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Correlates of Glucagon-Like Peptide-1 Receptor Agonist Use Among Patients With Atherosclerotic Cardiovascular Disease and Type 2 Diabetes Mellitus (from the Department of Veterans Affairs)

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This study used data from the Veterans Affairs administrative and clinical dataset to evaluate determinants of glucagon-like peptide-1 receptor agonist (GLP-1 RA) use among patients with concomitant atherosclerotic cardiovascular disease and diabetes mellitus and an antecedent primary care provider visit. The prevalence of GLP-1 RA use was 8.0%. In multivariable-adjusted models, White race, hypertension, obesity, higher hemoglobin A1c, ischemic heart disease, chronic kidney disease, a higher number of primary care provider visits, and previous cardiology or endocrinology visits were directly associated with GLP-1 RA use. Older age, having a physician primary care provider, and receiving care at a teaching facility were inversely associated with GLP-1 RA use. Our data can help inform targeted interventions to promote equitable access to GLP-1 RA and incentivize the adoption of these disease-modifying agents in high-risk patient populations. Published by Elsevier Inc. (Am J Cardiol 2022;00:1−4)

Introduction

Recent trends have demonstrated an increasing burden of atherosclerotic cardiovascular disease (ASCVD) and cardiovascular mortality that is paralleled by a rising prevalence of obesity and type 2 diabetes mellitus.[1] Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have protective cardiovascular effects as shown in recent randomized clinical trials.[2] GLP-1 RAs are also endorsed by the American Diabetes Association for secondary prevention of ASCVD and primary prevention in high-risk patients.[3] Furthermore, these medications should be considered early in the treatment strategy in patients with diabetes mellitus, including as first-line therapy if injectable therapy is warranted to reduce hemoglobin A1c (HbA1c).[4] However, few studies have examined the determinants of GLP-1 RA use in a contemporary real-world cohort of patients with ASCVD and diabetes mellitus.[5,6] Such data can help inform policy makers to ensure equitable delivery of these guideline-directed agents, especially among high-risk patients.

Methods

Data for this study were obtained from the nationwide Veterans Affairs (VA) administrative and clinical dataset. Veterans ≥18 years old with a diagnosis of ASCVD were assessed using International Classification of Diseases, Tenth Revision, Clinical Modification diagnosis and procedure codes and Current Procedural Terminology codes. Patients were included if they had a primary care provider (PCP) visit between January 1, 2020 and December 31, 2020 at 130 VA healthcare facilities including VA medical centers and their associated outpatient community-based clinics. PCP included both physician and nonphysician clinicians, including nurse practitioners and physician assistants. This time frame was chosen to evaluate the use of GLP-1 RA in a contemporary cohort of patients who met the current criteria for GLP-1 RA, which were approved by the Food and Drug Administration. Demographics and risk factors were extracted from the structured VA datasets. Type 2 diabetes mellitus was defined based on documented diabetes (2 outpatient or 1 inpatient International Classification of Diseases, Tenth Revision, Clinical Modification diagnosis code) or HbA1c ≥6.5%, fasting plasma glucose

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≥126 mg/dl, random plasma glucose ≥200 mg/dl, or the use of diabetes medications within 2 years before the index visit. Use of GLP-1 RA was assessed using prescription for the corresponding medications within 180 days before or up to 100 days after the index PCP visit. GLP-1 RA included injectables exenatide, liraglutide, lixisenatide, dulaglutide, and oral semaglutide.

Patients with ASCVD (n = 1,235,567) included those with a diagnosis of ischemic heart disease (IHD), peripheral arterial disease, or ischemic cerebrovascular disease identified using well-validated ICD-10 CM diagnosis codes and Current Procedural Terminology codes.[7] Patients with limited life expectancy (receiving hospice care within the preceding 12 months or have a history of metastatic cancer in the last 5 years) were excluded (n = 32,106). Among the remaining patients with ASCVD (n = 1,203,461), concomitant type 2 diabetes was identified in 537,980 patients.

