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Association of Second-line Antidiabetic Medications With Cardiovascular Events Among Insured Adults With Type 2 Diabetes

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Abstract

IMPORTANCE Understanding cardiovascular outcomes of initiating second-line antidiabetic medications (ADMs) may help inform treatment decisions after metformin alone is not sufficient or not tolerated. To date, no studies have compared the cardiovascular effects of all major second-line ADMs during this early decision point in the pharmacologic management of type 2 diabetes.

OBJECTIVE To examine the association of second-line ADM classes with major adverse cardiovascular events.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study among 132 737 insured adults with type 2 diabetes who started therapy with a second-line ADM after taking either metformin alone or no prior ADM. This study used 2011-2015 US nationwide administrative claims data. Data analysis was performed from January 2017 to October 2018.

EXPOSURES Dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, thiazolidinediones (TZDs), basal insulin, and sulfonylureas or meglitinides (both referred to as sulfonylureas hereafter). The DPP-4 inhibitors served as the comparison group in all analyses.

MAIN OUTCOMES AND MEASURES The primary outcome was time to first cardiovascular event after starting the second-line ADM. This composite outcome was based on hospitalization for the following cardiovascular conditions: congestive heart failure, stroke, ischemic heart disease, or peripheral artery disease.

RESULTS Among 132 737 insured adult patients with type 2 diabetes (men, 55%; aged 45-64 years, 58%; white, 63%), there were 3480 incident cardiovascular events during 169 384 person-years of follow-up. Patients were censored after the first cardiovascular event, discontinuation of insurance coverage, transition from *International Classification of Diseases, Ninth Revision* (*ICD-9*) to end of *ICD-9* coding, or 2 years of follow-up. After adjusting for patient, prescriber, and health plan characteristics, the risk of composite cardiovascular events after starting GLP-1 receptor agonists was lower than DPP-4 inhibitors (hazard ratio [HR], 0.78; 95% CI, 0.63-0.96), but this finding was not significant in all sensitivity analyses. Cardiovascular event rates after starting treatment with SGLT-2 inhibitors (HR, 0.81; 95% CI, 0.57-1.53) and TZDs (HR, 0.92; 95% CI, 0.76-1.11) were not statistically different from DPP-4 inhibitors. The comparative risk of cardiovascular events was higher after starting treatment with sulfonylureas (HR, 1.36; 95% CI, 1.23-1.49) or basal insulin (HR, 2.03; 95% CI, 1.81-2.27) than DPP-4 inhibitors.

(continued)

Key Points

Question Are second-line antidiabetic medications (ADMs) associated with cardiovascular events among insured adult patients with type 2 diabetes who are initiating second-line therapy?

Findings This cohort study of 132 737 adults with type 2 diabetes found that glucagon-like peptide 1 receptor agonists, dipeptidyl peptidase 4 inhibitors, and sodium-glucose cotransporter 2 inhibitors were associated with similar cardiovascular outcomes. Sulfonylureas and basal insulin were associated with comparatively higher cardiovascular risk.

Meaning Clinicians may consider prescribing newer ADM classes more routinely after metformin rather than sulfonylureas or basal insulin.

+ Invited Commentary

+ Supplemental content

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Abstract (continued)

CONCLUSIONS AND RELEVANCE Among insured adult patients with type 2 diabetes initiating second-line ADM therapy, the short-term cardiovascular outcomes of GLP-1 receptor agonists, SGLT-2 inhibitors, and DPP-4 inhibitors were similar. Higher cardiovascular risk was associated with use of sulfonylureas or basal insulin compared with newer ADM classes. Clinicians may consider prescribing GLP-1 receptor agonists, SGLT-2 inhibitors, or DPP-4 inhibitors more routinely after metformin rather than sulfonylureas or basal insulin.

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Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in type 2 diabetes, and reducing its burden is an important goal of antidiabetic medications (ADMs).[1,2] Metformin, which may have cardiovascular benefits, is widely recommended as first-line therapy.[2,3] However, there is a lack of consensus about choosing subsequent ADMs among patients who do not achieve adequate glycemic control with metformin or do not tolerate it.[2,4] Comparing cardiovascular outcomes of second-line ADMs during this early transition in diabetes pharmacotherapy may help improve treatment decisions after metformin or in place of it.

Use of ADMs has increased owing to the rising prevalence of diabetes and a proliferation of novel therapeutic classes. Recent placebo-controlled trials of dipeptidyl peptidase 4 (DPP-4) inhibitors generally found no cardiovascular benefits or harms.[5-7] However, some trials of glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT-2) inhibitors reported reductions in composite cardiovascular outcomes and some individual cardiovascular events.[8-14] These trials specifically recruited participants with a high burden of cardiovascular disease who were taking multiple ADMs. Therefore, it is not known whether their findings apply to the broader population with diabetes. Older research on second-line ADMs suggested cardiovascular harms associated with sulfonylureas, thiazolidinediones (TZDs), and insulin.[15] To date, no studies have directly compared the cardiovascular effects of all contemporary ADM options among patients starting second-line therapy.

