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RESEARCH

Clinical outcomes in heart failure patients with and without atrial fibrillation receiving sodium-glucose cotransporter-2 inhibitor

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Abstract

We report a retrospective analysis of a nationwide health database to study the association between sodium-glucose cotransporter-2 inhibitor (SGLT2I) use and the incidence of adverse clinical outcomes among heart failure (HF) patients with and without atrial fibrillation (AF) stratified by CHA2DS2–VASc score. The outcome of this study was on the development of adverse events, including acute myocardial infarction (AMI), hemorrhagic stroke, ischemic stroke, cardiovascular (CV) death, and all-cause mortality. By dividing the number of adverse events by the total person-years, the incidence rate was calculated. The hazard ratio (HR) was estimated by the Cox proportional hazard model. A total of 95% confidence interval (CI) was also presented to show the risk of adverse events for HF patients with and without AF taking SGLT2I. SGLT2I users had a lower risk of AMI (adjusted HR = 0.83; 95% CI = 0.74, 0.94), CV death (adjusted HR = 0.47; 95% CI = 0.42, 0.51), and all-cause death (adjusted HR = 0.39; 95% CI = 0.37, 0.41). Considering HF patients without AF and SGLT2I as the reference group, HF patients without AF but with SGLT2I had a reduced risk of adverse outcomes of 0.48 (95% CI = 0.45, 0.50), and HF patients with AF and SGLT2I had the decreased hazard ratio of 0.55 (95% CI = 0.50, 0.61). The adjusted HR of adverse outcomes for HF patients with CHA2DS2–VASc score less than 2 and SGLT2I without and with AF relative to HF patients without AF nor SGLT2I were 0.53 (95% CI = 0.41, 0.67) and 0.24 (95% CI = 0.12, 0.47), respectively. Compared to HF patients with no history of AF and SGLT2I, if patients additionally with SGLT2I and CHA2DS2–VASc score ≥ 2, the risk of the adverse outcomes was reduced with adjusted HR of 0.48 (95% CI = 0.45, 0.50); if patients additionally with AF and CHA2DS2–VASc score ≥ 2, the risk of the adverse outcomes was decreased with adjusted HR of 0.88 (95% CI = 0.80, 0.97); if patients additionally with AF, SGLT2I, and CHA2DS2–VASc score ≥ 2, the risk of the adverse outcomes was diminished with adjusted HR of 0.52 (95% CI = 0.47, 0.58). We concluded that SGLT2I has a protective effect in HF patients, and the risk reduction is greater with a score of < 2 and without AF.

Keywords Atrial fibrillation · Heart failure · SGLT2I

Introduction

Heart failure (HF) and atrial fibrillation (AF) are extremely closely linked (Anter et al. 2009; Lubitz et al. 2010; Kotecha and Piccini 2015; Ferreira and Santos 2015; Hu and Lin 2022). The situation would be very complicated when these two entities coexist (Anter et al. 2009; Lubitz et al. 2010; Kotecha and Piccini 2015; Ferreira and Santos 2015; Hu and Lin 2022). The vital role of sodium-glucose cotransporter-2 inhibitor (SGLT2I) in the HF population and the widespread use of SGLT2I in this population is well established (Packer et al. 2020; McMurray et al. 2019). However, a comparison of developing major adverse cardiac and cerebrovascular events (MACCE) in HF patients with and without AF who received SGLT2I remained unknown.

CHA2DS2–VASc score, once developed to quantify the comorbidity or complications in AF and potentially better predict the risk of stroke in people with AF, is widely penetrating into different risk stratification schemes currently (Hu and Lin 2019a, 2019b; Hu and Lin 2017; Yaşar et al. 2022a, 2022b). In general, it is also possible to use the above score as an indicator of patient selection for the further decision-making process.

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To identify this certainly novel research question of the role of SGLT2I for primary prevention of poor outcomes in a large HF cohort, the authors extracted data from Taiwan's National Health Insurance Research Database (NHIRD), a well-validated nationwide big database, to detect whether HF taking SGLT2I have a lower risk of adverse clinical events. Further subgroup analysis according to with and without AF and stratified by CHA2DS2–VASc score would also be performed.

