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Evidence-based SGLT2 inhibitor and GLP-1 receptor agonist use by race in the VA healthcare system☆

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ABSTRACT

Importance: Adoption of novel therapeutics often lags for Black versus non-Hispanic White patients. Seminal clinical trials established the cardiovascular efficacy of sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) in patients with type 2 diabetes (T2D) and established atherosclerotic cardiovascular disease. However, it is uncertain whether race influences the evidence-based prescription of these agents.

Objective: To determine whether evidence-based prescription of SGLT2i or GLP-1RA differs by Black versus White race in the Veterans Affairs (VA) healthcare system.

Design, Setting, and Participants: Retrospective cohort study of US Veterans with T2D and angiographically confirmed coronary artery disease (CAD) at 84 VA medical centers over the period 2015–2023. Data from the VA Clinical Assessment, Reporting, and Tracking Program were used to construct cohorts eligible for SGLT2i or GLP-1RA treatment based on eligibility criteria for the seminal Empagliflozin, Cardiovascular Outcomes, and Mortality in T2D (EMPA-REG OUTCOME) or the Liraglutide Effect and Action in Diabetes (LEADER) trial, respectively. Multivariable logistic regression estimated adjusted odds of trial-concordant SGLT2i or GLP-1RA prescription by race.

Exposures: Self-identified race.

Main Outcomes and Measures: SGLT2i or GLP-1RA prescription among those with an evidence-based (trial-concordant) indication.

Results: Of 63,561 Veterans with T2D and CAD, 3527 Black and 18,668 White patients met criteria for trial-concordant SGLT2i treatment and 2020 Black and 10,103 White patients for GLP1-RA treatment. Trial-concordant prescription of both classes increased over time for both races but reached only 42 % for SGLT2i and 15 % for GLP1-RA in 2023. Black versus White race was not associated with evidence-based SGLT2i prescription (adjusted odds ratio [OR] 0.96, 95 % CI 0.89–1.04, $P = 0.32$). However, Black Veterans were less likely than White to be provided with a trial-concordant GLP1-RA prescription (adjusted OR 0.85, 95 % CI 0.74–0.98, $P = 0.025$).

Conclusions and Relevance: Among patients with T2D and CAD in the VA healthcare system, evidence-based SGLT2i and GLP1-RA prescription increased over time, but many eligible patients remained untreated. Although SGLT2i prescription did not differ by race, Black versus White Veterans were less likely to receive evidence-based GLP1-RA prescription. Racial disparities in evidence-based cardiovascular drug prescription exist even in a healthcare system with few economic barriers and may be drug class-specific.

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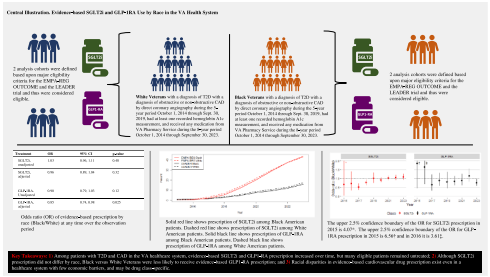

Central Illustration. Evidence-based SGLT2i and GLP-1RA Use by Race in the VA Health System

Key Takeaways: 1) Among patients with T2D and CAD in the VA healthcare system, evidence-based SGLT2i and GLP1-RA prescription increased over time, but many eligible patients remained untreated; 2) Although SGLT2i prescription did not differ by race, Black versus White Veterans were less likely to receive evidence-based GLP1-RA prescription; and 3) Racial disparities in evidence-based cardiovascular drug prescription exist even in a healthcare system with few economic barriers, and may be drug class-specific.

1. Introduction

In 2016 and 2017, respectively, the sodium-glucose cotransporter-2 inhibitor (SGLT2i) empagliflozin and the glucagon-like peptide-1 receptor agonists (GLP-1RA) liraglutide became the first drugs in their classes to be approved by the US Food and Drug Administration for cardiovascular risk reduction in patients with type 2 diabetes (T2D) [1,2]. The approvals followed the initial demonstration of cardiovascular efficacy of these agents in landmark, placebo-controlled trials published in 2015, the Empagliflozin, Cardiovascular Outcomes, and Mortality in T2D [3] (EMPA-REG OUTCOME) and the Liraglutide Effect and Action in Diabetes [4] (LEADER) trial. Both trials showed reductions in the endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke with active treatment in patients with T2D and established cardiovascular disease or high cardiovascular risk. Subsequent trials expanded the evidence base by demonstrating clinical efficacy of other agents in each drug class. In turn, clinical practice guidelines evolved to recommend SGLT2i and GLP-1RA use in patients with T2D and atherosclerotic cardiovascular disease (ASCVD), first as adjuncts to metformin (Glucophage) in 2018 and then as first line treatment beginning in 2021 [5–7]. However, despite high quality clinical trial evidence [3,4,8–10] and guideline recommendations, [5,7,11,12] overall prescribing of SGLT2i and GLP-1RA has lagged [13–15].

