Effect of SLGT2 Inhibitors on Patients with Atrial Fibrillation

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Abstract

Background: Sodium glucose cotransporter 2 (SGLT2) inhibitors have been associated with various cardiovascular benefits. There is limited data examining the effect of these medications on atrial fibrillation (AF) associated clinical outcomes. We compared ischemic stroke, acute coronary syndrome (ACS), cardioversion, and all-cause mortality outcomes in AF patients on SGLT2 inhibitors to propensity matched controls.

Materials and Methods: We conducted a retrospective study with a global medical research network database. AF patients were identified via ICD codes that must have been present for at least one month. Patients on SGLT2 inhibitors were identified as those on dapagliflozin, empagliflozin, or canagliflozin for at least one month. AF patients on SGLT2 inhibitors were propensity matched to those not on SGLT2 inhibitors based on age, race, ethnicity, cardiovascular comorbidities, valvular disease, pulmonary disease, urinary diseases, cardiovascular procedures, cardiovascular medications, and anticoagulants. We examined incidence of ischemic stroke, at least one ACS episode, cardioversion, and all-cause mortality.

Results: In 26,269 AF patients, SGLT2 inhibitors were associated with lower risk of cardioversion (HR 0.921, 95% CI 0.841 - 0.999, p = 0.0245) and all-cause mortality (HR 0.676, 95% CI 0.635 - 0.721, p < 0.0001). However, there was an association with increased risk for ischemic stroke (HR 1.081, 95% CI 1.012 - 1.154, p 0.0201). There was no clear association with ACS events.

Conclusion: In patients with AF, use of SGLT2 inhibitors was associated with a lower risk of cardioversion and all-cause mortality and higher probability of survival based on Kaplan-Meier analysis.

Introduction

Diabetes mellitus (DM) is a major cardiovascular risk factor; it is associated with increased cardiovascular events, mortality, and hospitalization [1]. DM is also an independent risk factor for atrial fibrillation (AF) [2]. It is associated with increase AF burden, lower quality of life, and worse AF associated morbidities [3-5]. While the pathophysiologyis not fully understood, it is thought to be due to hyperglycemic-induced myocardial remodeling and expansion of epicardial adipose tissue. This leads to inflammation-related cardiac fibrosis and changes in electrical conduction that may lead to AF [5,6]. Sodium glucose cotransporter 2 (SGLT2) inhibitors were developed to selectively inhibit these transporters, found exclusively in the proximal convoluted tubule of the kidneys, thereby preventing glucose reabsorption, increasing urinary glucose excretion, and decrease blood glucose levels [7]. Several trials, including the EMPA-REG OUTCOME [8], CANVAS [9], DECLARE-TIMI 58 [10], CREDENCE [11], DAPA-HF [12], and EMPEROR-Reduced [13] trials, have demonstrated various cardiovascular benefits of these medications. However, none of these trials formally evaluated SGLT2 inhibitor effects on atrial fibrillation.

A post-hoc analysis of the EMPA-REG OUTCOME trial found that in patients with type 2 DM and established cardiovascular disease, irrespective of AF presence, empagliflozin reduced heart failure (HF) related hospitalizations and renal events [14]. With regards to SGLT2 inhibitor direct effects on AF, a post-hoc analysis of the DECLARE-TIMI 58 trial found that dapagliflozin reduced incidence of AF and atrial flutter related events regardless of prior history of AF or atrial flutter in type 2 DM patients [15]. Recently, analysis of the CREDENCE trial examined the effect of canagliflozin on stroke and AF in type 2 DM patients with diabetic kidney disease [16]. This analysis found no significant effect of canagliflozin on risk of hemorrhagic stroke, total stroke, and AF. However, the study was not powered to evaluate this specific effect. A meta-analysis of 16 trials found that SGLT2 inhibitors in patients with type 2 DM may reduce atrial fibrillation and atrial flutter as well as all-cause mortality [17]. Currently, there has been no study examining the direct effect of SGLT2 inhibitors on atrial fibrillation related outcomes and complications, regardless of diabetes status.

