




Incidence of adverse cardiovascular events in type 2 diabetes mellitus patients after initiation of glucose-lowering agents: A population-based community study from the Shizuoka Kokuho database

Shun Kohsaka^{1,2*}, Hiraku Kumamaru^{2,3} , Shiori Nishimura^{2,3,4}, Satoshi Shoji¹, Eiji Nakatani² , Nao Ichihara^{2,3} , Hiroyuki Yamamoto^{2,3,4}, Yoshiki Miyachi², Hiroaki Miyata^{2,3,4}

¹Department of Cardiology, Keio University School of Medicine, Tokyo, Japan, ²Research Support Center, Shizuoka General Hospital, Shizuoka, Japan, ³Department of Healthcare Quality Assessment, The University of Tokyo Graduate School of Medicine, Tokyo, Japan, and ⁴Department of Health Policy and Management, Keio University School of Medicine, Tokyo, Japan

Keywords

Cardiovascular disease, Heart failure, Sodium–glucose cotransporter 2 inhibitors

*Correspondence

Shun Kohsaka
Tel: +81-3-5843-6702
Fax: +81-3-5363-3875
E-mail address: sk@keio.jp

J Diabetes Investig 2021; 12: 1452–1461

doi: 10.1111/jdi.13485

ABSTRACT

Aims/Introduction: Increased incidence of hospitalization for heart failure (HHF) among patients with diabetes is increasingly being reported. We investigated the incidence of adverse cardiovascular events including HHF among patients with type 2 diabetes mellitus, and the potential clinical improvement with sodium–glucose cotransporter 2 inhibitors (SGLT2i) using a contemporary administrative claims database from a large governmental district of Japan.

Materials and Methods: We included initiators of any oral glucose-lowering drugs between 2013 and 2018. We estimated the 5-year cumulative incidence of hospitalization for HF, myocardial infarction and stroke, treating death as a competing risk. We evaluated the possible impact of introducing SGLT2i to the potential recipients of the drug, using the inclusion criteria from Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) and Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trials, assuming the same risk reduction as theirs.

Results: Among 23,340 drug initiators (54.0% men, and 6.4% aged >85 years), the 5-year cumulative incidence was 5.4% (95% confidence interval 4.9–5.9%) for HHF, 1.9% (95% confidence interval 1.7–2.2%) for myocardial infarction admission and 6.1% (95% confidence interval 5.7–6.6%) for stroke admission. Among 6,192 patients with laboratory test data, 651 (10.5%) and 2,680 (43.3%) patients met the EMPA-REG-like and DECLARE-like criteria, respectively. The 5-year cumulative incidence among the 2,849 patients meeting either of the criteria was estimated to decrease from 97.1 to 75.6 events through 75% adoption of SGLT2i.

Conclusions: The incidence of HHF was similar to that of stroke. A significant portion of our cohort met the inclusion criteria for major randomized clinical trials for SGLT2i, and estimated reduction in the HHF events was substantial.

INTRODUCTION

Heart failure (HF) is a major cause of morbidity and mortality in people with diabetes. The incidence rates of hospitalization for HF (HHF) are twofold higher in patients with diabetes than

Received 21 September 2020; revised 6 December 2020; accepted 17 December 2020

in those without¹. However, despite increasing recognition of its importance, HF has not traditionally been considered as a primary target for reduction in the management of type 2 diabetes mellitus therapy. In addition, well-designed observational studies investigating the incidence of cardiovascular (CV) outcomes, including HHF in patients with diabetes, have not been carried out. In recent years, the aim of diabetic treatment has shifted drastically from simply focusing on the improvement of glycemic control to a reduction in CV outcomes. Newly introduced agents, such as sodium–glucose cotransporter 2 inhibitors (SGLT2i; e.g., empagliflozin, canagliflozin and dapagliflozin) have been shown to directly reduce the risk of HHF among people with type 2 diabetes mellitus and established CV disease (CVD) or multiple CV risk factors^{2–4}, along with a composite outcome involving CV death, myocardial infarction (MI) or stroke⁵, thus, SGLT2i have emerged as a potentially attractive option for initial therapy, particularly for patients with high-risk profiles⁶.