Methods

Data source

In 1995, the Taiwan government promoted a single-payer National Health Insurance program to improve the national welfare. The insurance information, which contains demographic data, disease diagnosis, medicine records, and therapy records, of beneficiaries has been collected and stored in NHIRD. Currently, NHIRD involves the medical history of the residents for at least two decades. The International Classification of Diseases, Ninth & Tenth Revision, and Clinical Modification (ICD-9-CM, ICD-10-CM) are used for the coding. This study was approved by the Institutional Review Board of China Medical University Hospital Research Ethics Committee (CMUH109-REC2-031(CR-2)).

Study population

Patients with at least three times of outpatient visits or one admission record of HF (ICD-9-CM code 428; ICD-10CM code I50) were enrolled for the study population in this cohort study. We further divided participants into SGLT2I users and non-users. The index date of the SGLT2I users was the first prescription day of SGLT2I, and that of the SGLT2I non-users was a random date after the diagnosis date of HF. The study period was between 2016 and 2019. Patients who were aged below 20, without information of gender, with an index date before 2016 or after 2018, or who developed outcomes before the index date were eliminated. SGLT2I non-users with similar characteristics, which is according to the propensity score calculated by the logistic model with covariates of sex, age, comorbidities, and medicines, to the SGLT2I users, were selected as the control group. The matched ratio was 1:1.

Main outcome and confounders

The primary outcome of the study was defined as patients with adverse events, including acute myocardial infarction (AMI) (ICD-9-CM code 410; ICD-10CM code I21, I22), hemorrhagic stroke (ICD-9-CM code 431,432; ICD-10-CM code I61, I62), ischemic stroke (ICD-9-CM code 433, 434, 436; ICD-10-CM code I63, I65, I66, I67.89), cardiovascular (CV) death, and all-cause mortality. Patients who developed any one of the events will be counted as the outcome occurs and the follow-up time will be recorded to the day of the first outcome. The following comorbidities which related to outcomes and developed before the index date were included for the adjustment, AF (ICD-9-CM code 427.3; ICD-10-CM code I48), diabetes (ICD-9-CM code 250; ICD-10-CM code E08-E13), hyperlipidemia (ICD-9-CM code 272; ICD-10-CM code E77, E78), hypertension (ICD-9-CM code 410–405; ICD-10-CM code I10-I15), chronic kidney disease (ICD-9-CM code 585; ICD-10-CM code N18), chronic obstructive pulmonary disease (COPD) (ICD-9-CM code 491, 492, 496; ICD-10-CM code J41-J44), AMI (ICD-9-CM code 410; ICD-10-CM code I21, I22), and stroke (ICD-9-CM code 430–438; ICD-10-CM code I60-I69). Medicines such as aspirin, colopidogrel, warfarin, novel oral anticoagulant drugs (NOACs), amiodarone, dronedarone, angiotensin-converting enzyme inhibitors(ACEIs), angiotensin II receptor blockers (ARBs), α-blockers, β-blockers, calcium channel blockers (CCBs), diuretics, sacubitril/valsartan, and statins used before the index date were considered too.

Statistical analysis

Baseline variables about the case group and control group were summarized by number with percentage for categorical variables and mean with standard deviation for continuous variables. To examine the difference in the characteristics between SGLT2I users and non-users, the standard mean difference was computed. By dividing the number of adverse events by the total person-years, we had the incidence rate. The hazard ratio (HR) was estimated by the Cox proportional hazard model. A total of 95% confidence interval (CI) was also presented. The univariable model was used for crude HR, and the multivariable model was used for adjusted HR. Kaplan–Meier method was adopted to plot the cumulative incidence curves of the outcomes. And the curves were asses by the Log-rank test. All statistical analyses were performed by SAS software, version 9.4 (SAS Institute Inc., Cary, NC). A significance level was set as a *p*-value less than 0.05.

Results

The cohort study consisted of 17,588 SGLT2I users and 17,588 SGLT2I non-users. As shown as Table 1, the distributions of gender and age group within two groups were similar. The proportions of each comorbidities had no difference between SGLT2I users and non-users. Besides,

Table 1 Demographic, comorbidities, and medications in HF patients with and without SGLT2is

