Use of SGLT2 Inhibitors Reduces Heart Failure and Hospitalization: A Multicenter, Real-World Evidence Study

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Christopher Antonio Blanco, MPH, was the lead author who was responsible for study conceptualization, data acquisition and analysis, and drafting of the final manuscript. Kara Garcia, PhD, participated in the study design, analysis of data, and editing of the final manuscript. William R Smith, MD, participated in the critical review and editing of the final manuscript. Adrian Singson, MD, participated in the review and editing of the final manuscript. All authors have given final approval to the manuscript.

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Abstract

BACKGROUND: New research has produced evidence to support the use of diabetic drugs to prevent heart failure (HF). However, evidence of their effect in real-world clinical practice is limited.

OBJECTIVE: The objective of this study is to establish whether real-world evidence supports clinical trial findings that use of sodium-glucose cotransporter-2 inhibitor (SGLT2i) reduces rate of hospitalization and incidence of HF for patients with cardiovascular disease and type 2 diabetes.

METHODS: This retrospective study used electronic medical records to compare rate of hospitalization and incidence of HF among 37,231 patients with cardiovascular disease and type 2 diabetes under treatment with SGLT2i, glucagon-like peptide-1 receptor agonist (GLP1-RA), both, or neither.

RESULTS: Significant differences were found between medication class prescribed and number of hospitalizations ($p < 0.0001$) and incidence of HF ($p < 0.0001$). Post-hoc tests revealed reduced incidence of HF in the group treated with SGLT2i relative to GLP1-RA alone ($p = 0.004$) or neither of these key drugs ($p < 0.001$). No significant differences were observed between the group receiving both drug classes compared to SGLT2i alone.

DISCUSSION: Results of this real-world analysis are consistent with clinical trial findings that SGLT2i therapy reduces incidence of HF. The findings also suggest the need for further points of research in demographic and socioeconomic status differences.

CONCLUSION: Real-world evidence supports clinical trial findings of SGLT2i reducing both incidence of HF and rate of hospitalization.

Introduction

Heart failure (HF) is a prevalent cardiovascular condition in the US population, with estimates showing that more than 6.2 million individuals are affected by HF.[1] In patients with cardiovascular disease (CVD) and type 2 diabetes (T2D), HF is one of the most common complications,

presenting with an incidence 2- to 5-fold greater than among the general population.[2] Nearly 25% of patients with HF are readmitted within 30 days, and of patients discharged with a primary diagnosis of HF, 30-day hospitalization readmission due to HF and all-cause accounted for 8.4% and 22.3%, respectively.[1] A growing body of evidence accumulated through several trials supports the claim that sodium-glucose cotransporter-2 inhibitors (SGLT2i) medication treatment is beneficial for patients with T2D and CVD, specifically heart failure with reduced ejection fraction (HFrEF).[3,4] The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG Outcomes) study included patients with T2D at high risk of cardiovascular events and concluded that long-term treatment with SGLT2i led to a lower occurrence of HF events, major decreases in the risk of HF requiring hospitalization, and the ability to prevent HF.[3] The Canagliflozin Cardiovascular Assessment Study (CANVAS) showed a beneficial synergistic effect of SGLT2 inhibition, when used in conjunction with glucagon-like peptide-1 receptor agonists (GLP1-RA), for cardiovascular risk.[5]

Reductions in incidence of HF and rate of hospitalization from use of SGLT2i have been observed in patients with T2D and CVD participating in randomized, controlled trials (RCTs) with stringent eligibility criteria. However, a gap exists in the understanding of how this drug performs when administered in a real-life clinical practice, with patients of varying demographic and socioeconomic status (SES). Real-world evidence (RWE) provides the opportunity to confirm the results seen in RCTs, such as the EMPA-REG Outcomes study, in real-world populations.[6] The FDA defines RWE as clinical evidence derived from sources other than RCTs, regarding the usage, benefits, or risks of a drug from analysis of real-world data (RWD).[7] RWD is considered data relating to patient health status and/or the delivery of health care, collected from a number of sources, including electronic health care records (EHR).[6] A critical benefit of utilizing RWE is that it can deliver outcomes from a heterogeneous patient population in real-world settings, effectively complementing clinical trials by generalizing their findings to the general population.[6]

To address this knowledge gap concerning the RWE of clinical benefits of SGLT2i seen in RCTs, the authors use diagnostic codes to identify a large, real-world study population, as this allows the study to attempt to design a standard metric that can be used to measure across different institutions because diagnostic coding in EHR is standardized. The authors conducted a retrospective study, utilizing de-identified patient EHR from a database of more than 3 million patients, to determine if RWD of use of SGLT2i reduces the incidence of HF and rate of hospitalization as seen in clinical trial studies, when compared to combination therapy with GLP1-RA, GLP1-RA alone, and neither therapy. The study is expected to produce RWE validating the published results of SGLT2i RCTs, as well as potential use case(s) for RWE in a hospital system.