Our study investigated the comparative effectiveness of all major second-line ADM classes on major adverse cardiovascular events among insured adult patients with type 2 diabetes. By examining cardiovascular outcomes among patients initiating second-line ADMs in the real world, this study aimed to complement findings from individual drug trials and further inform ADM choices for the broad population of patients currently receiving these medications.[16,17]

Methods

Study Design

We conducted a retrospective, cohort study using national administrative claims data collected from April 2011 to September 2015.[18] To minimize the potential for differences in diabetes duration and severity that may be related to ADM selection, we focused comparisons on patients with type 2 diabetes initiating second-line ADM therapy (ie, the first ADM other than metformin). Our analysis compared the cardiovascular effectiveness of the next ADM class started after metformin alone or no prior ADM: DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, TZDs, basal insulin, or sulfonylureas or meglitinides (both referred to as sulfonylureas hereafter). eTable 1 in the Supplement lists medications from each ADM class. The Northwestern University institutional review board deemed this study exempt from review and waived the need for patient informed consent.

Study Data and Setting

Data sources included patients' health plan enrollment files, laboratory claims, pharmacy claims, and medical claims provided from a large health payer. Medical diagnoses were coded according to the *International Classification of Diseases, 9th Revision* (*ICD-9*),[19] which was phased out in September 2015. Analyzing *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) data after that time would require differential ascertainment of outcomes and was therefore not performed. Pharmacy claims for individual second-line ADMs were grouped into 1 of the 6 classes. Hemoglobin A_{1c} (HbA_{1c}) values were available for a subset of patients based on their laboratory vendor. Information about patients' race/ethnicity was imputed by the data vendor. The data are described in-depth elsewhere.[20] We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[21]

Participants

The study population was derived from a nationwide database of US adults 18 years or older who were enrolled in commercial or Medicare Advantage health insurance plans. Inclusion criteria were (1) type 2 diabetes and a first pharmacy-dispensing event for second-line ADMs, occurring on the index date; (2) at least 12 months of enrollment before the index date; (3) no ADM prescription fills other than metformin before the index date; and (4) at least 2 prescription fills of the index ADM, which identifies early persistent users.[22] Individuals were considered to have type 2 diabetes if they had at least 1 medical claim associated with a corresponding diagnosis code occurring on or before the index date. We excluded patients with evidence of type 1 diabetes or secondary diabetes prior to the index date, more than 1 ADM class prescription filled on the index date, or pregnancy within 180 days before the index date or any time thereafter. Definitions of the eligibility criteria and study variables are provided in eTable 2 in the Supplement.

Exposure and Outcomes

The exposure was a categorical variable identifying which second-line ADM class was started on the index date, defined by the first prescription fill of the new ADM. The primary outcome was time to first major adverse cardiovascular event after starting the index ADM. Cardiovascular events were ascertained using diagnosis codes associated with inpatient medical claims, which are very specific and have higher positive predictive value for identifying events than ambulatory claims.[23,24]

The composite primary outcome included hospitalization for 1 of the following cardiovascular conditions: congestive heart failure, stroke, ischemic heart disease, and peripheral artery disease, which was added because a recent ADM trial reported increased amputation risk.[8] We examined each of these events individually as secondary outcomes. History of cardiovascular events before the index date was ascertained in the same manner. Patients were censored after the first cardiovascular event (n = 3483), discontinuation of insurance coverage (n = 86 411), transition to *ICD-10* (n = 7697), or 2 years of follow-up (n = 35 116). The last criterion was chosen to balance follow-up time across ADM groups given the introduction of SGLT-2 inhibitors in 2013.

Covariates

All covariates were assessed within the 12 months preceding the index date. Demographic data included patients' age, sex, and race/ethnicity. The most recent HbA_{1c} result was categorized: less than 8.0%, 8.0% to 10.0%, more than 10.0%, and a separate category for those without available values. We used diagnostic codes from inpatient and ambulatory medical claims to examine prevalent microvascular complications.[25] The following cardiovascular risk factors were also assessed at baseline and analyzed as covariates: chronic kidney disease, dyslipidemia, hypertension, obesity, and tobacco use. We examined patient use of the following medications known to affect cardiovascular risk: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists, antiplatelet drugs, β-blockers, calcium channel blockers, diuretics, statins, and other lipid-lowering drugs. Time-varying covariates were constructed to capture changes

in the use of these medications during follow-up as well as exposure to other ADMs started after the index date. Characteristics of prescribers (ie, area of clinical training) and health coverage (ie, payer, plan type, enrollment year, census division where enrolled, and mean medical expenses for all plan members in the previous year) were also analyzed as covariates.

Statistical Analysis

Data analysis was performed from January 2017 to October 2018. Summary statistics characterized the study population by second-line ADM class (**Table 1** and eTable 3 in the Supplement) and χ^2 tests were used to examine associations between baseline covariates and index ADM class. Cox proportional hazards regression was used to model the association between index ADM class and composite cardiovascular events (**Table 2**). To test the proportional hazards assumption, we generated and compared log-log plots for the 6 ADM classes, and tested Schoenfeld residuals.[26] The primary model included individual variables for all baseline patient characteristics listed in Table 1, in addition to prescribers' area of clinical training and health coverage characteristics listed in eTable 3 in the Supplement. Direct-adjusted cumulative incidence curves from the primary model were plotted (**Figure**).[27,28] Direct adjustment calculates a mean for the estimated survival curves for patients in each group rather than computing estimates at the mean value of the covariates. By using the same approach, individual cardiovascular events were modeled separately. The DPP-4 inhibitors served as the comparison group in all models, following trial evidence of their cardiovascular neutrality.[5-7] The primary analysis followed an intention-to-treat principle intended to reflect "real-world" clinical practice.

