000 PY	3.8 (3.6–4.0)	2.1 (2.0–2.3)	4.2 (4.0–4.5)	2.6 (2.4–2.9)	3.0 (2.7–3.4)	1.7 (1.4–1.9)	3.2 (2.5–4.1)	0.9 (0.6–1.4)	2.9 (2.1–4.1)	1.2 (0.6–2.0)
Unstable angina										
No. of events	194	130	121	83	51	27	19	12	3	8
Incidence per 1000 PY	0.5 (0.4–0.6)	0.4 (0.3–0.5)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.4 (0.3–0.6)	0.3 (0.2–0.4)	0.9 (0.5–1.4)	0.4 (0.2–0.7)	0.3 (0.1–0.7)	0.7 (0.3–1.5)
Percutaneous coronary interventions										
No. of events	389	165	283	109	82	50	24	6	0	0
Incidence per 1000 PY	1.0 (0.9–1.1)	0.5 (0.4–0.6)	1.2 (1.0–1.3)	0.6 (0.5–0.7)	0.7 (0.5–0.8)	0.5 (0.4–0.6)	1.1 (0.7–1.6)	0.2 (0.1–0.4)	0	0
Coronary artery bypass graft										
No. of events	852	256	550	163	246	64	40	19	16	10
Incidence per 1000 PY	2.1 (2.0–2.3)	0.7 (0.7–0.8)	2.2 (2.1–2.4)	0.8 (0.7–1.0)	2.0 (1.7–2.3)	0.6 (0.5–0.8)	1.8 (1.3–2.4)	0.6 (0.3–0.9)	1.3 (0.8–2.2)	0.9 (0.4–1.7)
Ischemic stroke										
No. of events	1725	1547	1239	1101	391	360	69	67	26	19
Incidence per 1000 PY	4.5 (4.3–4.8)	4.8 (4.6–5.0)	5.4 (5.1–5.8)	6.1 (5.7–6.4)	3.3 (3.0–3.6)	3.6 (3.3–4.0)	3.2 (2.5–4.0)	2.1 (1.6–2.7)	2.2 (1.4–3.2)	1.8 (1.1–2.7)
Hemorrhagic stroke										
No. of events	291	187	207	128	73	50	7	7	4	2
Incidence per 1000 PY	0.8 (0.7–0.9)	0.6 (0.5–0.7)	1.0 (0.8–1.1)	0.8 (0.6–0.9)	0.6 (0.5–0.8)	0.5 (0.4–0.7)	0.3 (0.1–0.7)	0.2 (0.1–0.5)	0.3 (0.1–0.9)	0.2 (0.02–0.7)
Transient ischemic attack										
No. of events	982	903	677	667	249	192	42	37	15	7
Incidence per 1000 PY	2.4 (2.3–2.6)	2.7 (2.5–2.8)	2.8 (2.6–3.0)	3.4 (3.2–3.7)	2.0 (1.8–2.3)	1.9 (1.6–2.2)	1.8 (1.3–2.5)	1.1 (0.8–1.6)	1.3 (0.7–2.1)	0.6 (0.3–1.3)
Heart failure										
No. of events	3988	3092	2861	2210	947	737	137	120	43	25
Incidence per 1000 PY	10.0 (9.7–10.3)	9.1 (8.8–9.5)	11.8 (11.4–12.3)	11.5 (11.0–12.0)	7.7 (7.2–8.2)	7.2 (6.7–7.7)	6.2 (5.2–7.3)	3.7 (3.0–4.4)	3.6 (2.6–4.9)	2.3 (1.5–3.4)

Data are provided as numbers of events or incidence rate (95% CI). DPP-4i indicates dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; PY, person-year; SGLT-2i, sodium-glucose-like transport-2 inhibitors; SU, sulfonylureas.

*Major cardiovascular events include nonfatal myocardial infarction, unstable angina, nonfatal ischemic and hemorrhagic stroke, and heart failure.