Equity in access to efficacious treatments is a pillar of public health policy. Yet evidence indicates that individuals from racial and ethnic minorities may be less likely than others to receive newer, more costly, or guideline-established medications, [16] particularly in the initial years of drug availability and/or evidence of efficacy [17–21]. Factors implicated in inequitable treatment include access to and cost of medications, as well as health team and system dynamics [22–24]. The national integrated health care system of the US Department of Veterans Affairs (VA) provides medical and pharmacy benefits with low or no out-of-pocket costs. With fewer economic barriers to care than systems reliant on commercial health insurance, the VA healthcare system might be less vulnerable to racial disparities in evidence-based care. However, a recent study in the VA healthcare system indicated that Black patients with T2D had significantly lower odds of being prescribed SGLT2i and GLP-1RA than White patients with T2D [23]. However, this analysis considered all prescriptions for these medication classes, including those that were not necessarily concordant with guidelines or with the seminal cardiovascular outcomes trials that established clinical efficacy. This is an important distinction because for many patients with T2D without established cardiovascular disease, initial lifestyle modification and metformin (Glucophage) treatment may be appropriate, and the absence of SGLT2i and GLP-1RA prescription may not reflect inferior treatment. Thus, pharmacoequity [16] in the use of these drug classes may be better evaluated by determining whether prescription aligned with high-quality clinical trial evidence is influenced by factors such as race.

To address this question, we examined prescription of SGLT2i and GLP-1RA among Black versus White Veterans with T2D and CAD diagnosed by coronary angiography, selecting an analysis cohort that was concordant with the eligibility criteria of the EMPA-REG OUTCOME and LEADER trials. We examined temporal trends in such trial-concordant prescription over an 8-year period following the publication of these trials.

2. Methods

2.1. Data source and analysis cohort

VA Clinical Assessment Reporting and Tracking (CART) Program is a national quality and safety program for several medical specialties, including invasive cardiology. To achieve its operational aims, the CART Program utilizes a clinical software application interfaced with the electronic health record to collect standardized data for all coronary angiography procedures performed in the 84 cardiac catheterization laboratories at VA medical centers nationwide [25]. Among data elements collected are demographic and clinical characteristics, procedural indications and descriptors, and coronary anatomic and physiological findings. The current retrospective cohort study was approved by the Colorado Multi-Institutional Review Board and VA Eastern Colorado Healthcare System Research and Development Committee as exempt from patient consent.

Fig. 1 schematizes the formation of the analysis cohorts. Using data from the CART Program, Veterans were identified with a diagnosis of T2D who self-identified as non-Hispanic Black (hereafter, Black) or non-Hispanic White (hereafter, White), had a diagnosis of obstructive or non-obstructive coronary artery disease by direct coronary angiography during the 5-year period October 1, 2014 through Sept. 30, 2019, had at least one recorded hemoglobin A1c (HbA1c) measurement, and received any medication from VA Pharmacy Service during the 8-year period October 1, 2014 through September 30, 2023. Individuals who self-reported being Hispanic or Latino, Asian, or of another race and ethnicity (such as American Indian, Alaska Native, Native Hawaiian, or Other Pacific Islander) were excluded. Obstructive CAD was defined as ≥50 % stenosis of the left main or ≥70 % stenosis in any other major epicardial coronary artery. Non-obstructive CAD was defined as ≥20 % stenosis in any major epicardial coronary artery that did not meet the definition of obstructive CAD.

Among these patients, two analysis cohorts were defined based upon fulfilment of the major eligibility criteria for the EMPA-REG OUTCOME or the LEADER trial [3,4], and thus were considered eligible for evidence-based treatment with an SGLT2i or GLP-1RA, respectively. Patients who fulfilled the criteria for both trials were included in both analysis cohorts.

2.2. Outcomes

Among the cohorts deemed eligible for evidence-based prescription of an SGLT2i or GLP-1RA, we assessed actual prescription of these drug classes from October 1, 2014 through September 30, 2023 (corresponding to Federal fiscal years 2015–2023). SGLT2i use was defined by prescription of empagliflozin, dapagliflozin, canagliflozin, or ertigliflozin. GLP-1RA use was defined by prescription of semaglutide, liraglutide, dulaglutide, or albiglutide. These data were used to create a patient-level binary indicator (any prescription yes/no) for use in logistic regression models.