To assess the robustness of our findings, we conducted multiple sensitivity analyses. In the full cohort, we stratified the primary model by the presence of prior cardiovascular events, prior metformin use, and available HbA_{1c} data (**Table 3**). Incomplete medication adherence or additional medications filled after the index date may have affected cardiovascular outcomes. Therefore, we conducted a sensitivity analysis accounting for time-varying exposure to all ADMs and cardiovascular medications filled during follow-up (Table 3). In addition, the subset of patients who were adherent to the index ADM, defined by possession of the medication for 80% or more of days,[29] and filled no other ADM during follow-up was examined (**Table 4**). Other sensitivity analyses added to the primary model HbA_{1c} values within the preceding 3 months (eTable 4 in the Supplement) and Charlson comorbidity score (eTable 5 in the Supplement). We also defined the index date based on the second fill of the index ADM (eTable 6 in the Supplement). We examined the association of ADM class with schizophrenia as a negative control outcome. Because there is no plausible mechanism by which ADMs are associated with schizophrenia risk, observed associations in this falsification test should be due to bias (eTable 7 in the Supplement). A 2-sided *P* value less than .05 was considered significant for all statistical testing. Analyses were conducted using SAS, version 9.4 (SAS Institute Inc).

Results

The total study cohort included 132 737 insured adult patients with type 2 diabetes (men, 55%; aged 45 to 64 years, 58%; white, 63%). Table 1 reports statistically significant associations between index ADM class and all listed baseline characteristics of patients. There were clinically meaningful differences between ADM groups with respect to some sociodemographic factors, prevalent clinical conditions, and cardiovascular medication use. Overall, 5.5% of patients had a history of cardiovascular events before starting treatment with the index ADM. Sulfonylureas composed 47.6% of index ADM fills, followed by DPP-4 inhibitors (21.8%), basal insulin (12.2%), GLP-1 receptor agonists (8.6%), TZDs (5.6%), and SGLT-2 inhibitors (4.3%). Almost three-quarters of index ADMs were prescribed by physicians trained in internal medicine or family medicine (eTable 3 in the Supplement). There were 3480 inpatient cardiovascular events during 169 384 person-years of follow-up (mean [SD], 1.3 [0.6] years). An omnibus hypothesis test demonstrated evidence of

