Sodium–glucose cotransporter 2 inhibitors compared with other glucose-lowering drugs in Japan: Subanalyses of the CVD-REAL 2 Study

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ABSTRACT

There are limited data on cardiovascular efficacy and safety of type 2 diabetes therapies in Japan, where treatments are characterized by lower metformin use and higher dipeptidyl peptidase-4 inhibitor (DPP4i) use versus other countries. We investigated the cardiovascular outcomes in Japanese patients with type 2 diabetes initiating sodium–glucose cotransporter 2 inhibitors (SGLT2i) matched 1:1 to patients initiating other glucose-lowering drugs (33,890 patients/group) or DPP4i (9,876 patients/group). SGLT2i initiation was associated with lower risks (hazard ratio of in-hospital death [death] 0.56, 95% confidence interval [CI] 0.47–0.67; hospitalization for heart failure 0.75, 95% CI 0.64–0.89; composite of hospitalization for heart failure or death 0.65, 95% CI 0.58–0.74 and stroke 0.66, 95% CI 0.52–0.84 versus other glucose-lowering drugs and lower risks of death 0.52, 95% CI 0.36–0.73) and composite of hospitalization for heart failure or death (0.65, 95% CI 0.51–0.83) versus DPP4i. In conclusion, SGLT2i initiators had lower risks of cardiovascular events versus other glucose-lowering drug initiators and, uniquely, versus DPP4i initiators in Japanese real-world practice.

INTRODUCTION

The incidences of heart failure (HF) and other cardiovascular diseases (CVD) are increasing in Japan[1], partly due to aging of the Japanese population and increasing incidence of type 2 diabetes[2]. Several large-scale international trials have investigated cardiovascular (CV) safety in patients treated with sodium–glucose cotransporter 2 inhibitors (SGLT2i)[3–5], which showed CV benefits in both prior CVD-dominant[3,4] and non-prior CVD-dominant populations[5]. However, few patients of Asian ethnicity were enrolled in these trials (12.7–21.6%). Therefore, there is limited insight into the CV safety of SGLT2i in Japan.

Data from Western studies cannot always be generalized to Japanese settings because of differences in patient characteristics, prescribing practices and management of diabetes[6,7]. Furthermore, Japanese clinical practice guidelines allow physicians to choose the first-line therapy based on their judgement[8]. Consequently, Japanese clinicians often favor dipeptidyl peptidase-4 inhibitors (DPP4i) and prescribe metformin to ~50% of patients[9,10]. Therefore, it is important to examine whether SGLT2i can benefit Japanese patients with type 2 diabetes in real-world settings by comparing the CV safety, including the impact of prior CVD, of SGLT2i against other glucose-lowering drugs (oGLD) and against DPP4i, separately.

The Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors (CVD-REAL 2) Study examined the CV outcomes of 470,128 patients with type 2 diabetes initiating SGLT2i or oGLD in Korea, Japan, Singapore, Australia, Israel and Canada[11]. That report did not include detailed analyses by baseline characteristics, such as history of CVD, at a country level. Considering that prior CVD is a risk factor for future CV events, we examined not only the CV outcomes of SGLT2i versus oGLD or DPP4i initiators, but also the impact of prior CVD on the CV safety of SGLT2i use in Japanese real-world settings.

METHODS

CVD-REAL 2 is a retrospective cohort study that collected data on SGLT2i, oGLDs and DPP4i initiators using a de-identified hospital claims database. For further details, see the Appendix S1 online and the original report[11].

Table 1 | Patient characteristics (matched patients)