Given the potential cardiovascular benefits of SGLT-2i, it is important to understand the potential impact associated with the use of these agents in real-world clinical practice⁷. In the present study, we investigated the following: (i) the incidence of HHF in patients with type 2 diabetes mellitus treated with glucose-lowering agents; and (ii) the use of SGLT2i and their potential improvement of clinical outcomes, based on a contemporary administrative database with complete registration of medical visits in a large governmental district of Japan.

METHODS AND MATERIALS

Data source

We used the Shizuoka Kokuho database for the present study. The database is an administrative claims database of enrollees in the municipal government health insurance program in Shizuoka Prefecture in Japan. The enrollees in the program could be categorized into those aged <75 years (National Health Insurance) and those ≥75 years (late-stage medical care system). The members of the <75 years group were mainly self-employed citizens, agricultural and fisheries workers, part-time workers, and unemployed individuals. Employees of large or small companies are not enrolled in the National Health Insurance program. All Japanese citizens aged ≥75 years are enrolled in an independent prefectural government health insurance program for the elderly. When National Health Insurance enrollees reach the age of 75 years and change programs, it is possible to track the same patients between the two programs. In the present study, we accessed all the data on all the procedures and diagnoses made for all enrollees between April 2012 and September 2018.

The database contains data on the members' enrollment and disenrollment dates, to assess their eligibility. In addition to the claims data component, which includes data on patients' diagnoses, procedures, devices used, laboratory tests ordered and drug dispensations, the database contains data from yearly health checkups for selected enrollees in the program.

The study was approved by the institutional review board of Shizuoka General Hospital (Shizuoka, Japan; SGHIRB#2019009). Based on the data use agreement with the regional insurers in the prefecture of Shizuoka, we are unable to make the analysis data accessible to the readers.

Participants

We selected patients aged ≥40 years who started oral glucose-lowering drugs for treating type 2 diabetes mellitus between April 2013 and March 2018. We identified each patient's first medication (biguanide, sulfonylurea, alpha glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor [DPP4i], thiazolidinedione, SGLT2i or a combination of these). We designated the prescription month of this first oral antidiabetic drug as the 'index month' (the database records only the month of prescription; the date of prescription is unknown), and the previous 12-month period as the 'baseline period'. Patients for whom the period between plan enrollment and the index month was <12 months were excluded. We also excluded patients with a diagnosis of type 1 diabetes mellitus or HF before or within the index month.

Patient characteristics

Data on each patient's sex and age were extracted from the enrollment data. We also extracted data for each patient's comorbidities during the baseline period from the claims data, using the following the International Classification of Diseases 10th version (ICD-10) codes: hypertension (I10), CVD (I20–22, I24, I60–67, I69), peripheral vascular disease (I73, I74), edema (R60), electrolyte and acid–base dysfunction (E87), hyperlipidemia (E78), chronic obstructive pulmonary disease (J41–44), pneumonia (J13, J15, J16, J18), sleep apnea syndrome (G473), malignancy (C00–C97), and chronic kidney disease (N18). Data on each patient's past and current medications were extracted from the database in a similar manner, using the following Anatomical Therapeutic Chemical codes: beta-blockers (C07), acetylcholinesterase (ACE) inhibitors (C09A), angiotensin II receptor blockers (C09D), calcium channel blockers (C08), statins (C10AA), nitrates (C01DA), anticoagulants (B01AA, B01AE, B01AF01–03) and antiplatelet agents (B01AC04–07, B01AC22–24).