Variable	Non-SGLT2is users *n* (%)/mean ± SD	SGLT2is users *n* (%)/mean ± SD	SMD
All	17,588	17,588	
Sex			0.0063
Female	7390 (42.02)	7335 (41.70)	
Male	10,198 (57.98)	10,253 (58.30)	
Age group (year)			
< 50	1942 (11.04)	2010 (11.43)	0.0122
50–59	3392 (19.29)	3555 (20.21)	0.0233
> 60	12,254 (69.67)	12,023 (68.36)	0.0284
Age (year)	65.29 ± 12.35	64.96 ± 12.43	0.0272
Comorbidities			
AF			0.0284
No	14,564 (82.81)	14,373 (81.72)	
Yes	3024 (17.19)	3215 (18.28)	
Diabetes			0.0115
No	948 (5.39)	903 (5.13)	
Yes	16,640 (94.61)	16,685 (94.87)	
Hyperlipidemia			0.0122
No	3983 (22.65)	4073 (23.16)	
Yes	13,605 (77.35)	13,515 (76.84)	
Hypertension			0.0192
No	1687 (9.59)	1788 (10.17)	
Yes	15,901 (90.41)	15,800 (89.83)	
Chronic kidney disease			0.0175
No	14,750 (83.86)	14,636 (83.22)	
Yes	2838 (16.14)	2952 (16.78)	
COPD			0.0094
No	13,556 (77.08)	13,486 (76.68)	
Yes	4032 (22.92)	4102 (23.32)	
AMI			0.0123
No	14,642 (83.25)	14,561 (82.79)	
Yes	2946 (16.75)	3027 (17.21)	
Stroke			0.0041
No	13,377 (76.06)	13,346 (75.88)	
Yes	4211 (23.94)	4242 (24.12)	
Medications			
Aspirin			0.0004
No	3385 (19.25)	3382 (19.23)	
Yes	14,203 (80.75)	14,206 (80.77)	
Clopidogrel			0.0028
No	10,099 (57.42)	10,075 (57.28)	
Yes	7489 (42.58)	7513 (42.72)	
Warfarin			0.0359
No	15,588 (88.63)	15,383 (87.46)	
Yes	2000 (11.37)	2205 (12.54)	
NOACs			0.0178
No	15,428 (87.72)	15,324 (87.13)	
Yes	2160 (12.28)	2264 (12.87)	
Amiodarone			0.0240
No	14,211 (80.80)	14,043 (79.84)	
Yes	3377 (19.20)	3545 (20.16)	

Table 1 (continued)

Variable	Non-SGLT2is users *n* (%)/mean ± SD	SGLT2is users *n* (%)/mean ± SD	SMD
Dronedarone			0.0089
No	17,453 (99.23)	17,439 (99.15)	
Yes	135 (0.77)	149 (0.85)	
ACEIs			0.0021
No	6957 (39.56)	6939 (39.45)	
Yes	10,631 (60.44)	10,649 (60.55)	
ARBs			0.0288
No	2108 (11.99)	2275 (12.93)	
Yes	15,480 (88.01)	15,313 (87.07)	
α-blockers			0.0000
No	10,471 (59.53)	10,471 (59.53)	
Yes	7117 (40.47)	7117 (40.47)	
β-blockers			0.0090
No	10,822 (61.53)	10,899 (61.97)	
Yes	6766 (38.47)	6689 (38.03)	
CCBs			0.0230
No	2911 (16.55)	3063 (17.42)	
Yes	14,677 (83.45)	14,525 (82.58)	
Diuretics			0.0015
No	2824 (16.06)	2814 (16.00)	
Yes	14,764 (83.94)	14,774 (84.00)	
Sacubitril/Valsartan			0.0148
No	17,119 (97.33)	17,076 (97.09)	
Yes	469 (2.67)	512 (2.91)	
Statins			0.0216
No	2997 (17.04)	3141 (17.86)	
Yes	14,591 (82.96)	14,447 (82.14)	
Follow-up period (year)	1.75 ± 1.01	1.99 ± 0.88	0.2572

SMD, standard mead difference; *AF*, atrial fibrillation; *COPD*, chronic obstructive pulmonary disease; *AMI*, acute myocardial infarction; *NOACs*, novel oral anticoagulant drugs; *ACEIs*, angiotensin-converting enzyme inhibitors; *ARBs*, angiotensin II receptor blockers; *CCBs*, calcium channel blockers

diabetes, hypertension, and hyperlipidemia were the most common comorbidities in this study. The drug prescription pattern in the two group was similar, and the most common medicines were ARBs. The mean of the follow-up time for SGLT2I users was 1.75(± 1.01) years and that for SGLT2I non-users was 1.99(± 0.88) years.