Therefore, we utilized a large medical research database to explore the effect of SGLT2 inhibitors on atrial fibrillation related outcomes

Key Words

Atrial Fibrillation; SGLT2 Inhibitors; Outcomes

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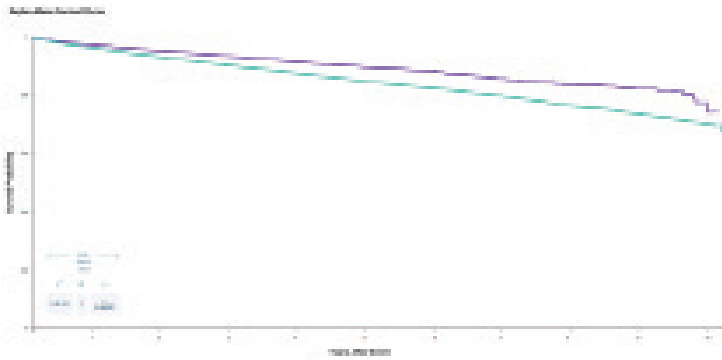7703 Floyd Curl Dr.San Antonio, TX 78229

Figure 1:   Kaplan-Meier Survival Curve for AF Patients With and Without SGLT2 Inhibitors.

Purple = Atrial Fibrillation patients with SGLT2 Inhibitors
Green = Atrial Fibrillation patients without SGLT2 Inhibitors

including stroke, acute coronary syndromes, cardioversion, and all-cause mortality in patients with atrial fibrillation. The goal of our study was to compare these outcomes in AF patients on SGLT2 inhibitors to propensity score matched patients with AF not on SGLT2 inhibitors.

Materials and Methods
Data Availability Statement
TriNetX global research network contains aggregate de-identified data from anonymously participating Healthcare Organizations (HCOs), mainly in the United States, but also throughout the world. TriNetX is compliant with the Health Insurance Portability and Accountability Act (HIPAA) and data displayed are in aggregate form, containing only de-identified data. Data can be accessed via TriNetX research network at https://live.trinetx.com. There may be costs and agreement forms needed to obtain data.

Patient Database
TriNetX (Cambridge, MA) is a global health research network with access to electronic medical records, including diagnoses, procedures, medications, laboratory values, and genomic information from 53 health care organizations (academic medical centers, physician practices, and community hospitals) with approximately 63,500,569 patients greater than or equal to 18 years old as of August 18, 2021. It is compliant with HIPAA, the US federal law which protects the privacy and security of healthcare data. Any data displayed on the TriNetX Platform in aggregate form, or any patient level data provided in a data set, only contains de-identified data as per the de-identification standard defined in HIPAA Privacy Rule.

Study Design
This is a retrospective observational study conducted via data from TriNetX Research Network. Inclusion criteria was: (1) patients having atrial fibrillation (AF) based on the International Classification of Diseases (ICD), Ninth and Tenth Revisions, Clinical Modification codes (I48.91, I48.0, I48.2, I48.1, I48.20, I48.19, I48.21, I48.11, I48.9, I48.21, I48.11) that was (2) present for at least one month. For the SGLT2 inhibitor cohort, we included (3) patients on SGLT2 inhibitors empagliflozin, dapagliflozin, or canagliflozin and (4) were on the medication for at least one month. These three were chosen due to being the most studied medications. The control cohort was designated as AF patients that were not on empagliflozin, dapagliflozin, or canagliflozin. We excluded patients that had a diagnosis of atrial flutter.

Outcomes were based on ICD codes and Common Procedure Coding System (CPT) codes that occurred at least one month after the diagnosis of AF with SGLT2 inhibitors or AF without SGLT2 inhibitors. Outcomes included ischemic stroke (I63, I63.50, G46.4, G46.3, I63.40, I63.239, I63.30, I63.139, I66.09, I63.139, I66.09, I63.59, I63.22, I63.219, I63.019, I63.20), acute coronary syndrome including unstable angina, non-ST elevation myocardial infarction, and ST elevation myocardial infarction (I20.0, I21.3, I21.1, I21.0, I21.19, I21.09, I21.2, I21.29, I21.11, I21.02, I21.21, I21.01, I21, I21.4, I25.110, I25.710, I25.700, I25.720, I25.790, I25.750, I25.760, I25.730), cardioversion (250980009, 5A2204Z, 1012978, 92960, 92961), and all-cause mortality.

Data Collection
TriNetX was accessed on August 18, 2021, and an anonymous data set from January 1, 2016, to August 18, 2021, was obtained. SGLT2 inhibitor cohort consisted of all patients greater than or equal to 18 years old with the diagnosis of AF, based on ICD codes above, and on either empagliflozin, dapagliflozin, or canagliflozin for at least 30 days. The control cohort was composed of all patients greater than or equal to 18 years old with the diagnosis of AF and not on empagliflozin, dapagliflozin, or canagliflozin. 48 participating health-care organizations had data available for this patient population. Afterwards, propensity-scored matching was conducted and outcomes were collected.