Table 1. Baseline Characteristics of the Study Population by ADM Class

Characteristic[a]	Total Cohort, No. (%)	ADM Class, No. (% of Total Cohort)					
		DPP-4 Inhibitors	GLP-1 Receptor Agonists	SGLT-2 Inhibitors	TZDs	Basal Insulin	SFUs
Participants (%)	132 737 (100)	28 898 (21.8)	11 351 (8.6)	5677 (4.3)	7368 (5.6)	16 249 (12.2)	63 194 (47.6)
Sex							
Women	58 935 (44.4)	12 628 (43.7)	7174 (63.2)	2589 (45.6)	2815 (38.2)	7231 (44.5)	26 478 (41.9)
Men	73 802 (55.6)	16 269 (56.3)	4177 (36.8)	3088 (54.4)	4553 (61.8)	9018 (55.5)	36 716 (58.1)
Age, y							
18-44	17 521 (13.2)	3236 (11.2)	2656 (23.4)	1028 (18.1)	729 (9.9)	3071 (18.9)	6762 (10.7)
45-64	76 589 (57.7)	17 714 (61.3)	7333 (64.6)	4195 (73.9)	3979 (54.0)	8807 (54.2)	34 567 (54.7)
≥65	38 627 (29.1)	7947 (27.5)	1362 (12.0)	454 (8.0)	2660 (36.1)	4371 (26.9)	21 865 (34.6)
Race/ethnicity[b]							
White	83 491 (62.9)	18 177 (62.9)	8059 (71.0)	3849 (67.8)	4502 (61.1)	10 302 (63.4)	38 548 (61.0)
Black	14 734 (11.1)	3091 (10.7)	1181 (10.4)	573 (10.1)	604 (8.2)	2015 (12.4)	7204 (11.4)
Hispanic	20 707 (15.6)	4306 (14.9)	1317 (11.6)	772 (13.6)	1341 (18.2)	2437 (15.0)	10 617 (16.8)
Unknown	13 805 (10.4)	3323 (11.5)	794 (7.0)	483 (8.5)	921 (12.5)	1495 (9.2)	6825 (10.8)
Diabetes complications[c]							
Prior cardiovascular events[d]	7301 (5.5)	1792 (6.2)	341 (3.0)	244 (4.3)	258 (3.5)	861 (5.3)	3855 (6.1)
Nephropathy	8761 (6.6)	1705 (5.9)	329 (2.9)	182 (3.2)	567 (7.7)	1397 (8.6)	4613 (7.3)
Neuropathy	11 415 (8.6)	2283 (7.9)	692 (6.1)	397 (7.0)	597 (8.1)	2047 (12.6)	5435 (8.6)
Retinopathy	8097 (6.1)	1705 (5.9)	409 (3.6)	278 (4.9)	376 (5.1)	1657 (10.2)	3665 (5.8)
Hemoglobin A_{1c}, %							
Result not available[e]	90 394 (68.1)	17 570 (60.8)	7412 (65.3)	2895 (51.0)	5232 (71.0)	12 496 (76.9)	44 867 (71.0)
<8	18 451 (13.9)	5404 (18.7)	2577 (22.7)	1288 (22.7)	1149 (15.6)	926 (5.7)	7078 (11.2)
8-10	13 937 (10.5)	3987 (13.8)	840 (7.4)	920 (16.2)	589 (8.0)	1056 (6.5)	6509 (10.3)
>10	9955 (7.5)	1936 (6.7)	522 (4.6)	568 (10.0)	398 (5.4)	1771 (10.9)	4740 (7.5)
Metformin use	79 377 (59.8)	19 535 (67.6)	5959 (52.5)	3957 (69.7)	4045 (54.9)	6630 (40.8)	39 307 (62.2)
Cardiovascular medication use							
ACE inhibitors/ARBs	62 785 (47.3)	14 189 (49.1)	4268 (37.6)	2753 (48.5)	3220 (43.7)	6093 (37.5)	32 229 (51.0)
Aldosterone antagonists	3584 (2.7)	809 (2.8)	443 (3.9)	153 (2.7)	162 (2.2)	439 (2.7)	1517 (2.4)
Antiplatelet drugs	6504 (4.9)	1358 (4.7)	306 (2.7)	159 (2.8)	324 (4.4)	959 (5.9)	3349 (5.3)
β-Blockers	32 521 (24.5)	7138 (24.7)	2111 (18.6)	1164 (20.5)	1533 (20.8)	3542 (21.8)	16 999 (26.9)
Calcium channel blockers	23 627 (17.8)	5288 (18.3)	1442 (12.7)	903 (15.9)	1238 (16.8)	2405 (14.8)	12 323 (19.5)
Diuretics	33 052 (24.9)	7456 (25.8)	2883 (25.4)	1391 (24.5)	1584 (21.5)	3217 (19.8)	16 557 (26.2)
Statins	65 041 (49.0)	16 038 (55.5)	4563 (40.2)	2861 (50.4)	3853 (52.3)	5801 (35.7)	31 913 (50.5)
Other lipid-lowering drugs	16 194 (12.2)	4508 (15.6)	1362 (12.0)	704 (12.4)	1164 (15.8)	1267 (7.8)	7267 (11.5)
Cardiovascular risk factors[c]							
Chronic kidney disease	16 592 (12.5)	3323 (11.5)	636 (5.6)	318 (5.6)	906 (12.3)	2746 (16.9)	8721 (13.8)
Dyslipidemia	81 766 (61.6)	19 795 (68.5)	6799 (59.9)	3968 (69.9)	4443 (60.3)	8092 (49.8)	38 675 (61.2)
Hypertension	93 049 (70.1)	21 385 (74.0)	7480 (65.9)	4332 (76.3)	4811 (65.3)	9993 (61.5)	44 994 (71.2)
Obesity	28 937 (21.8)	6300 (21.8)	4166 (36.7)	2186 (38.5)	1172 (15.9)	2746 (16.9)	12 386 (19.6)
Tobacco use	10 752 (8.1)	2312 (8.0)	851 (7.5)	573 (10.1)	442 (6.0)	1397 (8.6)	5182 (8.2)

Abbreviations: ACE, angiotensin-converting enzyme; ADM, antidiabetic medication; ARBs, angiotensin receptor blockers; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SFUs, sulfonylureas or meglitinides; SGLT-2, sodium-glucose cotransporter 2; TZDs, thiazolidinediones.

[a] All baseline characteristics were significantly associated with ADM class in bivariate analyses ($P < .001$).

[b] Race/ethnicity are not routinely collected in health plan administrative data sources but have been imputed by the data vendor from individual-level and area-level characteristics.

[c] Diagnostic codes used to define all clinical conditions are listed in eTable 2 in the Supplement.

[d] Prior cardiovascular events were defined using *International Classification of Diseases, Ninth Revision,* diagnosis codes associated with inpatient medical claims for any of the following conditions at baseline: congestive heart failure, stroke, ischemic heart disease, or peripheral artery disease.

[e] Laboratory values are not routinely available in health plan administrative data sources unless submitted by the laboratory vendor as part of their contract with the health payer; for these data, 31.9% of submitted laboratory claims nationally included a result.

cardiovascular outcome differences across the 6 antidiabetic medication groups (Wald statistic: χ^2_5, 486.85; score: χ^2_5, 530.07; likelihood ratio: χ^2_5, 551.10; all $P < .001$).

Table 2 and the Figure present the adjusted hazard ratios (HRs) of cardiovascular events for each second-line ADM class relative to DPP-4 inhibitors. Starting treatment with GLP-1 receptor agonists was associated with a lower incidence of composite cardiovascular events (HR, 0.78; 95% CI, 0.63-0.96). The cardiovascular event rates after starting treatment with SGLT-2 inhibitors (HR, 0.81; 95% CI, 0.57-1.53) and TZDs (HR, 0.92; 95% CI, 0.76-1.11) were not statistically different from DPP-4 inhibitors. The risk of composite cardiovascular events was 36% higher in the sulfonylureas group (HR, 1.36; 95% CI, 1.23-1.49) and more than 2 times higher in the basal insulin group (HR, 2.03; 95% CI, 1.81-2.27) than in the DPP-4 inhibitor group. This corresponds to numbers needed to harm during 2 years of treatment with sulfonylureas and basal insulin of 103 and 37, respectively. Increased relative cardiovascular risk associated with use of sulfonylureas or basal insulin was observed across all individual cardiovascular outcomes. Treatment with GLP-1 receptor agonists was associated with a significant reduction in stroke risk (HR, 0.65; 95% CI, 0.44-0.97). No other significant benefits of ADM class were observed for individual cardiovascular outcomes.

