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ORIGINAL ARTICLE

Reduction in cardiovascular disease events in patients with type 2 diabetes mellitus treated with a sodium–glucose cotransporter 2 inhibitor versus a dipeptidyl peptidase-4 inhibitor: A real-world retrospective administrative database analysis in Japan

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ABSTRACT

Aims/Introduction: To evaluate the benefit of sodium–glucose cotransporter 2 inhibitors (SGLT2i) versus dipeptidyl peptidase-4 inhibitors (DPP4i) in reducing cardiovascular disease (CVD) events in patients with type 2 diabetes mellitus with and without a CVD history.

Materials and Methods: This retrospective cohort study used Japanese hospital administrative data from the Medical Data Vision database (January 2015 to April 2020). Patients with type 2 diabetes mellitus (n = 625,739) who were new users of an SGLT2i (n = 57,070; 9.1%) or DPP4i (n = 568,669; 90.9%) were included. Outcomes included hospitalization for heart failure (hHF), all-cause death (ACD) and the composite of hHF or ACD. Hazard ratios (HR) were calculated using the inverse probability weighting Cox proportional hazards model to compare CVD event risks between treatment groups.

Results: Compared with DPP4i, SGLT2i was associated with a significant reduction in hHF risk among patients without a CVD history (HR 0.507, 95% confidence interval 0.283–0.907), but not in the full cohort or those with a CVD history. SGLT2i was associated with a significant risk reduction of ACD (HR 0.592, 95% confidence interval 0.481–0.729) and the composite of hHF or ACD (HR 0.712, 95% confidence interval 0.613–0.826), compared with DPP4i in the full cohort; similar results were observed among patients with and without a CVD history.

Conclusions: In this real-world study, SGLT2i versus DPP4i was associated with a significant reduction in hHF, ACD and hHF or ACD events in patients with type 2 diabetes mellitus without a CVD history.

INTRODUCTION

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have been shown to reduce cardiovascular disease (CVD) events and mortality in patients with type 2 diabetes mellitus in several randomized controlled trials (RCT) among patients with high CVD risks[1–6]. In real-world observational studies, the preventive effects of SGLT2i on various CVD events have also been shown compared with other glucose-lowering drugs in patients with and without pre-existing or prior CVD[7–9]. Furthermore, in a population-based observational study in Korea of older patients with type 2 diabetes mellitus, SGLT2i was significantly associated with a reduced risk of CVD events versus dipeptidyl

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peptidase-4 inhibitors (DPP4i) in those with a CVD history and those aged <75 years, but not in those without a CVD history[10]. Conversely, in other observational studies, including an analysis of Japanese patients, a significant reduction in the risk of various cardiovascular events were observed with SGLT2i versus DPP4i only in those without current or prior cardiovascular and renal diseases[11–13]. Therefore, despite this emerging evidence, the cardioprotective benefits of SGLT2i in type 2 diabetes mellitus patients with and without CVD remain controversial.

In Japan, SGLT2i is currently only recommended for type 2 diabetes mellitus patients with heart failure (HF) or a high risk of HF[14], and treatment selection is dependent on the physician's decision[15]; DPP4i is the most commonly prescribed antidiabetic drug[16], although it has not shown cardioprotective benefits in type 2 diabetes mellitus[14]. Therefore, further studies examining the association between SGLT2i use and CVD events, evaluated by a different methodology in real-world Japanese type 2 diabetes mellitus patients, might provide better insights into the role of SGLT2i in type 2 diabetes mellitus treatment, which might then help physicians choose the appropriate drugs for their patients.

Using an inverse probability weighting (IPW) Cox proportional hazards model, we analyzed a real-world Japanese administrative database to evaluate the risk of various CVD events in type 2 diabetes mellitus patients who were new users of SGLT2i compared with DPP4i. We also compared the cardioprotective effects of SGLT2i versus DPP4i among patients with and without a CVD history.

MATERIALS AND METHODS

Data source

This was a retrospective cohort study using real-world data from the Medical Data Vision Co., Ltd. (MDV) database in Japan. The MDV database is an administrative database of acute care hospitals in Japan that use the Diagnosis Procedure Combination system.[17] Health insurance claims data in this database are de-identified and comprise patients' characteristics (e.g., age and sex) and disease information (e.g., diagnosis, medication and procedure). As of March 2020, the MDV database contained hospital claims of >30 million patients from 399 Diagnosis Procedure Combination hospitals. Institutional ethics approval and informed consent were not required, because de-identified data were used.

Study population

In Japan, DPP4i and SGLT2i were first approved for clinical use in 2009 and 2014, respectively[18,19]. The present study, carried out between 1 January 2015 and 30 April 2020 (Figure S1), included patients aged ≥20 years who were newly prescribed an SGLT2i or a DPP4i on or after 1 January 2015 (see Table S1 for drug codes). As the nature of the MDV database prevents us from directly identifying patients newly prescribed these drugs, a '1-year washout period' was set as a surrogate to define 'new users'. Patients were excluded from this study if they had any of the following: prescription records of an SGLT2i or a DPP4i, including in a fixed-dose combination, during the pre-index period, defined as between 1 year and 1 day before the index date; simultaneous prescription records of both SGLT2i and DPP4i, or a fixed-dose combination containing both SGLT2i and DPP4i, at the index date; diagnosis of type 1 diabetes (International Classification of Diseases, 10th revision [ICD-10] code E10.x) on or before the index date; diagnosis of gestational diabetes (ICD-10 code O24.x) during the pre-index period or on the index date; or a record of hospitalization for HF (hHF) on or within 60 days preceding the index date. hHF was defined as HF (ICD-10 code I50) diagnosed by a doctor that required hospitalization.

Outcome measures

The primary end-point was the first record of hHF after the index date; the incidence rate (IR) of hHF was compared between treatment groups in all type 2 diabetes mellitus patients and in those stratified by CVD history (with and without a CVD history). Secondary end-points were the first record of all-cause death (ACD; defined as any death that occurred in hospital), a composite of hHF or ACD, hospitalization for myocardial infarction (MI; ICD-10 codes containing I21) and hospitalization for stroke (ICD-10 codes containing I60-I64) after the index date. The IRs of these CVD events were compared between treatment groups, in the full cohort, and in patients with and without a CVD history. Patients were considered to have a CVD history if they had one or more of the following conditions and/or procedures: MI, HF, unstable angina, stroke, atrial fibrillation and/or peripheral artery occlusion, percutaneous coronary intervention, or coronary artery bypass graft (Table S2).

Statistical analysis

Patients' baseline characteristics – including age, sex, body mass index, Charlson Comorbidity Index, adapted Diabetes Complications Severity Index[20], comorbidities and concomitant medications, from the data available on the index date or during the pre-index period – were summarized by treatment group (SGLT2i or DPP4i) and by treatment groups stratified by the time of the hHF event from the index date (post-hoc stratification: <30 and ≥30 days). Codes for variables used to calculate the Charlson Comorbidity Index and adapted Diabetes Complications Severity Index are shown in Tables S3 and S4. Weighted patient characteristics were calculated using IPW, which was estimated using logistic regression. Standardized mean difference was used to assess the degree of balance between treatment groups; standardized mean difference >0.1 between treatment groups was generally considered as covariate imbalance. Categorical variables are presented using frequencies and percentages; continuous variables are presented using the mean (standard deviation [SD]) and median (interquartile