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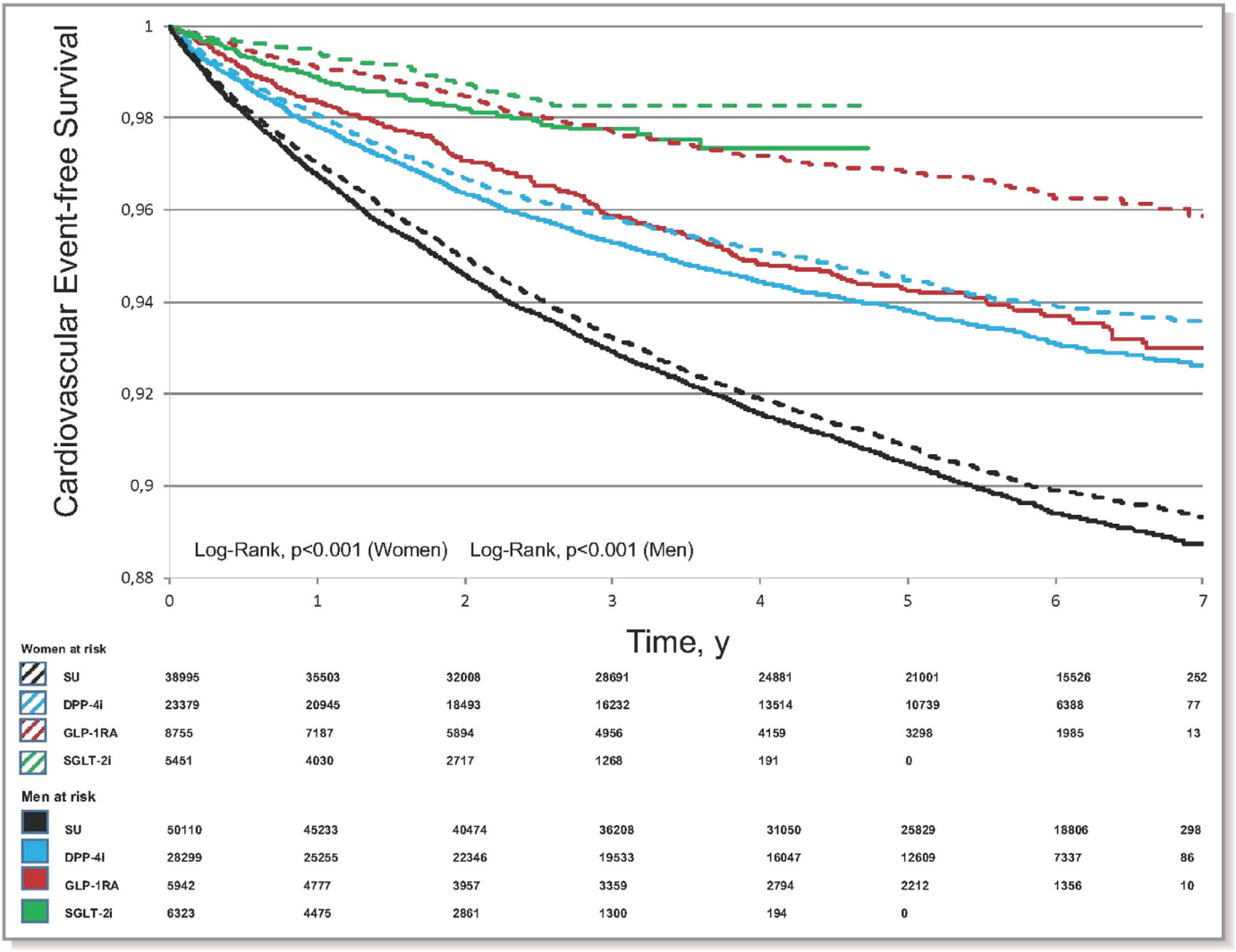

Figure 2. Kaplan–Meier curves for major cardiovascular events in women and men. DPP-4i indicates dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; SGLT-2i, sodium-glucose-like transport-2 inhibitors; SU, sulfonylureas.

are associated with reduced risks of major adverse cardiovascular outcomes in adults with T2DM and mostly without known established ASCVD. The magnitude of the risk reduction, relative to current sulfonylurea users, was greater in women users of GLP-1RA. Women experienced more side effects than men, regardless of the type of T2DM agent they initiated. However, as compared with sulfonylureas, newer glucose-lowering agents were associated with fewer adverse events in both men and women, without a clear difference in risk reductions between sexes.

Despite improved control of hypertension and other risk factors, individuals with diabetes mellitus continue to experience substantial excess of cardiovascular disease risk, especially women with double the risk of CVD events compared with men.[3–5] Therefore, in the past decade there has been substantial attention placed on the reduction of major cardiovascular events (including heart failure) seen in placebo-controlled RCTs of newer glucose-lowering agents in individuals at high cardiovascular risk.[22] The EMPA-REG (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) OUTCOME trial and the CANVAS (Canagliflozin and cardiovascular and renal events in type 2 diabetes) reported cardiovascular benefits, achieving a 14% relative risk reduction in the primary composite outcome with either empagliflozin or canagliflozin (both SGLT-2i) in individuals at high cardiovascular risk as compared with placebo.[17,18] A >30% relative risk reduction in hospitalization for heart failure was another key finding.[17,18] The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results**),** the SUSTAIN-6 trial (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide) and the HARMONY OUTCOMES (Trial to evaluate cardiovascular outcomes in T2DM and cardiovascular disease with albiglutide) reported a 13%, 27%, and 22% relative risk reduction in