Table 2 presents the associated of the covariates and the adverse outcomes. The adjusted hazard ratio of adverse events for SGLT2I users relative to SGLT2I non-users was 0.50 (95% CI = 0.48 0.53). Male patients were more likely to have an adverse outcome compared to female patients, and the adjusted HR was 1.18 (95% CI = 1.12, 1.25). If we consider patients younger than 50 years old as a reference group, 50–59-year-old patients and greater than 60-year-old patients increase the risk of adverse outcomes by 1.11 folds (95% CI = 1.00, 1.23) and 1.59 folds (95% CI = 1.45, 1.74), respectively. Patients with diabetes (adjusted HR = 1.25; 95% CI = 1.10, 1.41), chronic kidney disease (adjusted HR = 1.65; 95% CI = 1.56, 1.73), COPD (adjusted HR = 1.08; 95% CI = 1.03, 1.14), AMI (adjusted HR = 1.36; 95% CI = 1.28, 1.44), and stroke (adjusted HR = 1.56; 95% CI = 1.49, 1.64) will increase the risk of adverse outcomes. Patients with hyperlipidemia (adjusted HR = 0.84; 95% CI = 0.80, 0.89) reduce the risk of adverse outcomes. For the medications, clopidogrel (adjusted HR = 1.15; 95% CI = 1.09, 1.21), amiodarone (adjusted HR = 1.24; 95% CI = 1.16, 1.31), ACEIs (adjusted HR = 1.09; 95% CI = 1.04, 1.14), CCBs (adjusted HR = 1.08; 95% CI = 1.00, 1.16), and diuretics (adjusted HR = 2.22; 95% CI = 2.02, 2.43) were the risk factors of adverse outcomes. However, dronedarone (adjusted HR = 0.75; 95% CI = 0.59, 0.96), ARBs (adjusted HR = 0.87; 95% CI = 0.81, 0.94), β-blockers (adjusted HR = 0.90; 95% CI = 0.86, 0.95), and statins (adjusted HR = 0.84; 95% CI = 0.79, 0.89) were the protection factors of the adverse outcomes.

To look into the risk of the individual adverse outcome, SGLT2I users had a lower risk of AMI (adjusted HR = 0.83;

Table 2 Risk of adverse outcomes associated with SGLT2Is, demographics, comorbidities, and medications

Variable	Event $N=7892$	Person-years	IR 100 person-years	Crude HR (95% CI)	Adjusted HR (95% CI)
SGLT2is					
No	4956	30,758	16.11	1 (reference)	1 (reference)
Yes	2936	35,037	8.38	0.53 (0.51, 0.56)***	0.50 (0.48, 0.53)***
Sex					
Female	3137	27,914	11.24	1 (reference)	1 (reference)
Male	4755	37,882	12.55	1.11 (1.06, 1.16)***	1.18 (1.12, 1.25)***
Age (year)					
< 50	561	7934	7.07	1 (reference)	1 (reference)
50–59	1123	13,832	8.12	1.15 (1.04, 1.27)**	1.11 (1.00, 1.23)*
> 60	6208	44,030	14.10	1.95 (1.79, 2.12)***	1.59 (1.45, 1.74)***
Comorbidities					
AF					
No	6172	54,613	11.30	1 (reference)	1 (reference)
Yes	1720	11,182	15.38	1.34 (1.27, 1.41)***	1.01 (0.93, 1.09)
Diabetes					
No	261	3477	7.51	1 (reference)	1 (reference)
Yes	7631	62,318	12.25	1.64 (1.45, 1.86)***	1.25 (1.10, 1.41)***
Hyperlipidemia					
No	2034	14,672	13.86	1 (reference)	1 (reference)
Yes	5858	51,123	11.46	0.83 (0.79, 0.88)***	0.84 (0.80, 0.89)***
Hypertension					
No	564	6687	8.43	1 (reference)	1 (reference)
Yes	7328	59,108	12.40	1.46 (1.34, 1.59)***	0.96 (0.87, 1.06)
Chronic kidney disease					
No	5839	56,427	10.35	1 (Reference)	1 (Reference)
Yes	2053	9368	21.91	2.02 (1.92, 2.13)***	1.65 (1.56, 1.73)***
COPD					
No	5559	51,282	10.84	1 (Reference)	1 (Reference)
Yes	2333	14,513	16.08	1.46 (1.39, 1.53)***	1.08 (1.03, 1.14)**
AMI					
No	6129	55,368	11.07	1 (Reference)	1 (Reference)
Yes	1763	10,428	16.91	1.50 (1.42, 1.58)***	1.36 (1.28, 1.44)***
Stroke					
No	5023	51,578	9.74	1 (Reference)	1 (Reference)
Yes	2869	14,217	20.18	2.01 (1.92, 2.10)***	1.56 (1.49, 1.64)***
Medications					
Aspirin	1,183	13,083	9.04	1 (Reference)	1 (Reference)
No	6709	52,712	12.73	1.39 (1.31, 1.48)***	0.94 (0.88, 1.00)
Yes					
Clopidogrel					
No	3782	38,785	9.75	1 (Reference)	1 (Reference)
Yes	4110	27,010	15.22	1.54 (1.47, 1.61)***	1.15 (1.09, 1.21)***
Warfarin					
No	6787	58,000	11.70	1 (Reference)	1 (Reference)
Yes	1105	7795	14.18	1.21 (1.13, 1.29)***	0.98 (0.91, 1.05)
NOAC					
No	6724	58,098	11.57	1 (reference)	1 (reference)
Yes	1168	7697	15.17	1.28 (1.20, 1.36)***	0.94 (0.87, 1.02)
Amiodarone					
No	5857	53,698	10.91	1 (reference)	1 (reference)

