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Trends in First-Line Glucose-Lowering Drug Use in Adults With Type 2 Diabetes in Light of Emerging Evidence for SGLT-2i and GLP-1RA

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OBJECTIVE

We evaluated recent use trends and predictors of first-line antidiabetes treatment in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Using two large U.S. health insurance databases (Clinformatics and Medicare), we identified adult patients with type 2 diabetes who initiated antidiabetes treatment from 2013 through 2019. Quarterly trends in use of first-line antidiabetes treatment were plotted overall and stratified by cardiovascular disease (CVD). Multinomial logistic regressions were fit to estimate predictors of first-line antidiabetes treatment, using metformin, the recommended first-line treatment for type 2 diabetes, as the common referent.

RESULTS

Metformin was the most frequently initiated medication, used by 80.6% of Medicare beneficiaries and 83.1% of commercially insured patients. Sulfonylureas were used by 8.7% (Medicare) and 4.7% (commercial). Both populations had low use of sodium–glucose cotransporter 2 inhibitors (SGLT-2i, 0.8% [Medicare] and 1.7% [commercial]) and glucagon-like peptide 1 receptor agonists (GLP-1Ra; 1.0% [Medicare] and 3.5% [commercial]), with increasing trends over time ($P < 0.01$). Initiators of antidiabetes drugs with established cardiovascular benefits (SGLT-2i and GLP-1RA) were more likely to be younger and had prevalent CVD or higher socioeconomic status compared with initiators of metformin.

CONCLUSIONS

Among adult patients with type 2 diabetes, metformin was by far the most frequent first-line treatment. While the use of SGLT-2i and GLP-1RA was low from 2013 through 2019, it increased among patients with CVD.

Individuals with type 2 diabetes have an increased risk of cardiovascular (CV) disease (CVD) due to chronic hyperglycemia and a higher prevalence of CV risk factors, including obesity, hypertension, and various lipid abnormalities (1,2). CVD affects approximately one-third of the population with type 2 diabetes population (2) and accounts for 50–80% of their mortality (3–5). Given the burden of CVD in

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patients with type 2 diabetes, the recommendation for using metformin monotherapy as a first-line glucose-lowering treatment has been based on CV benefits, including reductions in the risk of myocardial infarction and CV death, in addition to efficacy and safety (6,7).

Since 2008, the U.S. Food and Drug Administration (FDA) has mandated long-term CV outcomes trials (CVOTs) to evaluate the safety of type 2 diabetes drugs in development (8). Among the completed trials, sodium–glucose cotransporter 2 inhibitors (SGLT-2i) demonstrated a significant decrease in major adverse CV events, and reductions in CV death, all-cause mortality, and hospitalization for heart failure (9–11). In addition, some glucagon-like peptide 1 receptor agonists (GLP-1RA) demonstrated a significant decrease in major adverse CV events, CV death, and all-cause mortality (12). As a result, the FDA has expanded the labels of SGLT-2i (empagliflozin, canagliflozin, and dapagliflozin) and some GLP-1RA (liraglutide, semaglutide, and dulaglutide) to reduce CV risk in adult patients with type 2 diabetes with CVD. These benefits have also prompted clinical guidelines to endorse SGLT-2i and GLP-1RA as the preferred second-line treatment among patients with CVD (6).

As the paradigm of second-line pharmacological treatment for type 2 diabetes has shifted to include the management of CV risk in addition to glycemic control (13) through the recommended use of SGLT-2i and GLP-1RA among patients with CVD, whether these agents should also be considered as first-line treatment for patients with type 2 diabetes with CVD or at high risk of CVD has been amply debated (14). However, little is known about patterns of current first-line type 2 diabetes treatment in real-world settings and about how the CV benefits of SGLT-2i and GLP-1RA may have influenced the choice of first-line antidiabetes medication among patients with type 2 diabetes with CVD.

We sought to analyze recent use trends in first-line antidiabetes medications among adult patients with type 2 diabetes and the effect of the prevalent CVD on medication choice, using large commercial and Medicare claims databases in the U.S. We assessed patient characteristics associated with the decision to initiate treatment for type 2 diabetes with alternatives to recommended metformin monotherapy.