2.3. Statistical analysis

In each cohort, we examined the prevalent use of a SGLT2i or GLP-

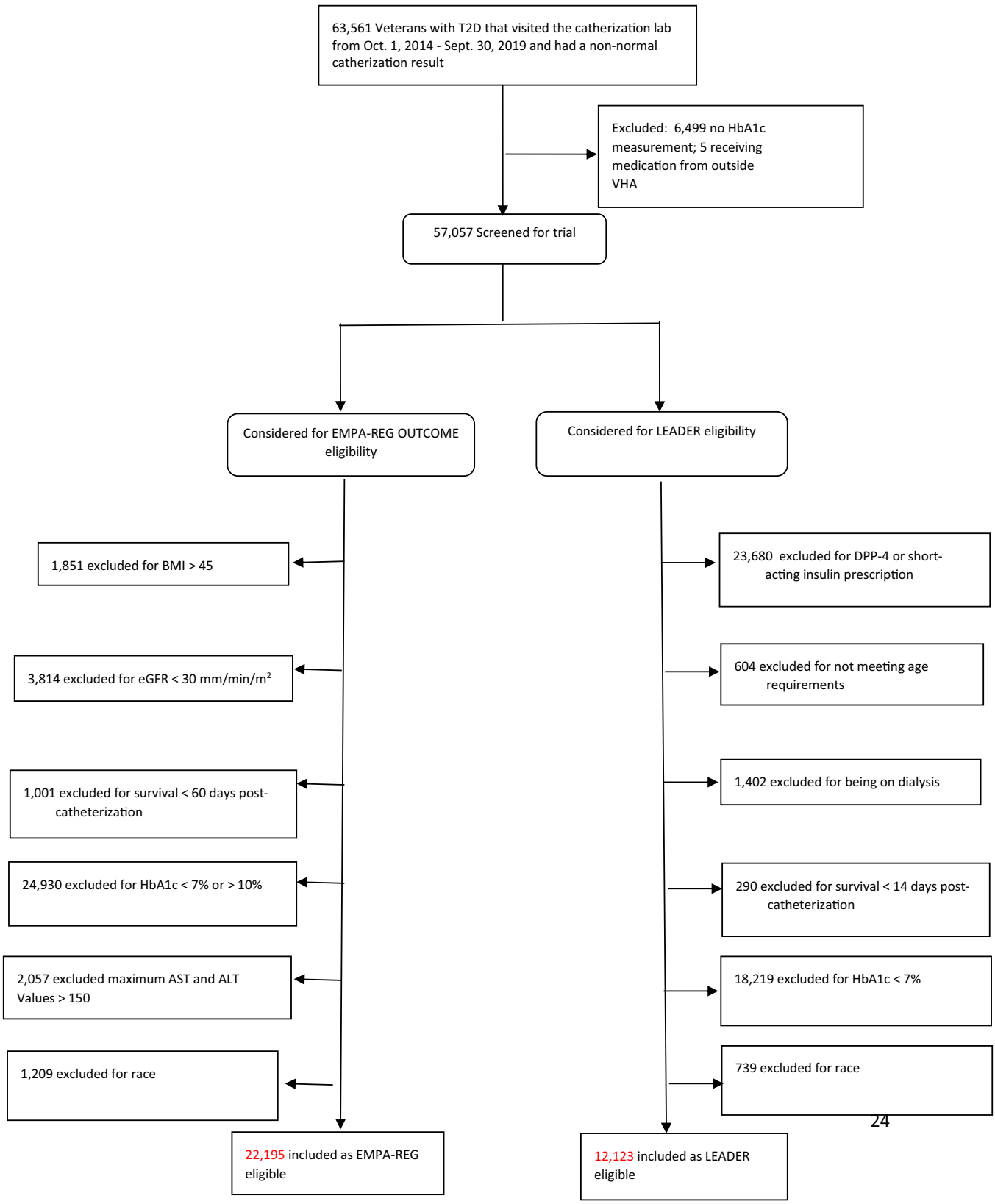

Fig. 1. Study flow diagram. The principal inclusion criteria applied from LEADER were age ≥18 years of age and had a HbA1c of at least 7.0 %. Patients were excluded if they were current users of a dipeptidyl peptidase-4 (DPP-4) inhibitor or short-acting insulin, if they were on dialysis, or if they had HbA1c <7 %. The principal inclusion criteria applied from EMPA-REG OUTCOME were age ≥18 years, body mass index (BMI) ≤45 kg/m2 and HbA1c 7 % to 10 %. Exclusions included BMI > 45, eGFR ⟨ 30 mm/min/m2, HbA1c < 7 % or ⟩ 10 %, maximum AST and ALT Values > 150. Patients were excluded across both cohorts if not self-identified as White or Black American race.

1RA at baseline (time of index angiography) and then annually until the end of the observation period. Odds ratios for the association between race and prescription of a SGLT2i or GLP 1RA were estimated using unadjusted and adjusted logistic regression models. Unadjusted models included a binary outcome for any prescription (yes/no) and a binary indicator for race (black/white). Covariates for the adjusted models were selected as *a priori* based on prior literature and clinical relevance. These included age, sex, insurance type (VA only or with additional coverage), number of cardiovascular medications (including anti-platelet agents, beta blockers, statins, inhibitor of the renin-angiotensin-aldosterone system, calcium channel blockers, and nitrates), insulin use, number of non-insulin anti-hyperglycemic medications (not including SGLT2i and GLP-1RA), and treatment site. All analyses were performed using R Statistical Software (v4.3.0).

3. Results

Of 63,561 patients with T2D and a diagnosis of coronary artery disease by angiography from October 1, 2014 through September 30, 2019 (Fig. 1), 6504 were excluded for absence of any HbA1c measurement or any VA Pharmacy prescription, leaving 57,057 patients who were screened for trial eligibility. The predominant reasons for further exclusion from the analysis cohorts were HbA1c levels outside the qualifying range or use of prohibited medications. A total of 22,195 (38.9 %) – 3527 Black (15.9 %) and 18,668 White (84.1 %) – patients met EMPA-REG OUTCOME eligibility criteria for SGLT2i treatment, and a total of 12,123 (21.2 %) – 2020 Black (16.7 %) and 10,103 (83.3 %) White – patients met LEADER eligibility criteria for GLP-1RA treatment.

3.1. Baseline characteristics of the analysis cohorts

Table 1 shows baseline characteristics of patients deemed eligible for evidence-based SGLT2i treatment in aggregate, by race, and according to actual treatment with an SGLT2i during the observation period. Table 2 shows the analogous data for patients deemed eligible for evidence-based GLP-1RA treatment. The cohorts had a median age of 69 years and 98 % were male. The most prominent differences in baseline characteristics of Black compared with White patients were the less frequent history of prior coronary revascularization, greater prevalence of chronic kidney disease, and differences in non-VA insurance coverage.

