Trends in prescriptions of cardio-protective diabetic agents after coronary artery bypass grafting among US Veterans

Brief title: Use of SGLT2i/GLP-1RA after CABG

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Abstract (153 words)

Introduction: Patients with type 2 diabetes mellitus (T2DM) undergoing coronary artery bypass grafting (CABG) are at risk of cardiovascular events. SGLT2i and GLP-1RA are effective cardio-protective agents, however, their prescription among CABG patients is uncertain.

Methods: We analyzed the nationwide Veteran Affairs database (2016 – 2019) to report trends and factors associated with SGLT2i or GLP1RA prescription after CABG.

Results: Among 5,109 patients operated at 40 different VA medical centers, 525/5109 (10.4%), 352/5109 (6.8%) and 91/5109 (1.8%) were prescribed SGLT2i, GLP-1RA and both respectively. Substantial increase in the quarterly SGLPT2i prescription rates (1.6% (2016Q1), 33% (2019Q4)) was present; less so for GLP-1RA (0.8% (2016Q1), 11.2% (2019Q4)). SGLT2i use was less likely with pre-existing vascular disease (OR 0.75-95%CI-[0.75,0.94]) or kidney disease (OR 0.72-95%CI-[0.58,0.88]), while GLP-1RA use was associated with obesity (OR 1.91-95%CI-[1.50,2.46]).

Conclusion: The overall utilization of SGLT2i or GLP-1RA drugs in US Veterans with T2DM undergoing CABG is low, with SGLT2i preferred over GLP-1RA.

Introduction

Coronary artery bypass grafting (CABG) is the preferred treatment for patients with type 2 diabetes mellitus (T2DM) and multivessel coronary artery disease (CAD) [1,2]. Sodium glucose cotransporter 2 receptor inhibitors (SGLT2i) and glucagon like peptide 1 receptor agonists (GLP-1RA) reduce cardiovascular risk in patients with T2DM and are, therefore, recommended for all T2DM patients with atherosclerotic vascular disease (ASCVD)[3 4]. However, their adoption post CABG is uncertain. We, therefore, analyzed patterns and trends for SGLT2i/GLP-1RA prescription in patients receiving CABG at Veterans Affairs (VA) medical centers nationwide. We evaluated longitudinal trends in SGLT2i / GLP-1RA use during the first post-operative year and studied clinical and socio-economic factors associated with the use of these cardio-protective medications.

Design and Methods

Our aims in this study were (i) to evaluate the overall use of SGLT2i / GLP-1RA after CABG and explore longitudinal trends, and (ii) examine patient related factors associated with the use of SGLT2i or GLP-1RA.

Study cohort: We analyzed patients with T2DM that underwent CABG (1st January 2016 through 31st December 2019) at VA medical centers nationwide (Figure S1). We excluded patients with unknown vital status during the first post-operative year and used outpatient pharmacy fill records to determine patients that filled prescriptions for either a SGLT2i (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin) or a GLP-1RA (semaglutide, liraglutide, exenatide, dulaglutide). We obtained the pre-operative clinical, laboratory and socio-economic

characteristics (community deprivation index, zip code derived median household income) for all patients (Table S1).

Statistical analysis: We present data as counts (percentages) or medians (interquartile range (IQR)). We calculated proportions (with 95% confidence intervals (CI)) for SGLT2i and GLP-1RA use (i) for the entire study period (ii) for every quarter year (Q) and (iii) for each VA medical center. We compared the use of SGLT2i and GLP-1RA for each VA medical center using a correlation test. To study the association between baseline characteristics and SGLT2i/GLP-1RA use, we fit a multi-variable binomial logistic regression model with patient demographics (age, sex, race, ethnicity), clinical characteristics (heart failure (HF), heart failure with reduced ejection fraction (HFrEF), peripheral arterial disease (PAD), cerebrovascular disease, chronic kidney disease (CKD) etc), and socioeconomic data (community deprivation index, zip-code derived median household income) as covariates and SGLT2i or GLP-1RA use as the endpoint. We report results as adjusted odds ratio (OR-(95% CI)). To evaluate whether prescription rates for SGLT2i and GLP-1RA changed over time, we initially fit separate generalized additive model (GAM) of the quarterly prescription rates for each drug against time. On observing a substantial non-linear increase in SGLT2i prescription rates over time, we performed a breakpoint analysis to identify the timepoint beyond which prescription rates increased.