Methods

DATA COLLECTION

This was a population-based retrospective review study utilizing RWD from a single schema electronic medical record system, implemented across the Cardiovascular Research Consortium's (CRC; Indianapolis, IN, USA)/SIDUS (formally known as GEMMS) national RWE research network. Real-time search and analysis was conducted using the de-identified EHR of more than 1.6 million patients from cardiology practices across multiple health care organizations, to identify patients who currently had a concomitant diagnosis of CVD and T2D between January 01, 2013 and December 31, 2020, based on the assignment of CVD and T2D specific International Classification of Diseases (ICD) codes. ICD-25 and all combination codes (I-25.1, I-25.2, etc.) were used to capture all subcategories of ischemic heart disease; ICD 429.2 coded for CVD, unspecified; ICD E11.9 coded for T2D mellitus without complication; ICD 429.2 coded for diabetes mellitus without mention of complication, type 2 or unspecified type, not stated as uncontrolled. During the same period, patients meeting diagnosis criteria and who had been started on a prescription of only SGLT2i, only GLP1-RA, both concomitant SGLT2i and GLP1-RA, and neither SGLT2i or GLP1-RA, were included and appropriately sorted into respective medication treatment groups. Placement on SGLT2i was based on patients' medication history of the brand or generic name for Farxiga (Dapagliflozin), Invokana (Canagliflozin), Invokamet (Canagliflozin/Metformin), Jardiance (Empagliflozin), Xigduo (Dapagliflozin/Metformin), Steglujan (Ertugliflozin/Sitagliptin), Qtern (Dapagliflozin/Saxagliptin), and Steglatro (Ertugliflozin). Placement on GLP1-RA was based on listing in patients' medication history of the brand or generic name for Trulicity (Dulaglutide), Ozempic (Semaglutide), Bydureon (Exenatide), Victoza (Liraglutide), Adylxin (Lixisenatide), and Byetta (Exenatide). Data were placed in the following medication treatment groups: "GLP1-RA" for patients

only on GLP1-RA prescriptions, "both" for patients on both SGLT2i and GLP1-RA, "neither" for patients who were not prescribed either SGLT2i or GLP1-RA, and "SGLT2i" for patients prescribed only SGLT2i.

There were 2 outcomes of interest for this study. One was capturing the total number of all-cause hospitalizations after starting their prescription. The results were collected under the heading "hospital visits total." The other outcome measured was the total number of diagnosed HFs after starting their medication. These results were collected under the heading "diagnosed heart failures." For the latter, ICD-50 and all combination codes were used to capture all subcategories of HF. Each outcome was captured for each medication treatment group as well as their respective averages (see Table 1). To improve clarity of data, subclassifiers of race as marked in the EHR were grouped into larger inclusive classes: "Asian" included Asian and Asian India, "Black" included Black or African American and African American, and "Other" included American Indian or Alaskan native, Middle East or North African, Native Hawaiian or Other Pacific Islander, Filipino, and American Indian. These larger inclusive classes were modeled after categories used in other prominent studies observing SGLT2i effects on HF incidence such as EMPA-REG Outcomes, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) clinical trials.[4,8,9] This study measured age distribution within each treatment group, with the 2 groups of ≥ 65 or < 65 seen in Figure 1, as this split in age range was studied in the aforementioned clinical trials.[4,8,9] All treatment groups had more than 50% of patients being 65 years or older.

DATA ANALYSIS

Data analysis was performed with IBM's SPSS Statistics 28 software. Per-patient data output from the CRC/SIDUS RWE database was collected and used in the software package to run significance tests. Grouped data of total count and averages were generated from the SQL software program used to collect the data output from the CRC/SIDUS RWE database (see Table 1). The patient data output for HF and all-cause hospitalizations was organized using the Excel statistical software package. The authors used Kruskal–Wallis and post-hoc significance testing through pairwise comparisons of treatment, controlling for multiple comparisons via the Bonferroni correction. The aim was to determine if medication groups were significantly different from one another in terms of all-cause hospitalizations and HF diagnosis after starting their group specified prescription(s). Further analysis included the ordinal logistic regression test, assessing the effect of covariates on the outcomes of all-cause hospitalizations and HFs. Included covariates were treatment, age, sex, race, and ethnicity. Regression coefficients and statistical significance were collected for each of the independent variables.

Results

POPULATION CHARACTERISTICS BY TREATMENT TYPE

Out of a registry of more than 1.6 million patients, the authors identified a total of 37,231 patients who had a concomitant diagnosis of CVD and T2D between 2013 and 2020, who additionally met the criteria to be included into either of the 4 medication treatment groups. Total patient counts in terms of treatment group and demographics are shown in Tables 1 and 2, respectively. Nearly 75% of all patients were between the ages of 66 and 81 years old. The youngest age was 28 and oldest was 90, with a mean age of 73. Figure 1 displays the age distribution within each treatment group, based on age being less than vs greater or equal to 65 years old. Of all study participants, 21% were < 65% and 79% were ≥ 65.

Drug treatment group	Patient count	Hospital visits total	Percent hospital visits	Diagnosed heart failures	Percent heart failures
GLP1-RA	1362	289	21.2%	357	26.2%
Both (GLP1-RA & SGLT2i)	736	79	10.7%	118	16.0%
Neither	32,402	19,489	60.1%	9593	29.6%
SGLT2i	2731	420	15.4%	539	19.7%
Total	37,231	20,277		10,607	

Table 1: Data collected from Cardiovascular Research Consortium SIDUS real-world evidence database

GLP1-RA = glucagon-like peptide-1 receptor agonists; SGLT2i = sodium-glucose cotransporter-2 inhibitors.