Identifying patients meeting SGLT2i indications

To assess the number of patients with possible indications for SGLT2i, we assessed the background factors of a subgroup of patients with data on hemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR) and smoking history, during health check-ups conducted within the 6 months preceding the index date. We then selected two sets of criteria as indications for SGLT2i, based on the enrollment and exclusion criteria for two clinical trials: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUT-COME; EMPA-REG)² and Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58

Table 1 | Baseline characteristics of the whole cohort and of those hospitalized for heart failure, myocardial infarction or stroke

	Total <i>n</i> = 23,340	HF admission <i>n</i> = 681	MI admission <i>n</i> = 267	Stroke admission <i>n</i> = 847
Age (years), mean (SD)	68.6 (10.3)	74.9 (11.2)	73.1 (11.4)	74.5 (10.5)
Age group, <i>n</i> (%)				
40–65 years	7,556 (32.4)	118 (17.3)	62 (23.2)	164 (19.4)
66–74 years	10,671 (45.7)	217 (31.9)	84 (31.5)	276 (32.6)
75–84 years	3,609 (15.5)	193 (28.3)	71 (26.6)	239 (28.2)
≥85 years	1,504 (6.4)	153 (22.5)	50 (18.7)	168 (19.8)
Sex, <i>n</i> (%)				
Male	12,595 (54.0)	417 (61.2)	178 (66.7)	515 (60.8)
First-prescribed oral GLD, <i>n</i> (%)				
DPP4i	14,810 (63.5)	430 (63.1)	160 (59.9)	554 (65.4)
Thiazolidinedione	430 (1.8)	9 (1.3)	7 (2.6)	13 (1.5)
Sulfonylurea	1,147 (4.9)	54 (7.9)	18 (6.7)	53 (6.3)
SGLT2i	597 (2.6)	6 (0.9)	4 (1.5)	6 (0.7)
OHA combination	119 (0.5)	3 (0.4)	2 (0.7)	6 (0.7)
Biguanide	2,165 (9.3)	38 (5.6)	17 (6.4)	48 (5.7)
Alpha-glucosidase inhibitor	1,190 (5.1)	35 (5.1)	11 (4.1)	44 (5.2)
≥Two drugs	2,673 (11.5)	99 (14.5)	42 (15.7)	115 (13.6)
Baseline comorbidities, <i>n</i> (%)				
Hypertension	14,855 (63.6)	499 (73.3)	181 (67.8)	637 (75.2)
Cardiovascular disease	6,520 (27.9)	279 (41.0)	113 (42.3)	406 (47.9)
Peripheral vascular disease	659 (2.8)	34 (5.0)	11 (4.1)	32 (3.8)
Edema	409 (1.8)	21 (3.1)	8 (3.0)	15 (1.8)
Fluid, electrolyte or acid–base disorder	344 (1.5)	20 (2.9)	4 (1.5)	15 (1.8)
Hyperlipidemia	14,145 (60.6)	351 (51.5)	137 (51.3)	480 (56.7)
COPD	1,368 (5.9)	72 (10.6)	16 (6.0)	63 (7.4)
Pneumonia	1,313 (5.6)	56 (8.2)	16 (6.0)	46 (5.4)
SAS	235 (1.0)	3 (0.4)	1 (0.4)	13 (1.5)
Cancer	6,377 (27.3)	196 (28.8)	76 (28.5)	242 (28.6)
Chronic kidney disease	471 (2.0)	41 (6.0)	7 (2.6)	32 (3.8)
Baseline medication use, <i>n</i> (%)				
Beta-blockers	1,418 (6.1)	53 (7.8)	16 (6.0)	43 (5.1)
ACEi	760 (3.3)	27 (4.0)	10 (3.7)	31 (3.7)
ARB	2,717 (11.6)	87 (12.8)	36 (13.5)	106 (12.5)
CCB	8,933 (38.3)	340 (49.9)	112 (41.9)	402 (47.5)
Statin	8,245 (35.3)	186 (27.3)	63 (23.6)	269 (31.8)
Nitrate	582 (2.5)	34 (5.0)	12 (4.5)	34 (4.0)
Anticoagulant	379 (1.6)	26 (3.8)	5 (1.9)	34 (4.0)
Antiplatelet agent	2,355 (10.1)	136 (20.0)	52 (19.5)	232 (27.4)
History of coronary revascularization, <i>n</i> (%)	28 (0.1)	3 (0.4)	1 (0.4)	0 (0.0)
Patients with available laboratory data, <i>n</i> (%)	6,192 (26.5)	112 (16.4)	49 (18.4)	180 (21.3)
BMI (kg/m ²), mean (SD)	24.5 (3.9)	24.0 (3.8)	24.1 (4.3)	24.3 (3.8)
BMI group, <i>n</i> (%) [†]				
<25 kg/m ²	3,706 (59.9)	71 (63.4)	29 (59.2)	114 (63.3)
25–<30 kg/m ²	1,997 (32.3)	35 (31.3)	17 (34.7)	54 (30.0)
≥30 kg/m ²	489 (7.9)	6 (5.4)	3 (6.1)	12 (6.7)
HbA1c (%), mean (SD)	7.5 (1.6)	7.6 (1.5)	7.8 (1.8)	7.6 (1.6)
HbA1c group, <i>n</i> (%) [†]				
<6.5%	1,148 (18.5)	23 (20.5)	8 (16.3)	33 (18.3)
6.5–<8%	3,590 (58.0)	57 (50.9)	26 (53.1)	100 (55.6)
≥8%	1,454 (23.5)	32 (28.6)	15 (30.6)	47 (26.1)
eGFR (mL/min/1.73 m ²), mean (SD)	74.0 (17.8)	66.0 (20.8)	69.8 (19.1)	69.2 (17.7)