Table 2 (continued)

Variable	Event $N=7892$	Person-years	IR 100 person-years	Crude HR (95% CI)	Adjusted HR (95% CI)
Yes	2035	12,097	16.82	1.52 (1.44, 1.59)***	1.24 (1.16, 1.31)***
Dronedarone					
No	7823	65,288	11.98	1 (reference)	1 (reference)
Yes	69	507	13.61	1.12 (0.88, 1.42)	0.75 (0.59, 0.96)*
ACEIs					
No	2644	26,589	9.94	1 (Reference)	1 (Reference)
Yes	5248	39,207	13.39	1.33 (1.27, 1.40)***	1.09 (1.04, 1.14)***
ARBs					
No	811	8405	9.65	1 (reference)	1 (reference)
Yes	7081	57,390	12.34	1.27 (1.18, 1.36)***	0.87 (0.81, 0.94)***
α-blockers					
No	3,997	40,408	9.89	1 (Reference)	1 (Reference)
Yes	3,895	25,387	15.34	1.52 (1.45, 1.59)***	1.04 (0.99, 1.10)
β-blockers					
No	4944	40,777	12.12	1 (reference)	1 (reference)
Yes	2948	25,019	11.78	0.97 (0.92, 1.01)	0.90 (0.86, 0.95)***
CCBs					
No	978	11,767	8.31	1 (reference)	1 (reference)
Yes	6914	54,028	12.80	1.52 (1.42, 1.62)***	1.08 (1.00, 1.16)*
Diuretics					
No	528	11,622	4.54	1 (reference)	1 (reference)
Yes	7364	54,173	13.59	2.92 (2.67, 3.19)***	2.22 (2.02, 2.43)***
Sacubitril/Valsartan					
No	7685	64,467	11.92	1 (reference)	1 (reference)
Yes	207	1328	15.58	1.15 (1.00, 1.33)*	1.08 (0.94, 1.25)
Statins					
No	1431	11,344	12.61	1 (reference)	1 (reference)
Yes	6461	54,451	11.87	0.94 (0.89, 1.00)*	0.84 (0.79, 0.89)***

IR, incidence rate; *HR*, hazard ratio; *CI*, confidence interval; *AF*, atrial fibrillation; *COPD*, chronic obstructive pulmonary disease; *AMI*, acute myocardial infarction; *NOACs*, novel oral anticoagulant drugs; *ACEIs*, angiotensin-converting enzyme inhibitors; *ARBs*, angiotensin II receptor blockers; *CCBs*, calcium channel blockers; *, p-value < 0.05; **, p-value < 0.01;***, p-value < 0.001

95% CI = 0.74, 0.94), CV death (adjusted HR = 0.47; 95% CI = 0.42, 0.51), and all-cause death (adjusted HR = 0.39; 95% CI = 0.37, 0.41), see Table 3. The cumulative incidence of adverse outcomes in SGLT2I users were lower than that of the SGLT2I non-users, see Fig. 1.