range; first quartile [Q1] and third quartile [Q3]). Missing data were imputed where required; for missing body mass index values, single imputation was applied by the mean in each stratum created by sex, age category and treatment group. Treatment persistence, defined as the time from index date to treatment discontinuation, was summarized using mean (SD) and median (Q1, Q3) and was estimated by having a grace period of 60 days. Therefore, patients were considered to have discontinued treatment when the period between the previous prescription date plus days' supply of the medication and the current prescription was >60 days, or if the patient switched to or added on the comparator drug. However, if this period was ≤60 days, patients were considered as continuing treatment. For both the primary and secondary end-points, the crude IR per 1,000 person-years for each CVD event of interest (hHF, ACD, a composite of hHF or ACD, MI and stroke) was calculated by dividing the number of CVD events occurring after the index date by the total duration from the index date to the end of follow-up, defined as the date when any of the following occurred: end of data period; first outcome event after the index date; or treatment discontinuation. The hazard ratios (HR) and 95% confidence intervals (CI) were calculated using an IPW Cox model to compare the risk of CVD events between treatment groups. Weighted Kaplan–Meier analyses were carried out using the estimated IPW at baseline to assess the time from treatment initiation to the occurrence of the CVD events. Patients were censored if they switched from an SGLT2i to a DPP4i or vice versa; analyses were carried out on data before censoring. Sensitivity analyses for crude IR and HR for hHF were carried out. A post-hoc subgroup analysis was carried out for HR for CVD events using the patient's age (<75 and ≥75 years). All analyses were performed for the full cohort and the CVD subcohorts using SAS Studio 3.8 (Basic Edition; SAS Institute, Cary, NC, USA).

RESULTS

Study population

The study included 625,739 patients with type 2 diabetes mellitus who met the eligibility criteria during the study period and had no records after death (Figure 1). Of these, 57,070 patients (9.1%) were newly treated with an SGLT2i, and 568,669 patients (90.9%) with a DPP4i. Among SGLT2i users, 23,015 patients (40.3%) had a CVD history, and 34,055 patients (59.7%) did not. Among DPP4i users, 237,923 patients (41.8%) had a CVD history, and 330,746 (58.2%) did not. After adjustment using IPW, the full cohort comprised 623,705 patients: 53,772 new users of an SGLT2i (with a CVD history: n = 21,651; without a CVD history: n = 33,159) and 569,933 new users of a DPP4i (with a CVD history: n = 238,574; without a CVD history: n = 330,996).

Patient demographic and baseline clinical characteristics

Weighted patient demographic and baseline clinical characteristics were generally similar between the SGLT2i and DPP4i groups in the full cohort and in the CVD subcohorts (Table 1). In the full cohort, the mean age of patients in the SGLT2i and

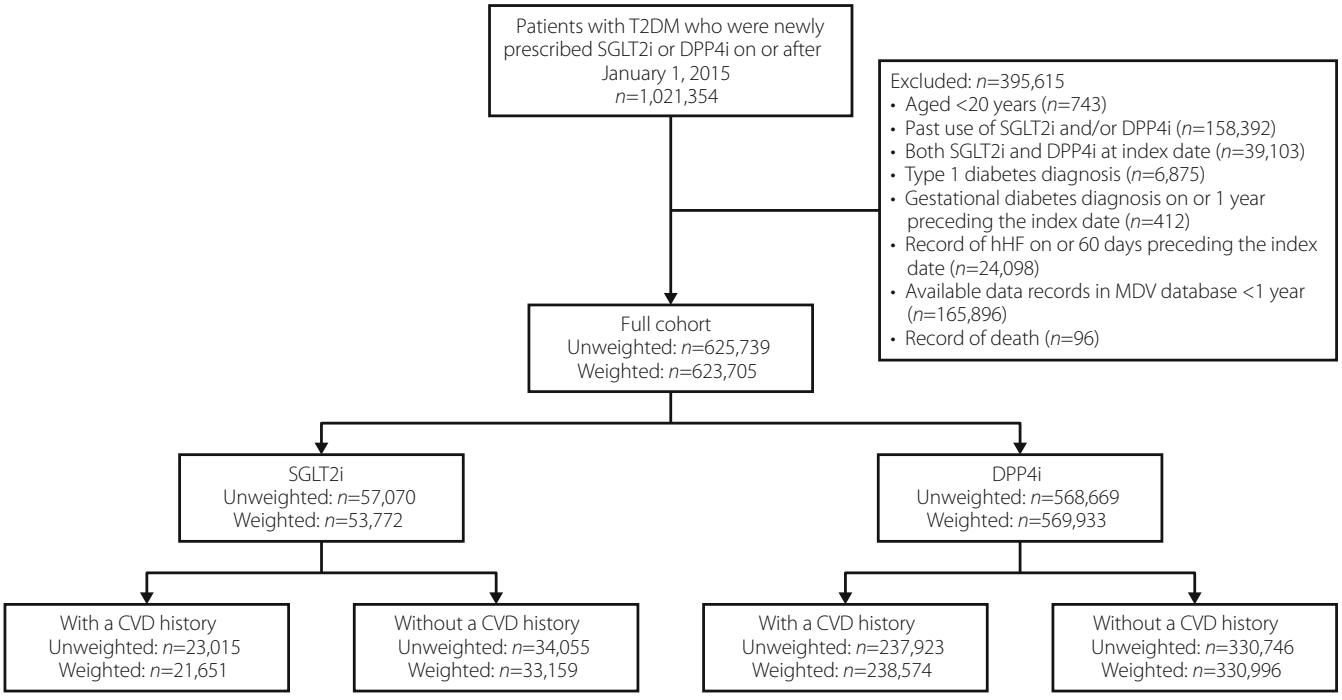

Figure 1 | Patient disposition. CVD, cardiovascular disease; DPP4i, dipeptidyl peptidase-4 inhibitor; hHF, hospitalization for heart failure; MDV, Medical Data Vision; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus.

Table 1 | Weighted patient demographics and baseline clinical characteristics[†]