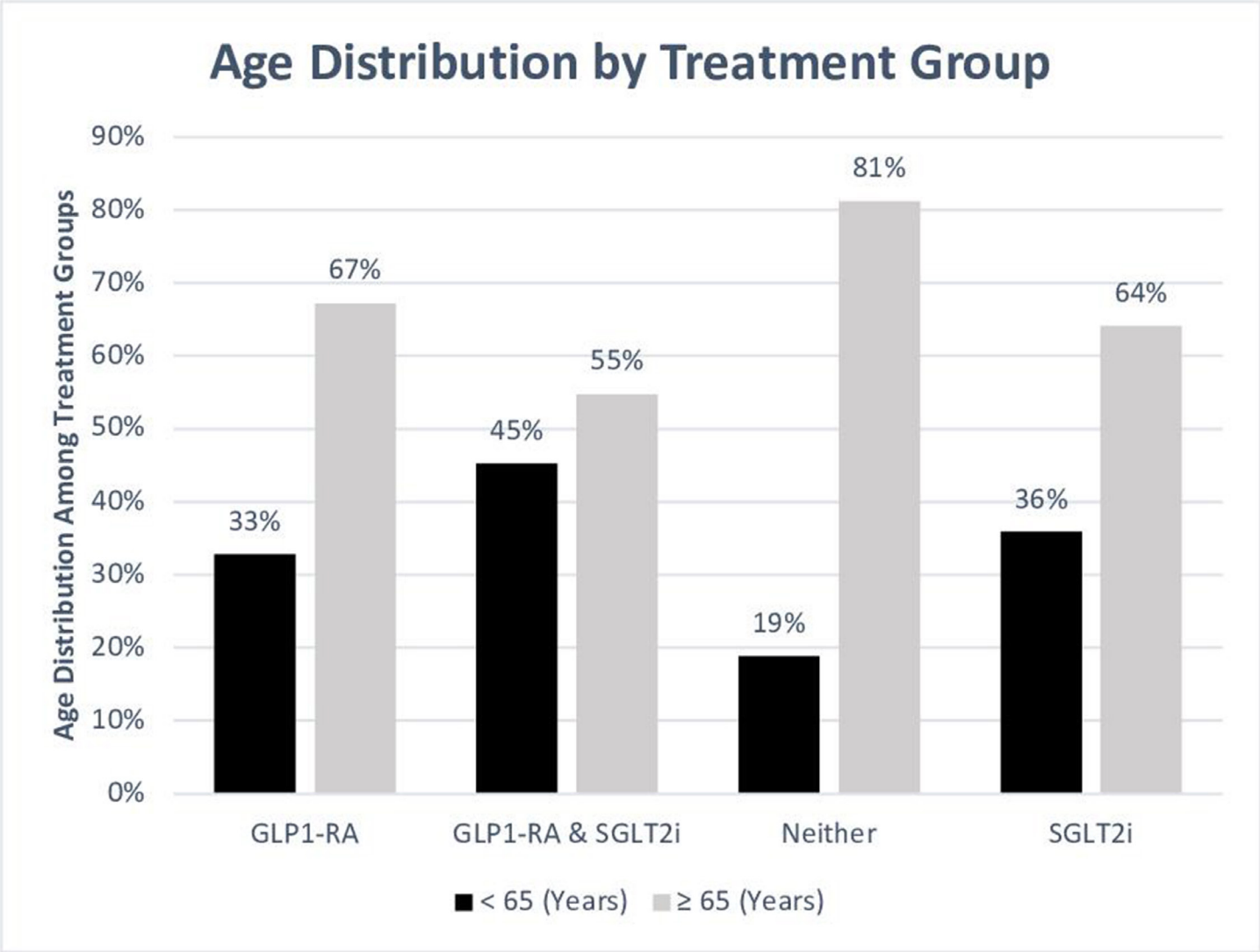

Figure 1: Age distribution by treatment group, demarcated by being either < 65 years old or ≥ 65 years old. GLP1-RA = glucagon-like peptide-1 receptor agonists; SGLT2i = sodium-glucose cotransporter-2 inhibitors.

GENERAL OUTCOMES BASED ON TREATMENT GROUPS

A Kruskal–Wallis test was conducted to determine whether differences in the number of hospital visits existed according to the type of medication received. A significant difference ($p < 0.0001$) was found between the type of medication prescribed and the number of hospital visits, and post-hoc tests were conducted to examine the differences between the types of medication: GLP1-RA, SGTL2i, both drugs, and neither drug. Significant reductions in rate of hospitalization were found between the group receiving SGLT2i and the group receiving neither drug ($p < 0.001$), the group receiving both drugs and the group receiving neither drug ($p < 0.001$), and the group receiving GLP1-RA and the group receiving neither drug ($p < 0.001$). No statistically significant difference in rate of hospitalization was found between the group receiving SGLT2i and the group receiving GLP1-RA ($p = 0.133$). Although a significant reduction in rate of hospitalization existed between the group receiving both drugs compared to GLP1-RA ($p = 0.021$), there was no statistically significant difference in rate of hospitalization between the group receiving both drugs compared to SGLT2i ($p = 0.992$). Figure 2 depicts the percentage of patients who had 1 all-cause hospitalization after starting treatment (during our specified time period), relative to their respective treatment group. Significance of differences between the treatment groups was determined by Kruskal–Wallis and post-hoc test analysis, conducted

Factor	n	Percent
Treatment		
GLP1-RA	1362	3.7%
GLP1-RA & SGLT2i	736	2.0%
Neither	32,402	87.0%
SGLT2i	2731	7.3%
Total	37,231	100.0%
Sex		
Female	12,607	33.9%
Male	24,602	66.1%
Undifferentiated	22	0.1%
Total	37,231	100.0%
Race		
Black	1673	4.5%
Asian	819	2.2%
Other race	3726	10.0%
Unknown	2963	8.0%
White	28,050	75.3%
Total	37,231	100.0%
Ethnicity		
Hispanic or Latino	1942	5.2%
Not Hispanic or Latino	29,865	80.2%
Unknown	5424	14.6%
Total	37,231	100.0%

Table 2: Overall demographics

GLP1-RA = glucagon-like peptide-1 receptor agonists; SGLT2i = sodium-glucose cotransporter-2 inhibitors.

in IBM SPSS Statistics 28 software package. The percentage was calculated by dividing the number of patients in the treatment group who only had 1 all-cause hospitalization by the total patient population in the respective treatment group.