According to Table 4, patients who used SGLT2I for 1–447 days had a reduced risk of adverse outcomes (adjusted HR = 0.88, 95% CI = 0.84, 0.93), and SGLT2I users for more than 448 days had a lower risk of adverse outcomes (adjusted HR = 0.15, 95% CI = 0.14, 0.17) compared to SGLT2I non-users.

Table 3 Risks of different types of adverse outcomes associated with SGLT2Is in HF patients

Variable	Non-SGLT2is users			SGLT2is users			Crude HR (95% CI)	Adjusted HR (95% CI)
	Event	Person-years	IR (100 person-years)	Event	Person-years	IR (100 person-years)		
Adverse outcomes								
Acute myocardial infarction	543	30,758	1.77	527	35,037	1.50	0.86 (0.77, 0.97)*	0.83 (0.74, 0.94)**
Hemorrhagic stroke	121	30,758	0.39	113	35,037	0.32	0.83 (0.64, 1.07)	0.78 (0.61, 1.02)
Ischemic stroke	534	30,758	1.74	622	35,037	1.78	1.03 (0.92, 1.16)	0.99 (0.89, 1.12)
CV death	1189	30,758	3.87	646	35,037	1.84	0.49 (0.45, 0.54)***	0.47 (0.42, 0.51)***
All-cause death	3811	30,758	12.39	1727	35,037	4.93	0.41 (0.39, 0.43)***	0.39 (0.37, 0.41)***