RESEARCH DESIGN AND METHODS

Data Sources

We used data from Optum Clinformatics Data Mart (Clinformatics, 1 January 2004 to December 31, 2019), a large commercial U.S. health insurance database, and Medicare Fee-For-Service (Centers for Medicare and Medicaid Services, 1 January 2012 to 31 December 2017), a U.S. federal health insurance database. Data from an additional large commercial U.S. health insurance database, IBM MarketScan (31 December 2002 to 31 December 2018), were used to confirm the robustness of our findings in Clinformatics. All sources contained deidentified data that were captured during billing of routine health care encounters. Commercial data sources included individuals with employer-sponsored commercial insurance, Medicare Advantage, or Medicare Supplemental health insurance plans from all 50 U.S. states and the District of Columbia. Medicare included individuals aged $\geq$65 and individuals $<$65 with disabilities or with end-stage renal disease. Comprehensive longitudinal information on baseline demographics, inpatient and outpatient diagnoses and procedures, and outpatient prescription dispensings were available for all enrollees. The study was approved by the Mass General Brigham Institutional Review Board, and licensing agreements were in place.

Study Population

We identified individuals who initiated any antidiabetes medications between 1 April 2013 (consistent with the launch of SGLT-2i in the U.S.) and 31 December 2019 (31 December 2018 for MarketScan and 31 December 2017 for Medicare). The cohort entry date was defined as the first antidiabetes drug dispensing date. To ensure first-line use, we required no use of any antidiabetes drugs for at least 365 days or more prior to cohort entry, depending on data availability. Patients who initiated more than one antidiabetes drug class on cohort entry were excluded. Additional eligibility criteria were at least one inpatient or outpatient diagnosis of type 2 diabetes (ICD-9 diagnosis codes 250.x0 or 250.x2 through 30 September 2015 and ICD-10 diagnosis code E11.xxx afterward) at any point prior to or on cohort entry (15,16); continuous health plan membership with complete medical coverage and pharmacy benefits in the 365 days preceding cohort entry; and age at cohort entry $\geq$18 years for Clinformatics and MarketScan, and $>$65 years for Medicare. We excluded patients with any diagnosis of type 1, gestational, or secondary diabetes, or history of malignancy, polycystic ovary syndrome, organ transplant, end-stage renal disease, or HIV/AIDS because these conditions could be associated with different patterns of glucose-lowering drug use from those patterns in type 2 diabetes. For example, combining metformin with some HIV medications should be avoided (17). We also excluded individuals with a history of nursing home admission because medication use cannot be reliably identified during a nursing home stay.

Study Drugs

All currently available antidiabetes drug classes in the U.S. were included except bile acid sequestrant (colesevelam), which could be administered for both type 2 diabetes and elevated LDL cholesterol levels (18). The following drug classes were included: biguanides (i.e., metformin), sulfonylureas, insulin, dipeptidyl peptidase-4 inhibitors (DPP-4i), GLP-1RA, SGLT-2i, thiazolidinediones (TZDs), α-glucosidase inhibitors, amylin mimetic agents, dopamine receptor agonists, and meglitinides. Among dopamine receptor agonists, we only included Cycloset (bromocriptine), which is exclusively indicated for type 2 diabetes treatment (19). Among GLP-1RA, we excluded Saxenda, a formulation of liraglutide approved in 2014 for weight loss (20). Because of the low frequency of use, we grouped α-glucosidase inhibitors, amylin mimetics, dopamine receptor agonists, and meglitinides in one group (hereafter referred to as "others").

To assess predictors of first-line antidiabetes drug initiation, drug classes were categorized into metformin, noninsulin agents with established CV benefits (SGLT-2i and GLP-1RA), noninsulin agents without CV benefits (sulfonylureas, DPP-4i, TZDs, and others), and insulin. Insulin was not categorized together with the agents without established CV benefits because first-line insulin is recommended for patients with a severely uncontrolled HbA_{1c} level ($\geq$10% [86 mmol/mol]) (21), and thus, insulin initiators were likely to present very distinct characteristics. Supplementary Table 1 shows the full list of included drugs.

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Covariates

We assessed the following baseline characteristics of patients initiating a first-line antidiabetes drug: Demographics, age, sex, geographic region (Supplementary Table 2), and race (available for Medicare); lifestyle risk factors, including alcohol or drug abuse or dependence, obesity or overweight, and smoking; claims-measured proxies of diabetes severity and duration, presence of diabetic microvascular complications (nephropathy, neuropathy, and retinopathy) and number of HbA_{1c} tests ordered; risk factors for prognosis of diabetes, presence of CVD or stages 1–4 chronic kidney disease (CKD); concomitant medications; claims-measured proxies of socioeconomic status (22), preventive health care services (flu or pneumococcal vaccination or cancer screening), measures of health care use (any hospitalizations 180 days prior to cohort entry, emergency department visits, number of outpatient visits), and measures of prior patient experience with brand name versus generic drugs (ratio); and any visits with specialists within 14 days prior to cohort entry.