Table 1 (Continued)

	Total <i>n</i> = 23,340	HF admission <i>n</i> = 681	MI admission <i>n</i> = 267	Stroke admission <i>n</i> = 847
eGFR group, <i>n</i> (%) [†]				
≥60 mL/min/1.73 m ²	4,996 (80.7)	67 (59.8)	33 (67.3)	125 (69.4)
30–<60 mL/min/1.73 m ²	1,176 (19.0)	41 (36.6)	16 (32.7)	53 (29.4)
<30 mL/min/1.73 m ²	20 (0.3)	4 (3.6)	0 (0.0)	2 (1.1)
Smoker, <i>n</i> (%) [†]	998 (16.1)	20 (17.9)	10 (20.4)	33 (18.3)

ACEi, acetylcholinesterase inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; DPP4i, dipeptidyl peptidase 4 inhibitor; GLD, glucose-lowering drugs; HF, heart failure; MI, myocardial infarction; OHA, oral hypoglycemic medication; SAS, sleep apnea syndrome; SD, standard deviation; SGLT2i, sodium–glucose cotransporter 2 inhibitors. [†]The percentages of patients in the body mass index (BMI) groups, hemoglobin A1c (HbA1c) groups, estimated glomerular filtration rate (eGFR) groups and smokers were calculated from the number of patients with laboratory data as the denominator.

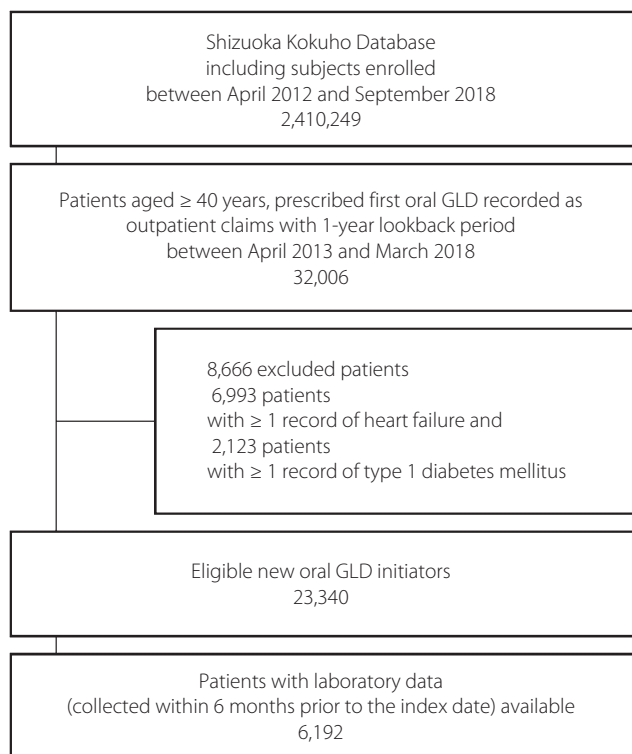


Figure 1 | Patient flow chart. GLD, glucose-lowering drugs.