	SGLT2i vs oGLD initiators			SGLT2i vs DPP4i initiators		
	SGLT2i initiator	oGLD initiator	St. Diff	SGLT2i initiator	DPP4i initiator	St. Diff
n	33,890	33,890		9,876	9,876	
Age (years)	59.1 (12.5)	58.9 (13.5)	1.4%	57.0 (12.9)	56.8 (14.1)	1.3%
Women	12,433 (36.7%)	12,522 (36.9%)	0.4%	3,710 (37.6%)	3,655 (37.0%)	0.9%
Time since first recorded A10 (years)	5.5 (5.7)	5.4 (5.8)	1.7%	4.4 (5.3)	4.3 (5.5)	1.6%
Index year			–			–
2014	1,558 (4.6%)	1,522 (4.5%)	–	581 (5.9%)	525 (5.3%)	–
2015	7,507 (22.2%)	7,335 (21.6%)	–	2,177 (22.0%)	2,051 (20.8%)	–
2016	14,356 (42.4%)	14,386 (42.4%)	–	4,123 (41.7%)	4,280 (43.3%)	–
2017	10,469 (30.9%)	10,647 (31.4%)	–	2,995 (30.3%)	3,020 (30.6%)	–
Frailty (≥3 days hospitalized)	6,982 (20.6%)	7,265 (21.4%)	1.7%	2,004 (20.3%)	2,110 (21.4%)	2.2%
Body mass index (kg/m^2)	27.7 (5.4)	27.7 (5.5)	0.9%	28.4 (5.6)	28.2 (5.7)	3.4%
	(*n* = 14,961)	(*n* = 15,068)		(*n* = 4,142)	(*n* = 4,107)	
Index drug at inpatient visit	3,255 (9.6%)	3,383 (10.0%)	1.0%	1,098 (11.1%)	1,151 (11.7%)	1.4%
Days hospitalized (days)	13.6 (6.9)	13.5 (6.9)	1.1%	13.2 (6.7)	13.4 (7.0)	2.8%
Index inpatient visit ending in death	0	0	–	0	0	–
HbA1c (%)	8.40 (1.59)	8.50 (1.80)	5.9%	8.29 (1.63)	8.18 (1.80)	6.3%
	(*n* = 4,508)	(*n* = 4,304)		(*n* = 1,322)	(*n* = 1,217)	
Glucose (mg/dL)	191.03 (76.09)	198.51 (89.46)	9.0%	188.20 (77.80)	181.97 (80.16)	7.9%
	(*n* = 3,819)	(*n* = 3,528)		(*n* = 1,071)	(*n* = 1,026)	
Baseline cardiovascular disease	5,568 (16.4%)	5,718 (16.9%)	1.0%	1,384 (14.0%)	1,432 (14.5%)	1.1%
Heart failure	3,008 (8.9%)	3,185 (9.4%)	1.5%	752 (7.6%)	792 (8.0%)	1.2%
Angina pectoris	2,931 (8.6%)	2,949 (8.7%)	0.2%	686 (6.9%)	709 (7.2%)	0.7%
Coronary revascularization	2,058 (6.1%)	2,179 (6.4%)	1.2%	476 (4.8%)	468 (4.7%)	0.3%
PCI with stent	1,954 (5.8%)	2,059 (6.1%)	1.1%	464 (4.7%)	456 (4.6%)	0.3%
Peripheral artery disease	1,325 (3.9%)	1,277 (3.8%)	0.6%	285 (2.9%)	279 (2.8%)	0.3%
Atrial fibrillation	1,253 (3.7%)	1,303 (3.8%)	0.6%	322 (3.3%)	357 (3.6%)	1.6%
Unstable angina	1,093 (3.2%)	1,120 (3.3%)	0.4%	249 (2.5%)	244 (2.5%)	0.3%
Myocardial infarction	1,002 (3.0%)	1,068 (3.2%)	0.9%	251 (2.5%)	258 (2.6%)	0.4%
Stroke	907 (2.7%)	903 (2.7%)	0.1%	218 (2.2%)	225 (2.3%)	0.4%
Ischemic	822 (2.4%)	825 (2.4%)	0.0%	198 (2.0%)	207 (2.1%)	0.5%
Hemorrhagic	100 (0.3%)	89 (0.3%)	0.5%	23 (0.2%)	21 (0.2%)	0.4%
Coronary artery bypass grafting	146 (0.4%)	165 (0.5%)	0.7%	21 (0.2%)	15 (0.2%)	1.2%
Transient ischemic attack	83 (0.2%)	83 (0.2%)	0.0%	20 (0.2%)	26 (0.3%)	1.0%
Microvascular disease	6,407 (18.9%)	6,502 (19.2%)	0.6%	1,608 (16.3%)	1,606 (16.3%)	0.0%
Cancer	418 (1.2%)	358 (1.1%)	1.4%	96 (1.0%)	95 (1.0%)	0.1%
Chronic kidney disease	374 (1.1%)	426 (1.3%)	1.1%	88 (0.9%)	112 (1.1%)	1.9%
COPD	151 (0.4%)	148 (0.4%)	0.1%	36 (0.4%)	33 (0.3%)	0.4%
Baseline glucose-lowering therapies	30,010 (88.6%)	30,276 (89.3%)	2.1%	6,209 (62.9%)	6,402 (64.8%)	3.3%
DPP4i	22,391 (66.1%)	22,304 (65.8%)	0.4%	0	0	–
Metformin	18,779 (55.4%)	18,600 (54.9%)	0.9%	4,640 (47.0%)	4,591 (46.5%)	0.8%
Sulfonylurea	11,887 (35.1%)	11,690 (34.5%)	1.0%	2,002 (20.3%)	1,957 (19.8%)	0.9%
Insulin	9,004 (26.6%)	9,238 (27.3%)	1.3%	2,551 (25.8%)	2,559 (25.9%)	0.2%
α-GI	6,721 (19.8%)	6,676 (19.7%)	0.3%	1,403 (14.2%)	1,385 (14.0%)	0.4%
Thiazolidinedione	4,398 (13.0%)	4,330 (12.8%)	0.5%	1,054 (10.7%)	1,023 (10.4%)	0.8%
GLP-1 RA	2,513 (7.4%)	2,564 (7.6%)	0.5%	875 (8.9%)	782 (7.9%)	2.8%
Glinide	2,173 (6.4%)	2,161 (6.4%)	0.1%	455 (4.6%)	443 (4.5%)	0.5%
SGLT2i	0	0	–	0	0	–
Cardiovascular therapies	25,410 (75.0%)	25,425 (75.0%)	0.1%	6,641 (67.2%)	6,625 (67.1%)	0.3%
Antihypertensives	20,763 (61.3%)	20,772 (61.3%)	0.0%	5,391 (54.6%)	5,412 (54.8%)	0.3%