A Kruskal–Wallis test was also conducted to determine whether differences in the number of I-50 (diagnosed HF) cardiac events existed according to the type of medication received. A significant difference ($p < 0.0001$) was found between the type of medication received and the number of I-50 cardiac events, and post-hoc tests were conducted to examine the differences between the types of medication: GLP1-RA, SGLT2i, both drugs, and neither drug. A significant reduction in incidence of HF was found between the group receiving SGLT2i compared to neither drug ($p < 0.001$), both drugs compared to neither drug ($p < 0.001$), and GLP1-RA compared to neither drug ($p = 0.018$). A significant reduction in incidence of HF existed between the group receiving both drugs compared to GLP1-RA ($p = 0.002$), as well as SGLT2i compared to GLP1-RA ($p = 0.004$). No statistically significant difference in incidence of HF was found between the group receiving SGLT2i and the group receiving both drugs ($p = 1.000$). Figure 3 illustrates the percentage of patients who only had 1 HF after starting treatment (during our specified time period), relative to their respective treatment group. Significance of differences between the treatment groups was determined by Kruskal–Wallis and post-hoc test analysis, conducted in IBM SPSS Statistics 28 software package. The percentage was calculated by dividing the number of patients in the treatment group who only had 1 HF by the total patient population in the respective treatment group.

EFFECTS OF COVARIATES ON OUTCOMES IN A LARGE, REAL-WORLD, HETEROGENEOUS POPULATION

To determine the impact of demographic differences across treatment groups, covariates were examined for their effects on the major outcomes of the study, all-cause hospitalizations, and incidence of HF. Covariates that were assessed included treatment, age, sex, race, and ethnicity. All covariates had a statistically significant main effect on both dependent variables, all-cause hospitalizations and incidence of HF.

Tables 3 and 4 include parameter estimates that display directionality and significance of each category of covariate based on comparison to the reference category. When assessing both hospitalization and HF, a statistically significant increase for each outcome was associated with an increase in age ($p < 0.001$) and for Black people compared to White people ($p < 0.001$ and $p < 0.001$, respectively). For hospitalizations, when compared to the SGLT2i treatment group, the groups receiving GLP1-RA and neither drug were associated with a statistically significant increased rate of hospitalization ($p < 0.001$ and $p < 0.001$, respectively). Compared to the SGLT2i group, the group receiving both drugs was associated with a significant decrease in rate of hospitalization ($p < 0.039$). Men were associated with statistically significant lower hospitalizations when compared to women ($p < 0.001$). For HF, when compared to the SGLT2i treatment group, the groups receiving GLP1-RA and neither drug were both associated with increased incidence of HF ($p < 0.001$ and $p < 0.001$, respectively). There was no statistically significant difference in incidence of HF between groups receiving both drugs and SGLT2i ($p = 0.281$) as well as no statistically significant differences in

