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Glucagon-like peptide-1 receptor agonist and sodium-glucose cotransporter 2 inhibitor use among adults with diabetes mellitus by cardiovascular-kidney disease risk: National Health and Nutrition Examination Surveys, 2015–2020

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HIGHLIGHTS

- GLP1-RAs and SGLT2Is lower the risk of adverse cardiac-kidney events in diabetes.
- Only 10 % used GLP1-RAs or SGLT2Is, regardless of level of cardiac-kidney risk.
- Few people who would benefit most from GLP1-RAs or SGLT2Is, were receiving them from 2015 to 2020.

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ABSTRACT

Objective: Glucagon-like peptide-1 receptor agonists (GLP1-RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2Is) lower adverse cardiac and kidney events among high-risk patients with diabetes mellitus (DM) and are now guideline-recommended as first-line therapy alongside metformin. However, the adoption of these new treatments from 2015 to 2020 among the highest-risk adults with DM remains unclear.

Methods: We performed a cross-sectional analysis of the National Health and Nutrition Examination Surveys (NHANES) 2015–2020 to estimate the use of GLP1-RAs and SGLT2Is among adults with DM overall and by level of cardiovascular and kidney risk (CKR). We defined high CKR by history of atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), heart failure, or age ≥55 years with at least 2 ASCVD risk factors (i.e., obesity, hypertension, hyperlipidemia, or current smoker).

Results: Overall, 2,432 participants with DM (mean age 60.6 years, 46.8 % female, 58.8 % Non-Hispanic White) were included, of which 1,869 and 563 were with and without high CKR, respectively. Participants with vs. without high CKR were more likely to be older, have higher systolic blood pressure, lower estimated glomerular filtration rate, use oral antidiabetic agents, and have health insurance. Overall, the weighted prevalence of GLP1-RA or SGLT2I was 9.0 % (95 % confidence interval [CI] 6.9–11.0): 4.8 % (95 % CI 3.6–6.1) took GLP1-RAs, and 5.1 % (95 % CI 3.3–7.0) took SGLT2Is. Use of GLP1-RAs or SGLT2Is did not differ between participants with vs. without high CKR (adjusted prevalence ratio [aPR] 1.00; 95 % CI 0.98–1.02). Participants with ASCVD were more likely to be on a GLP1-RA or SGLT2I (aPR 1.28; 95 % CI 1.25–1.31), while adults with CKD were less likely (aPR 0.84; 95 % CI 0.82–0.86).

Conclusion: Among US adults with DM, GLP1-RA and SGLT2I use was low regardless of CKR. Data since 2020 analyzing the utilization of GLP1-RAs and SGLT2Is among high-CKR patients with DM is needed to identify implementation strategies for increased utilization.

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1. Introduction

Adults with diabetes mellitus (DM) are 50 % more likely to have an adverse cardiovascular or kidney event compared to adults without DM [1]. Glucagon-like peptide-1 receptor agonists (GLP1-RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2Is) are recommended by clinical practice guidelines to reduce cardio-kidney risk (CKR) in patients with DM who have established, or are at high risk for, atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), or heart failure (HF) [2–5]. We estimated the prevalent use of GLP1-RAs and SGLT2Is among adults with DM overall and by CKR. This could help identify treatment gaps to prevent cardio-kidney events in patients with DM based on current recommendations.

1.1. Research design and methods

We used data from the National Health and Nutrition Examination Survey (NHANES) between 2015 and March 2020. The National Center for Health Statistics in the Centers for Disease Control and Prevention administers NHANES via a stratified, multistage probability sampling design [6]. We conducted a secondary analysis of NHANES data, using appropriate sampling weights to calculate nationally representative estimates. All estimates presented use appropriate NHANES sample weights [6].

The NHANES protocols, methodology, and data are publicly available [6]. Briefly, all NHANES participants provided informed consent to NHANES study investigators. Data were collected by trained interviewers who administered standardized questionnaires in participants' homes, followed by physical, anthropomorphic, and laboratory measurements in mobile examination centers. Medication use data from the previous 30 days were ascertained via medication container review.