In sensitivity analyses (Table 3), the increased cardiovascular risks associated with starting basal insulin or sulfonylurea treatment compared with DPP-4 inhibitors were robust. The lower risk of

Table 2. Adjusted HRs for Composite and Individual Cardiovascular Outcomes by ADM Class Among 132 737 Insured Adults With Type 2 Diabetes[a]

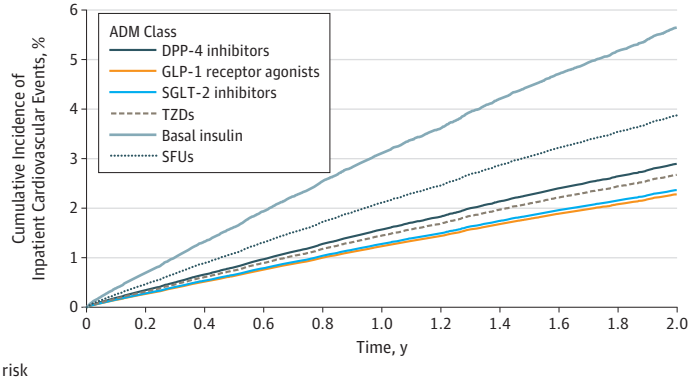
	Composite Cardiovascular Outcome[b]		Individual Cardiovascular Outcomes, HR (95% CI)			
ADM Class	No. of Events (%)	HR (95% CI)	Congestive Heart Failure	Stroke	Ischemic Heart Disease	Peripheral Artery Disease
DPP-4 inhibitors	543 (1.9)	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
GLP-1 receptor agonists	104 (0.9)	0.78 (0.63-0.96)	0.65 (0.42-1.02)	0.65 (0.44-0.97)	0.91 (0.67-1.24)	0.90 (0.42-1.95)
SGLT-2 inhibitors	34 (0.6)	0.81 (0.57-1.53)	0.54 (0.24-1.22)	0.56 (0.26-1.12)	1.18 (0.74-1.87)	1.11 (0.33-3.65)
TZDs	132 (1.8)	0.92 (0.76-1.11)	0.93 (0.63-1.36)	0.73 (0.51-1.05)	0.95 (0.71-1.28)	1.67 (0.94-2.97)
Basal insulin	721 (4.4)	2.03 (1.81-2.27)	2.33 (1.90-2.87)	1.77 (1.44-2.19)	1.92 (1.59-2.32)	2.92 (1.96-4.35)
SFUs	1946 (3.1)	1.36 (1.23-1.49)	1.47 (1.23-1.75)	1.28 (1.08-1.52)	1.35 (1.16-1.57)	1.65 (1.16-2.36)

Abbreviations: ADM, antidiabetic medication; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HR, hazard ratio; SFUs, sulfonylureas or meglitinides; SGLT-2, sodium-glucose cotransporter 2; TZDs, thiazolidinediones.

[a] All Cox proportional hazards models adjusted for patient baseline sociodemographic characteristics, hemoglobin A_{1c}, cardiovascular risk factors, diabetes complications including prior cardiovascular events, as well as prior use of metformin and cardiovascular medications included in Table 1. Models also adjusted for prescriber and health plan variables included in eTable 3 in the Supplement.

[b] Composite cardiovascular outcome included hospitalization for congestive heart failure, stroke, ischemic heart disease, or peripheral artery disease.

Figure. Adjusted Cumulative Incidence of First Cardiovascular Event After Starting the Second-line Antidiabetic Medication (ADM) Among Insured Adults With Type 2 Diabetes, by ADM Class



No. at risk

DPP-4	28 898	26 347	20 163	16 090	12 576	9674
GLP-1	11 351	10 051	7261	5668	4383	3361
SGLT-2	5677	4786	2597	1330	585	215
TZDs	7368	6783	5195	4256	3485	2769
Basal insulin	16 249	14 448	10 282	8090	6333	4802
SFU	63 194	57 239	43 304	34 951	28 064	21 991

This model was adjusted for patients' baseline sociodemographic characteristics, hemoglobin A_{1c} level, cardiovascular risk factors, diabetes complications (including prior cardiovascular events), prior use of metformin and cardiovascular medications, and prescriber and health plan variables. DPP-4 indicates dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SFUs, sulfonylureas or meglitinides; SGLT-2, sodium-glucose cotransporter 2; and TZDs, thiazolidinediones.

composite cardiovascular events associated with GLP-1 receptor agonist use was not statistically significant in all sensitivity analyses. In general, larger effect sizes were observed in the subgroup of patients who were 80% adherent and started treatment with no other ADMs during the follow-up period (Table 4). Other results from sensitivity analyses were substantively similar to the primary findings. In falsification testing, there were no significant associations between ADM class and schizophrenia (eTable 7 in the Supplement).