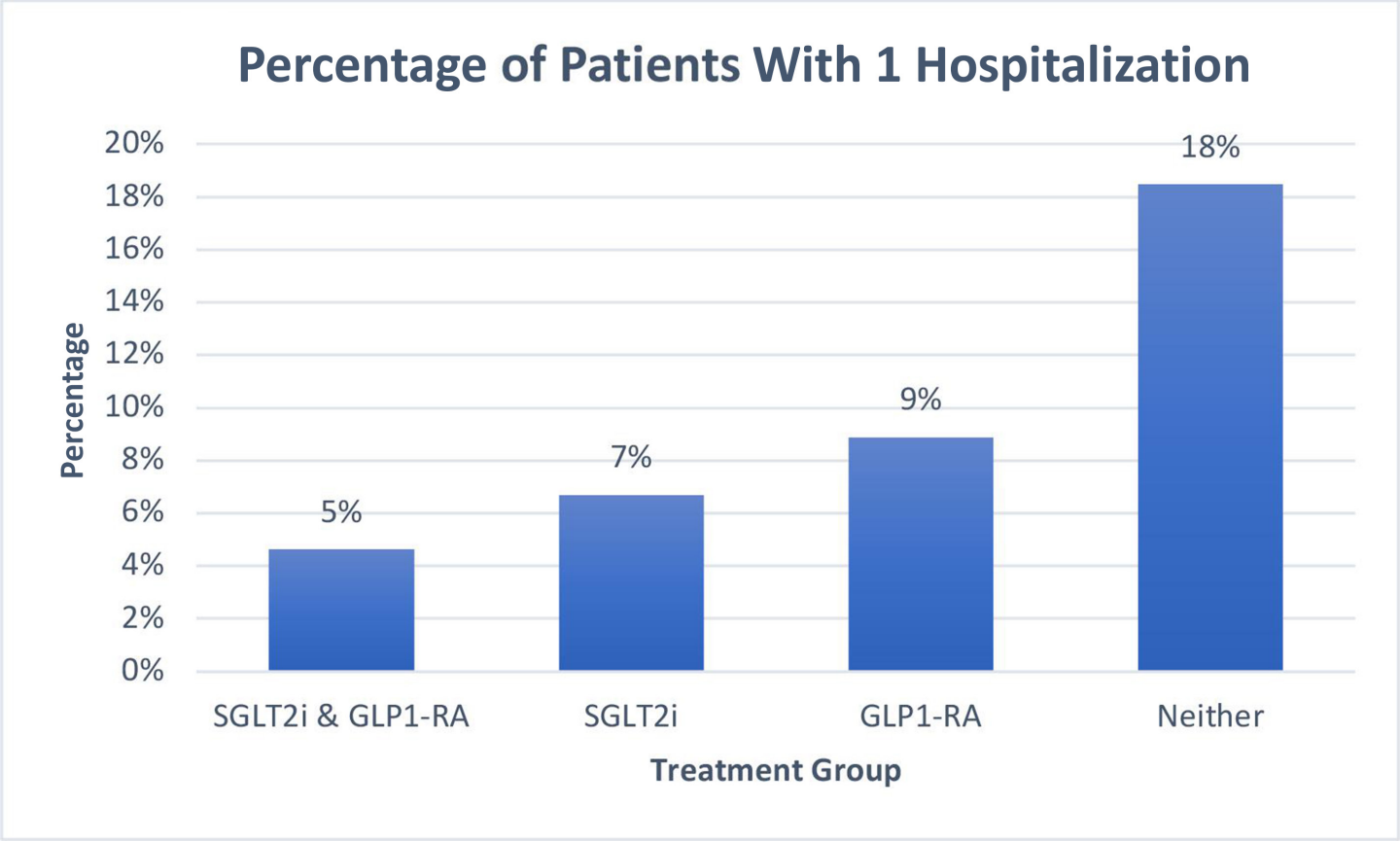

Figure 2: Percentage of patients with 1 all-cause hospitalization after starting treatment. GLP1-RA = glucagon-like peptide-1 receptor agonists; SGLT2i = sodium-glucose cotransporter-2 inhibitors.

incidence of HF between males and females ($p = 0.077$). When compared to Hispanic people, non-Hispanic people were associated with a statistically significant increase in incidence of HF ($p < 0.001$). Asian race was associated with statistically significant lower incidence of HF when compared to White people ($p = 0.002$).

Discussion

This study found that within an RWD database, use of SGLT2i (with or without GLP1-RA) significantly reduced all-cause hospitalization visits and incidence of HF diagnosis compared to GLP1-RA treatment or neither drug. Parameter estimates conducted during ordinal logistic regression analysis of covariates provided further support of this conclusion after accounting for demographic factors, including age, sex, race, and ethnicity. These results suggest that being placed on SGLT2i plays a role in lowering the risk of hospitalization and developing HF, consistent with RCT evidence from EMPA-REG Outcomes.[3]

Most importantly, RWE from this study supports the clinical benefit reported in RCTs that SGLT2i can lower incidence of HF and hospitalization in the uncontrolled lives of a heterogeneous patient population across multiple geographically dispersed cardiology clinics.

SGLT2i REDUCES INCIDENCE OF HF

Of note, the initial Kruskal–Wallis analysis to assess differences between treatment groups did not reveal a significant difference for hospitalizations when comparing SGLT2i to GLP1-RA. However, a significant difference did exist for HF, indicating SGLT2i are the superior medication for reducing incidence of HF. In subsequent parameter estimate analysis, when the GLP1-RA treatment group was compared to the SGLT2i treatment group, GLP1-RA only treatment was associated with increased incidence of HF. By reducing atherosclerotic ischemic events, GLP1-RA can help prevent events like myocardial infarctions in patients, therefore reducing the risk for hospitalization, but lack the ability to prevent