Table 1 (*Continued*)

	SGLT2i vs oGLD initiators			SGLT2i vs DPP4i initiators		
	SGLT2i initiator	oGLD initiator	St. Diff	SGLT2i initiator	DPP4i initiator	St. Diff
ARB	14,960 (44.1%)	14,884 (43.9%)	0.4%	3,803 (38.5%)	3,785 (38.3%)	0.3%
Calcium channel blocker	11,229 (33.1%)	11,241 (33.2%)	0.1%	2,932 (29.7%)	2,947 (29.8%)	0.3%
Beta blockers	6,253 (18.5%)	6,417 (18.9%)	1.0%	1,531 (15.5%)	1,556 (15.8%)	0.6%
ACEi	2,715 (8.0%)	2,713 (8.0%)	0.0%	739 (7.5%)	771 (7.8%)	1.0%
Thiazides	1,448 (4.3%)	1,494 (4.4%)	0.5%	442 (4.5%)	449 (4.5%)	0.3%
Statin	16,639 (49.1%)	16,702 (49.3%)	0.3%	4,140 (41.9%)	4,106 (41.6%)	0.6%
Loop diuretics	3,653 (10.8%)	3,765 (11.1%)	0.9%	867 (8.8%)	915 (9.3%)	1.4%
Low-dose aspirin	5,534 (16.3%)	5,604 (16.5%)	0.5%	1,306 (13.2%)	1,304 (13.2%)	0.0%
SGLT2i at baseline	33,890 (100.0%)	0	–	9,876 (100.0%)	0	–
Ipragliflozin	8,488 (25.0%)	0	–	2,325 (23.5%)	0	–
Dapagliflozin	8,408 (24.8%)	0	–	2,335 (23.6%)	0	–
Empagliflozin	6,633 (19.6%)	0	–	1,884 (19.1%)	0	–
Tofogliflozin	4,262 (12.6%)	0	–	1,515 (15.3%)	0	–
Canagliflozin	3,826 (11.3%)	0	–	1,147 (11.6%)	0	–
Luseogliflozin	2,273 (6.7%)	0	–	670 (6.8%)	0	–
Index GLD	0	33,890 (100.0%)	–	0	9,876 (100.0%)	–
DPP4i	0	6,757 (19.9%)	–	0	9,876 (100.0%)	–
Metformin	0	6,036 (17.8%)	–	0	0	–
Insulin	0	5,333 (15.7%)	–	0	0	–
Sulfonylurea	0	4,149 (12.2%)	–	0	0	–
α-GI	0	3,666 (10.8%)	–	0	0	–
Thiazolidinedione	0	2,995 (8.8%)	–	0	0	–
Glinide	0	2,895 (8.5%)	–	0	0	–
GLP-1 RA	0	2,059 (6.1%)	–	0	0	–