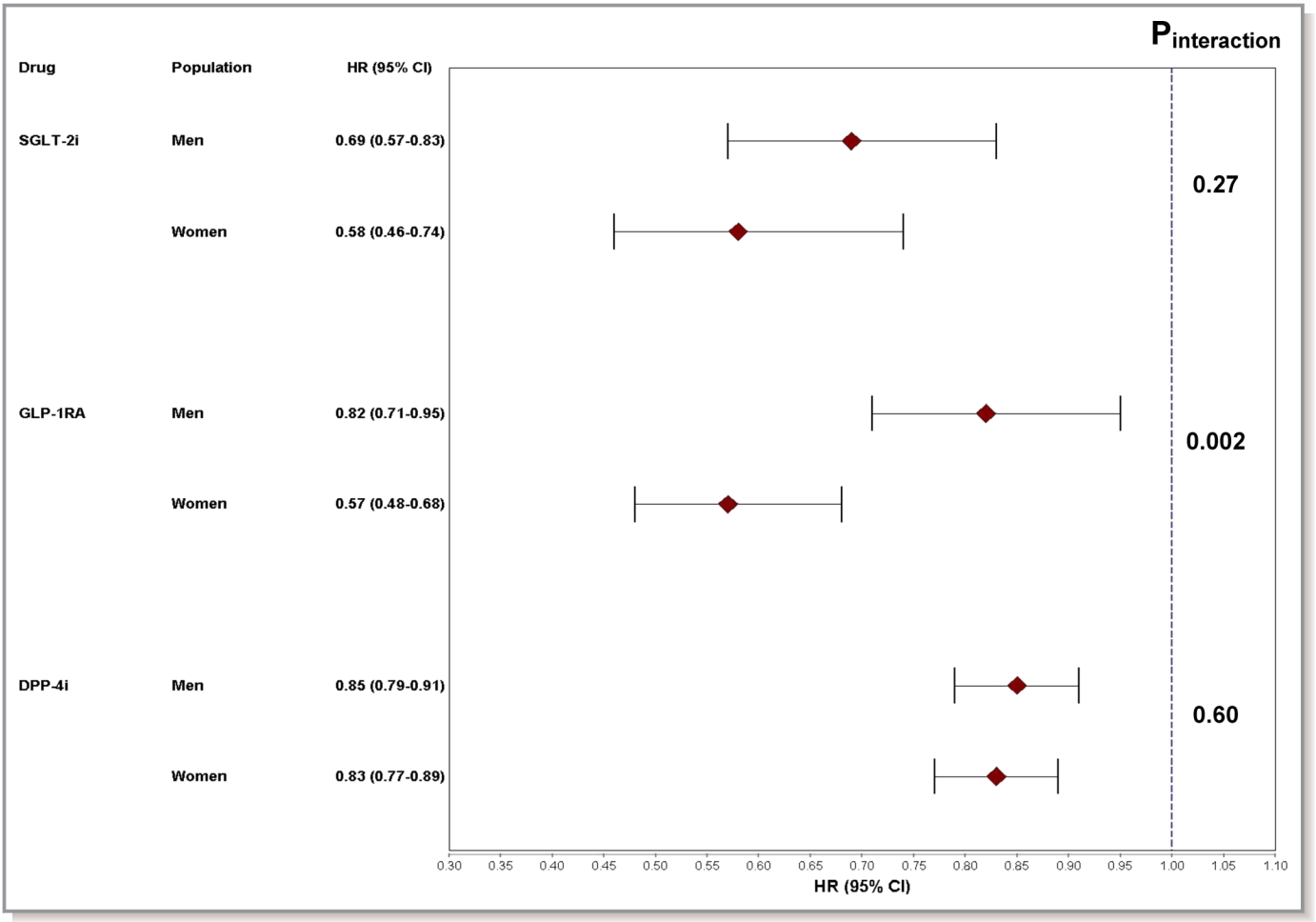

Figure 3. Adjusted hazard ratios (HR) relative to sulfonylureas for cardiovascular effectiveness outcomes in women and men. DPP-4i indicates dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; SGLT-2i, sodium-glucose like transport-2 inhibitors. The model was adjusted for age, baseline comorbidities, employment status, region, year entry, and sex-by-drug interactions.

major adverse events in users of liraglutide, semaglutide, and albiglutide (all GLP-1RA), as compared with placebo, respectively.[15,16,23] Overall, compared with placebo, DPP-4 inhibitors were not associated with benefits in terms of combined major adverse cardiovascular event and produced mixed results regarding heart failure.[24–26] Therefore, current guidelines recommended the use of SGLT-2i and GLP-1RA as second-line agents in T2DM adults with established ASCVD.[9] However, the choice of second-line drug is more challenging in individuals without established ASCVD because of the paucity of evidence. Specifically, data from RCTs or from observational cohort studies in low cardiovascular risk populations are available only for SGLT-2i. A recent meta-analysis from RCTs with SGLT-2i[27] showed that these agents are effective in reducing hospitalization for heart failure in primary prevention. Our cohort included predominantly adults with T2DM without established ASCVD, users of all the classes of new glucose-lowering agents, highlighting the need for confirming these overall and sex-specific results in RCTs specifically designed in individuals without established ASCVD.