The current analysis included NHANES participants >18 years with DM, defined as a self-reported history of diabetes, glycated hemoglobin level ≥6.5 %, fasting blood glucose ≥126 mg/dL, or current use of insulin or oral glucose-lowering medication. Participants were categorized as with or without high CKR, which we defined as the presence of any of the following: ASCVD, CKD, HF, or age ≥55 years and ≥2 risk factors. Risk factors included obesity (body mass index >30 kg/m^2), hypertension (systolic blood pressure (SBP) ≥140 mm Hg, diastolic BP ≥ 90 mm Hg, or self-report of high blood pressure or antihypertensive use), current smoker (self-report), or dyslipidemia (total cholesterol ≥200 mg/dL or statin use) [2]. ASCVD history and HF were defined by self-report of prior myocardial infarction or stroke, angina, or coronary heart disease and congestive heart failure, respectively. Estimated glomerular filtration (eGFR) <60 mL/min/1.73m^2 or urine albumin-creatinine ratio >30 mg/g was considered CKD [7]. Among 2442 study-eligible participants, 8 pregnant and 2 missing prescription data participants were excluded, totaling 2432 participants for analysis.

The primary outcome was prevalent use of GLP1-RA or SGLT2I. Poisson regression with robust error variance adjusted for age, sex, and race and ethnicity generated adjusted prevalence ratios (aPRs) and 95 % confidence intervals (CIs) for GLP1-RA or SGLT2I use associated with vs. without high CKR. The primary analysis was repeated in two sensitivity analyses with participants categorized into (1) ASCVD vs. no ASCVD history and (2) CKD vs. no CKD. Additionally, a subgroup analysis of the primary outcome among high-risk individuals (CKR, ASCVD, and CKD) between sex and race and ethnicity was performed. All analyses were performed in R v.4.1.3 (R Foundation).

2. Results

Of the 2432 participants included, the mean age was 60.6 years, 46.8 % were female, 58.8 % were Non-Hispanic White, 92.6 % had health insurance, 94.9 % had a routine location for healthcare, and the family income to poverty ratio was 2.9 (Table 1). Participants with high CKR (N = 1869, 72.9 % [95 % CI 70.0 %–75.7 %] vs. without high CKR (N = 563, 27.1 % [95 % CI 24.3 %–30.0 %] were more likely to be older, have a higher SBP, use oral anti-diabetes medications, have health insurance, and have lower eGFR. The most common reasons for inclusion in the high CKR cohort were having ≥2 risk factors (82.9 %, 95 % CI 79.6 %–85.7 %) and history of CKD (47.3 %, 95 % CI 43.2 %–51.5 %). The most common risk factors were hypertension (91.6 %, 95 % CI 88.1 %–94.1 %) and hyperlipidemia (81.5 %, 95 % CI 79.6–83.3).

Overall, 9.0 % (95 % CI 6.9 %–11.0 %) used either a GLP1-RA (4.8 %, 95 % CI 3.6 %–6.1 %) or SGLT2I (5.1 %, 95 % CI 3.3 %–7.0 %). The prevalence of use of either a GLP1-RA or SGLT2I for those with vs. without high CKR was 8.4 % (95 % CI 6.2 %–10.6 %) and 10.5 % (95 % CI 6.5 %–14.5 %), respectively (aPR 1.00, 95 % CI 0.98–1.02) (Fig. 1). GLP1-RA and SGLT2I use, individually, were estimated at 4.3 % (95 % CI 2.9 %–5.6 %) and 4.6 % (95 % CI 2.7 %–6.4 %), respectively, among those with high CKR.

In sensitivity analyses by history of ASCVD or CKD, results differed from the overall analysis. Participants with ASCVD history (vs. no ASCVD history) were more likely to have prevalent use of a GLP1-RA or SGLT2I (aPR 1.28, 95 % CI 1.25–1.31), whereas participants with CKD (vs. no CKD) were less likely to have prevalent use of these agents (aPR 0.84; 95 % CI 0.82–0.86).