CVD was defined as a composite of a history of myocardial infarction, unstable angina, other ischemic heart disease, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, and heart failure, based on the treatment guidelines for type 2 diabetes (6). All covariates were measured during the 365-day baseline period unless otherwise specified.

Statistical Analysis

We compared baseline characteristics of initiators of antidiabetes drug classes separately in three consecutive time blocks (1 April 2013–30 September 2015; 1 October 2015–31 December 2017; and 1 January 2018–31 December 2019). The first time block cut point of 30 September 2015 was chosen to examine trends prior to publication of the first results from a pivotal CVOT of SGLT-2i (9). The second cut point of 31 December 2017 was chosen to establish comparable time periods for the two data sources because of the limited data period of the Medicare database. This cut point also coincided with the change in clinical guidelines regarding a preferential prescribing of SGLT-2i and GLP-1RA among patients with established CVD (6). Patients were categorized by the class of the first antidiabetes drug prescription filled. We plotted temporal trends in first-line type 2 diabetes antidiabetes drug initiated by quarter, overall and stratified by CVD, using the number of initiators of each class as the numerator with the total number of initiators as the denominator. Trends were tested by the nonparametric Cox and Stuart trend test (23).

We also performed sensitivity analyses *1*) restricting the trend analyses to patients with a minimum health insurance enrollment period of 3 years prior to cohort entry with no use of any antidiabetes drugs to ensure the robustness of our findings to the possible inclusion of non–first-line antidiabetes drug initiators; and *2*) repeating the analyses using MarketScan to confirm the robustness of our findings in Clinformatics. Database-specific multinomial logistic regressions were fit to assess patient characteristics associated with the decision to initiate treatment for type 2 diabetes with alternatives (agents with established CV benefits, agents without CV benefits, or insulin) to the recommended first-line metformin (the common referent) during the three time blocks. Analyses were performed using R v3.6.2 software (24), with cohort and variable generation through the Aetion Evidence Platform v4.10 (25), which has been scientifically validated by accurately repeating a range of previously published studies (26) and by replicating (27) or predicting clinical trial findings (28).

RESULTS

Demographics

We identified 264,542 (commercial) and 285,213 (Medicare) patients with type 2 diabetes who initiated a first-line antidiabetes medication between 1 April 2013 and 31 December 2019 (31 December 2017 for Medicare) (Supplementary Fig. 1). Selected patient characteristics are presented in Table 1.

In the last time block (1 January 2018–31 December 2019 for Clinformatics and 1 October 2015–31 December 2017 for Medicare), among commercially insured patients mean age was 60 years and 56% were men; 48% had diagnosis codes for obesity or overweight, 13% had diabetic microvascular complications, 22% had CVD, and 8% had CKD. In addition, few commercially insured patients had visits with cardiologists (7%) or endocrinologists (2%), while many had visits with internists (56%) within 14 days prior to first-line antidiabetes drug initiation; 8% were hospitalized within 180 days prior to cohort entry, and 15% had at least three HbA_{1c} test orders within 365 days prior to cohort entry.

Medicare beneficiaries were older than commercially insured individuals (mean age, 73 years), were less likely to be men (47%), and most were White (82%); 34% had diagnosis codes for obesity or overweight, 15% had diabetic microvascular complications, 44% had CVD, and 14% had CKD. Medicare beneficiaries more likely visited cardiologists (10%), endocrinologists (3%), or internists (67%) within 14 days prior to first-line antidiabetes drug initiation; 11% were hospitalized within 180 days prior to cohort entry, and 29% had at least three HbA_{1c} test orders within 365 days prior to cohort entry. Supplementary Table 3 shows the full list of patient characteristics.

Antidiabetes Drug Use Trends

Figure 1 presents the trends, with proportions in Supplementary Tables 4–6, in antidiabetes drug class initiation by quarter. Metformin was the most frequent first-line type 2 diabetes treatment (Fig. 1*A* and *B*) in both commercially insured and Medicare beneficiaries. From the second quarter of 2013 to the fourth quarter of 2019 (2017 for Medicare), metformin was the choice of initial treatment with a single antidiabetes medication in between 79.9 and 83.1% of commercially insured beneficiaries (difference, 3.22 percentage points; 95% CI 2.10, 4.34), and between 77.0 and 80.6% with increased use over time (3.61; 2.48, 4.73) for Medicare beneficiaries. Sulfonylureas were the second most frequently used first-line antidiabetes medications in both populations, with a higher proportional share for Medicare that decreased over time (−3.56; −4.39, −2.74) compared with commercially insured, also decreasing over time (−4.58; −5.32, −3.84). The uptake of GLP-1RA increased in both populations, with a greater use in the commercially insured (2.23; 1.80, 2.66) versus Medicare (0.61; 0.35, 0.87). Likewise, the uptake of SGLT-2i increased (commercial: 1.46 [1.19, 1.72], Medicare: 0.78 [0.56, 1.00]). Nevertheless, in both populations, the use of SGLT-2i and GLP-1RA as a first-line antidiabetes treatment remained low. In both populations, a small proportion of patients