3.2. Odds of evidence-based prescription of SGLT2i and GLP-1RA by race

Evidence-based prescription of both drug classes increased over time for both races (Fig. 2A) but reached only approximately 40 % for SGLT2i and 15 % for GLP-1RA in 2023. For SGLT2i, the adjusted odds of evidence-based prescription by race approached 1.0 for the years 2019–2023 (Fig. 2B). For GLP-1RA, adjusted odds of evidence-based prescription were slightly lower for Black versus White patients but were not significantly different from 1.0 in any given year. Absolute differences in the adjusted odds ratio of GLP1RA prescribing by race did not change much year-to-year after 2017.

Considering the entire observation period, there was no association of race with evidence-based prescription of SGLT2i, either in unadjusted analysis [Black/White OR 1.03 (95 % CI: 0.96–1.11; $P = 0.40$)] or after adjustment for covariates [OR 0.96 (95 % CI: 0.89–1.04; $P = 0.32$)]. For GLP-1RA, the unadjusted odds of evidence-based prescription also did not differ for Black versus White patients [OR 0.90 (95 % CI: 0.79–1.03; $P = 0.12$)]. However, after adjustment for covariates, the odds of evidence-based prescriptions were lower for Black versus White patients [OR 0.85 (95 % CI: 0.74–0.98; $P = 0.025$; Table 3).

3. Discussion

This study examined racial differences in evidence-based, outcomes

Table 1
Baseline characteristics of patients eligible for evidence-based SGLT2i treatment.

Characteristic	Overall $n = 22,195$	White, $n = 18,668$	Black $n = 3527$	Treated, $n = 9562$	Untreated, $n = 12,633$
Demographics					
Age	69 (64, 73)	69 (65, 73)	66 (61, 71)	68 (63, 71)	69 (65, 74)
Female	433 (2.0 %)	301 (1.6 %)	132 (3.7 %)	184 (1.9 %)	249 (2.0 %)
Race					
White				8020 (83.9 %)	10,648 (84.3 %)
Black				1542 (16.1 %)	1985 (15.7 %)
Medical history, n (%)					
Prior CABG/PCI	14,392 (64.8 %)	12,691 (67.9 %)	1701 (48.2 %)	6055 (63.3 %)	8337 (65.9 %)
Prior stroke	2475 (11.2 %)	2017 (10.8 %)	458 (13.0 %)	848 (8.9 %)	1627 (12.9 %)
Peripheral artery disease	5276 (23.8 %)	4479 (24.0 %)	797 (22.6 %)	1851 (19.4 %)	3425 (27.1 %)
Hypertension	21,485 (96.8 %)	18,025 (96.6 %)	3460 (98.1 %)	9251 (96.7 %)	12,234 (96.8 %)
Chronic kidney disease	6368 (28.7 %)	5101 (27.3 %)	1267 (35.9 %)	2162 (22.6 %)	4206 (33.3 %)
Indication for index angiography, n (%)					
Acute coronary syndrome	4634 (20.9 %)	3911 (20.9 %)	723 (20.5 %)	1932 (20.2 %)	2702 (21.4 %)
Chest pain or stable angina pectoris	8733 (39.3 %)	7415 (39.7 %)	1308 (37.1 %)	3985 (41.7 %)	4748 (37.6 %)
Cardiomyopathy, valvular heart disease, or heart failure	2490 (11.2 %)	1971 (10.6 %)	519 (14.7 %)	954 (9.9 %)	1536 (12.2 %)
Other	2735 (12.3 %)	2282 (12.2 %)	453 (12.8 %)	1250 (13.1 %)	1485 (11.8 %)
Laboratory and biometric variables					
Body mass index, kg/m^2	32.1 (28.5, 36.0)	32.2 (28.6, 36.1)	31.5 (27.9, 35.5)	32.7 (29.2, 36.5)	31.6 (28.1, 35.6)
Hemoglobin A1c, %	7.9 (7.4, 8.6)	7.9 (7.4, 8.6)	7.9 (7.4, 8.7)	7.9 (7.4, 8.6)	7.8 (7.3, 8.5)
eGFR, ml/min/ $1.73m^2$	72 (56, 88)	71 (56, 87)	77 (59, 94)	75 (60, 91)	69 (54, 85)
Systolic blood pressure, mm Hg	135 (127, 144)	135 (126, 144)	138 (129, 146)	135 (127, 144)	136 (126, 145)
Diastolic blood pressure, mm Hg	74 (69, 80)	74 (69, 79)	78 (72, 83)	75 (70, 81)	74 (69, 79)
HDL-C, mg/dL	37 (32, 43)	36 (31, 43)	40 (34, 48)	36 (32, 43)	37 (32, 44)
LDL-C, mg/dL	79 (61, 102)	78 (60, 100)	86 (67, 112)	79 (61, 102)	79 (61, 102)
Medications					
Number of cardiovascular medications*	3.40 (2.35, 4.25)	3.35 (2.35, 4.25)	3.55 (2.50, 4.35)	3.55 (2.65, 4.35)	3.25 (2.20, 4.15)
Number of diabetes medications†	0.90 (0.35, 1.35)	0.95 (0.35, 1.40)	0.80 (0.25, 1.20)	1.00 (0.60, 1.60)	0.75 (0.20, 1.15)

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Table 1 (*continued*)

Characteristic	Overall *n* = 22,195	White, *n* = 18,668	Black *n* = 3527	Treated, *n* = 9562	Untreated, *n* = 12,633
Non-VA Health Insurance, n (%)					
Medicare or Medicaid	14,690 (66.2 %)	12,778 (68.4 %)	1912 (54.2 %)	5884 (61.5 %)	8806 (69.7 %)
Other‡	6665 (30.0 %)	5216 (27.9 %)	1449 (41.1 %)	3342 (35.0 %)	3323 (26.3 %)
None	840 (3.8 %)	674 (3.6 %)	166 (4.7 %)	336 (3.5 %)	504 (4.0 %)

Continuous variables are median (Q1, Q3). CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

* Anti-platelet agents, beta blockers, statins, inhibitor of the renin-angiotensin-aldosterone system, calcium channel blockers, and nitrates.