The distribution of various demographics and risk factors was compared by GLP-1 RA use. Multivariable-adjusted logistic regression models were used to study the association between patient and facility factors and GLP-1 RA use. A 2-sided $p < 0.05$ was used to define statistical significance.

Analyses were conducted using SAS version 9.1.3 (SAS Institute, Inc., Cary, North Carolina) and Stata version 14 (StataCorp, College Station, Texas). Approval for this study protocol and a waiver for informed consent were obtained from the institutional review boards at the Baylor College of Medicine and the Michael E. DeBakey VA Medical Center.

Results

The study population consisted of 537,980 patients with concomitant ASCVD and type 2 diabetes: mean (SD) age 72.6 years (9.0), 2.4% women, 70.8% White, 15.3% Black, and 8.0% were receiving GLP-1 RA. Compared with GLP-1 RA nonusers, those who used GLP-1 RA were younger, more likely to be White, had a higher burden of obesity (body mass index ≥30 kg/m^2), and a lower burden of peripheral arterial disease in the absence of IHD. However, GLP-1 RA users had a higher burden of hypertension, IHD, and systolic heart failure. GLP-1 RA users were more likely to be receiving insulin, metformin, and sodium-glucose cotransporter 2 (SGLT-2) inhibitors. GLP-1 RA users had a higher number of PCP visits and were more likely to have had a cardiology clinic visit or an endocrinology clinic visit in the 12 months before the index PCP visit (all $p < 0.01$) (Table 1).

In multivariable-adjusted models, factors directly associated with GLP-1 RA use included White race, hypertension, obesity, higher HbA1c, IHD, chronic kidney disease, a higher number of PCP visits, and previous cardiology or endocrinology visits (Table 2). Older age, having a physician PCP, and receiving care at a teaching facility were inversely associated with GLP-1 RA use.

Discussion

The present analysis from a VA cohort found that the utilization rate of GLP-1 RA was low (8.0%), similar to that reported in a previous study of patients with diabetes mellitus (7.7%) from a private payer claims database from 2015 to 2019,[5] and in the Getting to an Improved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia Management (GOULD) registry (7.9%).[6] These prevalence estimates were less than expected given that the use of GLP-1 RA has been endorsed by the American Diabetes Association for secondary prevention of ASCVD as of 2019.[3] The use of metformin was also low (58% among GLP-1 RA users and 46% among nonusers) even though it is guideline-endorsed for the management of patients with diabetes mellitus and ASCVD.[3] However, the prevalence of sulfonylurea use was much higher than GLP-1 RA in our study even though the former is not recommended as a first-line agent. In addition to the barriers identified in our study, clinical (therapeutic) inertia may have affected the adequate uptake of these guideline-endorsed medications.

Previous studies have often cited cost or lack of insurance coverage as a barrier to GLP-1 RA uptake and have suggested lowering the cost as a potential strategy to increase the use of GLP-1 RA. However, GLP-1 RA may not be cost-prohibitive in the VA healthcare system where copay amounts are generally low. This suggests that factors beyond cost may hinder adequate uptake of this class of medications as the present study suggests.

Even after accounting for other demographics and cardiovascular risk factors, non-Whites in our study were less likely to receive GLP-1 RA, similar to the study by Eberly et al.[5] Based on the present analysis, the reasons for these racial disparities are unclear; although efforts are warranted to understand reasons for this disparity to promote equitable access to GLP-1 RA in all demographic groups.