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Table 1—Patient characteristics at the time of first-line antidiabetes drug initiation (2013–2019)

	Clinformatics			Medicare	
Baseline characteristics	April 2013–September 2015, *n* = 88,873	October 2015–December 2017, *n* = 89,484	January 2018–December 2019, *n* = 86,185	April 2013–September 2015, *n* = 186,146	October 2015–December 2017, *n* = 99,067
Demographics					
Age, years, mean (SD)	58.87 (13.07)	58.92 (13.10)	59.63 (13.23)	73.16 (6.34)	73.09 (6.26)
Male sex	48,349 (54.4)	48,751 (54.5)	48,175 (55.9)	84,081 (45.2)	46,869 (47.3)
White race	—	—	—	150,883 (81.1)	80,978 (81.7)
Lifestyle risk factors					
Obesity or overweight	24,929 (28.1)	35,225 (39.4)	41,669 (48.3)	43,743 (23.5)	33,993 (34.3)
Comorbidities					
Microvascular complications*	9,307 (10.5)	10,274 (11.5)	11,524 (13.4)	17,922 (9.6)	15,189 (15.3)
CVD†	18,439 (20.7)	18,142 (20.3)	19,001 (22.0)	78,102 (42.0)	43,142 (43.5)
CKD	6,621 (7v.4)	6,745 (7.5)	7,256 (8.4)	20,418 (11.0)	13,352 (13.5)
Physician specialties‡					
Cardiologist	5,801 (6.5)	5,889 (6.6)	6,384 (7.4)	21,478 (11.5)	10,004 (10.1)
Endocrinologist	2,193 (2.5)	2,087 (2.3)	2,069 (2.4)	5,171 (2.8)	2.937 (3.0)
Internist	47,579 (53.5)	48,527 (54.2)	48,037 (55.7)	12,3537 (66.4)	66,010 (66.6)
Health care use					
Any hospitalization§	6,481 (7.3)	6,113 (6.8)	6,428 (7.5)	23,073 (12.4)	10,719 (10.8)
HbA_{1c} test orders ≥3	13,433 (15.1)	13,405 (15.0)	13,186 (15.3)	41,286 (22.2)	28,708 (29.0)

Data are *n* (%) unless otherwise specified. *Defined as history of diabetic nephropathy, neuropathy, and retinopathy. †Defined as history of myocardial infarction, unstable angina, other ischemic heart disease, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, and heart failure. ‡Defined as specialist visits that occurred within 14 days prior to cohort entry. §Defined as hospitalization that occurred within 180 days prior to cohort entry.

nitiated DPP-4i, insulin, TZDs, and others, with the trends relatively stable over the study period. MarketScan showed trends in first-line antidiabetes drug initiation similar to those observed in Clinformatics (Supplementary Fig. 2).

In the first quarter of 2015 for Clinformatics, the proportional share of metformin decreased considerably, explained by the acquisition of new claims data by Optum in addition to the influx of Medicare Advantage beneficiaries typically enrolled in the first quarter of each year (Fig. 1*A*).

Baseline CVD Status

Commercially insured and Medicare patients with CVD were both less likely to initiate metformin but more likely to initiate sulfonylureas, insulin, and DPP-4i, compared with those without CVD (Fig. 2*A* and *D* and Supplementary Tables 7–12). In both populations, the uptake of GLP-1RA did not differ by baseline CVD. However, the uptake of SGLT-2id appeared more evident among commercially insured patients with CVD. Other than differences in the proportional share, the order of first-line treatment choice showed no difference by baseline CVD. MarketScan showed patterns of first-line antidiabetes drug initiation by CVD similar to Clinformatics (Supplementary Fig. 2).

Sensitivity Analyses

Use trends remained consistent when we restricted the trend analyses to patients who had at least 3 years of contin uous health insurance enrollment prior to cohort entry, although the proportional shares of metformin initiation shifted slightly higher (e.g., from 79.9 to 82.8% in the second quarter of 2013 for Clinformatics), and those shares of other drugs shifted slightly lower (Supplementary Fig. 3 and Supplementary Tables 13–21).