† Not including SGLT2i or glucagon-like peptide-1 receptor agonists.

‡ Other includes private medical or dental insurance, military insurance (CHAMPUS), worker's compensation, indemnity, Medicare supplemental or other supplemental prescription coverage, and other insurance.

trial-concordant prescription of SGLT2i and GLP-1RA in Veterans with T2D and coronary artery disease diagnosed by angiography at 84 VA medical centers over an 8-year observation period following the initial publication of randomized, placebo-controlled clinical trials demonstrating the clinical efficacy of these drug classes [3,4]. There are two key observations. First, even in a healthcare system with few economic and access barriers, SGLT2i and GLP-1RA were underutilized in both Black and White patients. Although the uptake increased over the observation period, trial-concordant SGLT2i and GLP-1RA prescription reached only 42 % and 15 %, respectively, in the final year of observation (2023). Second, Black versus White race did not influence the odds of trial-concordant SGLT2i prescription, with or without adjustment for covariates. However, the odds of evidence-based GLP-1RA prescription were lower among Black versus White patients after adjustment for covariates. Even so, the absolute difference in trial-concordant prescription of GLP-1RA between Black and White patients was small compared with the gap between potential and achieved prescription in both racial groups.

The present analysis assessed evidence-based SGLT2i and GLP-1RA prescription in cohorts defined by eligibility criteria for the landmark trials that established the cardiovascular efficacy of treatment [3,4]. Accordingly, the patients who comprised the analysis cohorts had high-risk characteristics and would be expected to achieve meaningful clinical benefit of treatment [26]. This may explain the contrast between the present data and a cross-sectional analysis of all VA prescriptions for SGLT2i and GLP-1RA by race and ethnicity in 1197,914 Veterans with T2D [23]. In that analysis, racial and ethnic minorities had significantly lower adjusted odds of SGLT2i and GLP-1RA prescriptions compared with non-Hispanic White individuals. However, the analysis was not limited to guideline-based or trial-concordant prescriptions. Thus, it is difficult to infer differences in quality of care from differences in prescription rates according to race.

Although trial-concordant use of SGLT2i and GLP-1RA in patients with T2D and CAD was suboptimal in the current analysis, it was nonetheless higher than use in other, similar contemporary cohorts. Nanna and colleagues examined SGLT2i and GLP-1RA in 321,304 patients with T2D and ASCVD enrolled in 88 US healthcare systems [27]. Prescription rates for both classes reached only approximately 12 % in 2021. In a cohort of 324,706 patients with T2D and ASCVD from the National Patient-Centered Clinical Research Network, prescription of SGLT2i and GLP-1RA reached 2.8 % and 3.9 %, respectively, in 2020 [28]. In a privately insured US cohort of 416,149 patients with T2D and

Table 2
Baseline characteristics of patients eligible for evidence-based GLP-1RA treatment.