Statistical Analysis
Statistical analysis was conducted via the TriNetX online platform. Categorical variables were compared utilizing chi-square tests and continuous variables were compared utilizing independent sample t-tests. Propensity score matching at a 1:1 ratio was conducted with logistic regression to control for current age, age at AF diagnosis, gender, race, ethnicity, hypertensive diseases, hypertensive heart disease, ischemic heart disease, heart failure, valvular heart disease, metabolic syndrome (including, but not limited to hyperlipidemia, obesity, and overweight), type 2 diabetes mellitus, cerebrovascular disease, chronic kidney disease, respiratory disease, nervous system disease, neoplasms, disease of the urinary tract, cardiovascular procedures (including but not limited to echocardiography, cardiac catheterization, revascularization, coronary artery bypass grafts), cardiovascular medications (including, but not limited to: beta blockers, calcium channel blockers, antiarrhythmic drugs, antianginals), and anticoagulants (including, but not limited to: direct oral anticoagulants, warfarin, and heparin).

Cox proportioned hazards ratio with 95% confidence intervals (CI) for incidence of stroke, acute coronary syndrome (ACS), cardioversion, and all-cause mortality were generated after propensity score matching. Kaplan-Meier analysis was conducted to estimate all-cause mortality. Statistical significance was set at $p < 0.05$.

Results
Baseline Characteristics
A total of 48 HCOs provided data for patients with AF on SGLT2

| Table 1: | Baseline Characteristics of the AF Patients With and Without SGLT2 Inhibitors Before and AfterPropensity-Score Matching |

	Initial Populations			Propensity Score Matched Populations		
	AF and SGLT2i (n=26,294)	AF and No SGLT2i (n=1,368,518)	P-Value	AF and SGLT2 (n=26,269)	AF and No SGLT2 (n=26,269)	P-Value
Age (years) at Dx of AF (mean + SD)	66.2 + 10.5	71.3 + 12.9	< 0.0001	66.3 + 10.5	64.2 + 12.7	< 0.0001
Gender						
Male	68.5%	56.1%	< 0.0001	68.5%	70.7%	< 0.0001
Female	29.9%	43.4%	< 0.0001	29.9%	28.0%	< 0.0001
Unknown	1.5%	0.5%	< 0.0001	1.5%	1.3%	0.0347
Race/Ethnicity						
White	75.6%	79.6%	< 0.0001	75.7%	76.9%	0.0004
Black	12.5%	8.7%	< 0.0001	12.5%	11.9%	0.0809
Asian	1.3%	1.4%	0.6303	1.3%	1.2%	0.3536
Hispanic/Latino	4.9%	3.2%	< 0.0001	4.8%	4.6%	0.1878
Co-Morbidities						
HTN	80.5%	43.5%	< 0.0001	80.5%	78.3%	< 0.0001
Ischemic Heart Disease	54.4%	22.8%	< 0.0001	54.4%	53.4%	0.0177
Heart Failure	43.4%	15.1%	< 0.0001	43.4%	41.8%	0.0002
Metabolic Diseases	77.6%	39.3%	< 0.0001	77.6%	75.4%	< 0.0001
Nonrheumatic Mitral Valvular Disease	20.8%	8.8%	< 0.0001	20.8%	19.7%	0.0015
Nonrheumatic Aortic Valve Disease	13.8%	7.3%	< 0.0001	13.8%	12.6%	< 0.0001
Chronic Rheumatic Heart Disease	13.5%	5.7%	< 0.0001	13.5%	12.6%	0.0013
Type 2 Diabetes Mellitus	77.7%	17.4%	< 0.0001	77.7%	77.7%	0.8421
Cerebrovascular Disease	21.2%	11.7%	< 0.0001	21.2%	19.9%	0.0003
Chronic Kidney Disease	25.2%	11.4%	< 0.0001	25.2%	23.9%	0.0004
Respiratory Disease	58.1%	32.2%	< 0.0001	58.1%	56.2%	< 0.0001
Nervous System Disease	61.3%	32.1%	< 0.0001	61.3%	59.95%	0.0017
Neoplasms	34.1%	21.9%	< 0.0001	34.1%	33.1%	0.0114
Others						
Cardiovascular Procedures	67.7%	39.5%	< 0.0001	67.7%	66.0%	< 0.0001
Cardiovascular Medications	91.7%	57.0%	< 0.0001	91.7%	91.7%	0.8867
Anticoagulants	73.2%	36.1%	< 0.0001	73.2%	73.6%	0.2731