IR, incidence rate; *HR*, hazard ratio; *CI*, confidence interval

*, p-value < 0.05; **, p-value < 0.01;***, p-value < 0.001

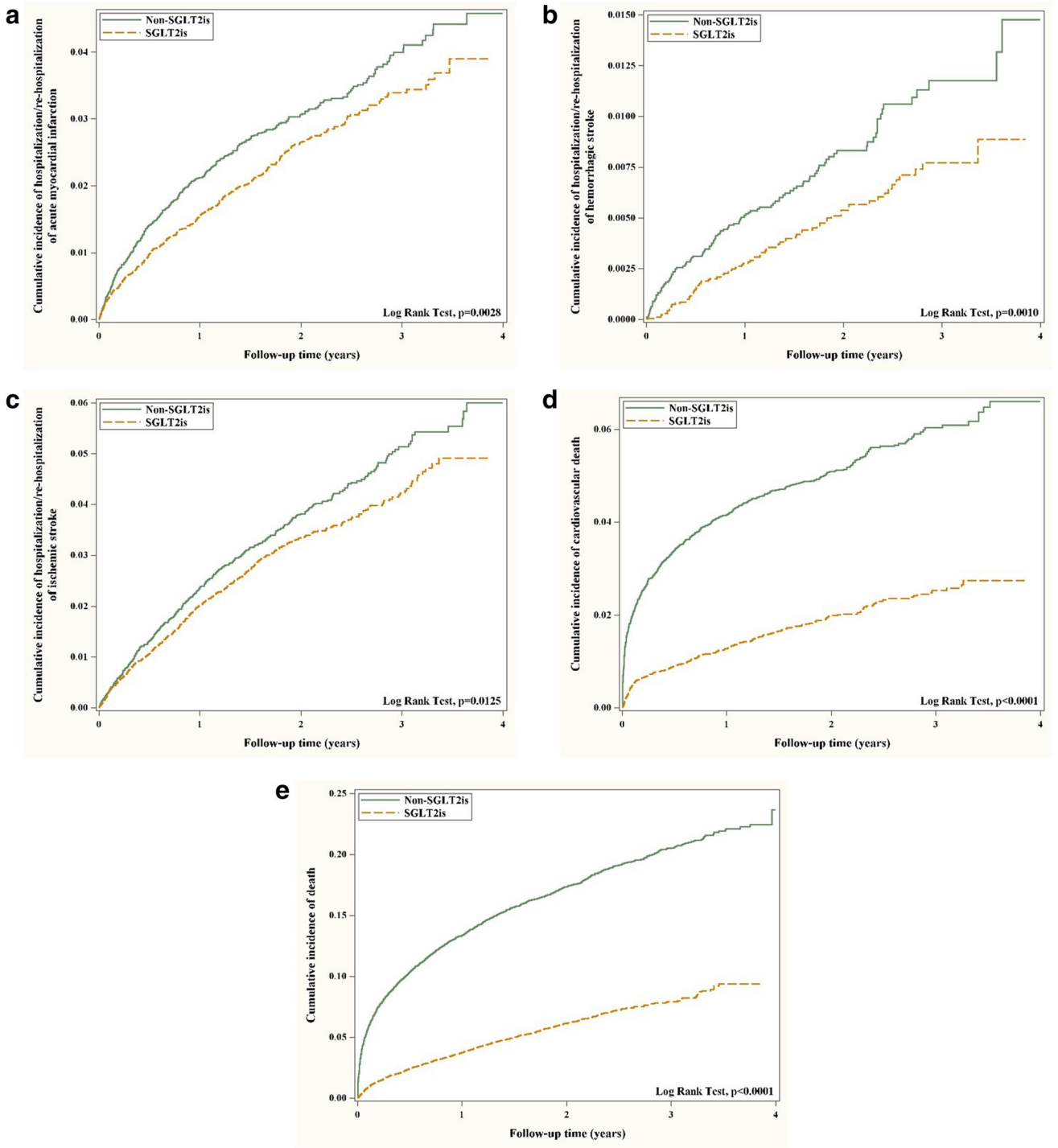

Fig. 1 The cumulative incidence curves of adverse outcomes in SGLT2Is users and non-users

Table 5 illustrates the relationship between SGLT2I and adverse outcomes stratified by AF and CHA2DS2-VASc score. When considering HF patients without AF and SGLT2I as the reference group, HF patients without AF but used SGLT2I reduce the risk of adverse outcomes to 0.48 (95% CI = 0.45, 0.50), and HF patients with AF and SGLT2I had the adjusted HR of 0.55 (95% CI = 0.50, 0.61). The adjusted HR of adverse outcomes for HF patients with CHA2DS2-VASc score less than 2 and SGLT2I without and with AF relative to HF patients without AF nor SGLT2I were 0.53 (95% CI = 0.41, 0.67) and 0.24 (95% CI = 0.12, 0.47), respectively. Compared to HF patients with no history of AF and SGLT2I, if patients

Table 4 Risk of adverse outcomes associated with different days' supply of SGLT2Is

Variable	Event $N=7892$	Person-years	IR 100 person-years	Crude HR (95% CI)	Adjusted HR (95% CI)
SGLT2is					
No	4956	30,758	16.11	1 (reference)	1 (reference)
1–447 days	2482	14,697	16.89	1.02 (0.97, 1.07)	0.88 (0.84, 0.93)***
> 448 days	454	20,340	2.23	0.15 (0.13, 0.16)***	0.15 (0.14, 0.17)***

IR, incidence rate; *HR*, hazard ratio; *CI*, confidence interval

*, p-value < 0.05; **, p-value < 0.01;***, p-value < 0.001

additionally with SGLT2I and CHA2DS2-VASc score ≥ 2, the risk of the adverse outcomes was reduced with adjusted HR of 0.48 (95% CI = 0.45, 0.50); if patients additionally with AF and CHA2DS2-VASc score ≥ 2, the risk of the adverse outcomes was diminished with adjusted HR of 0.88 (95% CI = 0.80, 0.97); if patients additionally with AF, SGLT2I, and CHA2DS2-VASc score ≥ 2, the risk of the adverse outcomes was decreased with adjusted HR of 0.52 (95% CI = 0.47, 0.58).

Discussion

In this study, the authors tried to evaluate the effect of SGLT2I on adverse events risk among patients with HF with/without AF. The authors reported that the use of SGLT2I in HF patients carried a lower risk for CV events, but not cerebrovascular events.

In this retrospective cohort study using the Taiwan NHIRD, HF patients were classified according to cormorbid AF or not stratified by a score of < 2 and ≥ 2. Even in patients with HF with AF, SGLT2I has been shown to improve the outcomes. In this study, the authors use CHA2DS2–VASc score as a surrogate marker for disease severity. The authors found that patients with a score ≥ 2 had a lower risk reduction rate of developing adverse outcomes if they were treated with SGLT2I. It seems that the risk reduction rate was attenuated in those with AF and especially in the score of ≥ 2.

There is sample data from randomized controlled trials on the value of SGLT2I in events protection (Packer et al. 2020; McMurray et al. 2019). Nonetheless, a properly conducted real-world study making a significant contribution is indeed important.