Characteristic	Overall *n* = 12,123	White, *n* = 10,103	Black *n* = 2020	Treated *n* = 2083	Untreated *n* = 10,040
Demographics					
Age	69 (64, 73)	69 (65, 74)	67 (61, 72)	68 (62, 71)	69 (65, 74)
Female	225 (1.9 %)	163 (1.6 %)	62 (3.1 %)	48 (2.3 %)	177 (1.8 %)
Race					
White				1760 (84.5 %)	8343 (83.1 %)
Black				323 (15.5 %)	1697 (16.9 %)
Medical history, n (%)					
Prior CABG/PCI	7345 (60.5 %)	6489 (64.2 %)	856 (42.4 %)	1178 (56.6 %)	6167 (61. %)
Prior stroke	1254 (10.3 %)	1021 (10.1 %)	233 (11.5 %)	166 (8.0 %)	1088 (10.8 %)
Peripheral artery disease	2782 (22.9 %)	2371 (23.5 %)	411 (20.3 %)	362 (17.4 %)	2420 (24.1 %)
Hypertension	11,633 (96.0 %)	9667 (95.7 %)	1966 (97.3 %)	2001 (96.1 %)	9632 (95.9 %)
Chronic kidney disease	2897 (23.9 %)	2269 (22.5 %)	628 (31.1 %)	443 (21.3 %)	2454 (24.4 %)
Indication for index angiography, n (%)					
Acute coronary syndrome	2750 (22.7 %)	2279 (22.6 %)	471 (23.3 %)	443 (21.3 %)	2307 (22.9 %)
Chest pain or stable angina pectoris	5169 (42.6 %)	4384 (43.4 %)	785 (38.9 %)	938 (45.0 %)	4231 (42.1 %)
Cardiomyopathy, valvular heart disease, or heart failure	1513 (12.5 %)	1205 (11.9 %)	308 (15.2 %)	215 (10.3 %)	1298 (12.9 %)
Other	1455 (12.0 %)	1207 (11.9 %)	248 (12.2 %)	292 (14.0 %)	1163 (11.6 %)
Biometric and laboratory variables					
Body mass index, kg/m^2	31.3 (27.9, 35.4)	31.4 (28.1, 35.4)	30.8 (27.2, 34.8)	33.3 (29.7, 37.4)	30.9 (27.7, 34.8)
Systolic blood pressure, mm Hg	136 (126, 145)	135 (126, 144)	138 (129, 147)	135 (127, 144)	136 (126, 145)
Diastolic blood pressure, mm Hg	74 (59, 90)	73 (58, 88)	80 (62, 96)	74 (60, 91)	74 (58, 90)
Hemoglobin A1c, %	7.70 (7.30, 8.50)	7.70 (7.30, 8.40)	7.80 (7.30, 8.70)	8.00 (7.40, 8.90)	7.70 (7.20, 8.40)
eGFR, ml/min/ 1.73m^2	75 (70, 81)	75 (69, 80)	78 (73, 84)	76 (71, 81)	75 (70, 81)
HDL-C, mg/dL	38 (32, 44)	37 (32, 43)	41 (34, 49)	37 (32, 43)	38 (32, 45)
LDL-C, mg/dL	82 (63, 105)	81 (62, 104)	87 (68, 112)	80 (62, 103)	82 (63, 106)
Medications					
Number of cardiovascular medications*	3.10 (2.00, 4.05)	3.10 (2.00, 4.00)	3.20 (2.10, 4.15)	3.35 (2.40, 4.25)	3.05 (1.95, 4.00)
Number of diabetes medications†	0.95 (0.45, 1.40)	0.95 (0.45, 1.45)	0.85 (0.40, 1.25)	1.15 (0.75, 1.75)	0.90 (0.35, 1.30)

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Table 2 (*continued*)

Characteristic	Overall *n* = 12,123	White, *n* = 10,103	Black *n* = 2020	Treated *n* = 2083	Untreated *n* = 10,040
Non-VA Health Insurance, n (%)					
Medicare or Medicaid	7953 (65.6 %)	6860 (67.9 %)	1093 (54.1 %)	1192 (57.2 %)	6761 (67.3 %)
Other[‡]	3735 (30.8 %)	2906 (28.8 %)	829 (41.0 %)	823 (39.5 %)	2912 (29.0 %)
None	435 (3.6 %)	337 (3.3 %)	98 (4.9 %)	68 (3.3 %)	367 (3.7 %)

Continuous variables are median (Q1, Q3). CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention.

[*] Anti-platelet agents, beta blockers, statins, inhibitor of the renin-angiotensin-aldosterone system, calcium channel blockers, and nitrates.

[†] Not including sodium-glucose cotransporter-2 inhibitors or GLP-1RA.

[‡] Other includes private medical or dental insurance, military insurance (CHAMPUS), worker's compensation, indemnity, Medicare supplemental or other supplemental prescription coverage, and other insurance.

prevalent or high risk for ASCVD, use of SGLT2i and GLP-1RA reached only 3.8 % and 4.6 %, respectively, in 2019 [29]. Greater use of these drugs in the VA healthcare system compared to other US healthcare systems may be due to fewer barriers to care [30,31]. However, even in Sweden and the United Kingdom, countries with government-funded, universal healthcare systems, recent evidence-based treatment has been disappointingly low. In Sweden, only one-quarter to one-third-of patients received treatment SGLT2i or GLP-1RA concordant with European guidelines [32]. In the United Kingdom National Health Service, only 9.8 % and 4.3 % of 44,808 patients with T2D and ASCVD were treated with SGLT2i and GLP-1RA, respectively, in 2020 [33].

The Swedish and UK data, in conjunction with the present findings in the VA healthcare system, suggest that factors other than access and medication cost may be culpable for low evidence-based use of these drug classes. Potential reasons for under-prescription include therapeutic inertia, [34–36] concerns about side effects, provider knowledge and confidence in prescribing these medications, [37,38] or obstacles in the processes of care such as requirements for step therapy with metformin (Glucophage) and administrative burden to obtain prior authorization that may increase probability of discontinued and delayed care [39,40]. In the VA healthcare system, requirements for background metformin (Glucophage) treatment and pharmacist approval were removed for SGLT2i in 2021 and may have contributed to rising trial-concordant prescription of that class thereafter. Both SGLT2i and GLP-1RA require patient education on side effects, proper administration, and self-monitoring [41]. As a result, time constraints in clinics and limited pharmacist resources may result in missed opportunities to counsel patients about benefits and adherence strategies [38]. Patient concerns over potential side effects of treatment or injection of GLP-1RA may also contribute to low prescribing rates [42,43]. Health literacy and awareness gaps may also affect uptake, including misconceptions that diabetes medications are only for lowering blood sugar rather than preventing cardiovascular events.

Our data indicates that trial-concordant SGLT2i and GLP-1RA treatment has not yet reached steady-state. Only in 2019 did the European Society of Cardiology/European Association for the Study of Diabetes endorse initial treatment with an SGLT2i or GLP-1RA (i.e., before metformin) in patients with T2D and established or high risk for cardiovascular disease [12]. Not until 2023 did the American Diabetes Association make a similar recommendation [44] and providers may not yet fully appreciate these paradigm changes [8,45,46]. While prescribing patterns in this study were not identified by clinical specialty, prescription of SGLT2i and GLP-1RA by US cardiologists still accounts for a small proportion of all use, contributing to the undertreatment of individuals with T2D at high cardiovascular risk [14].