AF = Atrial Fibrillation, SGLT2i = Sodium-Glucose Co-Transporter 2 inhibitor, Dx = Diagnosis, SD = Standard Deviation, HTN = Hypertension

inhibitors and not on SGLT2 inhibitors. There were 26,294 patients with AF and an SGLT2 inhibitor and 1,368,518 patients with AF and not on an SGLT2 inhibitor. After propensity score matching, both cohorts had a size of 26,269 patients (Table 1). The average age at the diagnosis of atrial fibrillation for patients in the SGLT2 inhibitor cohort and no SGLT2 inhibitor group was 66.3 + 10.5 years and 64.2 + 12.7 years respectively. The majority in each cohort were of male gender (68.5% and 70.7% respectively). 80% of patients in both cohorts had hypertension, approximately 79% had type 2 diabetes mellitus, 77% had metabolic diseases, 61% had nervous system diseases, and 57% had respiratory system diseases. Approximately 92% were on cardiovascular medications and 73% were on anticoagulants (Table 2).

Outcomes

In the cohorts of 26,269 AF patients, SGLT2 inhibitors were associated with a higher risk of ischemic stroke (HR 1.081, 95% CI 1.012 – 1.154, p 0.0201) based on Cox Proportioned Hazards Model. SGLT2 inhibitors were associated with a higher risk of acute coronary syndrome (HR 1.04, 95% CI 0.99 – 1.10, p 0.1458), although this did

not reach statistical significance. AF patients on SGLT2 inhibitors were also associated with lower risk for cardioversion (HR 0.912, 95% CI 0.841 - 0.999, p 0.0248). Lastly, SGLT2 inhibitors in AF patients were associated with lower all-cause mortality (HR 0.676, 95% CI 0.635 - 0.721, p < 0.0001) (Table 3). Kaplan-Meier analysis demonstrated survival probability was higher in patients with AF and SGLT2 inhibitors (74.1% vs. 67.6%, p < 0.0001) (Figure 1).

Discussion

This is the first observational study to examine the effect of SGLT2 inhibitors and outcomes on patients with atrial fibrillation. The main findings of this study show that patients with AF on these medications were associated with lower risk of cardioversion and all-cause mortality. There appears to be a higher tendency toward an ischemic stroke and acute coronary syndrome.

Ischemic Stroke

Atrial fibrillation is associated with increased risk of stroke, systolic embolism, and death [18,19]. Currently, the CHADS2VASc score has

Table 2: Cardiovascular Medications in Atrial Fibrillation Patients With and Without SGLT2 Inhibitors Before Propensity Matching		
Medications	**AF and SGLT2i (n=26,294)**	**AF and No SGLT2i (n=1,368,518)**
Cardiovascular Medications	92%	63%
Antilipemic Agents	78%	38%
Atorvastatin	55%	23%
Simvastatin	19%	12%
Rosuvastatin	18%	6%
Pravastatin	13%	6%
Fenofibrate	9%	2%
Ezetimibe	8%	3%
Beta Blockers/ Related	77%	43%
Metoprolol	57%	30%
Carvedilol	27%	9%
Labetalol	12%	6%
Diuretics	68%	35%
Loop Diuretics	54%	24%
Thiazides	36%	18%
Potassium Sparing Diuretics	27%	8%
ACE Inhibitors	52%	24%
Lisinopril	43%	20%
Enalapril	4%	2%
Benazepril	3%	2%
Calcium Channel Blockers	47%	27%
Amlodipine	28%	17%
Diltiazem	18%	9%
Verapamil	9%	3%
Nifedipine	3%	2%
Angiotensin II Inhibitors	42%	15%
Antianginals	35%	14%
Nitroglycerin	30%	12%
Isosorbide	11%	4%
Isosorbide Dinitrate	5%	1%
Ranolazine	3%	1%

AF = Atrial Fibrillation, SGLT2i = Sodium-Glucose Co-Transporter 2 inhibitor, ACE = Angiotensin Converting Enzyme

been utilized to assess risk of stroke in AF patients [20, 21]. Diabetes mellitus is one of the risk factors that is associated with a 2-fold risk of stroke alone [22]. SGLT2 inhibitors in diabetic patients has to been evaluated and found to have no significant differences in stroke risk from previous meta-analysis of 32 trials [23]. A recent post-hoc analysis of 142 patients from the CREDENCE trial found that there was no clear effect of SGLT2 inhibitors on stroke risk in patients with AF and diabetic kidney disease, but the study was not powered to assess this outcome [24]. Our study shows AF patients on SGLT2 inhibitors may be associated with a higher risk of ischemic stroke and appears to agree with the previous study. There have been previous data demonstrating glucose-lowering agents have limited effect on stroke prevention [35]. In previous studies, empagliflozin has been associated with systolic blood pressure reduction and hemoconcentration that may increase the risk for ischemic stroke [36]. Further data will be needed to examine this association and relationship.