Predictors for Choice of First-Line Antidiabetes Medications

Older and male patients were less likely to initiate antidiabetes drugs with CV benefits but more likely to initiate drugs without CV benefits compared with metformin, the common referent. Conversely, White and obese or overweight patients were more likely to initiate antidiabetes drugs with CV benefits but less likely to initiate drugs without CV

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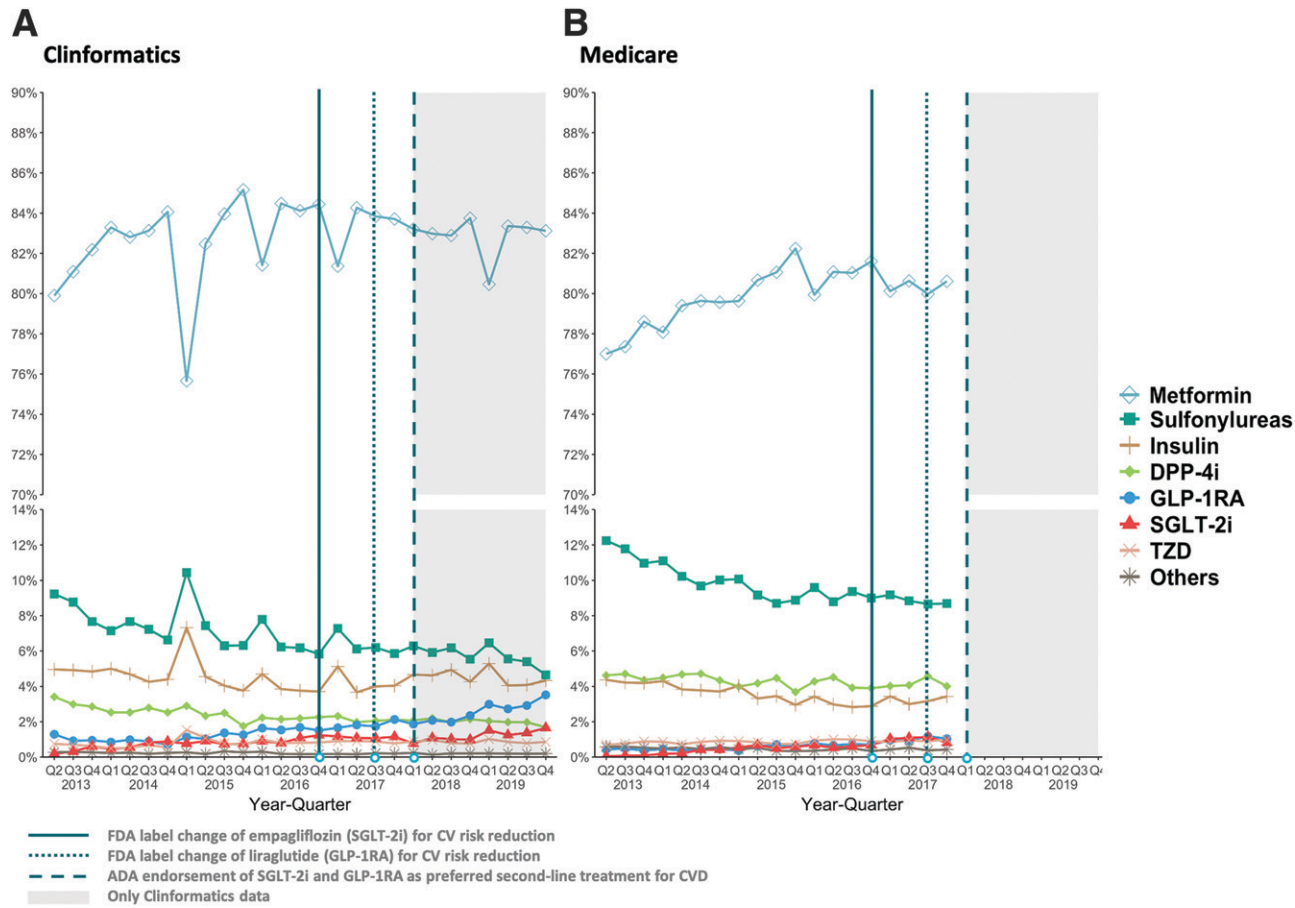

Figure 1—Trends in antidiabetes drug class initiation by quarter in Clinformatics (*A*) and Medicare (*B*) databases.

benefits compared with metformin (Fig. 3 and Supplementary Tables 22–24). Patients who had CVD, CKD, and diabetic microvascular complications were more likely to initiate both antidiabetes drugs with or without CV benefits compared with metformin, with particularly higher odds for antidiabetes drugs without CV benefits. Patients who had endocrinologist visits had higher likelihood of initiating both antidiabetes drugs with or without CV benefits instead of metformin, whereas the opposite was true for patients who had internist visits. Cardiologist visits decreased the likelihood of initiating antidiabetes drugs with CV benefits over metformin. Patients with any recent hospitalizations were less likely to initiate antidiabetes drugs with CV benefits but were more likely to initiate agents without CV benefits compared with metformin. Having three or more HbA_{1c} test orders indicated a preference for both antidiabetes drugs with or without CV benefits over metformin. MarketScan results for predictors of first-line antidiabetes medications were similar to Clinformatics and Medicare (Supplementary Fig. 4 and Supplementary Tables 22–24). Results for insulin are shown in Supplementary Fig. 5 and Supplementary Tables 22–24.