Discussion

In this large observational analysis of insured patients with type 2 diabetes who initiated second-line therapy, GLP-1 receptor agonist use was associated with significant reductions in the composite primary outcome compared with DPP-4 inhibitor use. However, this finding was not significant in some sensitivity analyses. There was a direction toward cardiovascular benefit among patients starting treatment with SGLT-2 inhibitors compared with DPP-4 inhibitors that did not achieve statistical significance. This study found consistent cardiovascular harms associated with use of basal insulin or sulfonylureas compared with DPP-4 inhibitors. Collectively, these findings raise concerns about the cardiovascular safety of sulfonylureas and basal insulin compared with newer ADMs and suggest that short-term cardiovascular outcomes of newer ADM classes may be similar among patients starting second-line treatment.

After metformin, current guidelines recommend selecting ADMs based on expected glycemic improvements, potential risks, and other factors, such as their effect on body weight.[2,4] Some experts suggest that clinicians also consider cardiovascular benefits and harms when prescribing second-line ADM therapy.[15] However, limited cardiovascular data are currently available for the large population of patients starting second-line ADMs after metformin alone is not sufficient or not tolerated. Our analysis provides preliminary evidence needed by patients, clinicians, insurance plans, and pharmacy benefit managers to weigh the comparative cardiovascular harms and benefits of each second-line ADM class in this understudied population.

Recent randomized clinical trial results (eTable 8 in the Supplement) provide some context for interpreting our findings. Although the trials used the highest level of methodologic rigor, they have limitations. First, the major cardiovascular outcome trials compared a single medication to placebo,

Table 3. Adjusted HRs for Composite CV Outcome by ADM Class and Selected Patient Characteristics Among 132 737 Insured Adults With Type 2 Diabetes[a]

	Composite CV Outcome, HR (95% CI)[b]						
	Time-Varying Model (N = 132 737)[c]	Prior CV Events[d]		Prior Metformin Use[e]		Baseline HbA_{1c} Data[f]	
ADM Class		History (n = 7301)	No History (n = 125 436)	History (n = 79 377)	No History (n = 53 360)	Available (n = 42 343)	Not Available (n = 90 394)
DPP-4 inhibitors	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
GLP-1 receptor agonists	0.81 (0.61-1.08)	0.78 (0.43-1.42)	0.81 (0.65-1.01)	0.92 (0.70-1.22)	0.66 (0.48-0.90)	0.60 (0.39-0.94)	0.78 (0.63-0.97)
SGLT-2 inhibitors	0.89 (0.57-1.39)	0.36 (0.09-1.45)	0.91 (0.63-1.31)	0.84 (0.55-1.30)	0.74 (0.40-1.37)	1.13 (0.69-1.82)	0.84 (0.59-1.20)
TZDs	0.88 (0.68-1.15)	0.88 (0.49-1.58)	0.94 (0.77-1.15)	0.90 (0.68-1.18)	0.94 (0.73-1.23)	0.83 (0.55-1.27)	0.92 (0.76-1.12)
Basal insulin	1.57 (1.32-1.88)	1.68 (1.29-2.20)	2.07 (1.82-2.35)	1.85 (1.54-2.22)	2.10 (1.81-2.45)	1.96 (1.53-2.51)	2.06 (1.84-2.31)
SFUs	1.27 (1.09-1.47)	1.29 (1.04-1.61)	1.38 (1.24-1.53)	1.32 (1.15-1.51)	1.39 (1.21-1.59)	1.32 (1.10-1.59)	1.36 (1.24-1.50)

Abbreviations: ADM, antidiabetic medication; CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HbA_{1c}, hemoglobin A_{1c}; HR, hazard ratio; SFUs, sulfonylureas or meglitinides; SGLT-2, sodium-glucose cotransporter 2; TZDs, thiazolidinediones.

[a] With exceptions noted below, all Cox proportional hazards models adjusted for the following baseline covariates: sociodemographic characteristics, HbA_{1c}, CV risk factors, diabetes complications including prior CV events, as well as prior use of metformin and CV medications listed in Table 1. Models also adjusted for prescriber and health plan variables listed in eTable 3 in the Supplement.

[b] Composite CV outcome included hospitalization for congestive heart failure, stroke, ischemic heart disease, or peripheral artery disease.

[c] This Cox proportional hazards model also adjusted for time-varying covariates capturing exposure to all CV medications and ADMs during follow-up. Total length of exposure to the medication was defined as the prescription supply duration (number of days' supply) plus 30 days.

[d] These models adjusted for all covariates in the primary model, with the exception of prior CV events.

[e] These models adjusted for all covariates in the primary model, with the exception of prior metformin use.

[f] These models adjusted for all covariates in the primary model. The stratified model including participants without available HbA_{1c} values did not adjust for this variable.

hindering comparisons across ADM classes. Second, most participants had known cardiovascular disease, which affects only 18% of all US adults with diabetes.[30] Therefore, trial findings may not apply to patients with a lower short-term risk of cardiovascular events.[31] Future cardiovascular outcome trials in this broader population are unlikely because of the resources required, limited interest among funders, and the lack of a regulatory requirement to conduct such trials for older ADMs.[32] Randomized clinical trials also may overestimate medication effects observed in clinical practice by selecting highly adherent participants and other study procedures that are not replicable during routine care.[33]

This context highlights an important role for observational research comparing the cardiovascular effectiveness of ADMs in more typical patients receiving medication in real-world conditions.[34,35] Our findings will be complemented by an ongoing randomized clinical trial comparing the glucose-lowering effects of all ADMs studied here, except TZDs and SGLT-2 inhibitors, among participants who initiate second-line treatment after metformin monotherapy.[36] When available, results from that ongoing trial will provide evidence about the glycemic efficacy of these drugs among adherent research volunteers and under ideal conditions.