Characteristic[‡]	Full cohort			With a CVD history			Without a CVD history		
	SGLT2i (*n* = 53,772)	DPP4i (*n* = 569,933)	SMD	SGLT2i (*n* = 21,651)	DPP4i (*n* = 238,574)	SMD	SGLT2i (*n* = 33,159)	DPP4i (*n* = 330,996)	SMD
Age (years)									
Median (Q1, Q3)	71 (62, 78)	72 (63, 80)	0.0580	73 (66, 80)	74 (67, 81)	0.0575	69 (60, 76)	70 (60, 78)	0.0568
Mean[§] (SD)	69.4 (12.4)	70.2 (13.0)		72.3 (11.1)	72.9 (11.4)		67.5 (12.6)	68.2 (13.6)	
Sex (male)	34,550 (64.3)	352,051 (61.8)	0.0514	14,499 (67.0)	156,066 (65.4)	0.0328	20,500 (61.8)	195,678 (59.1)	0.0554
Mean BMI, kg/m^2 (SD)	24.7 (3.6)	24.4 (3.9)	0.0879	24.4 (3.6)	24.1 (3.8)	0.0894	24.8 (3.7)	24.6 (4.0)	0.0655
HbA1c (%), *n*	4,442	48,734	–	1,930	21,228	–	2,571	27,462	–
Mean (SD)	8.0 (1.8)	7.7 (1.8)	0.1761	7.9 (1.6)	7.5 (1.5)	0.2917	8.2 (1.9)	7.9 (1.9)	0.1315
Mean CCI score (SD)	2.9 (2.0)	2.8 (2.0)	0.0122	3.5 (2.0)	3.5 (2.0)	0.0034	2.4 (1.8)	2.4 (1.8)	0.0038
Mean adapted DCSI score (SD)	1.4 (1.5)	1.3 (1.5)	0.0323	2.5 (1.3)	2.5 (1.4)	0.0087	0.5 (0.9)	0.5 (0.9)	0.0151
Smoking status, *n*	34,751	415,478	–	14,344	185,330	–	21,759	230,028	–
Smoker	16,901 (48.6)	187,209 (45.1)	0.0717	7,048 (49.1)	87,465 (47.2)	0.0388	10,386 (47.7)	99,547 (43.3)	0.0895
Comorbidities									
Chronic kidney disease	4,505 (8.4)	44,878 (7.9)	0.0184	2,632 (12.2)	28,074 (11.8)	0.0119	1,793 (5.4)	16,811 (5.1)	0.0147
Nephropathy	8,400 (15.6)	84,638 (14.9)	0.0215	4,187 (19.3)	44,071 (18.5)	0.0221	4,186 (12.6)	40,516 (12.2)	0.0116
Retinopathy	5,553 (10.3)	59,692 (10.5)	0.0048	2,126 (9.8)	23,304 (9.8)	0.0018	3,520 (10.6)	36,328 (11.0)	0.0116
Myocardial infarction	1,977 (3.7)	18,547 (3.3)	0.0231	1,781 (8.2)	18,377 (7.7)	0.0193	0	0	0
Stroke	6,633 (12.3)	67,022 (11.8)	0.0177	6,147 (28.4)	67,153 (28.1)	0.0054	0	0	0
Heart failure	9,241 (17.2)	91,116 (16.0)	0.0322	8,427 (38.9)	90,981 (38.1)	0.0162	0	0	0
Angina pectoris	9,143 (17.0)	92,078 (16.2)	0.0228	8,482 (39.2)	91,907 (38.5)	0.0134	0	0	0
Atrial fibrillation	4,349 (8.1)	44,035 (7.7)	0.0134	3,965 (18.3)	44,040 (18.5)	0.0038	0	0	0
Peripheral artery disease	648 (1.2)	7,233 (1.3)	0.0058	591 (2.7)	7,240 (3.0)	0.0183	0	0	0
Hypertension	28,248 (52.5)	303,667 (53.3)	0.0150	15,083 (69.7)	165,478 (69.4)	0.0066	13,012 (39.2)	138,084 (41.7)	0.0504
Dyslipidemia	21,717 (40.4)	232,223 (40.7)	0.0073	11,532 (53.3)	126,323 (52.9)	0.0063	9,929 (29.9)	105,694 (31.9)	0.0430
Procedures									
Coronary artery bypass graft	280 (0.5)	1,945 (0.3)	0.0274	257 (1.2)	1,942 (0.8)	0.0374	0	0	0
PCI	2,182 (4.1)	20,060 (3.5)	0.0282	1,955 (9.0)	19,907 (8.3)	0.0244	0	0	0
Carotid intervention	83 (0.2)	644 (0.1)	0.0113	77 (0.4)	627 (0.3)	0.0164	1 (0.0)	20 (0.0)	0.0034
Bariatric surgery	0	6 (0.0)	0.0014	0	1 (0.0)	0.0001	0	3 (0.0)	0.0008
Medications									
Biguanides	11,715 (21.8)	123,027 (21.6)	0.0049	3,942 (18.2)	40,447 (17.0)	0.0329	8,189 (24.7)	82,413 (24.9)	0.0047
Sulfonylurea	9,777 (18.2)	96,099 (16.9)	0.0348	3,958 (18.3)	39,431 (16.5)	0.0463	6,097 (18.4)	56,654 (17.1)	0.0333
GLP-1 receptor agonists	870 (1.6)	9,754 (1.7)	0.0073	348 (1.6)	4,023 (1.7)	0.0062	527 (1.6)	5,786 (1.7)	0.0125
Glinides	3,009 (5.6)	30,000 (5.3)	0.0147	1,322 (6.1)	12,840 (5.4)	0.0312	1,763 (5.3)	17,149 (5.2)	0.0061
Thiazolidinedione alone/with BG or SU	3,032 (5.6)	28,380 (5.0)	0.0294	1,162 (5.4)	11,275 (4.7)	0.0293	1,936 (5.8)	17,068 (5.2)	0.0300
Alpha-glucosidase inhibitor	6,488 (12.1)	65,577 (11.5)	0.0174	3,038 (14.0)	29,471 (12.4)	0.0497	3,675 (11.1)	36,089 (10.9)	0.0057
Insulins	18,178 (33.8)	190,820 (33.5)	0.0069	7,612 (35.2)	82,978 (34.8)	0.0079	11,105 (33.5)	107,868 (32.6)	0.0192
Lipid-lowering therapy	22,113 (41.1)	229,906 (40.3)	0.0160	11,228 (51.9)	120,877 (50.7)	0.0238	10,930 (33.0)	108,804 (32.9)	0.0019
Alpha-blocker	1,788 (3.3)	18,037 (3.2)	0.0090	876 (4.0)	9,975 (4.2)	0.0067	888 (2.7)	8,066 (2.4)	0.0153

Table 1. (*Continued*)

Characteristic‡	Full cohort			With a CVD history			Without a CVD history		
	SGLT2i (*n* = 53,772)	DPP4i (*n* = 569,933)	SMD	SGLT2i (*n* = 21,651)	DPP4i (*n* = 238,574)	SMD	SGLT2i (*n* = 33,159)	DPP4i (*n* = 330,996)	SMD
Beta-blocker	9,437 (17.5)	92,921 (16.3)	0.0332	6,566 (30.3)	70,619 (29.6)	0.0159	2,551 (7.7)	22,051 (6.7)	0.0399
Calcium channel blocker	18,525 (34.5)	193,392 (33.9)	0.0109	8,925 (41.2)	95,871 (40.2)	0.0211	9,812 (29.6)	97,445 (29.4)	0.0033
ACE inhibitors	3,365 (6.3)	34,639 (6.1)	0.0075	2,236 (10.3)	24,323 (10.2)	0.0044	1,030 (3.1)	10,170 (3.1)	0.0019
ARBs	13,021 (24.2)	140,743 (24.7)	0.0112	6,277 (29.0)	69,619 (29.2)	0.0042	6,942 (20.9)	71,138 (21.5)	0.0136
ARBs with CCB	2,636 (4.9)	26,123 (4.6)	0.0150	1,064 (4.9)	11,318 (4.7)	0.0080	1,625 (4.9)	14,779 (4.5)	0.0206
ARBs with diuretics	1,027 (1.9)	10,232 (1.8)	0.0086	438 (2.0)	4,743 (2.0)	0.0024	601 (1.8)	5,493 (1.7)	0.0117
Diuretics	9,848 (18.3)	95,946 (16.8)	0.0389	5,928 (27.4)	63,498 (26.6)	0.0172	3,837 (11.6)	32,364 (9.8)	0.0581
Aldosterone antagonists	3,023 (5.6)	29,041 (5.1)	0.0234	1,971 (9.1)	20,655 (8.7)	0.0156	1,020 (3.1)	8,345 (2.5)	0.0336

‡Data were derived from data available on the index date or on the date closest to the index date during the pre-index period. Index date was defined as the date of the first recorded receipt of an sodium–glucose cotransporter 2 inhibitor (SGLT2i) or a dipeptidyl peptidase-4 inhibitor (DPP4i). Pre-index period was defined as the period between 1 year and 1 day before the index date. †Data are *n* (%) unless otherwise indicated. §Mean age >100 years was rounded to 100 years. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BG, biguanide; BMI, body mass index; CCB, calcium channel blockers; CCI, Charlson Comorbidity Index; CVD, cardiovascular disease; DCSI, Diabetes Complications Severity Index; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; PCI, percutaneous coronary intervention; Q, quartile; SD, standard deviation; SMD, standardized mean difference; SU, sulfonylurea.