Patients with more frequent visits to a PCP, cardiologist, and especially, an endocrinologist were more likely to receive GLP-1 RA. The presence of an efficient network with these multiple nodes of care will increase the likelihood of increased use of these cardioprotective agents by primary care clinician or specialists. GLP-1 RA were first studied as glucose-lowering drugs before their cardiovascular benefit was proved. The significant effect of GLP-1 RA on cardiovascular and renal outcomes must result in expanded use of these agents. As cardiologists are 5 times more likely to see patients with concomitant diabetes mellitus and ASCVD than endocrinologists,[8] they are well-positioned to prescribe these agents, given the high burden of diabetes mellitus and renal disease in patients with ASCVD. However, the present study demonstrates that endocrinologists were more likely to prescribe GLP-1 RA than cardiologists likely because they are more knowledgeable about this class of medications and are, therefore, more comfortable prescribing them.

Coordinated efforts including primary care clinicians, specialists, patients, payers, professional societies, and health systems must be implemented to promote the adaptation of GLP-1 RA. Educating clinicians about the various cardiovascular and renal benefits of GLP-1 RA,[9,10] in addition to effects on appetite and weight loss,[11] may help promote uptake of these medications. Improving knowledge about injections and management of rare side effects may also help clinicians be more comfortable prescribing GLP-1 RA. Single or multiple payer systems may also consider the use of cardioprotective glucose-lowering agents as a performance measure. Lastly, mitigating the barriers and

Table 1
Baseline characteristics of the study population by GLP-1 RA use

Variable	GLP-1 RA users n=43,118	GLP-1 RA nonusers n=494,862	P-value
Age (years), mean (SD)	69.6 (8.0)	72.8 (9.0)	<0.01
Men	41,681 (96.7%)	483,542 (97.7%)	<0.01
			<0.01
Non-Hispanic White	31,902 (74.0%)	349,104 (70.6%)	
Non-Hispanic Black	5,374 (12.4%)	77,150 (15.6%)	
Other racial/ethnic groups	5,842 (13.6%)	68,608 (13.8%)	
Hypertension	40,526 (94.0%)	447,646 (90.5%)	<0.01
Body mass index (kg/m^2), mean (SD)	33.9 (6.5)	31.0 (6.2)	<0.01
Body mass index ≥30 kg/m^2	30,551 (70.9%)	258,276 (52.2%)	<0.01
Hemoglobin A1c (%), mean (SD)	8.0 (1.5)	7.2 (1.4)	<0.01
Ischemic heart disease (IHD)	35,960 (83.4%)	391,849 (79.2%)	<0.01
Peripheral arterial disease (in the absence of IHD)	3,506 (8.1%)	49,582 (10.0%)	<0.01
Ischemic cerebrovascular disease (in the absence of IHD)	4,301 (10.0%)	63,112 (12.8%)	<0.01
Systolic heart failure	8,965 (20.8%)	80,286 (16.2%)	<0.01
Physician primary care provider	32,461 (75.3%)	373,819 (75.5%)	0.24
eGFR (ml/min/m^2), mean (SD)	62.0 (22.5)	63.8 (22.5)	<0.01
eGFR <60 ml/min/m^2	19,780 (45.9%)	189 (38.3%)	<0.01
Glucose lowering medications			
Insulin	32,051 (74.3%)	160,407 (32.4%)	<0.01
Biguanides	24,813 (57.6%)	229,224 (46.3%)	<0.01
Sulfonylureas	9,693 (22.5%)	106,676 (21.6%)	<0.01
Thiazolidinediones	2,190 (5.1%)	11,913 (2.4%)	<0.01
DPP-4 inhibitors	3,084 (7.2%)	48,673 (9.8%)	<0.01
SGLT2- inhibitors	12,440 (28.9%)	48,052 (9.7%)	<0.01
Receipt of care at a teaching facility	14,950 (34.7%)	168,309 (34.0%)	<0.01
Number of PCP visits (primary care) in the 12 months prior to the index PCP visit, mean (SD)	11.0 (7.6)	7.4 (6.1)	<0.01
Number of cardiology visits in the 12 months prior to the index PCP visit, mean (SD)	1.0 (2.3)	0.7 (1.8)	<0.01
Number of endocrinology visits in the 12 months prior to the index PCP visit, mean (SD)	0.6 (1.6)	0.2 (0.8)	<0.01

Categorical variables are presented as counts (percentage).
Abbreviations: DPP-4 inhibitors: Dipeptidyl peptidase 4 (DPP-4); SGLT2-inhibitors: Sodium-glucose co-transporter 2 PCP: Primary care provider.

promoting the facilitators identified in our study may help improve use of these medications in clinical practice.