The paucity of prior evidence for or against sex differences in the cardiovascular effectiveness and safety of strategies to improve CVD outcomes is an alarming issue.[8] In the last decade, the US Food and Drug Administration advocated for a higher participation of women in clinical trials for US Food and Drug Administration drug approval.[28–30] Simultaneously, the US Food and Drug Administration also released specific guidance requiring pharmaceutical agencies testing new glucose-lowering drugs to assess major adverse cardiovascular events.[31] However, RCTs of the new glucose-lowering agents enrolled a relatively low proportion of women (from 20% to 40%) and thus are far from being adequately powered to verify potential sex difference in their cardiovascular efficacy or safety.[15–18,22,27,32]

To address the issue of underrepresentation of women in RCTs,[28] the inclusion of sex as a biological variable in clinical research has been promoted by the World Health Organization

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Table 3. Safety Outcomes According to Sex and Glucose-Lowering Agent Prescribed at the Cohort Entry

	Men Overall (n=90 674)	Women Overall (n=76 580)	Men SU (n=50 110)	Women SU (n=38 995)	Men DPP-4i (n=28 299)	Women DPP-4i (n=23 379)	Men GLP-1RA (n=5942)	Women GLP-1RA (n=8755)	Men SGLT-2i (n=6323)	Women SGLT-2i (n=5451)
Safety composite outcome*										
No. of events	10 110	9471	6974	6154	2498	2435	455	696	183	186
Incidence per 1000 PY	27.7 (27.1–28.2)	31.2 (30.6–31.9)	32.1 (31.3–32.8)	36.5 (35.6–37.4)	21.7 (20.9–22.6)	26.0 (25.0–27.1)	21.7 (19.8–23.8)	22.9 (21.2–24.7)	15.6 (13.5–18.1)	17.6 (15.2–20.4)
Hypoglycemia										
No. of events	2269	1815	1775	1377	409	333	76	90	9	15
Incidence per 1000 PY	5.8 (5.6–6.1)	5.5 (5.3–5.8)	7.6 (7.2–7.9)	7.4 (7.0–7.8)	3.4 (3.1–3.7)	3.3 (3.0–3.7)	3.5 (2.7–4.3)	2.8 (2.2–3.4)	0.8 (0.3–1.4)	1.4 (0.8–2.3)
Urosepsis										
No. of events	5222	6158	3630	3994	1284	1626	235	448	76	90
Incidence per 1000 PY	13.1 (12.7–13.4)	18.3 (17.8–18.7)	15.0 (14.5–15.5)	20.8 (20.2–21.5)	10.4 (9.8–11.0)	15.9 (15.2–16.7)	10.5 (9.2–12.0)	13.7 (12.5–15.0)	6.4 (5.0–8.0)	8.3 (6.7–10.2)
Genital infections										
No. of events	881	1027	560	633	242	265	45	77	34	52
Incidence per 1000 PY	2.2 (2.1-2.4)	3.1 (2.9–3.3)	2.4 (2.2–2.6)	3.4 (3.1–3.6)	2.0 (1.7–2.2)	2.6 (2.3–3.0)	2.0 (1.5–2.7)	2.4 (1.9–3.0)	2.8 (2.0–4.0)	4.8 (3.1–3.6)
Acute renal failure										
No. of events	4531	3128	3136	2139	1124	777	199	177	72	35
Incidence per 1000 PY	11.8 (11.5–12.2)	9.9 (9.6–10.3)	13.6 (13.1–14.1)	12.1 (11.6–12.6)	9.4 (8.9–10.0)	8.1 (7.5–8.7)	9.2 (8.0–10.6)	5.7 (4.9–6.6)	6.1 (4.8–7.6)	3.3 (2.3–4.6)
Pancreatitis										
No. of events	705	497	437	281	190	147	50	50	28	19
Incidence per 1000 PY	1.8 (1.6–1.9)	1.5 (1.3–1.6)	1.8 (1.6–2.0)	1.4 (1.3–1.6)	1.5 (1.3–1.8)	1.4 (1.2–1.7)	2.2 (1.7–3.0)	1.5 (1.1–2.0)	2.3 (1.6–3.4)	1.7 (1.1–2.7)
Lower limb amputation										
No. of events	378	192	261	127	89	47	19	15	9	3
Incidence per 1000 PY	0.9 (0.9–1.0)	0.6 (0.5–0.7)	1.1 (0.9–1.2)	0.7 (0.5–0.8)	0.7 (0.6–0.9)	0.5 (0.3–0.6)	0.9 (0.5–1.3)	0.5 (0.3–0.8)	0.8 (0.3–1.4)	0.3 (0.1–0.8)

Data are provided as numbers of events or incidence rate (95% CI). DPP-4i indicates dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; PY, person-year; SGLT-2i, sodium-glucose-like transport-2 inhibitors; SU, sulfonylureas.