CONCLUSIONS

In two large U.S. commercial and public health insurance databases, metformin was by far the most frequently initiated first-line type 2 diabetes treatment, followed by sulfonylureas. Sulfonylurea initiation was more frequent in older patients, represented by Medicare, and patients with CVD compared with younger patients and patients without CVD. The use of SGLT-2i and GLP-1RA as a first-line antidiabetes treatment remained low in both commercially insured and Medicare; however, since 2017, the use of SGLT-2i and GLP-1RA steadily increased. The uptake of SGLT-2i appeared higher among patients with CVD. The use of antidiabetes drugs with established CV benefits (SGLT-2i and GLP-1RA) compared with the use of metformin as first-line therapy was associated with younger age, prevalent CVD, and higher socioeconomic status.

Our findings of lower metformin use among older patients and patients with CVD are likely attributable to its contraindications (e.g., renal dysfunction) (21), which are prevalent in these populations. Nevertheless, we also observed an increase in the use of metformin in these populations, perhaps encouraged by the FDA revision of the metformin label in 2016 allowing its use in patients with mild-to-moderate renal dysfunction associated with increased CVD risk (29,30). Prediction models showed that older age and underlying conditions such as CVD and CKD predicted lower use of metformin compared with other drug classes, in particular sulfonylureas, which might be seen as an affordable alternative compared with more expensive agents, including SGLT-2i and GLP-1RA, in patients who had contraindications for metformin. However, sulfonylureas can be a suboptimal first-line antidiabetes treatment choice in certain subpopulations

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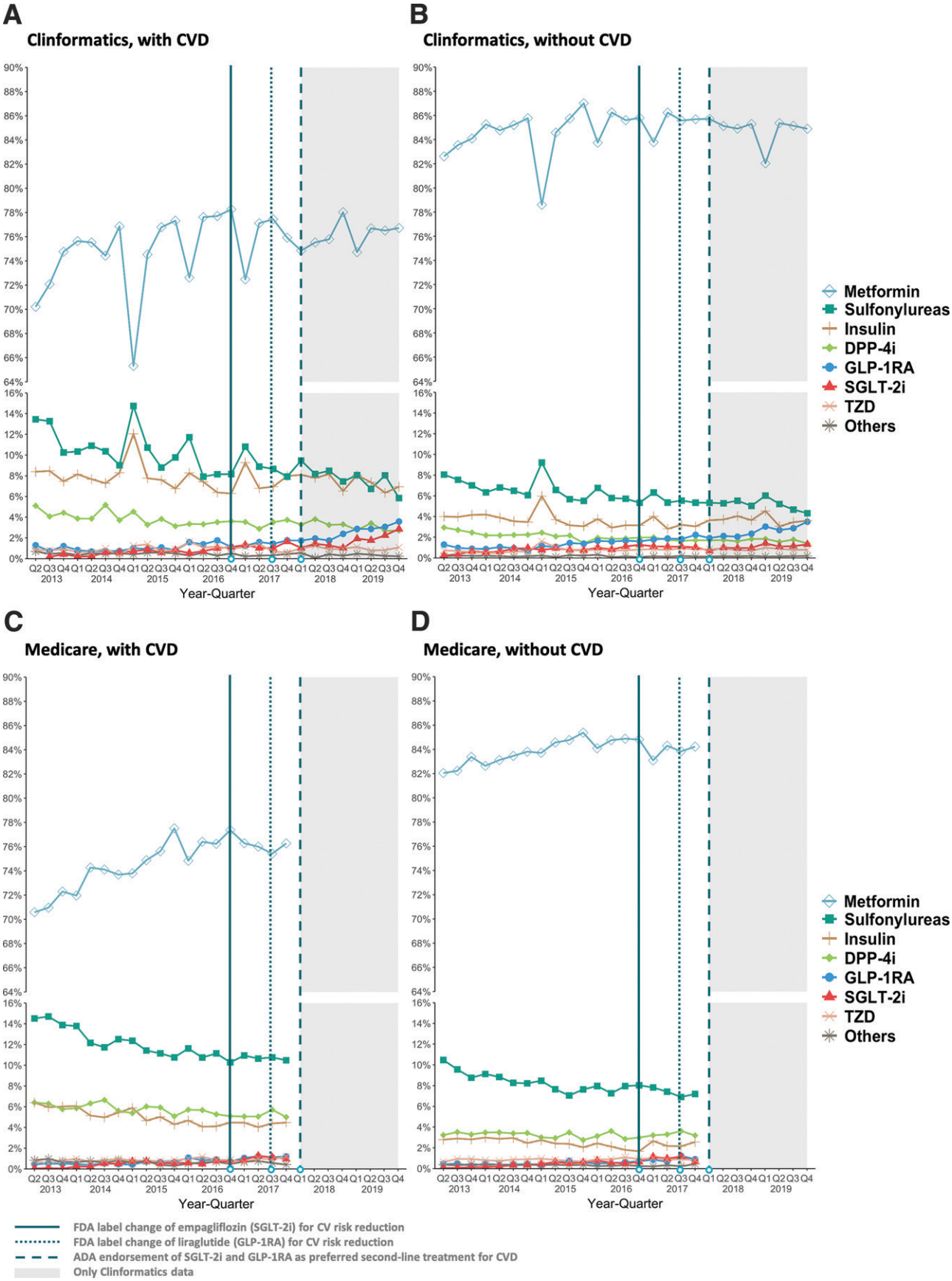