DPP4i groups was 69.4 years (SD 12.4 years) and 70.2 years (SD 13.0 years), respectively; >60% of patients were men. Hemoglobin A1c levels were higher in the SGLT2i group versus the DPP4i group in the full cohort and in the CVD subcohorts. However, hemoglobin A1c was not used to estimate IPW, because patients' baseline hemoglobin A1c records were limited. The most common index SGLT2i and DPP4i drugs were empagliflozin (32.3%) and sitagliptin (38.2%), respectively (Table S5).

Treatment persistence

The mean time from the index date to discontinuation was generally similar or slightly longer with SGLT2i-treated patients versus DPP4i-treated patients in the full cohort and both CVD subcohorts (Table S6).

Crude IR of CVD events of interest

In the full cohort, SGLT2i-treated patients had a lower crude IR of hHF versus DPP4i-treated patients (SGLT2i: 10.97 per 1,000 person-years; DPP4i: 15.26 per 1,000 person-years; Table 2). Similarly, the crude IR of hHF was numerically lower in SGLT2i-treated patients than DPP4i-treated patients among those without a CVD history (1.42 vs 5.18 per 1,000 person-years), but was similar among those with a CVD history (26.21 vs 28.72 per 1,000 person-years). Furthermore, the crude IR of ACD, the composite of hHF or ACD and hospitalization for stroke were also lower in SGLT2i-treated patients versus DPP4i-treated patients in the full cohort and both CVD subcohorts. However, the crude IR of hospitalization for MI was lower in SGLT2i-treated patients versus DPP4i-treated patients only among patients without a CVD history; similar crude IRs between treatment groups were observed in the full cohort and both CVD subcohorts.

Reduction in the risk of hHF

The IPW Cox model showed that there was a significant reduction in the risk of hHF in SGLT2i-treated patients versus DPP4i-treated patients among patients without a CVD history (HR 0.507, 95% CI 0.283–0.907), but not in the full cohort (HR 0.936, 95% CI 0.765–1.146) or among patients with a CVD history (HR 0.978, 95% CI 0.707–1.353; Figure 2). Consistent results were observed in the three sensitivity analyses of IPW HR for hHF in the full cohort and both CVD subcohorts (Table S7).

In Kaplan–Meier analyses, the weighted cumulative rate of hHF appeared higher in the SGLT2i-treated patients versus the DPP4i-treated patients, up to approximately 60 days after treatment initiation, for the full cohort and among patients with a CVD history (Figure 3a,b; Tables S8 and S9). Among patients without a CVD history, the weighted cumulative rate of hHF tended to be lower in SGLT2i-treated patients than in DPP4i-treated patients at almost all time points from 90 days after treatment initiation (Figure 3c; Table S10).

Table 2 | Crude incidence rates of cardiovascular disease events of interest

	Full cohort		With a CVD history		Without a CVD history	
	SGLT2i (*n* = 57,070)	DPP4i (*n* = 568,669)	SGLT2i (*n* = 23,015)	DPP4i (*n* = 237,923)	SGLT2i (*n* = 34,055)	DPP4i (*n* = 330,746)
hHF (Primary analysis)						
Events, *n*	390	4,708	359	3,795	31	913
Person-years	35,557.4	308,481.8	13,698.6	132,143.6	21,858.8	176,338.2
Incidence rate† (95% CI)	10.97 (9.91–12.11)	15.26 (14.83–15.70)	26.21 (23.57–29.06)	28.72 (27.81–29.65)	1.42 (0.96–2.01)	5.18 (4.85–5.52)
hHF (sensitivity analysis)‡						
Events, *n*	359	4,125	329	3,345	30	780
Person-years	33,231.4	285,361.8	12,946.2	122,692.7	20,285.2	162,669.1
Incidence rate† (95% CI)	10.80 (9.71–11.98)	14.46 (14.02–14.90)	25.41 (22.74–28.31)	27.26 (26.35–28.20)	1.48 (1.00–2.11)	4.80 (4.46–5.14)
ACD						
Events, *n*	260	10,486	162	5,300	98	5,186
Person-years	35,777.2	312,419.8	13,891.5	135,121.2	21,885.7	177,298.6
Incidence rate† (95% CI)	7.27 (6.41–8.21)	33.56 (32.92–34.21)	11.66 (9.94–13.60)	39.22 (38.18–40.29)	4.48 (3.64–5.46)	29.25 (28.46–30.06)
hHF or ACD						
Events, *n*	631	14,651	503	8,649	128	6,002
Person-years	35,580.1	309,104.0	13,708.8	132,431.5	21,871.3	176,672.6
Incidence rate† (95% CI)	17.73 (16.38–19.17)	47.40 (46.63–48.17)	36.69 (33.55–40.04)	65.31 (63.94–66.70)	5.85 (4.88–6.96)	33.97 (33.12–34.84)
Hospitalization for MI						
Events, *n*	69	733	52	476	17	257
Person-years	35,747.8	311,902.6	13,871.4	134,770.9	21,876.4	177,131.7
Incidence rate† (95% CI)	1.93 (1.50–2.44)	2.35 (2.18–2.53)	3.75 (2.80–4.92)	3.53 (3.22–3.86)	0.78 (0.45–1.24)	1.45 (1.28–1.64)
Hospitalization for stroke						
Events, *n*	173	3,672	117	2,689	56	983
Person-years	35,714.9	310,206.9	13,846.2	133,530.8	21,868.6	176,676.2
Incidence rate† (95% CI)	4.84 (4.15–5.62)	11.84 (11.46–12.23)	8.45 (6.99–10.13)	20.14 (19.38–20.91)	2.56 (1.93–3.33)	5.56 (5.22–5.92)

†Incidence rate was the number of events per 1,000 person-years. ‡Sensitivity analysis using a grace period of 30 days. ACD, all-cause death; CI, confidence interval; CVD, cardiovascular disease; DPP4i, dipeptidyl peptidase-4 inhibitor; hHF, hospitalization for heart failure; MI, myocardial infarction; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

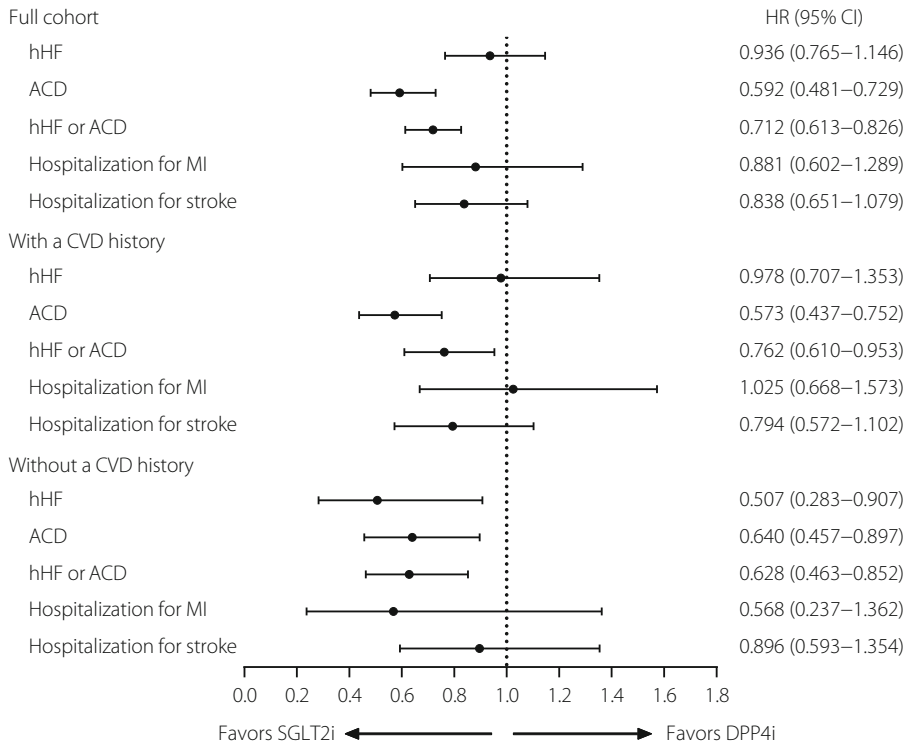

Figure 2 | Forest plot of the risk of hospitalization for heart failure (hHF), all-cause death (ACD), a composite of hHF or ACD, hospitalization for myocardial infarction (MI) and hospitalization for stroke, in the full cohort and in patients with and without a cardiovascular disease (CVD) history. CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitor; HR, hazard ratio; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