Utilizing data from the VA healthcare system, we found no disparity by race in trial-concordant prescription of SGLT2i, but a disparity of modest magnitude disfavoring Black patients in trial-concordant prescription of GLP-1RA. In contrast, a study in a broader US cohort by Cromer et al. found that evidence-based prescription of both drug classes was lower in communities of color [47]. Those investigators examined Medicare data (2016–2019) for 4057,725 US individuals age >65 years with T2D for SGLT2i or GLP-1RA prescription within 180 days of a new diagnosis of ASCVD or heart failure. Compared with non-Hispanic White individuals, medication was initiated significantly less often among Black individuals and those of other race/ethnicity, with estimated hazard ratios of 0.81 and 0.84, respectively.

It is uncertain why there is an apparent disparity by race in trial-concordant prescription of GLP-1RA, but not SGLT2i prescription, in the VA healthcare system. For most patients with T2D and CAD, the use of GLP-1RA in the VA healthcare system continues to require stepped care with metformin (Glucophage) and prior approval by a pharmacist, while such requirements have been removed for SGLT2i. GLP1-RA are typically prescribed as injectable agents requiring gradual, multi-step titration and often down-titration of other glucose-lowering agents to avoid hypoglycemia. In contrast, SGLT2i are oral agents usually given at fixed doses, with smaller effects on glycemic control. Accordingly, the initiation and management of GLP-1RA is more complex than SGLT2i, requiring more provider time and greater collaboration among various providers. We could not measure the number or duration of patient appointments or the degree of co-management by specialty providers to assess whether those factors varied by race and might have influenced our findings. Nor could we assess contextual provider or patient-related factors not discernible through quantitative data that might influence initiation or persistence of treatment by race, including implicit bias, effectiveness of provider-patient communication, health literacy, socioeconomic status, and patient prescription abandonment [26,48–54].

4.1. Strengths and limitations

Strengths of the current analysis include a large sample size of veterans across 84 VA medical centers. The study specifically examines trial-concordant use of SGLT2i and GLP-1RA and thus determines whether any disparities in drug utilization correspond to disparities in evidence-based care, and by extension to disparities in cardiovascular risk reduction. Such inference is not possible when all prescriptions are considered, irrespective of indication [23]. The current study spanned an 8-year observation period, allowing for assessment of temporal trends in prescription.

Several limitations of our retrospective observational cohort analysis should also be noted. First, we considered a subset of evidence-based use of SGLT2i and GLP-1RA in patients with T2D and CAD. In recent years, evidence supporting use of these classes has expanded to include patients with chronic kidney disease, [55] heart failure, [56] and obesity, [57] as well as atherosclerotic cardiovascular disease without T2D [58]. Future expansion of the evidence-based use of these classes is possible [59,60]. Second, only about half of the 172 VA medical centers have cardiac catheterization laboratories and only patients who undergo procedures in a VA laboratory are included in the CART Program dataset. Thus, Veterans who receive medications through VA but had coronary angiography at a non-VA facility were not included in the analysis. Third, our cohort of Veterans with T2D and CAD was predominantly male, there were too few patients of race other than Black or White for meaningful analysis, and ethnicity was not considered. Finally, the present analysis did not estimate potential clinical consequences of lower trial-concordant prescription of GLP-1RA in Black versus White Veterans. However, in a recent analysis comprising patients of all races and ethnicities with T2D and CAD receiving care at VA