(DECLARE-TIMI 58; DECLARE)⁴. We then calculated the number and percentage of patients meeting these criteria among the cohort enrollees, as follows:

1. EMPA-REG-like criteria: HbA1c ≥6.5%, with at least one recorded diagnosis of CVD (stroke, MI, arteriosclerosis obliterans [1,709], history of coronary revascularization) and eGFR ≥30 mL/min/1.73 m².
2. DECLARE-like criteria: HbA1c ≥6.5%, with at least one recorded diagnosis of CVD (as defined above) OR CV risk

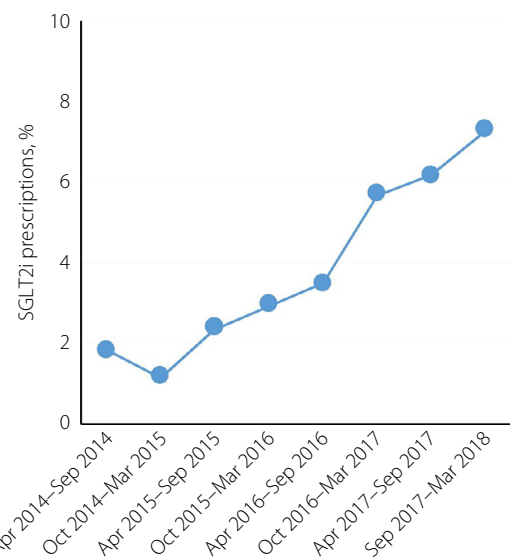


Figure 2 | Trend in the proportion of initial sodium–glucose cotransporter 2 inhibitor (SGLT2i) users among oral glucose-lowering drug initiators in the Shizuoka Kokuho database between April 2014 and March 2018.

factors, defined as male aged ≥55 years or female aged ≥60 years with at least one recorded risk factor (prescribed lipid-lowering drug, prescribed antihypertensive drug, self-reported tobacco use) and eGFR ≥60 mL/min/1.73 m².

Outcomes

The primary outcome of interest of the present study was hospitalization for HF. We identified this outcome using the Japanese electronic claims code corresponding to the ICD-10 codes for HF (I50), which was used for diagnosis during a hospitalization episode. Hospitalization claims are also bundled together

for each month in the database. As a secondary outcome, we assessed the occurrence of hospitalization with a diagnosis for MI (codes I21–22) or stroke (codes I60–64).

Statistical analysis

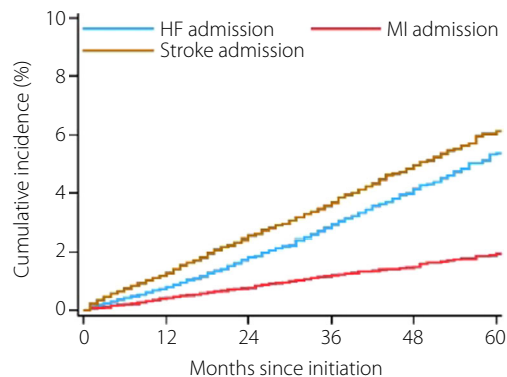
We tabulated the background characteristics of all patients selected for the study cohort, using counts and percentages for categorical variables, and means and standard deviations for continuous variables. We also tabulated the backgrounds of those patients for whom the outcomes of interest during the follow-up period were available, separately for hospitalization for HF, MI and stroke.