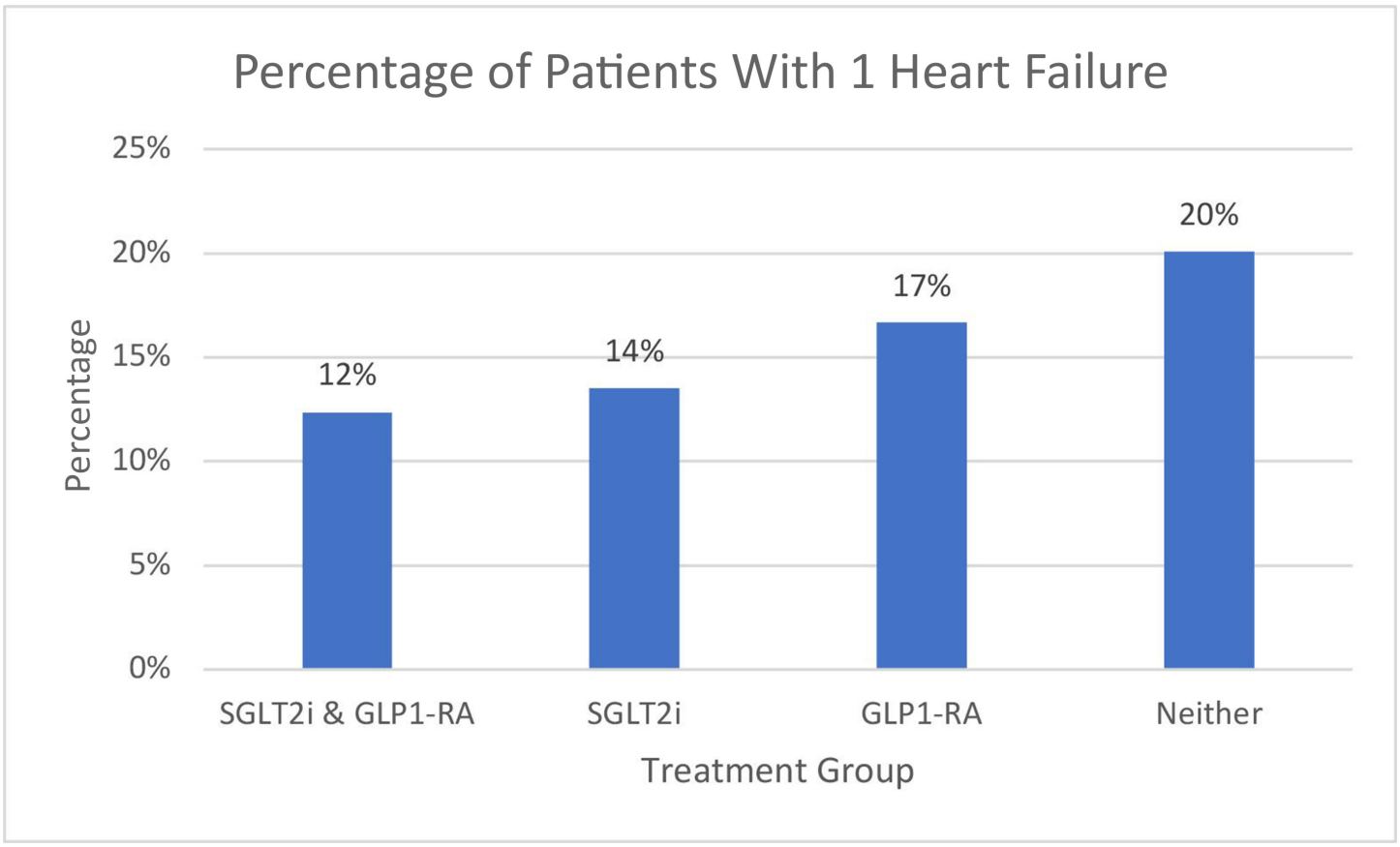

Figure 3: Percentge of patients with 1 heart failure after starting treatment. GLP1-RA = glucagon-like peptide-1 receptor agonists; SGLT2i = sodium-glucose cotransporter-2 inhibitors.

the varying other etiologies of HF. Patients receiving both classes or either class of medication were associated with fewer HFs and hospitalization events, when compared to patients receiving neither class, who are assumed to have been receiving other diabetes medication. This study found no significant difference in the number of HFs between the group that received both drugs and the group receiving only SGLT2i, indicating that there may be no additional clinically significant benefit related to reducing incidence of HF from adding GLP1-RA to a patient already receiving SGLT2i. This study found that the rate of hospitalization was higher in those who received only GLP1-RA when compared to those who received SGLT2i and GLP1-RA. Although initial Kruskal–Wallis analyses did not reveal a significant difference between SGLT2i only and GLP1-RA only ($p = 0.133$), subsequent parameter analysis suggests a statistically significant benefit in reducing all-cause hospitalizations by initiating SGLT2i compared to GLP1-RA. Further research is needed to establish clear clinical significance.

DEMOGRAPHIC CONSIDERATIONS

In this study, the authors analyzed demographic covariates utilizing ordinal logistic regression and parameter estimation. The study concluded that treatment group was still statistically significant after accounting for available demographic covariates. Importantly, however, the study found that hospitalizations and incidence of HF were significantly increased in Black people when compared to White people, and all-cause hospitalization was significantly increased in women. HF was significantly lower in Asian people when compared to White people, and in Hispanic people when compared to non-Hispanic people.

Increased age was associated with increases in both hospitalization and incidence of HF. In all treatment groups, more than 50% of patients included in this study were ≥ 65 years old. However,

Parameter estimates				
		95% Wald confidence interval		
Parameter	B	Lower	Upper	Hypothesis test sig
[Treatment = GLP1-RA]	0.347	0.145	0.549	< 0.001
[Treatment = GLP1-RA & SGLT2i]	−0.329	−0.641	−0.017	0.039
[Treatment = Neither]	1.360	1.230	1.490	0.000
[Treatment = SGLT2i]	0[a]			
[Sex = Undifferentiated]	0.616	−0.235	1.468	0.156
[Sex = Male]	−0.101	−0.149	−0.054	< 0.001
[Sex = Female]	0[a]			
[Race = Black]	0.290	0.185	0.394	< 0.001
[Race = Asian]	−0.109	−0.269	0.052	0.184
[Race = Other race]	−0.270	−0.360	−0.180	< 0.001
[Race = Unknown]	−0.879	−1.015	−0.744	0.000
[Race = White]	0[a]			
[Ethnicity = Unknown]	−0.162	−0.295	−0.029	0.017
[Ethnicity = Not Hispanic or Latino]	0.046	−0.060	0.151	0.399
[Ethnicity = Hispanic or Latino]	0[a]			
Age	0.023	0.021	0.025	0.000
(Scale)	1[b]			

Table 3: Effect of covariates on all-cause hospitalization

Dependent variable = hospitalizations; Model = treatment, sex, race, ethnicity, age.

[a]Set to zero because this parameter is redundant.

[b]Fixed at the displayed value.

GLP1-RA = glucagon-like peptide-1 receptor agonists; SGLT2i = sodium-glucose cotransporter-2 inhibitors.

in the group receiving neither drug, 81% of patients were ≥ 65 years old, the highest among all groups. Patients receiving both drugs represented the youngest population, with 45% of patients under 65, followed closely by the SGLT2i group with 36% of patients under 65. Between SGLT2i and GLP1-RA, age distribution was relatively similar, consisting of 64% vs 67% of patients ≥ 65 years old, respectively. These differences between the group age distributions may have contributed to differences in primary outcomes.