Results: From 2016 - 2019, 5,109 patients with T2DM underwent CABG (median age 68 (IQR: 63, 71) years, 98.6 % male, 77.8% white, 11.6% Hispanic) at 40 VA medical centers. CKD, PAD, heart failure with reduced ejection fraction, and cerebrovascular disease were present in 38.6%, 27.9%, 9% and 6.8%, respectively (Table S2). Overall, 10.4% (95% CI: 9.6, 11.4)

[535/5,109] and 6.8% (95% CI: 6.2, 7.6) [352/5,109] received a prescription for SGLT2i and GLP-1RA, respectively, and 1.8% (95% CI: 1.5, 2.2) [94/5,109] received both. Variation in prescription rates between VA medical centers was large (Figure S2), with poor correlation between SGLT2i and GLP-1RA prescription rates in each VA medical center (correlation coefficient: 0.08 (95%CI: -0.23,0.38) (Figure S3). A higher median income [OR 1.08 (1.03, 1.13) per 5,000 USD increase in median income], living in less deprived neighborhoods [OR 1.19 (0.98, 1.44)] and obesity [OR 1.39 (1.15, 1.69)] were factors associated with receiving SGLT2i, while patients with pre-existing PAD [OR 0.75 (0.60, 0.94)] or CKD [OR 0.72 (0.58, 0.88)] were less likely to receive SGLT2i. We did not observe any association between pre-existing HF [OR 1.10 (0.85, 1.40)] or HFrEF [OR 0.86 (0.59, 1.27)] and SGLT2i prescription. With the black race as reference, whites [OR 1.64 (1.11, 2.51)] were more likely to receive GLP-1RA therapy. Obesity [OR 1.91 (1.50, 2.46)] was associated with GLP-1RA prescription while patients with cerebrovascular disease [OR 0.59 (0.32, 0.99)] were less likely to receive GLP-1RA prescription (Table S3).

From 2016 Q1 to 2019 Q4, prescription rates per quarter increased for both medications; however, this effect was far greater for SGLT2i (20-fold increase, from 1.6% to 33%) than GLP-1RA (14-fold increase, from 0.8% to 11.2%) (Figure 1A, Table S4). Since 2018 Q1, we observed a non-linear increase in prescription rates for SGLT2i (GAM smoothing parameter p-value: 0.03). While GLP-1RA prescriptions also increased over time, they did not increase with the same rate and prescription rates appear to stabilize from 2019 Q1 (Figure 1B). The exploratory breakpoint analysis model further supports the GAM model by defining 2018 Q1 as the breakpoint for SGLT2i prescriptions (Figure 1C).

Conclusions

From over 5000 patients receiving CABG at 40 different VA medical centers, we observed low utilization of SGLT2i or GLP-1RA therapy after surgery. SGLT2i was more likely to be prescribed vs GLP-1RA and prescription rates for SGLT2i rapidly increased since 2018 Q1.

Current guidelines recommend SGLT2i or GLP-1RA for all patients with T2DM and established ASCVD [3,4]. In CABG patients, T2DM is independently associated with future cardiovascular risk [5], thus, surgery provides an opportunity to initiate guideline-directed care. Therefore, it is unfortunate that the overall prescription rates among CABG patients are not higher than T2DM with stable coronary artery disease [6]. While the observed 20-fold increase in SGLT2i use over a four-year study period is encouraging, two thirds of patients with T2DM undergoing CABG remained untreated with either recommended drug, suggesting a significant opportunity to improve cardiovascular outcomes in this high-risk group. Like a prior study from Denmark, we observed higher prescription rates for SGLT2i compared with GLP1-RA[7]. Possible reasons for preferring SGLT2i in our study may be the advantage of oral therapy and more familiarity among cardiologists for SGLT2i. Drug cost is unlikely to play a role, as Veterans have the same co-pay for either medication.