Values are the number (percentage) or mean (standard deviation). A10, glucose-lowering drug (Anatomical Therapeutic Chemical Classification System codes A10); α-GI, alpha-glucosidase inhibitor; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; oGLD, other glucose-lowering drug; PCI, percutaneous coronary intervention; SGLT2i, sodium–glucose cotransporter 2 inhibitor; St. Diff, standardized difference (a standardized difference >10% represents a non-negligible difference).

RESULTS

Dapagliflozin, ipragliflozin and empagliflozin were the most frequently prescribed SGLT2i (Table 1). The most frequently prescribed oGLDs were DPP4i (19.9%), metformin (17.8%) and insulin (15.7%). For the SGLT2i versus oGLD comparison, of 456,271 GLD initiators, 33,890 were matched (Figure 1; total SGLT2i exposure time 26,529 years). For the SGLT2i versus DPP4i comparison, of 145,050 SGLT2i or DPP4i initiators, 9,876 were matched (Figure 1; total SGLT2i exposure time 7,478 years). The groups were generally well matched with standardized differences of <10% (Table 1).

Compared with oGLD initiators, the SGLT2i initiators were associated with lower risks (hazard ratio) of death (0.56, 95% confidence interval [95% CI] 0.47–0.67), hospitalization for heart failure (HHF; 0.75, 95% CI 0.64–0.89), the composite of HHF or death (0.65, 95% CI 0.58–0.74) and stroke (0.66, 95% CI 0.52–0.84; Figures 2,S1). Similar trends were also apparent in patients with and without a history of CVD (Figure 2).

SGLT2i initiators were associated with lower risks of death (0.52, 95% CI 0.36–0.73) and the composite of HHF or death

(0.65, 95% CI 0.51–0.83) versus DPP4i (Figures 3,S2). These trends were also observed in patients with and without a history of CVD (Figure 3).

DISCUSSION

Results from this Japanese cohort were consistent with the overall pooled results of CVD-REAL 2[11], showing that SGLT2i initiation was associated with lower risks of in-hospital death, HHF, composite of HHF or death, myocardial infarction and stroke compared with oGLD initiation overall, and in patients with or without a history of CVD (Figure 2). These results are similar to those of major CV outcome trials[3–5] and meta-analyses[12,13]. Uniquely, we showed that SGLT2i initiation was associated with a lower risk of death and the composite of HHF or death versus DPP4i initiation in a country where DPP4is are frequently used to treat type 2 diabetes[9,10].