For patients with a CVD history and a hHF event <30 days from the index date, the presence of hypoglycemia was higher in SGLT2i-treated patients (37.8%; 54/143) versus DPP4i-treated patients (1.2%; 8/642; Table S11). Similarly, the mean age of SGLT2i-treated patients with hypoglycemia was higher than those treated with DPP4i (84.7 vs 78.6 years), and a greater proportion of patients had an index year of 2015 (97.5% vs 24.1%). SGLT2i-treated patients also had a higher prevalence of comorbid chronic kidney disease, nephropathy and dyslipidemia and used multiple antidiabetic drugs, including insulins, than DPP4i-treated patients. Conversely, hypoglycemia was present in just 3.2% of SGLT2i-treated patients with a CVD history and a hHF event ≥30 days from the index date, which was similar to DPP4i-treated patients (1.9%; Table S12).

Reduction in the risk of ACD

The risk of ACD was significantly reduced in SGLT2i-treated patients versus DPP4i-treated patients in the full cohort (HR 0.592, 95% CI 0.481–0.729), both with (HR 0.573, 95% CI 0.437–0.752) and without (HR 0.640, 95% CI 0.457–0.897) a CVD history (Figure 2). The weighted cumulative rate of ACD was lower in SGLT2i-treated patients versus DPP4i-treated patients at all time points after treatment initiation in the full cohort and both CVD subcohorts (Figure 4, Tables S8–S10).

Reduction in the risk of the composite of hHF or ACD

A significant reduction in the risk of the composite of hHF or ACD was observed in SGLT2i-treated patients versus DPP4i-treated patients in the full cohort and both CVD subcohorts (Figure 2). The weighted cumulative rate of the composite of hHF or ACD was also lower in SGLT2i-treated patients versus DPP4i-treated patients at almost all time points after treatment initiation in the full cohort and both CVD subcohorts (Figure 5; Tables S8–S10).

Reduction in the risk of hospitalization for MI or stroke

No significant reduction in the risk of hospitalization for MI or stroke in SGLT2i-treated patients versus DPP4i-treated patients was observed in the full cohort and both CVD subcohorts (Figure 2). Cumulative rates of hospitalization for MI or stroke were similar between both treatment groups at all time points after treatment initiation in the full cohort and both CVD subcohorts (Tables S8–S10).

Subgroup analysis

In the full cohort and among patients with a CVD history, the risk of all CVD events, except for hospitalization for MI, was significantly reduced with SGLT2i versus DPP4i in patients aged <75 years, but not in those aged ≥75 years (Figure 6).

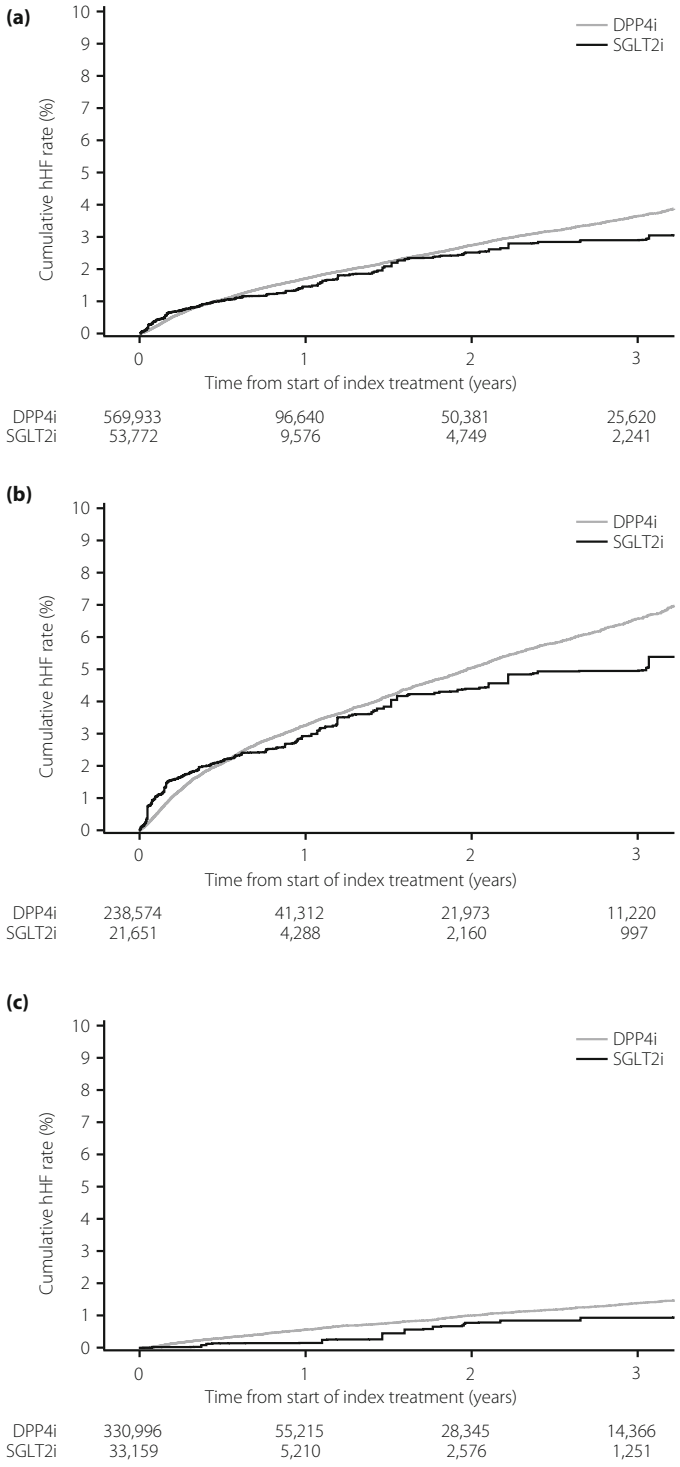

Figure 3 | Kaplan–Meier curve of cumulative rate of hospitalization for heart failure (hHF) in (a) the full cohort, (b) patients with a cardiovascular disease (CVD) history and (c) patients without a CVD history. The weighted cumulative hHF rate in sodium–glucose cotransporter 2 inhibitor (SGLT2i)-treated patients was higher than that in dipeptidyl peptidase-4 inhibitor (DPP4i)-treated patients 30–60 days after the index date, in the full cohort and in patients with a CVD history; the cumulative hHF rate tended to be lower in SGLT2i-treated patients than in DPP4i-treated patients after 1 year from the index date. In contrast, among patients without a CVD history, the cumulative hHF rate in SGLT2i-treated patients was lower at almost all time points from 90 days after the index date than in DPP4i-treated patients.

Among patients without a CVD history, the risk of ACD and the composite of hHF or ACD were significantly reduced with SGLT2i versus DPP4i only in patients aged <75 years. However, the risk of hospitalization for MI or stroke was significantly reduced with SGLT2i only in patients aged ≥75 years.