Increased median household income was associated with SGLT2i use, while obesity was associated with GLP-1RA use. Compared to black patients, whites were also more likely to receive GLP-1RA therapy. These findings support prior observations from commercially insured patients [8]. That these socio-economic disparities should exist among Veterans is perhaps surprising, as co-pay amounts are highly subsidized. However, data from Denmark, a country

with a universal healthcare system also report similar observations [9]. SGLT2i use was lower among patients with CKD and PAD, both high risk subgroups, that derive high absolute benefits with SGLT2i therapy [10,11]. While the low use of SGLT2i use in PAD patients is likely related concerns of increased amputation rates observed in the CANVAS trial, neither the CREEDENCE trial nor results from large retrospective data support these findings [12,13].

Retrospective data analysis, a predominantly male cohort, use of ICD codes to define T2DM and the reliance on pharmacy fill data are limitations of our study. Our study is, however, likely, the first to evaluate the use of SGLT2i / GLP-1RA among patients with T2DM following CABG, a high-risk cohort, with considerable potential to benefit from receiving either cardio-protective agent.

In conclusion, between 2016 and 2019, SGLT2i use, and to a lesser extent GLP1-RA use, increased substantially among US Veterans undergoing CABG, with SGLT2i use accelerating rapidly since 2018. However, socio-economic disparities exist and opportunities for improvement remain.

Disclosures:
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Author contributions statement: SD designed the study, did the statistical analysis and wrote the manuscript, DM designed the study and reviewed/edited the manuscript, SK wrote the manuscript, YE reviewed/edited the manuscript, DC reviewed/edited the manuscript, JP designed the study, reviewed/edited the manuscript, NS designed the study, reviewed/edited the manuscript.

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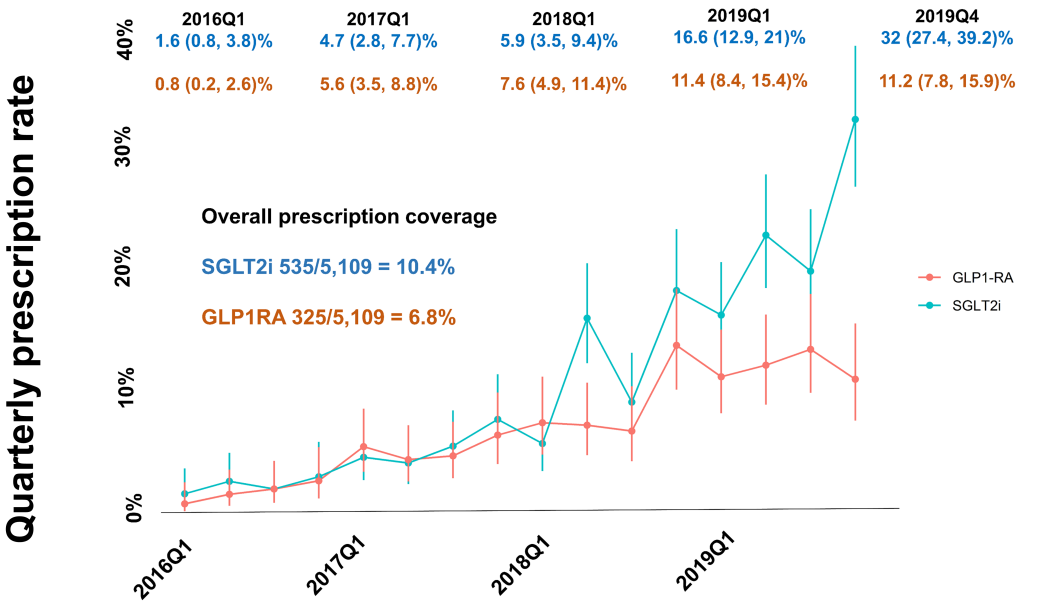
Figure 1.