*Safety composite outcome includes any hospitalization or emergency room visit for hypoglycemic episode, pancreatitis, urosepsis, lower limb amputation, genital yeast infection, or acute renal failure.

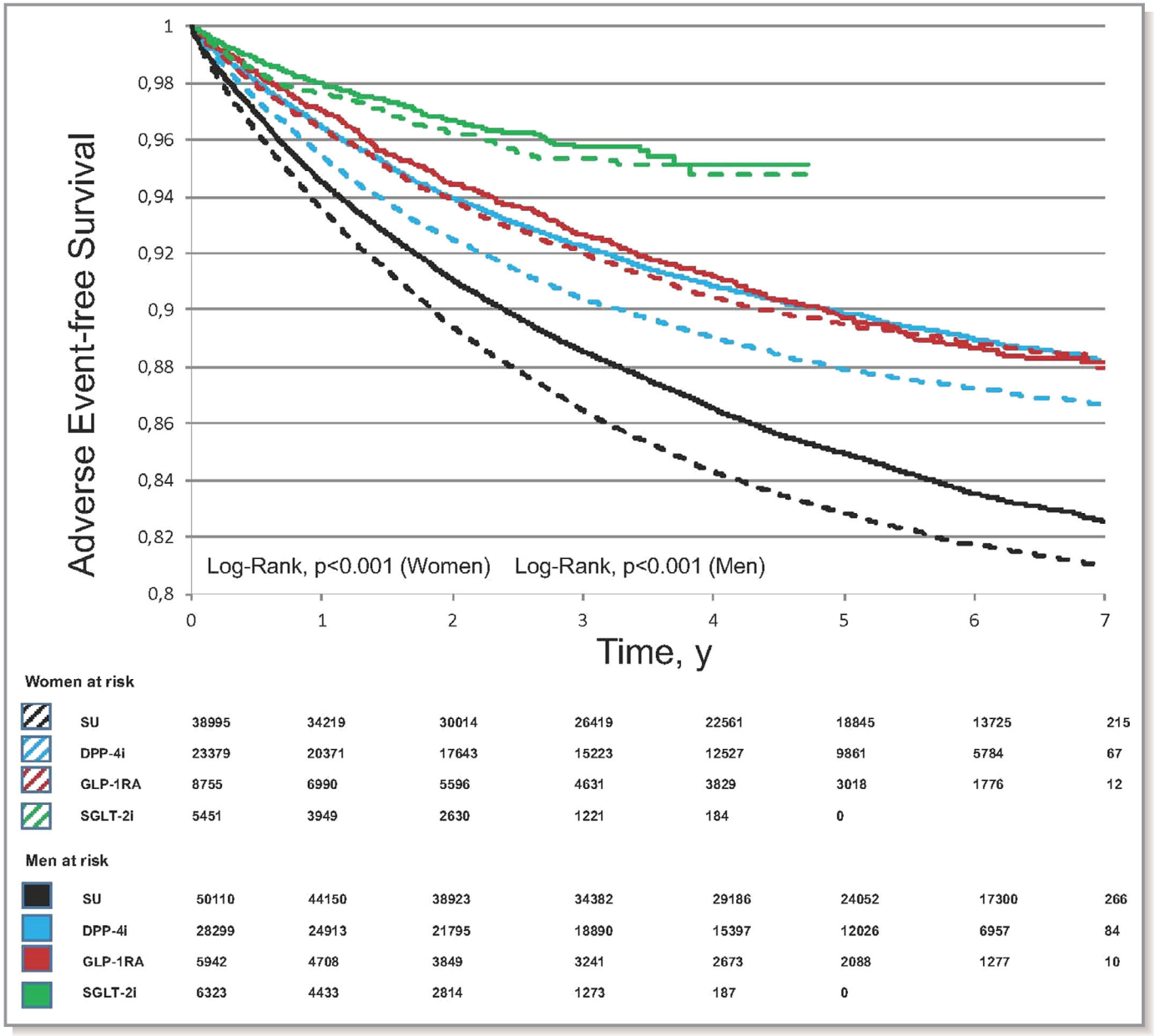

Figure 4. Kaplan–Meier curves for safety outcomes in women and men. DPP-4i indicates dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide 1 agonists; SGLT-2i, sodium-glucose-like transport-2 inhibitors; SU, sulfonylureas.

and other international societies.[33–35] Almost half of our cohort comprised women, whereas the proportion of women in RCTs of glucose-lowering agents is on average 30%. We found that women with T2DM using GLP-1RA, DPP-4i, and SGLT-2i (versus sulfonylureas) gained greater cardiovascular benefit than men in term of reduction of nonfatal major adverse events, with a sex-by-drug interaction significant for GLP-1RA.This observation extends our knowledge regarding the specific drug nonglycemic effect based on sex beyond the data available from landmark RCTs in adults with T2DM. Of note, our findings are in accordance with prior efforts[7,8,36] aimed at addressing therapeutic approaches for managing diabetes mellitus–associated cardiovascular complications and how differences in sex-gender can influence the existing therapeutic approaches. Furthermore, the present analysis is based on data from women with diabetes mellitus whose age ranges from 51 to 68 years, which presumably includes some premenopausal women. Nevertheless, the beneficial effect of new glucose-lowering agents cannot be biased by the inclusion of premenopausal women, traditionally considered to be at lower risk for CVD, because diabetes mellitus is the only condition that counteracts the beneficial cardiovascular effects of sex hormonal status.