The prevalence of stroke is generally higher in Asian populations than in Western populations[14,15]. The present findings suggest that SGLT2i might lower the risk of stroke in Japanese real-world clinical settings. The mechanism underlying the
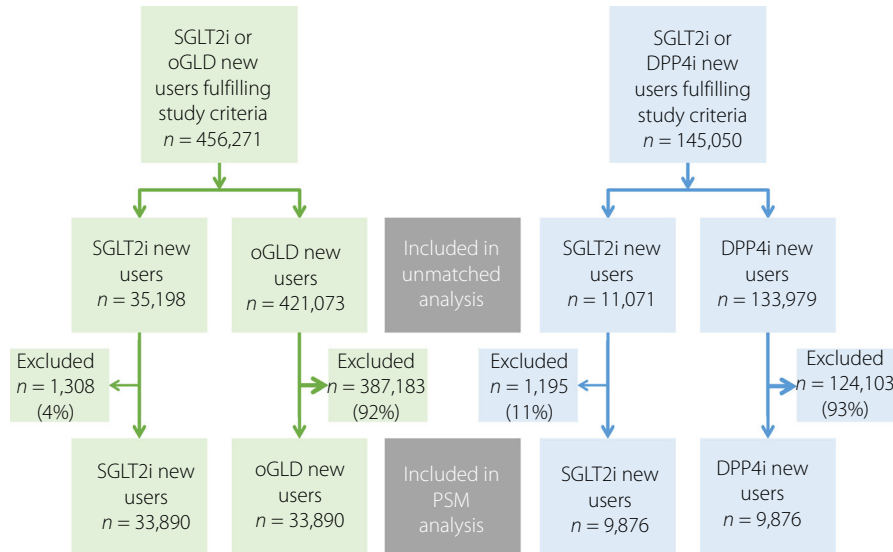
Figure 1 | Patient disposition. DPP4i, dipeptidyl peptidase-4 inhibitor; oGLD, other glucose-lowering drug; PSM, propensity score matching; SGLT2i, sodium–glucose cotransporter 2 inhibitor.
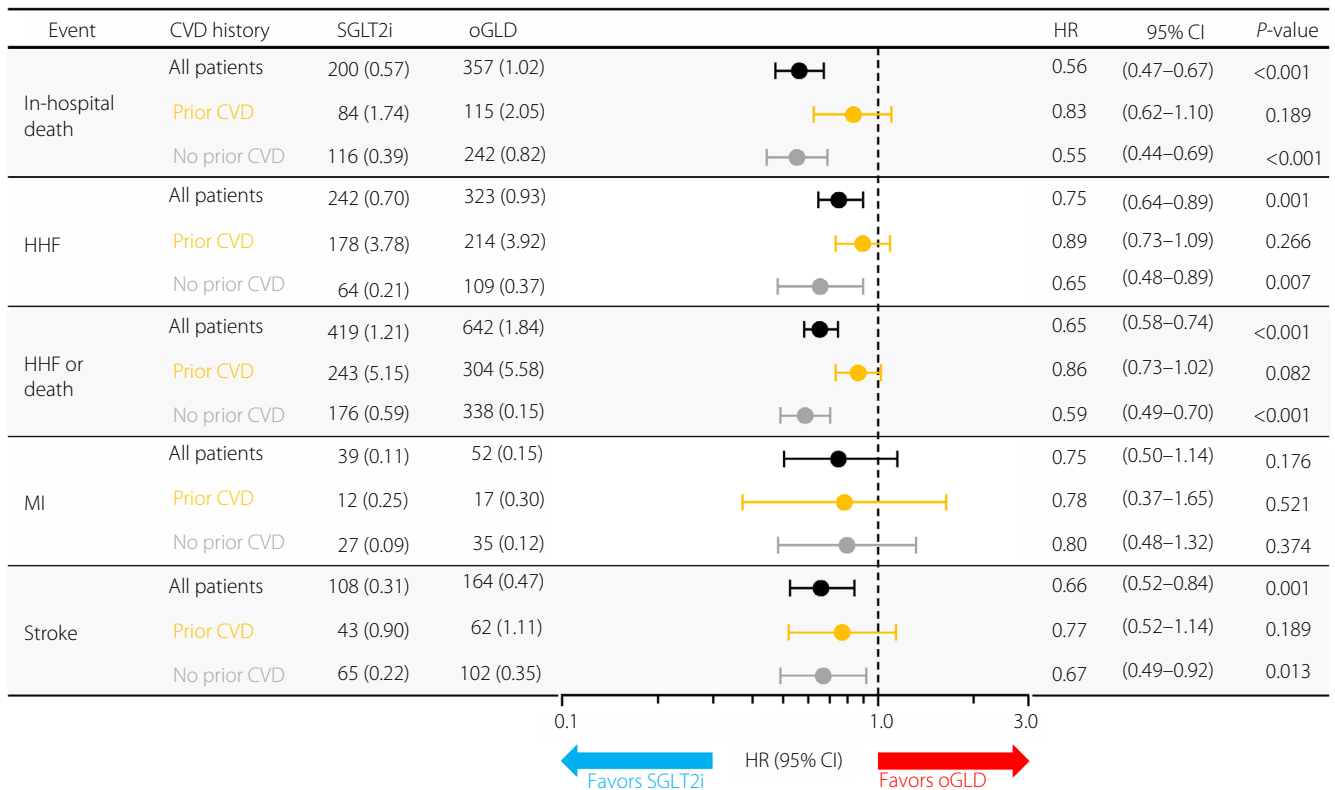