We assessed the incidence of admission for HF, MI or stroke during the follow-up period. We assessed the cumulative incidence of the outcomes during a follow-up period of 5 years, treating death as a competing risk factor for the three outcomes, and repeated the analysis in a restricted group of patients with no previous diagnosis of CVD. We censored patients when their enrollment in the municipal government insurance plan was terminated. We fitted Fine–Gray proportional subdistribution hazard models separately for the three outcomes from patients' demographic variables, comorbidities and whether patients were initiated on combination drug therapy or not to identify strong predictors of these outcomes, and report their subdistribution hazard ratios and 95% confidence intervals. All analyses were carried out with SAS version 9.4 (SAS Institute, Cary, NC, USA).

We also evaluated the possible impact of introducing SGLT2i to the potential recipients of the drug, identified using the EMPA-REG-like and DECLARE-like criteria described above. We used the relative risk reduction values for SGLT2i estimated in the two trials (0.65 for EMPAREG and 0.73 for DECLARE) to estimate the numbers of cases that would be observed if 75%, 50% or 25% of the patients meeting these criteria were treated with SGLT2i and would, therefore, benefit from the risk reduction estimated in the trials. Those already taking SGLT2i were considered to receive no additional benefit. To assess the total number of patients with a reduced risk of each event, those meeting both the EMPA-REG-like and DECLARE-like criteria were treated as 'EMPA-REG-like' patients.

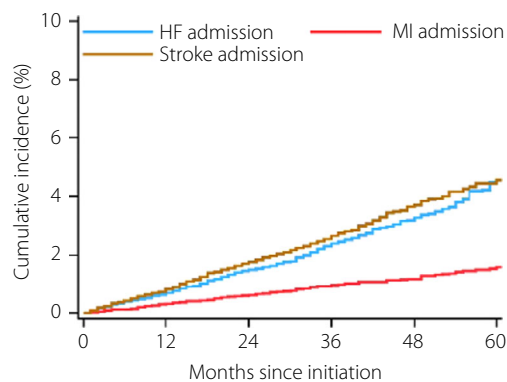
RESULTS

We identified 23,340 patients who were started on oral glucose-lowering drugs. In total, 54.0% of the patients were men, and the proportions of patients aged 75–84 and ≥ 85 years were 15.5 and 6.4%, respectively (Table 1). For 6,192 patients, data were available for serum creatinine, HbA1c and body mass index (BMI) from health checkups carried out within 6 months preceding the index date (Figure 1). The mean (\pm standard deviation) BMI was 24.5 ± 3.9 kg/m², and BMI was ≥ 25.0 kg/m² in 40.2% of the patients. HbA1c was 6.5–8.0% in the majority (58.0%) of patients, and $\geq 8.0\%$ in 23.5% of the patients. The proportion of patients with eGFR of 30–60 mL/min/1.73 m² was 19.0%, and eGFR was <30 mL/min/1.73 m² in 0.3%. Of all



	No. at risk					
HF admission	23,340	19,879	15,032	10,687	6,397	2,068
MI admission	23,340	19,930	15,161	10,834	6,530	2,140
Stroke admission	23,340	19,792	14,943	10,622	6,343	2,058

Figure 3 | Cumulative incidence of primary and secondary outcomes in patients initially treated with an oral glucose-lowering drug. HF, heart failure; MI, myocardial infarction.



	No. at risk					
HF admission	16,820	14,316	10,846	7,701	4,635	1,510
MI admission	16,820	14,353	10,925	7,795	4,713	1,559
Stroke admission	16,820	14,304	10,827	7,698	4,620	1,526

Figure 4 | Cumulative incidence of primary and secondary outcomes among oral glucose-lowering drug initiators without cardiovascular disease during the baseline period. HF, heart failure; MI, myocardial infarction.

the patients, 16.1% had a history of smoking. Most (63.5%) of the patients initiated treatment with DPP4i, and 2.6% of those initiated treatment with SGLT2i. Prescriptions of SGLT2i increased from approximately 2% in April 2014 to September 2014 to slightly more than 8% in September 2017 to March 2018 (Figure 2).