DISCUSSION

The present large retrospective cohort study based on hospital administrative data investigated the risk of developing CVD events in >600,000 patients with type 2 diabetes mellitus newly treated with either an SGLT2i or a DPP4i, using IPW Cox models. In this study, the risk of hHF, ACD and the composite of hHF or ACD were significantly reduced with SGLT2i versus DPP4i among patients without a CVD history. Compared with DPP4i, SGLT2i was also associated with a significant reduction in the risk of ACD and the composite of hHF or ACD, but not hHF, in the full cohort and among those with a CVD history. These results suggest that early treatment with SGLT2i might help prevent the development of hHF and ACD in type 2 diabetes mellitus patients who have no CVD history. Furthermore, these findings highlight the benefit of SGLT2i and support the use of this drug class in Japanese patients with type 2 diabetes mellitus.

To date, the beneficial effects of SGLT2i for the prevention of hHF in type 2 diabetes mellitus are controversial. Four RCTs have shown the benefits of SGLT2i in reducing the incidence of hHF versus placebo in type 2 diabetes mellitus patients with high CVD risk[1–6]; relatively similar percentage reductions in hHF events were observed across these studies[21]. Similarly, two observational studies (CVD-REAL, CVD-REAL 2) showed a significantly lower risk of hHF in type 2 diabetes mellitus patients treated with SGLT2i versus other glucose-lowering drugs, regardless of patients' pre-existing CVD[7–9]. In the present study, SGLT2i significantly reduced the risk of hHF by almost 50% in patients without a CVD history, which was consistent with the results from a large multinational observational study of SGLT2i use in type 2 diabetes mellitus patients without cardiovascular and renal diseases[12]. These results also reflect those from a recent observational study reporting that left ventricular function was significantly improved in the empagliflozin group versus the control group, particularly in early versus advanced diabetes-related cardiomyopathy[22]. Furthermore, in the present study, SGLT2i was associated with a significantly reduced risk of hHF in type 2 diabetes mellitus patients aged <75 years, but not in those aged ≥75 years, suggesting that the beneficial effects of SGLT2i might be age-dependent in the type 2 diabetes mellitus population[10]. Therefore, although the effect of SGLT2i in preventing hHF is potentially affected by other factors – including age, CVD severity, the presence of micro- and macrovascular complications, and ethnicity – which in addition to the stricter eligibility criteria of RCTs might also explain the differences observed between the RCTs and observational studies, findings from the present study showed that early treatment with SGLT2i might be beneficial in reducing hHF risk in patients without a CVD history.

In the present study, the cumulative IR of hHF was higher with SGLT2i than DPP4i in the early phases of treatment in the full cohort and among patients with a CVD history. These results could be partly explained by the fact that SGLT2i-treated patients with a CVD history and a hHF event very soon after treatment initiation had baseline characteristics indicative of higher risks of hHF versus DPP4i-treated patients. Compared with the DPP4i-treated patients, these SGLT2i-treated patients were older and had a higher prevalence of hypoglycemia, because they were treated with multiple antidiabetic drugs with or without insulins. The prevalence of comorbidities, including chronic kidney disease and nephropathy, was also higher in these SGLT2i-treated patients than DPP4i-treated patients, and almost all had started their treatment in 2015, which was relatively soon after SGLT2i was first launched in Japan. Furthermore, given that results from the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study were published in 2015[1], physicians at that time possibly would have preferred to prescribe SGLT2i to patients with a higher severity of diabetes and CVD. Nevertheless, a lower cumulative hHF event rate was observed in the later phase, suggesting that long-term use of SGLT2i might show greater benefits in reducing hHF risk regardless of patients' CVD history.

Similar to previous studies, SGLT2i initiation was associated with a significant reduction in the risk of ACD, and the composite of hHF or ACD, compared with DPP4i initiation among patients without a CVD history[12,13,23]. In the present study, the cumulative rates of ACD and the composite of hHF or ACD were also lower at all time points after treatment initiation. In Japan, prescription of SGLT2i remains low compared with DPP4i[16,24]. There is no specific treatment regimen for type 2 diabetes mellitus in the current Japanese diabetes treatment guideline, and drug selection is by the treating physician taking into consideration the drugs' pharmacological and safety profiles and patients' age and disease condition[15]. In fact, SGLT2i is recommended over other antidiabetic drugs only in patients with atherosclerotic CVD or high/very high CV risk in the European guideline[25], and in patients with HF or a high risk of HF in the Japanese consensus statement[14]. Therefore, the results from this current study highlighted that SGLT2i might also be recommended for a broader patient population. Furthermore, SGLT2i is a potential first-line treatment for type 2 diabetes mellitus in Japan to prevent hHF, ACD and the composite of hHF or ACD, even in patients without a CVD history.

In the present study, SGLT2i was not associated with a significant reduction in the risk of hospitalization for MI or stroke versus DPP4i in the full cohort and both CVD subcohorts. These results were similar to those from previous observational studies[11,12]. However, conflicting results were observed in the subanalysis of the Comparative Effectiveness of Cardiovascular