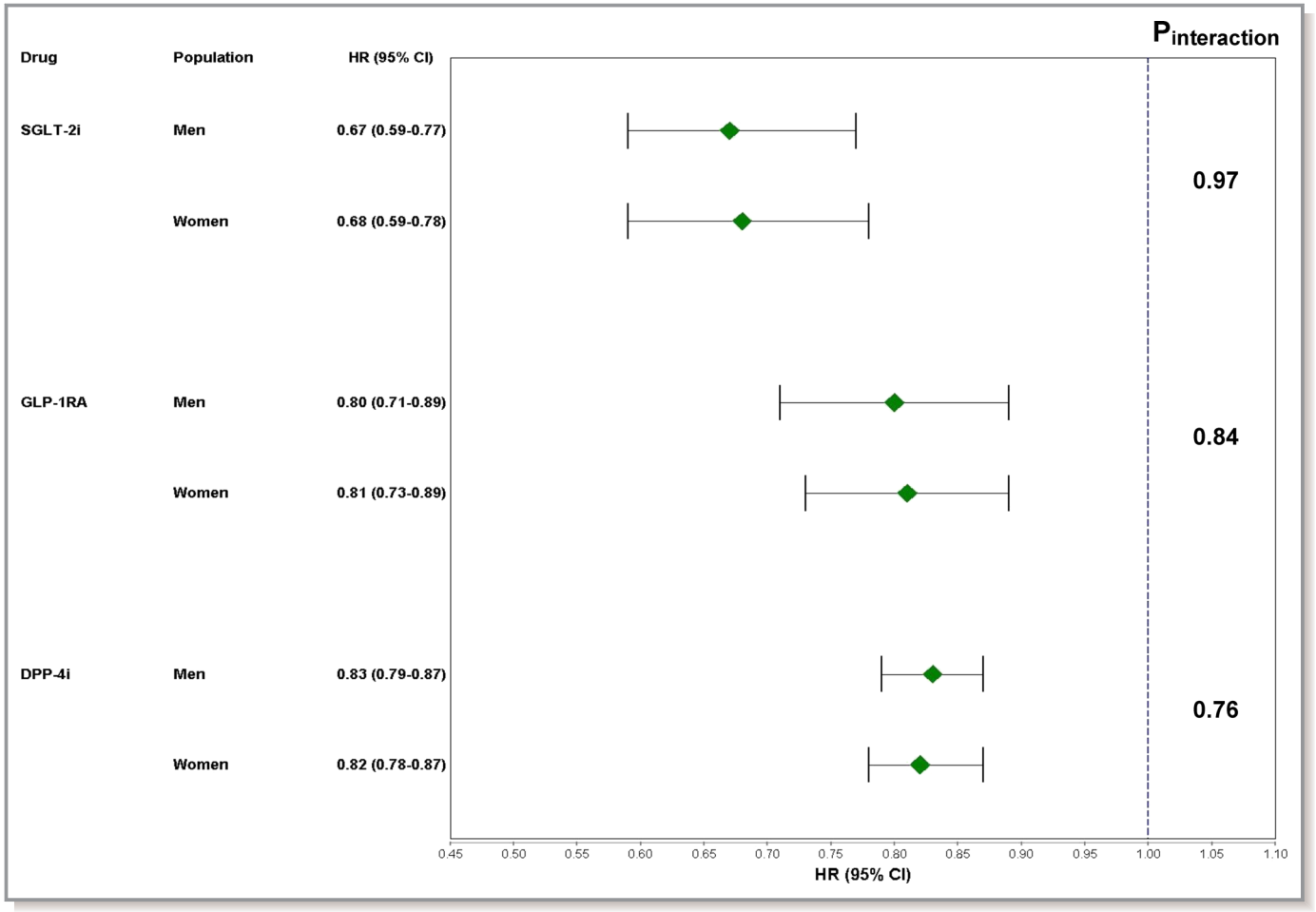

Figure 5. Adjusted HR relative to sulfonylureas for safety outcomes in women and men. DPP-4i indicates dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; HR, hazard ratios; SGLT-2i, sodium-glucose-like transport-2 inhibitors. The model was adjusted for age, baseline comorbidities, employment status, region, year entry, and sex-by-drug interactions.

Finally, we found a short-term cardiovascular beneficial effect of DPP4-I relative to sulfonylureas in US individuals in accordance with data of a recent network meta-analysis[37] and a Taiwanese study.[38] Nevertheless, the impact of DPP-4i on cardiovascular risk of individuals with T2DM remains a controversial issue that deserves further investigation.