Our primary model showed significantly lower risk of composite cardiovascular events associated with GLP-1 receptor agonist use compared with DPP-4 inhibitor use. Improved cardiovascular outcomes among those who initiated treatment with GLP-1 receptor agonists who did not take metformin previously, relative to those who did, may reflect time-lag bias with a longer duration of diabetes among metformin users. Recent placebo-controlled trials of semaglutide and liraglutide therapy also showed reductions in composite fatal and nonfatal cardiovascular events.[12,13] Like the semaglutide trial,[13] this study found a significant decrease in the incidence of stroke among patients starting treatment with GLP-1 receptor agonists. Reductions in stroke risk approached statistical significance in other GLP-1 receptor agonist trials despite not being designed to detect this outcome.[10-12,37] Our analysis likely had greater statistical power because there was follow-up of many more patients receiving treatment than past cardiovascular outcome trials. Interestingly, none of the patients in our GLP-1 receptor agonist group filled a prescription of semaglutide (data not shown).

Table 4. Adjusted HRs for Composite CV Outcome by ADM Class Among 58 744 Adherent, Insured Adult Patients With Type 2 Diabetes[a]

ADM Class	Composite CV Outcome, HR (95% CI)
DPP-4 inhibitors	1 [Reference]
GLP-1 receptor agonists	0.74 (0.50-1.10)
SGLT-2 inhibitors	0.62 (0.32-1.23)
TZDs	0.71 (0.47-1.07)
Basal insulin	2.29 (1.87-2.79)
SFUs	1.31 (1.10-1.56)

Abbreviations: ADM, antidiabetic medication; CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HR, hazard ratio; SFUs, sulfonylureas or meglitinides; SGLT-2, sodium-glucose cotransporter 2; TZDs, thiazolidinediones.

[a] This sensitivity analysis included only patients who were adherent to the index ADM medication, defined as exposure to the medication for at least 80% of days. Total length of exposure to the medication was defined as the prescription supply duration (number of days' supply) plus 30 days. In addition, this subgroup filled no additional ADM medication class during the follow-up period. Cox proportional hazards model adjusted for patient baseline sociodemographic characteristics, hemoglobin A_{1c}, CV risk factors, diabetes complications including prior CV events, as well as prior use of metformin and CV medications included in Table 1. This model also adjusted for prescriber and health plan variables included in eTable 3 in the Supplement. Composite CV outcome included hospitalization for congestive heart failure, stroke, ischemic heart disease, or peripheral artery disease.

Although preliminary, these findings suggest a potential class effect of GLP-1 in reducing stroke risk that requires confirmation.

Compared with DPP-4 inhibitors, we found no statistically significant cardiovascular benefit from SGLT-2 inhibitor therapy. Our analysis included relatively few data on SGLT-2 inhibitors because of their introduction in 2013. Therefore, including longer follow-up in this group may have increased statistical power to detect significant cardiovascular benefits from these medications. Treatment with SGLT-2 inhibitors and GLP-1 receptor agonists has shown improvements in mortality and some individual cardiovascular events among trial participants with a high burden of cardiovascular disease.[14] Prior observational analyses that included patients taking sulfonylureas or insulin in their comparison groups have generally reached similar findings.[38-42] If sulfonylureas and insulin are more harmful than other ADMs, this finding may have accentuated estimates of comparative cardiovascular benefit associated with GLP-1 receptor agonists and SGLT-2 inhibitors. Furthermore, observational analyses examining the subgroup of patients without prior cardiovascular disease reported smaller or no benefits on composite cardiovascular outcomes when initiating treatment with these 2 drug classes, which is more similar to our findings.[38,39] Finally, most previous research included Europeans, whose cardiovascular outcomes may differ from this US cohort.

Sulfonylureas constituted almost half of the second-line ADM prescriptions in our cohort, which is comparable with prior reports.[43] We found increased cardiovascular risk with sulfonylureas compared with DPP-4 inhibitors, which was robust across all analyses. This risk is consistent with a large number observational studies describing cardiovascular harms of sulfonylureas, many of which were conducted before statins were widely used in diabetes care.[44] Our comparison of sulfonylureas with all newer ADMs in the poststatin era shows continued widespread use despite comparatively greater cardiovascular harms.

We also found that basal insulin treatment was associated with higher cardiovascular risk than DPP-4 inhibitor treatment. Recent trials studying insulin as part of intensive diabetes treatment have reported conflicting findings on cardiovascular outcomes.[45] However, a large body of research reveals common mechanisms linking basal insulin and sulfonylureas with increased cardiovascular risk, namely, hyperinsulinemia, weight gain, and hypoglycemia.[45-47] Hypoglycemia may be most important for short-term cardiovascular outcomes.[48] Despite the observed cardiovascular harms associated with initiating sulfonylureas and basal insulin, prescriptions for these 2 ADM classes were filled by 60% of patients in our nationwide analysis. The cardiovascular effects of TZDs have been debated for many years,[49-53] and we found no significant associations in this group.