Figure 2—Trends in patients with (*A*) and without (*B*) CVD initiating metformin in Clinformatics and with (*C*) and without (*D*) CVD in Medicare database.

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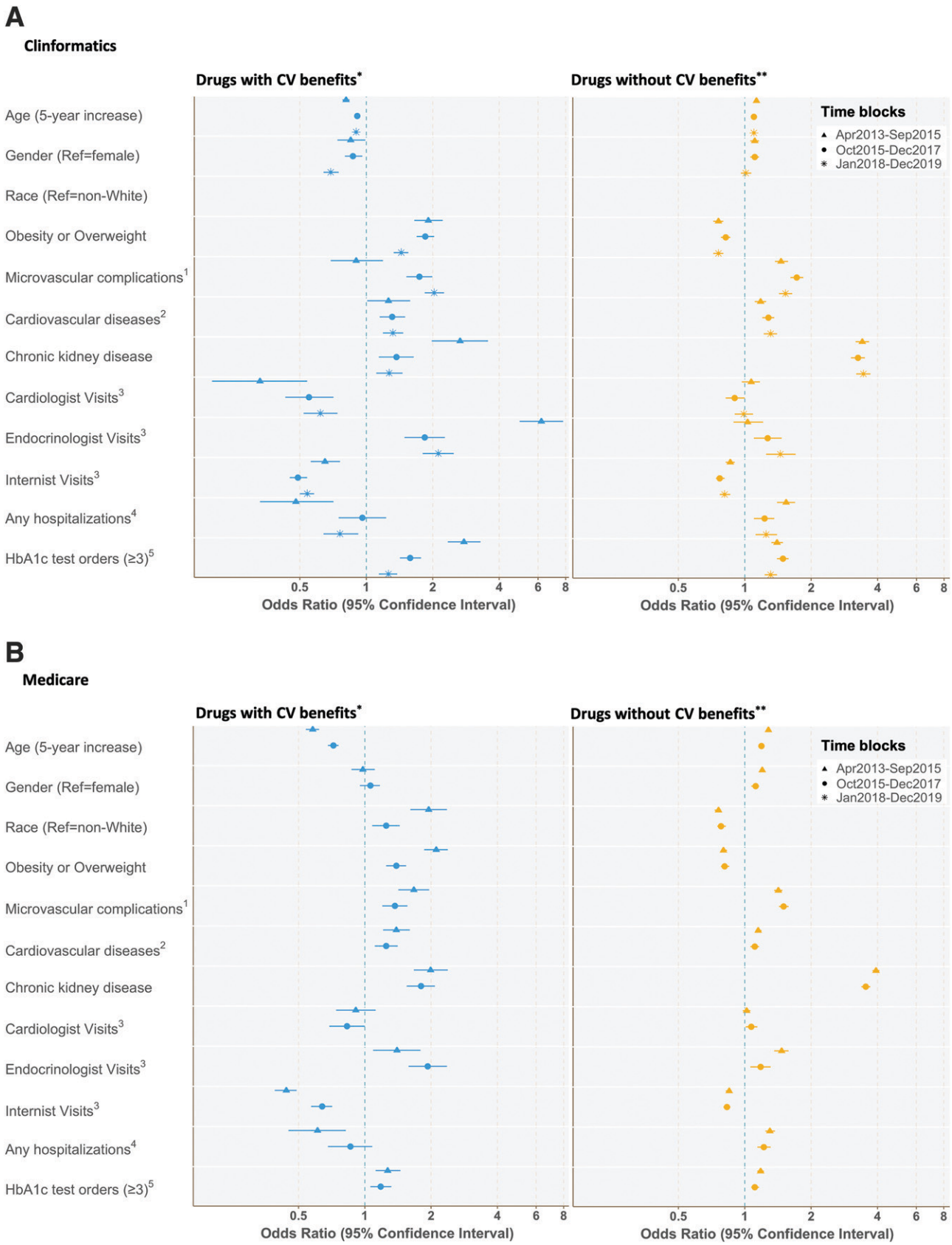