Factors associated with lower GLP1-RA or SGLT2I use among those with vs. without high CKR included sex, race, and ethnicity. Female sex (vs. male, aPR 0.91, 95 % CI 0.86–0.95) as well as Non-Hispanic Black (aPR 0.82, 95 % CI 0.79–0.86), Hispanic (aPR 0.80; 95 % CI 0.78–0.82), and Other Race or Ethnicity (aPR 0.50, 95 % CI 0.49–0.52) individuals vs. Non-Hispanic White individuals had lower utilization of these agents.

Due to recommendations against or limited available data on the use GLP1-RAs and SGLT2Is in patients with an eGFR<25 mL/min/1.73m2 a sensitivity analysis was performed in those with an eGFR ≥25 mL/min/

Table 1
Characteristics of US adults with DM by CKR, NHANES 2015-Mar 2020.

Characteristic	High CKR Risk* With (unweighted N = 1869)	Without (unweighted N = 563)
Age, years	65.0 (64.0, 65.9)	48.7 (47.5, 50.0)
Female sex	45.5 (41.4, 49.7)	50.2 (44.7, 56.0)
Race and ethnicity, self-reported		
Hispanic	15.5 (12.3, 19.3)	21.3 (16.4, 27.2)
Non-Hispanic Asian	5.5 (4.1, 7.2)	7.5 (4.8, 11.6)
Non-Hispanic Black	13.4 (10.3, 17.1)	13.0 (9.8, 17.1)
Non-Hispanic White	60.2 (54.8, 65.3)	54.9 (47.2, 62.4)
Other race or ethnicity or multi-racial†	5.5 (4.2, 7.3)	3.3 (2.0, 5.3)
eGFR[c], mL/min/1.73m^2	77.8 (75.9, 79.6)	100.3 (98.2, 102.5)
SBP, mm Hg	130.9 (129.5, 132.4)	122.8 (120.5, 125.0)
Hemoglobin A1c,%	7.3 (7.2, 7.4)	7.2 (7.0, 7.4)
Antidiabetic use		
Oral anti-diabetes medications	76.1 (73.7, 78.5)	65.4 (60.2, 70.2)
Insulin	25.7 (23.2, 28.4)	27.2 (21.7, 33.4)
Current smoker	12.4 (10.3, 14.9)	17.5 (13.8, 21.9)
Less than high school education	18.2 (15.9, 20.7)	17.5 (13.5, 22.3)
Routine location for healthcare	95.5 (93.7, 96.8)	93.2 (89.9, 95.5)
Health insurance	95.4 (93.6, 96.7)	85.8 (81.1, 89.5)
Family income to poverty ratio	2.8 (2.6, 2.9)	3.0 (2.8, 3.3)

Continuous data are presented as weighted mean (95 % CI) and categorical data are presented as weighted proportion (95 % CI). *High CKR was defined presence of any of the following: ASCVD, CKD, HF, or age ≥55 years and ≥2 risk factors. Risk factors include obesity, hypertension, current smoker, or dyslipidemia. † Other race or ethnicity includes the following options from NHANES: "Non-Hispanic Asian" and "Other Race – Including Multi-Racial" [c] Calculated based on CKD-EPI equation [7].

ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; CKD = chronic kidney disease; CKR = cardio-kidney risk; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HF = heart failure NHANES = National Health and Nutrition Examination Survey; SBP = systolic blood pressure.

1.73m2. The primary outcome between use of these agents in participants with and without high CKR did not qualitatively change (aPR 1.03, 95 % CI 0.99, 1.06).