Event	CVD history	SGLT2i	oGLD		HR	95% CI	P-value
In-hospital death	All patients	200 (0.57)	357 (1.02)		0.56	(0.47–0.67)	<0.001
	Prior CVD	84 (1.74)	115 (2.05)		0.83	(0.62–1.10)	0.189
	No prior CVD	116 (0.39)	242 (0.82)		0.55	(0.44–0.69)	<0.001
HHF	All patients	242 (0.70)	323 (0.93)		0.75	(0.64–0.89)	0.001
	Prior CVD	178 (3.78)	214 (3.92)		0.89	(0.73–1.09)	0.266
	No prior CVD	64 (0.21)	109 (0.37)		0.65	(0.48–0.89)	0.007
HHF or death	All patients	419 (1.21)	642 (1.84)		0.65	(0.58–0.74)	<0.001
	Prior CVD	243 (5.15)	304 (5.58)		0.86	(0.73–1.02)	0.082
	No prior CVD	176 (0.59)	338 (0.15)		0.59	(0.49–0.70)	<0.001
MI	All patients	39 (0.11)	52 (0.15)		0.75	(0.50–1.14)	0.176
	Prior CVD	12 (0.25)	17 (0.30)		0.78	(0.37–1.65)	0.521
	No prior CVD	27 (0.09)	35 (0.12)		0.80	(0.48–1.32)	0.374
Stroke	All patients	108 (0.31)	164 (0.47)		0.66	(0.52–0.84)	0.001
	Prior CVD	43 (0.90)	62 (1.11)		0.77	(0.52–1.14)	0.189
	No prior CVD	65 (0.22)	102 (0.35)		0.67	(0.49–0.92)	0.013

0.1   1.0   3.0

HR (95% CI)