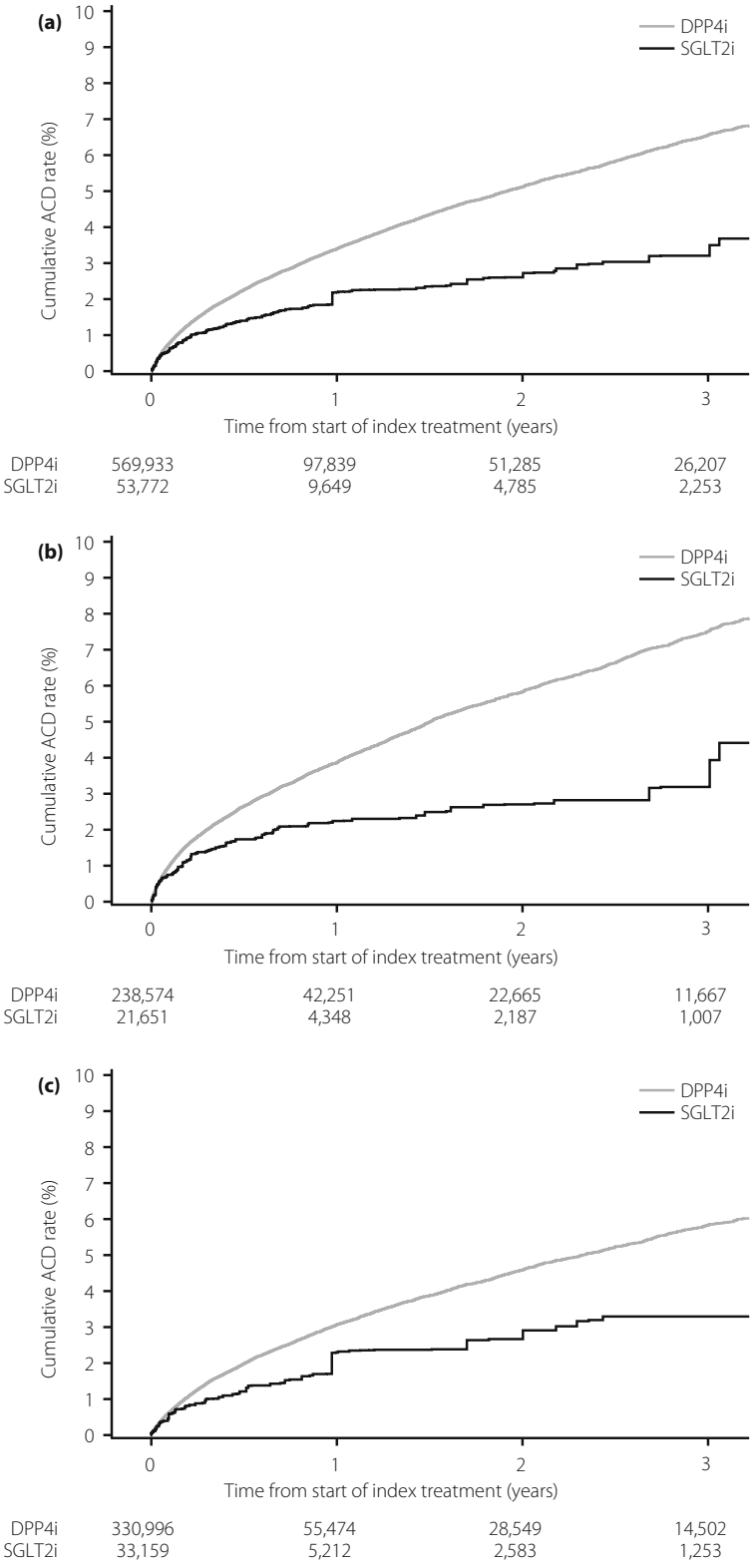

Figure 4 | Kaplan–Meier curve of cumulative rate of all-cause death (ACD) in (a) the full cohort, (b) patients with a cardiovascular disease (CVD) history, and (c) patients without a CVD history. The weighted cumulative rate of ACD was lower in sodium–glucose cotransporter 2 (SGLT2i)-treated patients compared with dipeptidyl peptidase-4 inhibitor (DPP4i)-treated patients at all time points after initiation of the respective drugs in the full cohort and both CVD subcohorts.

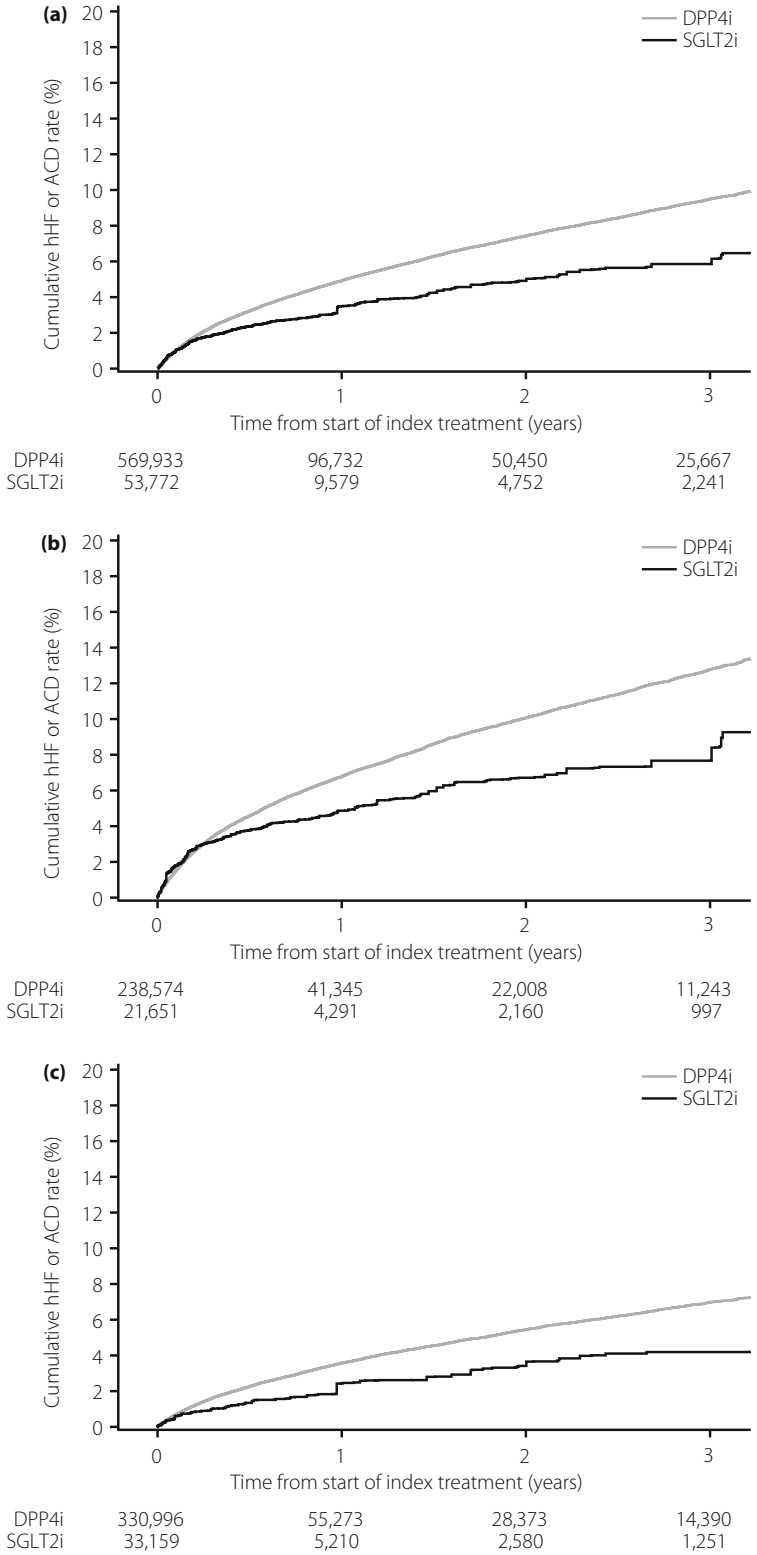

Figure 5 | Kaplan–Meier curve of cumulative rate of the composite of hospitalization for heart failure (hHF) or all-cause death (ACD) in (a) the full cohort, (b) patients with a cardiovascular disease (CVD) history and (c) patients without a CVD history. The weighted cumulative rate of the composite of hHF or ACD was lower in sodium–glucose cotransporter 2 inhibitor (SGLT2i)-treated patients compared with dipeptidyl peptidase-4 inhibitor (DPP4i)-treated patients at almost all time points after initiation of the respective drugs in the full cohort and both CVD subcohorts.