3. Discussion

Despite data from a multitude of trials showing the benefits of GLP1-RAs and SGLT2Is for high-risk DM patients, our results show their usage remains low, at around 10 %, regardless of CKR level [4,5,8–12]. These medications have been recommended as first-line therapy in high-risk individuals since 2020 [2,3]. Continued underutilization of these protective medications represents a missed opportunity to significantly reduce population-wide CKR. Moreover, among adults with DM and high CKR, usage of these agents was only 8.4 %, showing no significant difference compared to those without high CKR.

In the current analysis, the use of these agents was even lower among patients with CKD, whereas patients with a history of ASCVD had increased utilization of GLP1-RA or SGLT2Is. This could be attributable to various factors, including cost, safety concerns, or lack of awareness of the cardio-kidney benefits. Additionally, recent use of these medications expands their application beyond diabetes treatment exclusively, and prescribing patterns for these agents differ between specialties (eg, cardiology vs. endocrinology vs. nephrology) [13]. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-II receptor blockers (ARBs), other CKR-protective agents, also have low use among CKD patients with or without diabetes. In a 1999–2014 NHANES analysis, prevalent use of ACEI or ARB was only 35 % [14]. Previous studies by Nelson et al. also found <10 % utilization of these agents in patients with a history of ASCVD from the National Patient-Centered Clinical Research Network cohort as well as a claims from a large commercial insurer [13,15]. Addressing these gaps in optimal pharmacotherapy is pivotal to improve patient outcomes.

Low utilization of GLP1-RA and SGLT2I is likely influenced by multiple factors such as clinician familiarity, out-of-pocket cost, or lack of access to healthcare. Retrospective analyses of DM patients from 2015 to 2020 revealed low usage rates (3.2–11.9 %) with Asian, Black, and Hispanic adults being 5–40 % less likely to use these agents compared to White adults [16,17]. Moreover, individuals from high-income areas had higher use (9–13 %) than those from low-income areas. For these agents, Medicare beneficiaries face annual out-of-pocket expenses ranging from $1000–2500, and high co-payments are associated with lower long-term utilization [18,19]. In the present analysis, over 90 % of participants had health insurance and had a routine location for healthcare, indicating that access to care and cost may not be the sole drivers of utilization. Furthermore, these drivers may contribute to the sex-, race-, and ethnic-disparities seen within our study. Despite the low utilization from 2015 to 2020, use of GLP1-RAs and SGLT2Is have increased since 2015 due to their incorporation into guidelines, medication formularies, and even media [2,3,20]. These data could serve as a framework for comparison for future analyses to determine the degree of increased utilization since 2020.

Limitations to this analysis include potential reporting bias for medication use, ASCVD, and HF history. The prevalence estimates in this study are derived from data collected from medication containers, which does accurately estimate those prescribed these agents but did not pick them up from the pharmacy due to primary non-adherence, cost, or other barriers. Next, SGLT2I use is not recommended in patients with type 1 diabetes, but NHANES data does not differentiate between type 1 and type diabetes. Furthermore, clinicians have significantly increased their prescribing of these agents in recent years (ie, post-2020), which