Future research should investigate stratification by additional comorbidities, SES, and demographics. Future study designs can look to build upon these results by controlling for the effect that covariates of age, sex, race, and ethnicity have on key outcomes such as hospitalization and HF when assessing clinical significance of treatment modality. These covariates should be further studied to assess if any specific group is at higher incidence of either HF or all-cause hospitalization, and if certain groups display clinically significant differences in outcomes based on treatment modality. Results from these studies would be useful in generating evidence-based targeting of treatment strategies. Employing a study designed for RWE would allow for better measurement of adverse events, such as HF, among a more heterogeneous population in real-life settings because they are of longer duration and rarely depend on strict eligibility criteria that could exclude older patients or those with comorbidities that may influence an adverse event.[6]

STRENGTHS AND LIMITATIONS

Key strengths of the study included the large, retrospective design, which allowed the high power of the study. Due to the design of the SIDUS data platform, the authors had access to information on more than 1.6 million cardiovascular patients across multiple health care systems. This lends confidence to the generalizability of the data to other EHR platforms as well as individual hospital system's cardiovascular patient populations. Upon review of the SQL data, the researchers found that several drugs included in the SGLT2i category were drugs that combined SGLT2i with either metformin or dipeptidyl peptidase-4 inhibitors. However, after removing all SQL language that included SGLT2i combination drugs and rerunning the program, the study population did not change, therefore confirming no patients included in the original data analysis were on an SGLT2i combination drug.

Parameter estimates				
Parameter	B`	95% Wald confidence interval		Hypothesis test sig
		Lower	Upper	
[Treatment = GLP1-RA]	0.307	0.140	0.474	< 0.001
[Treatment = GLP1-RA & SGLT2i]	−0.128	−0.360	0.105	0.281
[Treatment = Neither]	0.379	0.272	0.486	< 0.001
[Treatment = SGLT2i]	0[a]			
[Sex = Undifferentiated]	0.704	−0.115	1.522	0.092
[Sex = Male]	−0.046	−0.097	0.005	0.077
[Sex = Female]	0[a]			
[Race = Black]	0.371	0.261	0.480	< 0.001
[Race = Asian]	−0.296	−0.481	−0.112	0.002
[Race = Other race]	0.121	0.030	0.213	0.009
[Race = Unknown]	−0.390	−0.530	−0.251	< 0.001
[Race = White]	0[a]			
[Ethnicity = Unknown]	−0.003	−0.150	0.145	0.972
[Ethnicity = Not Hispanic or Latino]	0.300	0.179	0.420	< 0.001
[Ethnicity = Hispanic or Latino]	0[a]			
Age	0.024	0.022	0.027	0.000
(Scale)	1[b]			

Table 4: Effect of covariates on heart failure

Dependent variable = heart failures; Model = treatment, sex, race, ethnicity, age.

[a]Set to zero because this parameter is redundant.

[b]Fixed at the displayed value.

GLP1-RA = glucagon-like peptide-1 receptor agonists; SGLT2i = sodium-glucose cotransporter-2 inhibitors.

A major limitation of this study is the effect of confounding variables on the major outcomes. Data analysis found that additional covariates of age, sex, race, and ethnicity had a significant effect on both rate of hospitalization and incidence of HF. In addition to the relatively small number of study participants receiving either or both drug classes, a disproportionate amount of study participants (75%) were White. Treatment with the 2 classes of medication in this study may be cost-prohibitive, an important reason for their limited use, and is a limitation because the researchers were unable to stratify by SES. Further, data analysis and study design were limited by the ability to recruit patients based on covariates, as the SIDUS database serves only as repository for patient data, whose accumulation of new patients stems from new partnerships and independent physician practices acquiring more patients.

The treatment group labeled "neither," referred to patients who did not receive either drug class. The coding process included patients who could have been on other forms of diabetes management but did not exclude patients who were on no diabetes medication or on certain medications. This introduced additional confounding variables to why the "neither" group had such high rates of HF and hospitalization, as this group contained a multitude of variables, including individualized diabetes care. This study did not collect A1c levels on patients, so the researchers were unable to assess level of diabetes management across treatment groups. This makes it possible that higher rates of elevated A1c levels could have been concentrated in the "neither" group due to some patients not being on any medication or having poorly managed T2D, further confounding the results. It may be possible that patients who are on novel medications are more attentively followed, further confounding the study's claim. Lastly, the authors were unable to discern if a cardiologist or other practitioner initiated SGLT2i/GLP1-RA therapy due to limitations of the data repository program.

During the time frame in which the researchers gathered data, a switch in ICD codes occurred. Therefore, the coding process to generate data output in the SIDUS platform leaned on the use of multiple ICD codes from different generations of ICD codes, best matched to the diagnostic criteria of the research question. Human errors in the data collection may have occurred during the query construction in the SQL program for SIDUS. Additionally, it is possible

that practitioner error resulted in miscoding when the patient was admitted. To generate a sufficiently large patient population and to ensure the collection of an accurate count of HFs, the researchers used "I50%" to catch every subcategory of ICD coding of HF. This limitation may have introduced bias into the study, as "I50%" would include HFrEF and heart failure with persevered ejection fraction (HFpEF), and SGLT2i have not been shown to have clear benefits in the HFpEF population.[2] Because the authors did not exclude HFpEF, the reduction in incidence of HF among HFrEF may be larger than observed in the current analysis. Alternately, it is possible that additional benefits of SGLT2i are present in other conditions, such as HFpEF. This more detailed analysis is worthy of exploration in future studies.