Figure 3—Trends in patients initiating antidiabetes drugs with or without CV benefits compared with metformin in Clinformatics (*A*) and Medicare (*B*) databases. *SGLT-2i and GLP-1RA. **Sulfonylureas, DPP-4i, TZD, and others (α-glucosidase inhibitors, amylin mimetics, dopamine receptor agonists, and meglitinides). [1]Defined as a history of diabetic nephropathy, neuropathy, or retinopathy. [2]Defined as a history of myocardial infarction, unstable angina, other ischemic heart diseases, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, or heart failure. [3]Defined as specialist visits occurred within 14 days before cohort entry. [4]Defined as hospitalization occurred within 180 days before cohort entry. [5]Defined as having three or more HbA_{1c} test orders within 365 days before cohort entry.

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for several reasons: increased hypoglycemia risk (27,31), in particular among older patients (32), inconsistent findings for CV safety (33), and weight gain (6), which makes blood glucose control more difficult in some patients (34).

Our results of a low use of SGLT-2i and GLP-1RA as first-line antidiabetes treatment were consistent with previous findings (35). The FDA approved GLP-1RA in 2005 and SGLT-2i in 2013, and CVOT results for these agents were only recently released, in contrast to more than 60 years of established clinical experience with metformin or sulfonylureas (36). Indeed, our results showed that internists and cardiologists showed a preference for metformin over SGLT-2i and GLP-1RA despite their established CV benefits, perhaps partly driven by lack of familiarity (37,38) in addition to compliance with clinical guidelines (6). High cost could have limited widespread use of SGLT-2i and GLP-1RA, with a considerably higher annual expenditure compared with metformin (39). Additionally, formulary restrictions might also have limited patient access to SGLT-2i and GLP-1RA compared with more affordable options such as metformin or sulfonylureas (40).

Although we included patients who had not filled any antidiabetes drug prescriptions for at least the preceding 365 days or beyond, some patients might not have been first-time antidiabetes users. A sensitivity analysis, requiring 3 years of prior health insurance enrollment without any use of antidiabetes medications, produced results consistent with the primary findings. Another limitation of this study stemmed from potential misclassification of baseline CVD status due to the inaccuracy of coding in the databases. However, these possible misclassifications were unlikely to affect results. Finally, although our study cohort represented a wide-ranging population, the results may not be generalizable to all populations, including uninsured patients.

To conclude, among adult patients with type 2 diabetes, metformin was the most frequently chosen first-line treatment by far, followed by sulfonylureas. Sulfonylurea use was higher among older patients and patients with CVD, who might have higher prevalence of contraindications to metformin (e.g., CKD). The use of SGLT-2i and GLP-1RA as first-line treatment remained low, although we observed a steady increase during the study period particularly in patients with existing CVD.

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Duality of Interest. E.P. is an investigator of investigator-initiated grants to Brigham and Women's Hospital from Boehringer Ingelheim, not directly related to the topic of the submitted work. S.S. is an investigator of investigator-initiated grants to Brigham and Women's Hospital from Bayer, Vertex, and Boehringer Ingelheim unrelated to the topic of this study and is a consultant to Aetion Inc., a software manufacturer of which he owns equity. R.J.G. has received funding from grants to Brigham and Women's Hospital from AstraZeneca, Kowa, Pfizer, and Novartis unrelated to the topic of this study. No other potential conflicts of interest relevant to this article were reported.

These interests were declared, reviewed, and approved by Brigham and Women's Hospital and Partners HealthCare System in accordance with their institutional compliance policies.

Author Contributions. All authors contributed to the design, analysis, and interpretation of the results as well as provided feedback on the drafted manuscript. All authors approved of and agreed to submit the manuscript. H.S. and E.P. are the guarantors of this work, and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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