We analyzed data from 5,109 US Veterans that received coronary artery bypass grafting at 40 different VA medical centers nationwide. We identified those patients that receiving a prescription for SGLT2i or GLP-1RA drugs during the first postoperative year and calculated quarterly prescription rates for each cardio-protective drug group. (A) The overall prescription coverage for both drugs (SGLT2i – 10.4% and GLP-1RA – 6.8%) was low. the quarterly prescription rates increased for both SGLT2i (1.6% (2016 Q1) to 32% (2019 Q4)) and GLP-1RA (0.8% (2016Q1) to 11.2% (2019Q4)) during the 4-year study period. (B) We observed a non-linear increase in SGLT2i prescriptions rates (GAM model smoothing parameter p-value = 0.03), which was clearly evident from 2018Q1. (C) Exploratory breakpoint analysis demonstrates a breakpoint of 2018Q1 for SGLT2i prescription rates; while GLP-1RA prescription rates also increased, the model did not define a breakpoint for this drug class.

A



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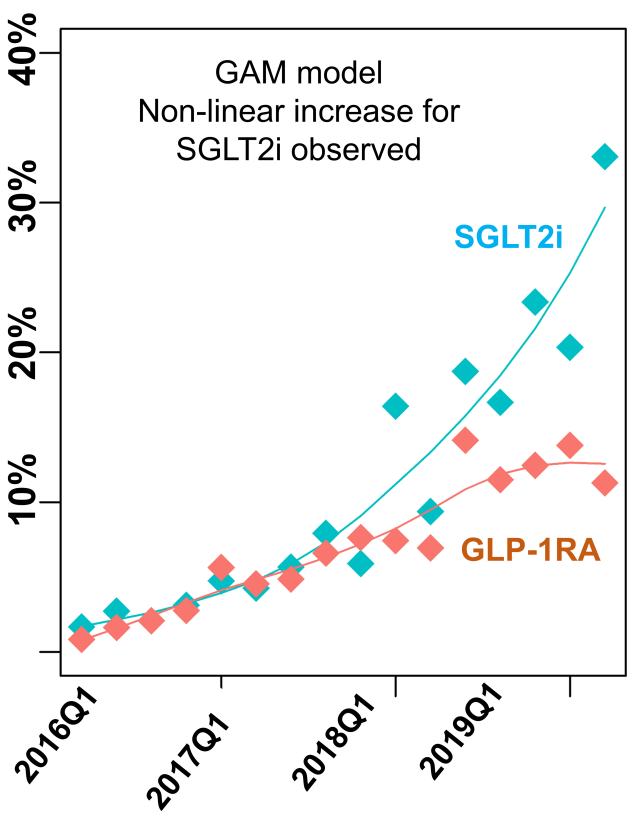

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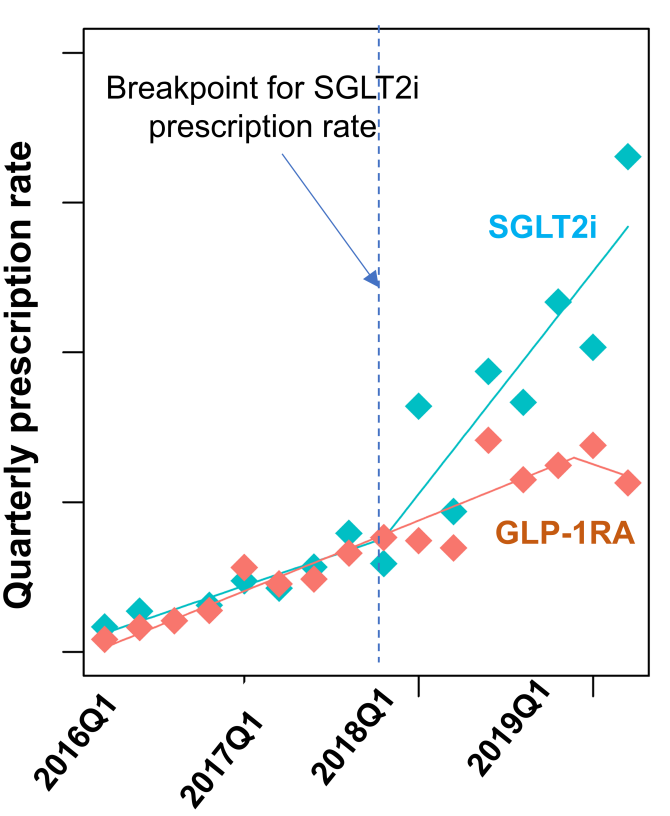

Quarterly time period