The most likely hypothesis for the increased risk of ischemic stroke is the blood pressure lowering effect associated with SGLT2 inhibitors. Lower blood pressure poses a risk for hypovolemia and hypotension leading to hypoperfusion and ischemic stroke. The major mechanism for this blood pressure effect may be related to natriuresis, osmotic diuresis, and reduction in body weight [37,38]

Acute Coronary Syndrome

There have been multiple trials with results on major adverse cardiovascular events, including myocardial infarction (MI). The EMPA-REG OUTCOME trial demonstrated 14% relative risk reduction in major adverse cardiovascular events (MACE) including MI [8]. Specifically for myocardial infarction, there was no statistically significant difference in findings. The CANVAS trial demonstrated 14% relative risk reduction of a major adverse cardiovascular event but also demonstrated no statistically significant difference in MI events [9,32]. Similarly, the CREDENCE trial demonstrated a relative risk reduction in cardiovascular death, MI, or stroke [11]. The DECLARE-TIMI 58 provided the largest trial and still found a non-statistically significant risk reduction in MACE, including MI [15]. Our study demonstrated a non-significant association of SGLT2 inhibitors and ACS events in patients with atrial fibrillation. Again, this may be related to diabetic related microvascular disease. Currently, SGLT2 inhibitors have been thought to have anti-atherosclerotic effects through glucose control, blood pressure control, and weight loss [39]. However, patients on SGLT2 inhibitors may have already worsened diabetic microvascular disease that may be confounding the outcome of ACS events. Further trials will be needed to examine the association with ACS events and SGLT2 inhibitors.

Cardioversion

Currently, direct-current cardioversion is a Class 1 recommendation for pursuing rhythm-control strategies for AF patients [33]. The findings of this study present that AF patients taking SLGT2 inhibitors are associated with lower risk of cardioversion compared to AF patients not taking these medications (HR 0.921, 95% CI 0.841 - 0.999, p = 0.0245). Therefore, this study presents new data that SGLT2 inhibitors are associated with lower risk for cardioversion and may affect the morbidity of AF patients. Further data should be explored to closely examine the association and relationship.

With regards to mechanism, there are currently animal models that have found SGLT2 inhibitors to suppress inflammation and oxidative stress in diabetic rodents [40]. A hypothesis is that this decreases inflammation and myocardial fibrosis. This decrease in fibrosis can lead to less alterationin the electrical properties of the atrial tissue and could be a possible explanation for the associated lower risk for cardioversion.

All-Cause Mortality

SGLT2 inhibitors have been associated with lower cardiovascular mortality in various patient populations including diabetes, chronic kidney disease, and heart failure [8-13]. Similarly, our study demonstrated that SGLT2 inhibitors are associated with lower mortality in AF patients (HR 0.676, 95% CI 0.635 - 0.721, p < 0.0001) compared to those not on them. This provides further evidence that supports previous studies, including a meta-analysis demonstrating an association of SGLT2 inhibitors with lower risk of sudden cardiac death [33].

Table 3:	Outcomes of AF Patients With and Without SGLT2 Inhibitors After Propensity-Score Matching		
	HR	95% CI	P-Value
Ischemic Stroke	1.08	1.01 – 1.15	0.0201
ACS	1.04	0.99 – 1.10	0.1458
Cardioversion	0.91	0.84 – 0.99	0.0248
Mortality	0.68	0.64 – 0.72	< 0.0001

HR = Hazards Ratio, CI = Confidence Interval, ACS = Acute Coronary Syndrome

There are multiple hypotheses as to the overall mortality benefit in cardiovascular patients. SGLT2 inhibitors have been associated with lower blood pressure, increased diuresis, improved cardiac energy metabolism, decreased inflammation, weight loss, improved glucose control, improved cardiac remodeling, preventing ischemic myocardial injury, decreased epicardial fat, and decreased oxidative stress [41]. These effects are likely to extend to atrial fibrillation patients, who are also likely to have many similar cardiovascular morbidities that SGLT2 inhibitors are known to impact. In addition, SGLT2 inhibitors may affect left atrial appendage (LAA) remodeling either directly, by reducing cardiac remodeling, or indirectly, by lowing blood pressure and in turn LAA pressure. Further studies are needed to explain the mechanism of SGLT2 inhibitors impact on atrial fibrillation related mortality.