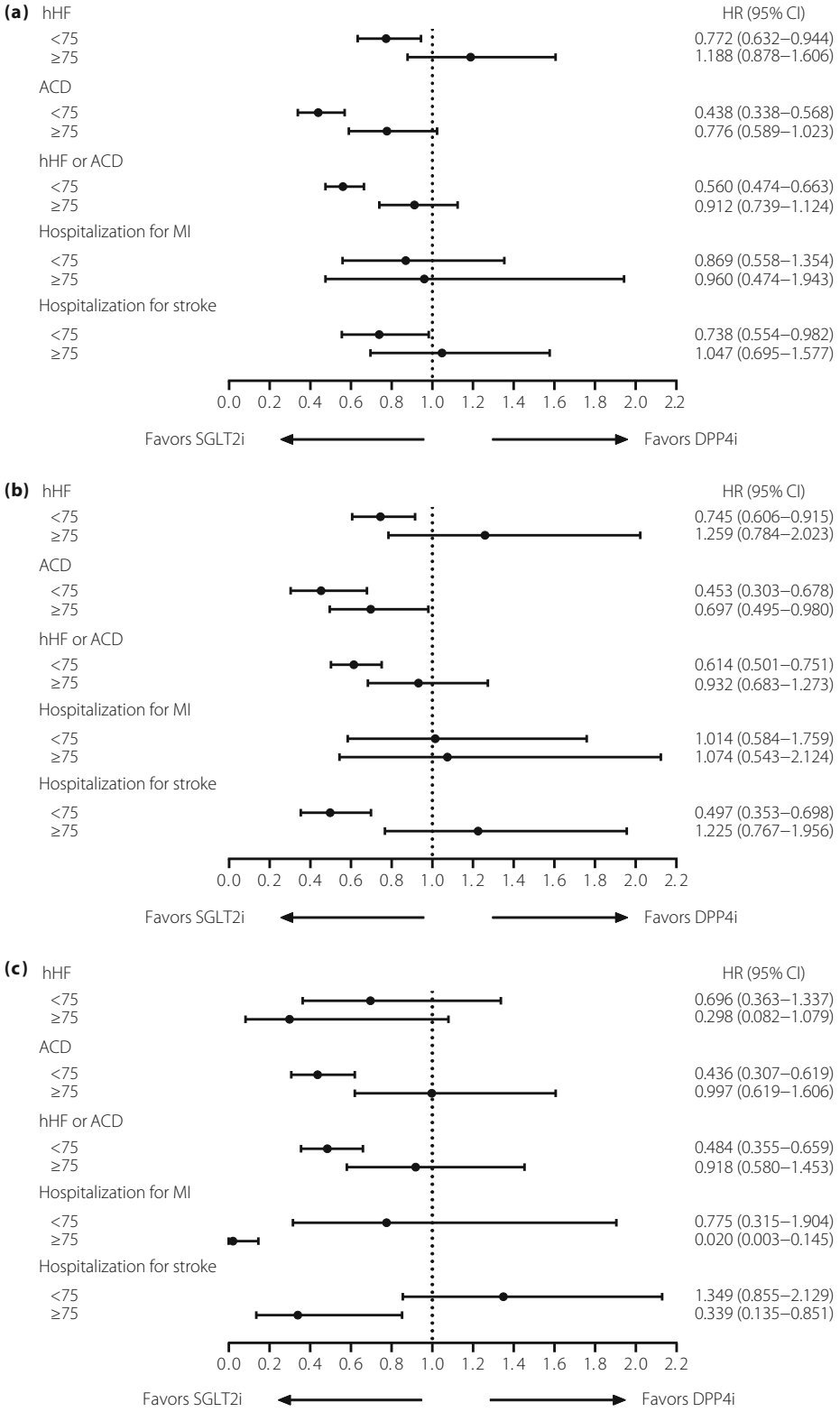

Figure 6 | Subgroup analysis (<75 years; ≥75 years). Forest plot of the risk of hospitalization for heart failure (hHF), all-cause death (ACD), hHF or ACD, hospitalization for myocardial infarction (MI), and hospitalization for stroke in (a) the full cohort, (b) patients with a cardiovascular disease (CVD) history and (c) patients without a CVD history. CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitor; HR, hazard ratio; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Outcomes in New Users of Sodium–Glucose Cotransporter-2 Inhibitors (CVD-REAL 2) study, which showed that SGLT2i significantly reduced the risks of MI and stroke versus DPP4i[23]. Furthermore, a Korean retrospective cohort study of older type 2 diabetes mellitus patients, and a recent Japanese cohort study of type 2 diabetes mellitus patients without established CVD and renal diseases showed that SGLT2i was associated with a significantly reduced risk of stroke, but not MI, versus DPP4i[10,13]. In the present study, the risk of hospitalization for stroke was significantly reduced in patients aged <75 years treated with SGLT2i versus DPP4i, in the full cohort and among patients with a CVD history, but hospitalization for both MI or stroke was significantly reduced with SGLT2i versus DPP4i in patients aged ≥75 years without a CVD history. Therefore, the benefits of SGLT2i on these CVD events might also be affected by patient characteristics, including age and comorbidities.

The strengths of the present study included the statistical methods; IPW was used to estimate treatment effect in patients with type 2 diabetes mellitus from the MDV database, and the treatment effects of SGLT2i and DPP4i were compared using the real-world characteristics of patients newly treated with either SGLT2i or DPP4i. This study included 57,070 and 568,669 new users of SGLT2i and DPP4i, respectively. Patients' mean ages were higher than those in previous studies[12,13,23], which appears to better reflect the true age of the Japanese type 2 diabetes mellitus population. Therefore, the IPW approach might have given more generalizability of the study results than previous studies that generally used propensity score matching. Additionally, previous studies should have addressed the 'immortal time bias'[26]; in the present study, because the new-user design was selected, we were not required to address this bias.

The limitations of the present study included the administrative database. We were unable to account for any unknown confounding factors that potentially guided therapy selection and outcomes. As important clinical and disease information, including the severity of patients' underlying CVD history, was not available from the MDV database, this study was also unable to evaluate how CVD severity might have impacted outcomes. The database also does not track patients if they change hospitals; therefore, patients might have been counted and recorded multiple times. Furthermore, deaths that occurred outside of hospitals were not recorded. Nevertheless, as most deaths in Japan occur in hospitals[27], the impact of this limitation is assumed to be small.

In conclusion, the present study further confirmed that SGLT2i is associated with a significant reduction in CVD events in a broader type 2 diabetes mellitus population in Japan, particularly in those without a history of CVD. Findings suggest that early initiation of SGLT2i might provide cardioprotective effects in patients without a CVD history. Collectively, SGLT2i should not be excluded as a first-line treatment option for improved and integrated management of both type 2 diabetes mellitus control and CVD prevention, especially hHF and ACD, in patients with type 2 diabetes mellitus.

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DISCLOSURE

AK has received funding as an advisor for Sunstar group. SS, SO, YK, and YI are employees of Astellas Pharma Inc. MW is a former employee of Astellas Pharma Inc. MW has changed affiliation since the completion of the study; her current affiliation is as follows: Director, Health Economics and Outcomes Research, Medical Affairs, Alexion Pharma GK Alexion-AstraZeneca Rare Disease, AstraZeneca.

Approval of the research protocol: The Medical Affairs Japan Protocol Review Committee reviewed and approved the study protocol prior to study initiation.

Informed consent: N/A.

Approval date of registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

DATA AVAILABILITY STATEMENT

Researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Study design. The pre-index period, defined as the period between 1 year and 1 day before the index date, and the index date were used to confirm that an sodium–glucose cotransporter 2 inhibitor (SGLT2i) or a dipeptidyl peptidase-4 inhibitor (DPP4i) was not previously prescribed and to establish patients' baseline characteristics.

Table S1 | Treatment category: sodium–glucose cotransporter 2 or dipeptidyl peptidase-4 inhibitor codes.

Table S2 | Cardiovascular disease history: variables and codes.

Table S3 | Charlson Comorbidity Index diagnostic codes.

Table S4 | Adapted Diabetes Complications Severity Index codes[†].

Table S5 | Unweighted index treatment.

Table S6 | Treatment persistence.

Table S7 | Sensitivity analysis: hospitalization for heart failure inverse probability weighting hazard ratios.

Table S8 | Weighted Kaplan–Meier estimate of cumulative rates of cardiovascular disease events of interest over time in the full cohort.

Table S9 | Weighted Kaplan–Meier estimate of cumulative rates of cardiovascular disease events of interest over time in patients with a cardiovascular disease history.

Table S10 | Weighted Kaplan–Meier estimate of cumulative rates of cardiovascular disease events of interest over time in patients without a cardiovascular disease history.

Table S11 | Weighted patient demographics and baseline clinical characteristics in patients with a cardiovascular disease history who had a hospitalization for heart failure event <30 days from treatment initiation.

Table S12 | Weighted patient demographics and baseline clinical characteristics in patients with a cardiovascular disease history who had a hospitalization for heart failure event ≥30 days from treatment initiation.