IMPLICATION FOR RESEARCH AND/OR PRACTICE

Although RCTs are necessary for studying a new drug's safety and efficacy, they also require a good study design to have strong internal validity from having strict inclusion and exclusion criteria, controlled settings, and a selective patient population.[6] Patients with specific comorbidities, who live in a remote geographic location, are of a certain race or ethnicity, belong to particular SES, or are of an age range not included in any RCTs may not respond to the medical therapy as expected. Ultimately, this lowers the generalizability of the findings to the general population, as results derived from such stringent eligibility criteria could not truly represent the actual general population.[6] RWE provides answers to these problems by analyzing effects of treatments over longer periods, among a broad and diverse patient population, and without the limitations of unrealistic controlled settings. Studies designed to produce RWE can perfectly complement RCTs because they can generalize the findings of clinical trials to a more diverse patient population of a particular disease.[6]

Developing similar organizational studies that utilize hospital system's EHR may serve as a tool to increase implementation of proven clinical treatments into routine clinical practice. Hospitals could replicate the framework of this study to analyze RWD collected in their EHR database to assess the real-world efficacy of adding, reducing, or switching medications to improve treatment management and health outcomes. This RWE can be used to develop clinical guidelines, decision support tools used in real-world clinical practice, support patient-centered outcomes, analyze health economics, and better understand efficacy of current health care services.[6,7] Potential early adopters may be persuaded more effectively with RWE that supports the benefits of a treatment found in a clinical trial, especially when that RWE is generated from the community the provider serves. As data-gathering software and EHR improve, hospital organizations should seek to merge the two to improve patient outcomes and reduce health care costs. Hospital organizations serve as a wealth of RWD, and by allowing access to researchers to conduct data analysis, they can provide critical insight into true clinical significance of existing research literature and produce useful RWE.

With the advent of SGLT2i, clinicians, especially cardiologists, can prevent HF hospitalization with improved targeting of this treatment to the populations at highest risk for HF events, such as patients with CVD and T2D. However, a 2017 study found that only 5.2% of all eligible patients from a large US-based outpatient registry were prescribed SGLT2i.[10] In this large study population of cardiology clinic patients who met indications for SGLT2i therapy, barely 10% of patients were receiving treatment with SGLT2i. One potential explanation for why only a small portion of patients in clinical practice who meet established clinical trial eligibility are treated with SGLT2i is underprescribing on behalf of cardiologists.[11] Cardiologists represent a key prescribing pathway because they treat many patients with T2D.[11] Future research should focus around detailing barriers to increasing prescribing rates of these life-saving medications among cardiologists. Increasing the prescribing rates of SGLT2i can help improve mortality and quality of life for patients, reduce the all-cause hospitalizations and HF readmission rates, and lower the overall economic burden on both patients and the hospital system.[1-4]

Conclusion

The goal of this study was to determine if the real-world use of SGLT2 inhibitors reduces the rate of HF in a real-world cardiology clinic setting for patients with CVD and T2D. This study derived RWE from RWD of a large, heterogeneous patient population, supporting SGLT2i benefits of reducing both HF and hospitalization, initially found in highly controlled clinical trials with stringent eligibility criteria. The results also suggest that SGLT2i therapy is just as beneficial as using

both SGLT2i and GLP1-RA, and that there may exist a benefit of reduction in incidence of HF from initiating SGLT2i over GLP1-RA. The results of this study suggest that benefits of SGLT2i found in clinical trials exist in the real world. This study demonstrates the utility of RWD for corroborating research findings from controlled trials with RWE.

REFERENCES

1. Kilgore M, Patel HK, Kielhorn A, Maya JF, Sharma P. Economic burden of hospitalizations of medicare beneficiaries with heart failure. Risk Manag Healthc Policy. 2017;10:63–70. DOI: https://doi.org/10.2147/RMHP.S130341
2. Nakagawa Y, Kuwahara K. Sodium-glucose cotransporter-2 inhibitors are potential therapeutic agents for treatment of non-diabetic heart failure patients. J Cardiol. 2020;76(2):123–131. DOI: https://doi.org/10.1016/j.jjcc.2020.03.009
3. Packer M, Anker SD, Butler J, Filippatos G, Zannad F. Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure: Proposal of a novel mechanism of action. JAMA Cardiol. 2017;2(9):1025–1029. DOI: https://doi.org/10.1001/jamacardio.2017.2275
4. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008. DOI: https://doi.org/10.1056/NEJMoa1911303
5. Arnott C, Neuen BL, Heerspink HJL, et al. The effects of combination canagliflozin and glucagon-like peptide-1 receptor agonist therapy on intermediate markers of cardiovascular risk in the CANVAS program. Int J Cardiol. 2020;318:126–129. DOI: https://doi.org/10.1016/j.ijcard.2020.06.011
6. Chodankar D. Introduction to real-world evidence studies. Perspect Clin Res. 2021;12(3):171–174. DOI: https://doi.org/10.4103/picr.picr_62_21
7. Real-world evidence [Internet]. U.S. Food and Drug Administration. FDA. 2022. Accessed January 14, 2023. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
8. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117–2128. DOI: https://doi.org/10.1056/NEJMoa1504720
9. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–1424. DOI: https://doi.org/10.1056/NEJMoa2022190
10. Arnold SV, Inzucchi SE, Tang F, et al. Real-world use and modeled impact of glucose-lowering therapies evaluated in recent cardiovascular outcomes trials: An NCDR® Research to Practice project. Eur J Prev Cardiol. 2017;24(15):1637–1645. DOI: https://doi.org/10.1177/2047487317729252
11. Vaduganathan M. SGLT2 inhibitor prescription rates low among cardiologists [Internet]. Healio. 2018. Accessed July 8, 2020. https://www.healio.com/cardiology/diabetes/news/online/{771f96e4-5fe2-4231-8778-1dcdc9fe7755}/sglt2-inhibitor-prescription-rates-low-among-cardiologists