Limitations

Aside from the inherent limitation of retrospective analysis there are several other limitations to this study. First, these results are based on aggregate data of ICD and CPT codes. There is a possibility of underreporting patients due to timing and number of diagnosis codes as well as CPT codes. We attempted to address these issues by utilizing time constraints when possible. For example, we included only patients with ICD codes for atrial fibrillation that was present for at least one month. Similarly, we only included patients that were on SGLT2 inhibitors for at least one month. This also limited the evaluation of cardiovascular specific mortality as there is no specific code for that. Second, when utilizing the TriNetX data platform, we are limited to use the platform analytical power and limiting us to their calculations and methods. Thirdly, we were unable to directly compare dapagliflozin, canagliflozin, and empagliflozin due to the limitation of the analytical software. Another limitation of this study was the inability to account for socioeconomic status (SES) risk factors in atrial fibrillation. It has been established that SES plays a role in AF burden [34] and plays a role in access to SGLT2 inhibitors. Despite these limitations, and with a comprehensive propensity score matching to any possible confounding factors, this study does provide evidence of the benefit of SGLT2 inhibitors in AF patients, and it should pave the way for prospective trials to provide further proof of this association.

Conclusion

In 26,269 patients with atrial fibrillation, use of SGLT2 inhibitors was associated with lower risk of all-cause mortality. This study provides further evidence for the benefits of SGLT2 inhibitors in patients with atrial fibrillation. Further data should be examined prior to determination of the full effect of SGLT2 inhibitors for this patient population.

References

1. Benjamin E.J., Muntner P., Alonso A., Bittencourt M.S. and Callaway C.W. : "Heart disease and stroke statistics—2019 update: a report from the American Heart Association". Circulation 2019; 5: 56.

2. Echouffo-Tcheugui J.B., Shrader P., Thomas L.et.al. : "Care patterns and outcomes in atrial fibrillation patients with and without diabetes: ORBIT-AF Registry". J Am Coll Cardiol 2017; 70: 1325.

3. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic featuresof chronic atrial fibrillation: the Framingham study. N Engl J Med.1982;306:1018-1022.

4. Fangel MV, Nielsen PB, Kristensen JK, Larsen TB, Overvad TF, Lip GYH,Jensen MB.Glycemic status and thromboembolic risk in patients with atrialfibrillation and type 2 diabetes mellitus. Circ ArrhythmElectrophysiol.2019;12:e007030.

5. Wang A, Green JB, Halperin JL, Piccini JP Sr. Atrial fibrillation and diabetesmellitus: JACC review topic of the week. J Am Coll Cardiol.2019;74:1107–1115.

6. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr,Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRSfocused update of the 2014 AHA/ACC/HRS guideline for the managementof patients with atrial fibrillation: a report of the American Collegeof Cardiology/American Heart Association Task Force on ClinicalPractice Guidelines and the Heart Rhythm Society in collaboration withthe Society of ThoracicSurgeons. Circulation. 2019;140:e125–e151. doi:10.1161/CIR.0000000000000665

7. Zelniker TA, Braunwald E. Cardiac and renal effects of sodium-glucoseco-transporter 2 inhibitors in diabetes: JACC state-of-the-art review. J AmColl Cardiol. 2018;72:1845–1855.

8. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S,Mattheus M, Devins T,Johansen OE, Woerle HJ, et al; EMPA-REGOUTCOME Investigators. Empagliflozin,cardiovascular outcomes, andmortality in type 2 diabetes. N Engl J Med. 2015;373:2117–2128. doi:10.1056/NEJMoa1504720

9. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, ShawW, Law G,Desai M, Matthews DR; CANVAS Program Collaborative Group.Canagliflozin and cardiovascular and renal events in type 2 diabetes. N EnglJ Med. 2017;377:644–657. doi: 10.1056/NEJMoa1611925

10. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG,ZelnikerTA, Kuder JF, Murphy SA, et al; DECLARE–TIMI 58 Investigators.Dapagliflozin andcardiovascular outcomes in type 2 diabetes. N Engl J Med.2019;380:347–357. doi:10.1056/NEJMoa1812389

11. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, CharytanDM, Edwards R,Agarwal R, Bakris G, Bull S, et al; CREDENCE TrialInvestigators. Canagliflozin and renaloutcomes in type 2 diabetesand nephropathy. N Engl J Med. 2019;380:2295–2306. doi:10.1056/NEJMoa1811744

12. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008. doi: 10.1056/ NEJMoa1911303. Epub 2019 Sep 19. PMID: 31535829.

13. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, et al; EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes

with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383(15):1413-1424. doi: 10.1056/NEJMoa2022190. Epub 2020 Aug 28. PMID: 32865377.