Strengths and Limitations

To our knowledge, this is the first study comparing cardiovascular outcomes among initiators of all major second-line ADM. Examining a large, population-based, nationwide cohort enabled the ascertainment of sufficient cardiovascular events to perform this current analysis. Our study design provided adequate power to examine stroke as an individual outcome, which was not possible in clinical trials with smaller numbers of participants receiving treatment. Our rates of nonfatal cardiovascular events were comparable with those observed in the UK Prospective Diabetes Study and prior analyses of similar populations.[54-56] The consistency of this study's findings across multiple cardiovascular outcomes, modeling approaches, and subpopulations supports its internal validity. Our observational design also captured real-world conditions that randomized clinical trials do not, which promotes generalizability of the results in diverse US practice settings. This analysis is also timely, providing data on all major ADMs in a contemporary context where prescribers have little available cardiovascular evidence to inform initiation of second-line therapy.

Our study also has limitations. Patients were required to fill the index ADM at least twice, which was chosen to represent a level of exposure that has been associated with cardiovascular outcomes.[8,9,12,13] This requirement may have introduced bias if reasons for discontinuation after the first fill were correlated with cardiovascular outcomes.[57] Although this is likely not the case for most ADMs studied here,[2] the systematic exclusion of some patients with early discontinuation of

sulfonylureas and basal insulin owing to hypoglycemia may have underestimated the cardiovascular harms reported.[58,59] We analyzed administrative claims data, which may be prone to misclassification and do not include granular information used by clinicians when prescribing second-line ADMs. Medical record data, which may contain some of these factors, have been used in similar studies but were not available in our data source.[60] Nonrandomized studies like ours are also prone to selection bias. Multivariable adjustment for observed differences in cardiovascular risk among ADM groups, as well as falsification testing to address potential unobserved confounders, were approaches used to mitigate selection bias.[61] Propensity score matching was not used because it would have limited statistical power for comparing 6 ADM groups,[62] especially those with relatively smaller numbers of patients. Like similar observational studies, we had no body weight data. Although we used diagnosis codes to ascertain obesity identically for all ADM groups, this strategy underestimates its true prevalence and lacks detail about obesity severity.[63]

Our data sources included HbA_{1c} values for one-third of the study population, which represents a proportion comparable to similar cohort studies using claims data.[64] Compared with patients who had no HbA_{1c} data, those with available values were younger with a higher burden of other cardiovascular risk factors (eTable 9 in the Supplement). However, the cardiovascular effectiveness of ADM classes was similar in these 2 subpopulations (Table 3). Furthermore, adjustment for HbA_{1c} in the primary model did not change our findings, which supports a growing consensus that short-term cardiovascular events are not primarily mediated by glycemic control and its association with atherosclerosis progression.[65] A large body of research has identified other mechanisms that may explain the short-term association of ADM with cardiovascular outcomes.[48,50,66-70] Although the mean duration of follow-up in our was 1.3 years, this represents a comparable or longer time interval than other recent observational analyses of second-line ADMs.[38,39,41,71]

We also had no information on diabetes duration, which is an important determinant of cardiovascular risk.[72] However, our selection of patients who were early in their medical treatment of diabetes was intended to compare those at a similar disease stage. In addition, all analyses adjusted for individual cardiovascular risk factors and evidence of existing microvascular and macrovascular complications that are a proxy for diabetes duration. Because we selected patients at a relatively early point in their pharmacologic management of diabetes, our findings may not apply to patients who have a longer duration of diabetes, are already taking multiple ADMs, or have a higher risk of cardiovascular events. Such populations have been studied elsewhere.[5-14,38-42,71] Our data source did not allow us to examine mortality, hindering comparisons with studies that assessed fatal cardiovascular events. We did not analyze individual drugs within ADM classes or total costs of diabetes care. These are important directions for future research.

Conclusions

Among the large population of insured adult patients with type 2 diabetes who initiated second-line antidiabetic medication therapy, an increased risk of cardiovascular events was associated with starting sulfonylureas or basal insulin treatment compared with newer ADM alternatives. Therefore, clinicians may consider prescribing GLP-1 receptor agonists, DPP-4 inhibitors, or SGLT-2 inhibitors more routinely after metformin rather than sulfonylureas or basal insulin. Furthermore, our findings may suggest a role for these newer ADMs in managing cardiovascular risk among patients with type 2 diabetes who either are taking metformin alone or have received no ADM previously. Although our findings should be interpreted with some caution due to the observational design of this study, they were robust to several rigorous sensitivity analyses and are supported by prior mechanistic and clinical evidence. Future research should compare ADM classes on glycemic effectiveness and additional metabolic end points.

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SUPPLEMENT.

eTable 1. Individual Medications Within Each Antidiabetic Medication Class
eTable 2. Diagnosis Codes Used to Define Study Variables
eTable 3. Characteristics of Prescribers and Health Insurance Plans for the Study Population by Antidiabetic Medication Class
eTable 4. Adjusted Hazard Ratios from Primary Model But Adjusting for HbA_{1c} Within the Last 3 Months
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eTable 9. Baseline Characteristics of the Study Population by Availability of Hemoglobin A_{1c} Data