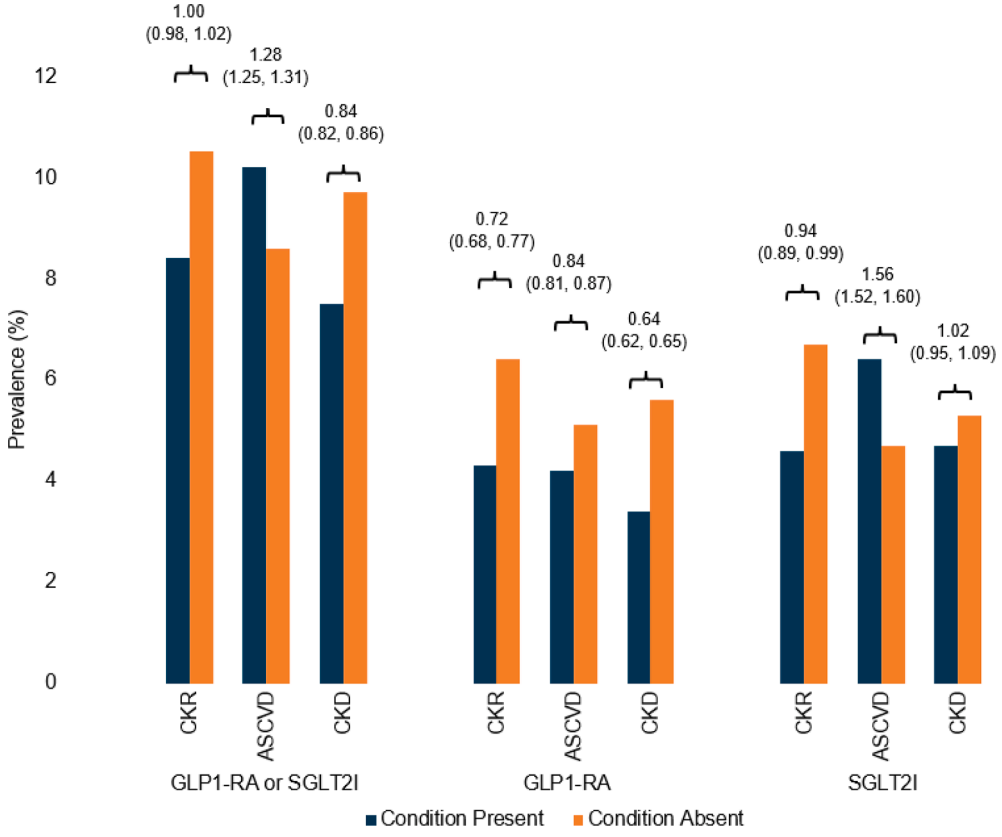

Fig. 1. Association between high CKR, ASCVD, and CKD and GLP1-RA or SGLT2I use, NHANES 2015-March 2020
Date are presented as adjusted PRs (95 % CI). ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CKR = cardio-kidney risk; CI = confidence interval; DM = diabetes mellitus; GLP1-RA = glucagon-like peptide-1 receptor agonist; NHANES = National Health and Nutrition Examination Survey; PR = prevalence ratio; SGLT2I = sodium-glucose cotransporter 2 inhibitor.

we could not incorporate in the current analysis. Therefore, these data may not reflect the most current use patterns. Due to small sample sizes, subgroup results should be interpreted with caution.

4. Conclusion

Use of GLP1RA and SGLT2Is among US adults with DM from 2015 to 2020 was low regardless of CKR risk level. Contemporary data are needed to assess the degree of increased utilization of these agents by CKR.

5. Author declaration

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.

CRediT authorship contribution statement

Joshua A. Jacobs: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Alexander R. Zheutlin:** Conceptualization, Investigation, Methodology, Validation, Writing – review & editing. **Catherine G. Derington:** Conceptualization, Investigation, Methodology, Visualization, Writing – review & editing. **Jordan B. King:** Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Ambarish Pandey:** Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. **Adam P. Bress:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Catherine G. Derington reports a relationship with Amarin Pharma Inc that includes: funding grants. Jordan B. King reports a relationship with National Heart Lung and Blood Institute that includes: funding grants. Adam P. Bress reports a relationship with National Heart Lung and Blood Institute that includes: funding grants. Adam P. Bress reports a relationship with Amarin Pharma Inc that includes: consulting or advisory and funding grants. Adam P. Bress reports a relationship with Amgen Inc that includes: funding grants. Ambarish Pandey reports a relationship with i) Gilead Sciences that includes: funding grants. ii) National Institute on Aging that includes: funding grants iii) Applied Therapeutics Inc that includes: funding grants iv) Tricog Health Inc. that includes: consulting or advisory v) Eli Lilly and Company that includes: consulting or advisory vi) Cytokinetics Inc that includes: consulting or advisory vii) Rivus that includes: consulting or advisory viii) Roche Diagnostics Corp that includes: consulting or advisory.ix) Pfizer Inc that includes: non-financial support x) Merck & Co Inc that includes: non-financial support.

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