The mechanisms by which newer glucose-lowering agents achieve cardiovascular benefits are unknown. Overall, the observed cardiovascular effects are believed to be almost certainly unrelated to the glucose-lowering effects of these drugs and most likely driven by benefits on various other factors including weight loss, blood pressure, lipid profile, inflammatory markers, and renal disease as well as by direct effects on the heart and vasculature.[39,40] Interventions aimed at weight loss have a greater benefit in terms of clinical and psychological parameters for women with diabetes mellitus than for men with diabetes mellitus.[41] Interestingly, a sex imbalance in the prescription of incretin-based therapy has been previously reported: DPP-4i were more often prescribed to men of older age with T2DM and with comorbidities,[42] while GLP-1RA were more often prescribed to obese young women.[43] In our analysis, among the new glucose-lowering agents, GLP-1RA users were more commonly women and the larger sample size allowed identification of a sex-by-drug interaction for this drug class.

Our findings are certainly hypothesis-generating and, at the moment, we can only speculate on the reasons underlying the greater effect of GLP-1RA in women.[44,45] A study reported that the function of the receptor for glucagon-like peptide can be modified by sex hormones,[44] while some authors proposed the hypothesis that GLP-1 receptor stimulation may have the potential to reduce platelet aggregation,[45] resulting in the lower cardiovascular risk especially in women who have higher baseline platelet activation than men.[46] Unfortunately, no data on the sex of cells and human platelets used to perform such experiments are reported. Nonglycemic effects of GLP-1RA have been recently reviewed and GLP-1RA seems to counteract endothelial dysfunction and inflammatory response,[39] which could also lower the risk of cardiovascular events, yet no data are available based on sex.

The beneficial effect of SGLT-2i on major cardiovascular outcomes, especially on heart failure, has been recently highlighted[27,32]; both hemodynamic and metabolic explanations have been proposed as underlying mechanisms.[40] Observational data showed that the clinical benefit occurred within the first year.[47] Hemodynamic benefits, related to salt and water elimination, may explain this early clinical improvement observed that could be greater in women. Recently, the ability of SGLT-2i to reduce left ventricular mass index has been reported as a main contributor to cardiovascular benefits in the long-term follow-up for patients with established ASCVD.[48] In our population, we found a lower rate of heart failure events in SGLT-2i users, especially in women. However, the absolute numbers of events during follow-up was low, and we can only speculate on the reasons for the lower incidence of heart failure admissions. Further mechanistic studies are needed to understand the greater heart failure benefit in women users of SGLT-2i versus sulfonylureas that we observed.

Data from clinical trials and observational studies have indicated that the new glucose-lowering agents could be associated with serious adverse events including lower limb amputation, acute kidney injury, serious genital and urinary infections, and acute pancreatitis.[49]Specifically, in a recent network meta-analysis, SGLT-2i were associated with a 4-fold increased relative risk of genital infections, not associated with a significant increase in lower limb amputation or urinary infections, while DPP-4i were associated with a 2-fold increased relative risk of acute pancreatitis.[49] However, safety data reported by sex are lacking. This issue is particularly relevant because during the postmarketing phase of drugs, more side effects are commonly reported in women,[50] which could be responsible for the higher medication discontinuation and nonadherence in women with diabetes mellitus.[51] In our cohort, regardless of the class of second-line glucose-lowering agents, women experienced a higher rate of side effects. However, sulfonylureas were associated with even greater risk than the newer agents, in both men and women**.** Of note, for men, SGLT-2i seem to be the optimal choice because they are equally effective but safer than GLP-1RA. For women, the choice of the add-on drug may require assessing the trade-off between higher effectiveness of GLP-1RA and the better safety profile of SGLT-2i.

The present analysis has clinical relevance because it specifically assessed sex differences in the cardiovascular effectiveness and safety of new glucose-lowering agents, as second-line as compared with sulfonylureas. An important strength of the study is the large sample size, with a representation of women that provides the power to detect the existence of sex differences. Other strengths of this study are the population-based, unselected real-world design, which provides good external validity.