14. Böhm M, Slawik J, Brueckmann M, Mattheus M, George JT, Ofstad AP, Inzucchi SE, Fitchett D, Anker SD, Marx N, Wanner C, Zinman B, Verma S. Efficacy of empagliflozin on heart failure and renal outcomes in patients with atrial fibrillation: data from the EMPA-REG OUTCOME trial. Eur J Heart Fail. 2020 Jan;22(1):126-135. doi: 10.1002/ejhf.1663. Epub 2019 Dec 9. PMID: 31820559.

15. Zelniker TA, Bonaca MP, Furtado RHM, Mosenzon O, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Budaj A, Kiss RG, Padilla F, Gause-Nilsson I, Langkilde AM, Raz I, Sabatine MS, Wiviott SD. Effect of Dapagliflozin on Atrial Fibrillation in Patients With Type 2 Diabetes Mellitus: Insights From the DECLARE-TIMI 58 Trial. Circulation. 2020 Apr 14;141(15):1227-1234. doi: 10.1161/CIRCULATIONAHA.119.044183. Epub 2020 Jan 27. PMID: 31983236.

16. Zhou Z, Jardine MJ, Li Q, Neuen BL, Cannon CP, de Zeeuw D, Edwards R, Levin A, Mahaffey KW, Perkovic V, Neal B, Lindley RI; CREDENCE Trial Investigators*. Effect of SGLT2 Inhibitors on Stroke and Atrial Fibrillation in Diabetic Kidney Disease: Results From the CREDENCE Trial and Meta-Analysis. Stroke. 2021 May;52(5):1545-1556. doi: 10.1161/STROKEAHA.120.031623. Epub 2021 Apr 20. PMID: 33874750; PMCID: PMC8078131.

17. Li WJ, Chen XQ, Xu LL, Li YQ, Luo BH. SGLT2 inhibitors and atrial fibrillation in type 2 diabetes: a systematic review with meta-analysis of 16 randomized controlled trials. Cardiovasc Diabetol. 2020 Aug 26;19(1):130. doi: 10.1186/s12933-020-01105-5. PMID: 32847602; PMCID: PMC7448518.

18. Wolf PA, Dawber TR, Thomas HE, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology. 1978; 28:973–977.

19. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham heart study. Circulation. 1998; 98:946–952.

20. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor–based approach: the Euro heart survey on atrial fibrillation. Chest. 2010; 137:263–272. doi: 10.1378/chest.09-1584.

21. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. ThrombHaemost. 2012; 107:1172–1179. doi: 10.1160/TH12-03-0175.

22. Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes andincidence of cardiovascular diseases: a cohort study in 1.9 millionpeople. Lancet Diabetes Endocrinol. 2015;3:105-113.

23. Guo M, Ding J, Li J, Wang J, Zhang T, Liu C, Huang W, Long Y, Gao C, Xu Y. SGLT2 inhibitors and risk of stroke in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes ObesMetab. 2018 Aug;20(8):1977-1982. doi: 10.1111/dom.13295. Epub 2018 Apr 16. PMID: 29573118.

24. Zhou Z, Jardine MJ, Li Q, Neuen BL, Cannon CP, de Zeeuw D, Edwards R, Levin A, Mahaffey KW, Perkovic V, Neal B, Lindley RI; CREDENCE Trial Investigators*. Effect of SGLT2 Inhibitors on Stroke and Atrial Fibrillation in Diabetic Kidney Disease: Results From the CREDENCE Trial and Meta-Analysis. Stroke. 2021 May;52(5):1545-1556. doi: 10.1161/STROKEAHA.120.031623. Epub 2021 Apr 20. PMID: 33874750; PMCID: PMC8078131.

25. Nassif ME, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE, McGuire DK, Pitt B, Scirica BM, Austin B, Drazner MH, Fong MW, Givertz MM, Gordon RA, Jermyn R, Katz SD, Lamba S, Lanfear DE, LaRue SJ, Lindenfeld J, Malone M, Margulies K, Mentz RJ, Mutharasan RK, Pursley M, Umpierrez G, Kosiborod M. Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial. Circulation. 2019 Oct 29;140(18):1463-1476. doi: 10.1161/CIRCULATIONAHA.119.042929. Epub 2019 Sep 16. PMID: 31524498.

26. Writing Committee, Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, Fonarow GC, Ibrahim NE, Lindenfeld J, Masoudi FA, Motiwala SR, Oliveros E, Patterson JH, Walsh MN, Wasserman A, Yancy CW, Youmans QR. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021 Feb 16;77(6):772-810. doi: 10.1016/j.jacc.2020.11.022. Epub 2021 Jan 11. PMID: 33446410.