Incidence of HF, stroke and MI admissions

During the follow-up period (mean 2.8 years; total 65,567 years), we identified 681 admissions for HF, 267

Table 2 | Fine–Gray model for predictors of the primary and secondary outcomes

	HF admission		MI admission		Stroke admission	
	sHR	95% CI	sHR	95% CI	sHR	95% CI
Age group						
40–65 years	1	Reference	1	Reference	1	Reference
66–74 years	1.40	1.11–1.75	1.04	0.75–1.45	1.23	1.01–1.50
74–85 years	2.84	2.23–3.6	2.17	1.51–3.11	2.49	2.01–3.08
≥85 years	5.68	4.4–7.33	3.88	2.60–5.78	4.45	3.53–5.61
Sex						
Male	1	Reference	1	Reference	1	Reference
Female	0.69	0.59–0.81	0.54	0.42–0.70	0.68	0.59–0.79
Baseline comorbidities						
Hypertension	1.31	1.1–1.56	1.04	0.80–1.37	1.39	1.17–1.63
Cardiovascular disease	1.31	1.11–1.54	1.60	1.24–2.07	1.88	1.63–2.18
Peripheral vascular disease	1.27	0.9–1.79	1.09	0.58–2.03	0.93	0.65–1.33
Edema	1.23	0.77–1.97	1.40	0.68–2.87	0.73	0.44–1.22
Fluid, electrolyte or acid–base disorder	1.24	0.78–1.97	0.85	0.32–2.26	0.87	0.51–1.45
Hyperlipidemia	0.72	0.62–0.84	0.76	0.59–0.97	0.84	0.73–0.96
COPD	1.45	1.12–1.87	0.82	0.49–1.37	0.98	0.75–1.28
Pneumonia	1.14	0.86–1.50	0.91	0.54–1.52	0.76	0.56–1.03
SAS	0.57	0.18–1.80	0.45	0.06–3.17	1.89	1.09–3.28
Chronic kidney disease	2.45	1.76–3.42	1.09	0.52–2.28	1.62	1.13–2.32
Cancer	0.87	0.73–1.03	0.91	0.70–1.19	0.90	0.77–1.04
Initiated on combination therapy	1.55	1.25–1.93	1.54	1.10–2.16	1.41	1.16–1.73

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HF, heart failure; MI, myocardial infarction; SAS, sleep apnea syndrome; sHR, subdistribution hazard ratio.

admissions for MI and 847 admissions for stroke, resulting in incidence rates of 10.4/1,000 person-years for HF admission, 4.1/1,000 person-years for MI admissions and 12.9/1,000 person-years for stroke admissions. The 5-year cumulative incidence was 5.4% (95% confidence interval [CI] 4.9–5.9%) for HF admission, 1.9% (95% CI 1.7–2.2%) for MI admission and 6.1% (95% CI 5.7–6.6%) for stroke admission (Figure 3). Figure S1 shows the 5-year cumulative incidence of the three outcomes by age group and sex. When we restricted the cohort to patients without a diagnosis of CVD during the baseline period, the cumulative incidence of HF, MI and stroke admissions at 5 years was 4.6% (95% CI 4.0–5.1%), 1.6% (95% CI 1.3–1.9%) and 4.5% (95% CI 4.1–5.1%), respectively (Figure 4).

Patients experiencing these events were older than the overall cohort and were more likely to be men (Table 1). They also had a higher prevalence of CV and non-CV comorbidities at baseline. Those hospitalized for HF included the highest proportion of patients aged ≥85 years and with hypertension. The proportion of patients with past CVD was highest among patients hospitalized for stroke during the follow-up period. The BMI and HbA1c values of those experiencing the outcomes did not differ greatly from those who did not. Patients with reduced eGFR (<60 mL/min/1.73 m²) were substantially more frequent among the patients experiencing these events during the follow-up period, accounting for 40.2% of the HF

admission group, 32.7% of the MI admission group and 30.5% of the stroke admission group.