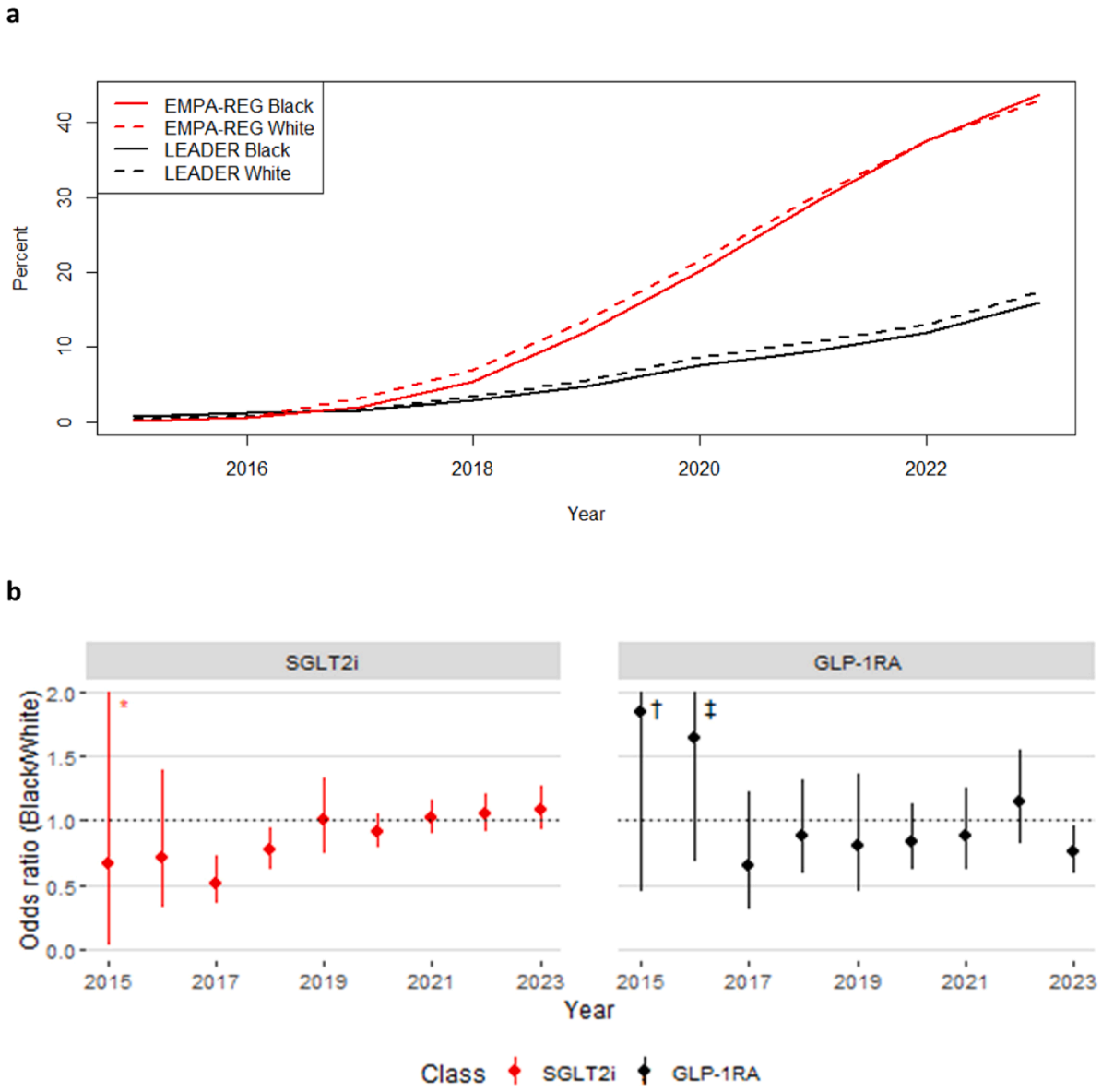

Fig. 2. *Racial difference in odds of receiving an evidence-based SGLT2i or GLP-1RA prescription.* **(a)** Percentage of Trial-Eligible Patients Treated by Race and Sodium-Glucose Cotransporter-2 Inhibitor (SGLT2i) or Glucagon-like Peptide-1 Receptor Agonist (GLP-1RA) and Prescriptions by Year and **(b)** Adjusted odds ratio (OR) of evidence-based prescription by race (Black/White) and year.
(a) Solid red line shows prescription of SGLT2i among Black American patients. Dashed red line shows prescription of SGLT2i among White American patients. Solid black line shows prescription of GLP-1RA among Black American patients. Dashed black line shows prescription of GLP-1RA among White American patients. (b) * *The upper 2.5 % confidence boundary of the OR for SGLT2i prescription in 2015 is 4.07.* †*The upper 2.5 % confidence boundary of the OR for GLP-1RA prescription in 2015 is 6.56;* ‡ *is 3.61.*

Table 3
Odds ratio (OR) of evidence-based prescription by race (Black/White) at any time over the observation period.

Treatment	OR	95 % CI	p-value
SGLT2i, unadjusted	1.03	0.96, 1.11	0.40
SGLT2i, adjusted	0.96	0.89, 1.04	0.32
GLP-1RA, Unadjusted	0.90	0.79, 1.03	0.12
GLP-1RA, adjusted	0.85	0.74, 0.98	0.025

Covariates in adjusted models are age, sex, age, sex, insurance type (VA with or without additional coverage), number of cardiovascular medications (anti-platelet agents, beta blockers, statins, inhibitor of the renin-angiotensin-aldosterone pathway, calcium channel blockers, and nitrates), insulin use, number of non-insulin anti-hyperglycemic medications (not including sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists), and treatment site. OR, odds ratio; CI, confidence interval.

facilities between 2015 and 2021, we projected that broader use of GLP-1RA could have prevented a substantial number of deaths [26]. Therefore, the current findings suggest that disparities in trial-concordant GLP-1RA prescription may result in a disproportionate excess of adverse events in Black patients.

5. Conclusions

Evidence-based prescription of SGLT2i and particularly GLP-1RA was low among patients with T2D and coronary artery disease treated in the VA healthcare system. Black and White patients had similar odds of evidence-based treatment with SGLT2i. In contrast, Black patients had lower adjusted odds of evidence-based treatment with GLP-1RA. Further work is needed to identify factors responsible for treatment disparities by race and develop interventions to promote equitable

access to evidence-based cardioprotective therapies.

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CRediT authorship contribution statement

Demetria M. Bolden: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization. **Vanessa Richardson:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Taufiq Salahuddin:** Writing – review & editing, Writing – original draft. **Kamal Henderson:** Writing – review & editing, Writing – original draft. **Paul L. Hess:** Writing – review & editing, Writing – original draft. **Sridharan Raghavan:** Writing – review & editing, Writing – original draft, Conceptualization. **David R. Saxon:** Writing – review & editing, Conceptualization. **P. Michael Ho:** Writing – review & editing. **Stephen W. Waldo:** Writing – review & editing, Investigation, Data curation. **Gregory G. Schwartz:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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