Observational big-data studies can be valuable resources for teasing out signals regarding rare or unexpected outcomes. SGLT2I is indicated in HF patients according to the current practice guidelines (Li et al. 2021; Heidenreich et al. 2022). This analysis of Taiwan's large health database is important as it confirms the protective effect of SGLT2I in HF patients. In addition, the sufficiencies in the study's methodology and statistical planning empowered the confidence in the stated conclusions.

Concerning the role of SGLT2I therapy in HF ± AF and stratified by CHA2DS2–VASc score, there is no significant

Table 5 Risk of adverse outcomes associated with SGLT2Is among HF patients stratified by AF

Variable	Event $N=7892$	Person-years	IR 100 person-years	Crude HR (95% CI)	Adjusted HR (95% CI)
AF/SGLT2is					
No/no	3,989	25,653	15.55	1 (reference)	1 (reference)
No/yes	2,183	28,960	7.54	0.50 (0.47, 0.52)***	0.48 (0.45, 0.50)***
CHA_2DS_2-VASc score					
< 2	79	1,661	4.75	0.31 (0.25, 0.39)***	0.53 (0.41, 0.67)***
2 +	2,104	27,298	7.71	0.51 (0.48, 0.54)***	0.48 (0.45, 0.50)***
Yes/no	967	5,105	18.94	1.20 (1.12, 1.29)***	0.92 (0.84, 1.00)
CHA_2DS_2-VASc score					
< 2	17	268	6.33	0.42 (0.26, 0.67)***	0.62 (0.38, 1.02)
2 +	950	4,837	19.64	1.23 (1.15, 1.32)***	0.88 (0.80, 0.97)*
Yes/yes	753	6,077	12.39	0.80 (0.74, 0.87)***	0.55 (0.50, 0.61)***
CHA_2DS_2-VASc score					
< 2	9	310	2.90	0.20 (0.10, 0.38)***	0.24 (0.12, 0.47)***
2 +	744	5,768	12.90	0.84 (0.77, 0.90)***	0.52 (0.47, 0.58)***

IR, incidence rate; *HR*, hazard ratio; *CI*, confidence interval; *AF*, atrial fibrillation

*, p-value < 0.05; **, p-value < 0.01;***, p-value < 0.001

data from randomized controlled trial or mendelian studies or prospective observational studies. Thus, using the Taiwan NHI database, the aim of the study might be powerful, full of interest for the scientific community, and also be important for everyday clinical practice, and SGLT2I-associated risk reduction phenomenon was reported. The reasons for the alleviated protective effect of SGLT2I in patients with the higher scores or AF might be due to the diluted effect resulting from multiple comorbid illnesses. Moreover, the protective effect of the medication can be achieved over enough time.

Taken together, it was understood that the study suggested that the onset of adverse events in HF patients could be prevented and that SGLT2I prescription might be involved, especially in cases with no AF and with lower scores. Our observation further emphasizes the important role of this drug in HF patients for adverse outcomes prevention and SGLT2I should be initiated in the HF population as early as possible so that the beneficial effect would not be attenuated.

Limitations

Despite its large population, this claimed database is severely limited in that no detailed laboratory information is available.

In addition, the lack of data regarding the disease duration and severity which might probably make an inconclusive result. Finally, the authors collected the study population simply by ICD-9/ICD-10 codes but not by left ventricular ejection fraction per se. Other echocardiografic parameters such as left atrium volume, akinesia, hypokinesia, and thickness of the interventricular septum were also unavailable. Moreover, there is not any mention about forms of AF. Furthermore, the events of death were also collected only by ICD codes which should be underestimated such as out-of-hospital events.

Conclusions

SGLT2I is beneficial in HF population, and the effect is greater for those with a CHA2DS2–VASc score of < 2 and with no AF.

Author contribution All authors contributed to the manuscript. All were involved in the design of the study, collected the data, performed statistical analysis, and wrote the manuscript, and all authors were involved in the final approval of the manuscript.

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Data availability Data are available upon reasonable request.

Declarations

Ethical approval This study was approved by the Institutional Review Board of China Medical University Hospital Research Ethics Committee (CMUH109-REC2-031(CR-2)).

Consent to participate Not required.

Consent for publication Not required.

Competing interests The authors declare no competing interests.

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