This study also had some limitations to consider in the interpretation of the results. Nonrandomized and observational studies have inherent biases and limitations. However, adjustment for potential available confounders was done to limit such biases. Still, our observational data on sex differences reinforce the need for future RCTs to enroll enough women to enable measurement of potential differences in drug cardiovascular effectiveness and/or safety for men versus women. The administrative data sources that we used tend to have short periods of observation, because people may change their insurance plan. Thus, Marketscan may be of limited use in studying long-term outcomes. Furthermore, because of the limitations of administrative data, some relevant information was not available. We do not have outpatient mortality data that could clarify whether the nonfatal benefit in cardiovascular outcomes is conditioned by increased long-term outpatient mortality. In-hospital death occurred in few individuals (0.6%), as expected given the baseline low risk of this young population. Therefore it is unlikely that an analysis accounting for the competing risk of death would be informative in our specific cohort. We also did not have information regarding some important clinical confounding factors (eg, severity of disease, body mass index, systolic and diastolic blood pressure, duration of diabetes mellitus or other cardiovascular risk factors such as hypertension and obesity) and laboratory data (eg, hemoglobin A1C, glomerular filtration rate, etc.) that might have helped in interpreting the greater benefit achieved by women and to better control for confounding and baseline risk. However, to account for the severity of diabetes mellitus and based on our main focus on the add-on therapy when metformin alone fails to achieve long-term glycemic control, we decided to exclude any individuals with prior use of insulin. We also did not have information on smoking, which itself might be a confounder for the main effect observed, and/or details on adherence, a complex and important factor potentially correlated with other important and missing variables such as body mass index and smoking. However, it is unlikely that these variables could be confounders for the sex–drug interactions we observed.[52] The generalizability of these findings is potentially limited because the MarketScan includes only data of US individuals treated within a multipayer healthcare system, so these data require external validation in cohorts from different countries with different demographics and types of healthcare systems. Furthermore, because of the calendar year availability of data, the group of users of SGLT-2i was smaller compared with other glucose-lowering agents. Finally, because sulfonylureas was used as reference group, we cannot exclude that the cardiovascular harm of this drug category[53] may have influenced the great risk reduction observed for newer glucose-lowering agents.

In the cohort derivation, we have not accounted for individuals with surgically induced T2DM or steroid-induced DM whose disease course might be different from that of individuals with typical T2DM. However, these groups would likely be a small component of the cohort. Therefore, it is unlikely that the results might be biased. Our results required careful interpretation, because we are reporting only associations between treatment and outcomes. Therefore, causality cannot be established by this observational study.

Conclusions

Newer glucose-lowering agents used with metformin were associated with a lower risk of major adverse cardiovascular events, as compared with sulfonylureas. This beneficial effect was more pronounced in women than in men, especially for GLP-1RA users. Newer agents were also associated with a lower risk of adverse events, with no clear sex–drug interactions. These findings highlight the importance of a personalized approach that considers patients' sex in the choice of the most appropriate diabetes mellitus therapy. In clinical practice, the selection of the add-on therapy in metformin users should be guided by the estimate of the net benefit in terms of effectiveness and safety in both men and women.

Our findings suggest the need for ongoing evaluation of possible interactions with sex in all drug safety and effectiveness analyses, including randomized trials.

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Disclosures

None.

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Supplemental Material

Table S1. Detailed list of codes for outcomes definition.

Condition	Diseases		Procedures
	ICD-9	ICD-10	CPT-4/HCPCS/ICD-9
Acute Myocardial Infarction*	410.xx	I21–I22	
Unstable angina*	411.1x	I20	
Silent Myocardial Infarction		I25.6	
Ischemic stroke*	433.x1, 434.x1, or 436	I63	
Hemorrhagic stroke*	431	I61	
Heart failure	428.x	150.x	
Coronary artery bypass graft			36.10-36.19 plus CPT-4 codes 33510-33519, 33521-33523, 33533-33536
Percutaneous coronary intervention			00.66, 36.01-36.09 plus CPT-4 codes 92980-92982, 92984, 92995, 92996 92920-92944
Transient Ischemic Attack*	435.x	G45.x	
Hypoglycemia	251.0x, 251.1x, 251.2x, and 250.8x	E15-E16	
Amputation of lower limb			ICD-9: 84.10, 84.12, 84.14, 84.15, 84.3, 84.91, 84.11 † CPT: 27590-27592, 27880-27882, 28800, 28805, 28810, 28820, and 28825
Pancreatitis	577.0	K85.0,K85.3,K85.8,K85.9	
Urosepsis	599.0, 020.0x (septicemic), 038.xx	R78.81 (bacteremia), A41.9 (septicemia),	

	(septicemia and its subtypes), 785.52 (septic shock), 790.7x (bacteremia), 995.91 (sepsis), 995.92 (severe sepsis), and 780.6 (fever of unknown origin).	A41.51 (E.coli), R65.10-65.11 (SIRS), T65.20 (severe sepsis), R65.21 (septic shock)
Genital infection	112.1, 616.1 (female); 607.1 (male)	B37.3, N77.1, (Female), B37.4, N37.0, N51.2 (male), B36.9 (unspecified), B36.8 (other specified superficial mycoses). B35.6 (tinea inguinalis)
Acute renal failure	584.5 – 584.9	N17

ICD, International Classification of Diseases; CPT, Current Procedural Terminology; HCPCS, Health Care Procedures Classification System.
*For hospital records, only the main diagnosis was selected. For outpatient records, only emergency room visit records were selected.
† Must be accompanied by one of the following codes: 440.20, 440.21, 440.22, 440.23, 440.24.