Favors SGLT2i   Favors oGLD

Figure 2 | Hazard ratios for the study outcomes in sodium–glucose cotransporter 2 inhibitor (SGLT2i) initiators versus other glucose-lowering drug (oGLD) initiators in all patients and according to history of cardiovascular disease (CVD). See Figure S1 for the Kaplan–Meier plots showing the cumulative event rates for each event type. CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction.
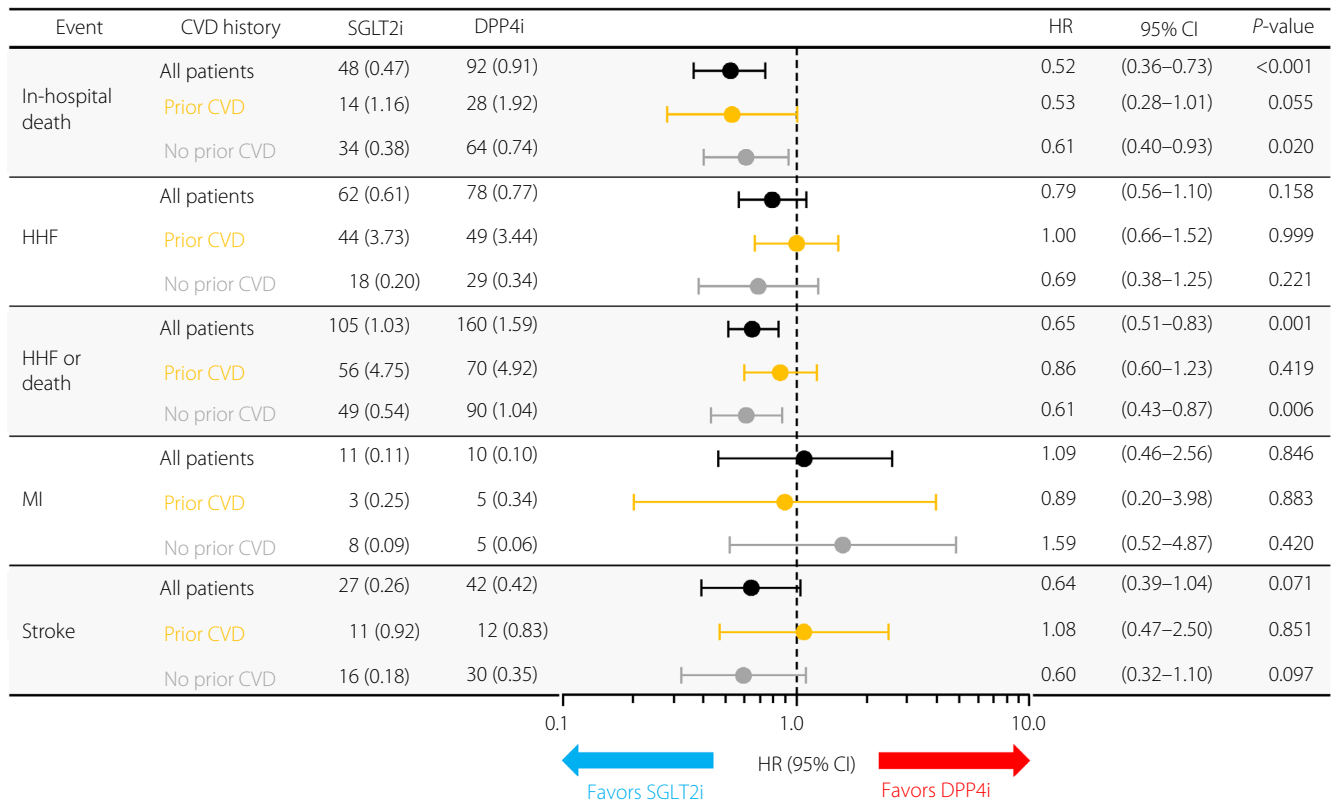
Event	CVD history	SGLT2i	DPP4i		HR	95% CI	P-value
In-hospital death	All patients	48 (0.47)	92 (0.91)		0.52	(0.36–0.73)	<0.001
	Prior CVD	14 (1.16)	28 (1.92)		0.53	(0.28–1.01)	0.055
	No prior CVD	34 (0.38)	64 (0.74)		0.61	(0.40–0.93)	0.020
HHF	All patients	62 (0.61)	78 (0.77)		0.79	(0.56–1.10)	0.158
	Prior CVD	44 (3.73)	49 (3.44)		1.00	(0.66–1.52)	0.999
	No prior CVD	18 (0.20)	29 (0.34)		0.69	(0.38–1.25)	0.221
HHF or death	All patients	105 (1.03)	160 (1.59)		0.65	(0.51–0.83)	0.001
	Prior CVD	56 (4.75)	70 (4.92)		0.86	(0.60–1.23)	0.419
	No prior CVD	49 (0.54)	90 (1.04)		0.61	(0.43–0.87)	0.006
MI	All patients	11 (0.11)	10 (0.10)		1.09	(0.46–2.56)	0.846
	Prior CVD	3 (0.25)	5 (0.34)		0.89	(0.20–3.98)	0.883
	No prior CVD	8 (0.09)	5 (0.06)		1.59	(0.52–4.87)	0.420
Stroke	All patients	27 (0.26)	42 (0.42)		0.64	(0.39–1.04)	0.071
	Prior CVD	11 (0.92)	12 (0.83)		1.08	(0.47–2.50)	0.851
	No prior CVD	16 (0.18)	30 (0.35)		0.60	(0.32–1.10)	0.097

Figure 3 | Hazard ratios for the study outcomes in sodium–glucose cotransporter 2 inhibitor (SGLT2i) initiators versus dipeptidyl peptidase-4 inhibitor (DPP4i) initiators in all patients and according to history of cardiovascular disease (CVD). See Figure S2 for the Kaplan–Meier plots showing the cumulative event rates for each event type. CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction.