Reassuringly, higher HbA1c, hypertension, obesity, IHD, and chronic kidney disease in our study were associated with higher use of GLP-1 RA. In a previous study of VA patients, we found similar determinants of SGLT-2 inhibitor use except that chronic kidney disease was inversely associated with the receiving of SGLT-2 inhibitors.[7] This suggests that clinicians may be less reluctant to use GLP-1 RA among patients with chronic kidney disease than SGLT-2 inhibitors.

Clinicians may be reluctant to start GLP-1 RA among older patients as the present study demonstrates despite that the effect of GLP-1 RA on major adverse cardiovascular events does not differ by age as demonstrated in a meta-analysis of randomized controlled trials of GLP-1 RA (p for

Table 2
Multivariate logistic regression analyses for the use of GLP-1 RA in patients with ASCVD and type 2 diabetes

Variable	OR/95% CI	P- value
Age (per 5-year increase)	0.873 (0.867-0.879)	<0.01
Women (men as referent)	0.99 (0.93-1.06)	0.80
Race (Whites versus others)	1.33 (1.30-1.37)	<0.01
Hypertension	1.16 (1.10-1.21)	<0.01
BMI >=30 Kg/m^2	1.83 (1.78-1.87)	<0.01
Hemoglobin A1c (per 0.5% increase) Scale this one	1.254 (1.246-1.261)	<0.01
IHD versus PAD or ICVD only	1.258 (1.222-1.295)	<0.01
Physician PCP	0.96 (0.94-0.99)	<0.01
eGFR<60 ml/min/m^2	1.33 (1.30-1.36)	<0.01
Receipt of care at a teaching facility	0.93 (0.91-0.95)	<0.01
Number of PCP visits (per PCP visit)	1.056 (1.055-1.057)	<0.01
Presence of cardiology visit (Yes/No)	1.05 (1.03-1.08)	<0.01
Presence of endocrinology visit (Yes/No)	2.78 (2.71-2.86)	<0.01

BMI = body mass index; IHD = ischemic heart disease; PAD = peripheral arterial disease; ICVD = ischemic cerebrovascular disease; PCP = primary care provider; eGFR = estimated glomerular filtration rate.

interaction = 0.79).[2] It is unclear why older patients were less likely to receive GLP-1 RA; considerations are high costs, administering drugs through subcutaneous injections, concern for drug-drug interactions, and concern for risk for hypoglycemia in older patients. These may discourage prescription of these agents in this patient population. Unexpectedly, having a physician PCP and receiving care at a teaching facility were associated with lower use of GLP-1 RA. However, there are likely significant variations in practicing patterns across VA facilities in the United States of which the present study does not evaluate.[12]

Our results should be interpreted in the context of limitations. We were unable to reliably assess and adjust for additional variables such as doses of respective antidiabetic medications, which raises the possibility of residual confounding. We could not ascertain whether other risk factors such as hypertension or hyperlipidemia were adequately controlled. The majority of our study population consisted of men and non-Hispanic Whites, which may limit generalizability of our results. Furthermore, we used data from a single healthcare system, and results may not apply to other settings. Lastly, our study occurred during the initial phase of the COVID-19 pandemic when quarantine requirements may have affected some of our results.

In summary, our study performed in 1 of the largest health care systems in the United States identified several barriers and facilitators associated with the use of GLP-1 RA among patients with ASCVD and concomitant type 2 diabetes mellitus.

Disclosures

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