27. Middlekauff HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure: a study of 390 patients. Circulation. 1991; 84: 40–48.

28. Carson PE, Johnson GR, Dunkman WB, Fletcher RD, Farrell L, Cohn JN. The influence of atrial fibrillation on prognosis in mild to moderate heart failure: the V-HeFT Studies: the V-HeFT VA Cooperative Studies Group. Circulation. 1993; 87 (suppl): VI-102–VI-110.

29. Mahoney P, Kimmel S, DeNofrio D, Wahl P, Loh E. Prognostic significance of atrial fibrillation in patients at a tertiary medical center referred for heart transplantation because of severe heart failure. Am J Cardiol. 1999; 83: 1544–1547. CrossrefMedlineGoogle Scholar

30. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MM. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation. 1998; 98: 2282–2289.

31. Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the Veterans Affairs Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT): the Department of Veterans Affairs CHF-STAT Investigators. Circulation. 1998; 98: 2574–2579.

32. Mahaffey KW, Neal B, Perkovic V, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Fabbrini E, Sun T, Li Q, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation. 2018 Jan 23;137(4):323-334. doi: 10.1161/CIRCULATIONAHA.117.032038.

33. Fernandes GC, Fernandes A, Cardoso R, Penalver J, Knijnik L, Mitrani RD, Myerburg RJ, Goldberger JJ. Association of SGLT2 inhibitors with arrhythmias and sudden cardiac death in patients with type 2 diabetes or heart failure: A meta-analysis of 34 randomized controlled trials. Heart Rhythm. 2021 Jul;18(7):1098-1105.

34. Mou L, Norby FL, Chen LY, O'Neal WT, Lewis TT, Loehr LR, Soliman EZ, Alonso A. Lifetime Risk of Atrial Fibrillation by Race and Socioeconomic Status: ARIC Study (Atherosclerosis Risk in Communities). Circ ArrhythmElectrophysiol. 2018 Jul;11(7):e006350. doi: 10.1161/CIRCEP.118.006350. PMID: 30002066; PMCID: PMC6053683.

35. Zinman B, Inzucchi SE, Lachin JM, Wanner C, Fitchett D, Kohler S, Mattheus M, Woerle HJ, Broedl UC, Johansen OE, Albers GW, Diener HC; EMPA-REG OUTCOME Investigators (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients). Empagliflozin and Cerebrovascular Events in Patients With Type 2 Diabetes Mellitus at High Cardiovascular Risk. Stroke. 2017 May;48(5):1218-1225. doi: 10.1161/STROKEAHA.116.015756. Epub 2017 Apr 6. PMID: 28386035; PMCID: PMC5404404.

36. Ricci F, Fedorowski A, Radico F, Romanello M, Tatasciore A, Di Nicola M, Zimarino M, De Caterina R. Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. Eur Heart J. 2015 Jul 1;36(25):1609-17. doi: 10.1093/eurheartj/ehv093. Epub 2015 Apr 6. PMID: 25852216.

37. Malyszko J, Muntner P, Rysz J, Banach M. Blood pressure levels and stroke: J-curve

phenomenon? CurrHypertens Rep. 2013 Dec;15(6):575-81. doi: 10.1007/s11906-013-0402-z. PMID: 24158455; PMCID: PMC3838583.

38. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. J Am Soc Hypertens. 2014 Apr;8(4):262-75.e9. doi: 10.1016/j.jash.2014.01.007. Epub 2014 Jan 26. PMID: 24602971.

39. Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, Espadero RM, Woerle HJ, Broedl UC, Johansen OE. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. Diab Vasc Dis Res. 2015 Mar;12(2):90-100. doi: 10.1177/1479164114559852. Epub 2015 Jan 14. PMID: 25589482; PMCID: PMC4361459.

40. Oelze M, Kröller-Schön S, Welschof P, Jansen T, Hausding M, Mikhed Y, Stamm P, Mader M, Zinßius E, Agdauletova S, Gottschlich A, Steven S, Schulz E, Bottari SP, Mayoux E, Münzel T, Daiber A. The sodium-glucose co-transporter 2 inhibitor empagliflozin improves diabetes-induced vascular dysfunction in the streptozotocin diabetes rat model by interfering with oxidative stress and glucotoxicity. PLoS One. 2014 Nov 17;9(11):e112394. doi: 10.1371/journal.pone.0112394. PMID: 25402275; PMCID: PMC4234367.

41. Lopaschuk GD, Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. JACC Basic Transl Sci. 2020 Jun 22;5(6):632-644. doi: 10.1016/j.jacbts.2020.02.004. PMID: 32613148; PMCID: PMC7315190.