potential benefit on stroke risk is unclear, but we hypothesize the following. Atrial fibrillation (AF) and hypertension are possible risk factors and causal factors leading to stroke. The incidence of AF is high in Asian countries[16], and it was reported that 73% of cases of cardiogenic brain embolism occurred in patients with AF[17]. Results of a DECLARE-TIMI 58 subanalysis showed that dapagliflozin reduces the risk of AF[18]. Additionally, SGLT2i might reduce the risk of stroke through their effects on blood pressure[19–21]. These properties of SGLT2i might have contributed to the lower incidence of stroke in patients with type 2 diabetes.

Few studies have compared the CV safety of SGLT2i and DPP4i in Asian populations. Here, initiation of SGLT2i versus DPP4i was associated with lower risks of in-hospital death and composite of HHF or death, findings that were apparent in patients with and without a history of CVD. These results are also consistent with those reported in another real-world study comparing SGLT2i use and DPP4i use[22]. However, the present comparison of SGLT2i and DPP4i initiators involved fewer patients than the comparison of SGLT2i and oGLD initiators, potentially reducing statistical power. Furthermore, patients included in the SGLT2i versus DPP4i analysis were younger

(by ~2 years), had a shorter duration of diabetes and were treated with fewer GLDs or CV drugs at baseline than those included in the SGLT2i versus oGLD comparison. This suggests that the SGLT2i versus DPP4i comparison involved patients earlier in the course of type 2 diabetes.

Future analyses comparing SGLT2i and oGLD/DPP4i initiators from different patient backgrounds, such as patients with/ without metformin, with/without multiple CV risk factors, with lower body mass index (BMI) and with each component of established CVD might provide more insight into the potential CV benefits of SGLT2i.

As this was a retrospective analysis of a hospital-based database, some limitations should be considered. It might be difficult to extrapolate the results to patients treated by general practitioners. It is possible that we did not exclude unmeasured confounders, such as sociodemographic status or physical conditions, although we adjusted confounding factors using propensity scores and carried out some sensitivity analyses. Mortality was assessed as in-hospital death, because the database only recorded in-hospital death, which accounts for the vast majority of deaths in Japan[11,23]. Nevertheless, these limitations should not greatly affect the results, because they apply

randomly to both groups. We also acknowledge that the patients in the present study were matched based on SGLT2i use, and their BMI could be higher than that of average Japanese type 2 diabetes patients. It was reported that the glucose-lowering effect of DPP4i is higher in Asian populations with a lower BMI[24]. However, large-scale CV outcome trials of DPP4i have reported neutral or inferior effects on CV safety[25–28]. Furthermore, the beneficial effects on CV outcomes shown in the subanalysis of SGLT2i CV outcome trials were independent of glycemic control[29] and baseline BMI[30]. Thus, these limitations might not have affected the CV safety results. Finally, observational real-world studies can only evaluate association and not causality.

In conclusion, the present retrospective analysis of a Japanese cohort showed consistent findings with the overall pooled results of CVD-REAL 2. Initiation of SGLT2i was associated with lower risks of CV events, including HHF, in-hospital death and stroke, when compared with initiation of oGLD or DPP4i in real-world clinical practice.

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DISCLOSURE

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SUPPORTING INFORMATION

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

Appendix S1 | Supplementary methods.
Figure S1 | Kaplan–Meier plots comparing the cumulative event rates for (a) in-hospital death, (b) hospitalization for heart failure (HHF), (c) composite of in-hospital death and HHF, (d) myocardial infarction (MI), and (e) stroke between sodium–glucose cotransporter 2 inhibitor (SGLT2i) and other glucose-lowering drug (oGLD) initiators.
Figure S2 | Kaplan–Meier plots comparing the cumulative event rates for (a) in-hospital death, (b) hospitalization for heart failure (HHF), (c) composite of in-hospital death and HHF, (d) myocardial infarction (MI), and (e) stroke between sodium–glucose cotransporter 2 inhibitor (SGLT2i) and dipeptidyl peptidase-4 inhibitor (DPP4i) initiators.