Predictors of CVD events

In the Fine–Gray model, age was identified as the strongest predictor of admission for HF, and age ≥85 years had a subdistribution hazard ratio (sHR) of 5.45 (95% CI 4.23–7.03; Table 2). Women had a substantially lower sHR than men (sHR 0.69, 95% CI 0.59–0.81). Other strong predictors of HF admission included chronic kidney disease (sHR 2.41, 95% CI 1.73–3.36), chronic obstructive pulmonary disease (sHR 1.44, 95% CI 1.12–1.86) and CVD (sHR 1.30, 95% CI 1.11–1.53). Those started on combination drug therapy were more likely to experience HHF compared with those not (sHR 1.55, 95% CI 1.25–1.93). Age and sex were also strong predictors of the secondary outcomes, hospital admission for MI or stroke. Previous CVD was a strong predictor of admission for stroke (sHR 1.87, 95% CI 1.62–2.16), as were sleep apnea syndrome (sHR 1.85, 95% CI 1.07–3.22) and chronic kidney disease (sHR 1.60, 95% CI 1.12–2.28). Patients started on combination drug therapy were also at increased risk of both MI (sHR 1.54, 95% CI 1.10–2.16) and stroke (sHR 1.41, 95% CI 1.16–1.73). No comorbidities correlated strongly with the incidence of admission for MI, except for a previous diagnosis of CVD.

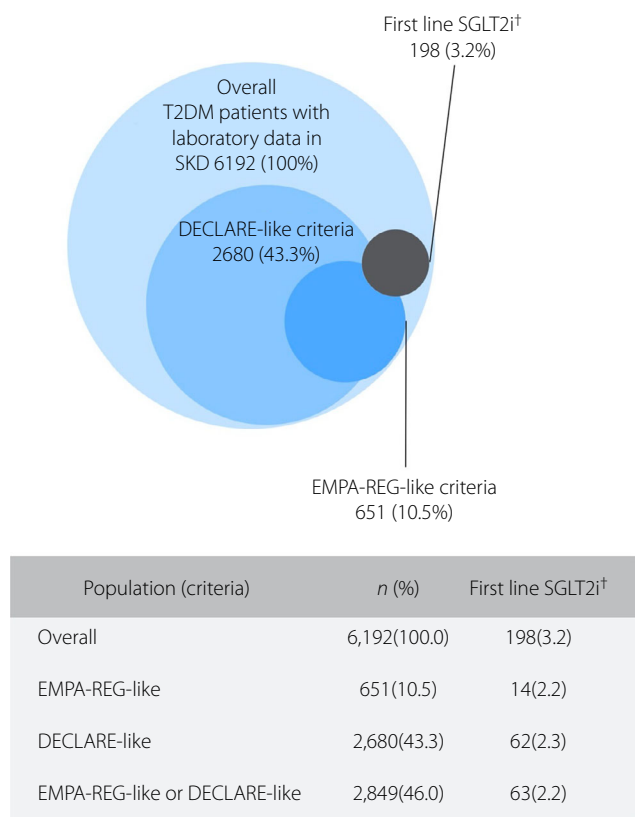


Figure 5 | Number of patients with type 2 diabetes mellitus (T2DM) meeting each set of cardiovascular disease risk criteria. The circles are proportional to the population sizes of each criteria. †Including first-line treatment of mono- or combination sodium–glucose cotransporter 2 inhibitor (SGLT2i) therapy. DECLARE, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58); EMPA-REG, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME); SKD, Shizuoka Kokuho database.

Identification of SGLT2i-eligible patients

From the health checkup data, we identified 6,192 patients with information on eGFR, HbA1c and smoking history. Of these, 651 (10.5%) patients met the EMPA-REG-like criteria, and 2,680 (43.3%) patients met the DECLARE-like criteria (Figure 5). Many of the patients in the cohort who initiated treatment with SGLT2i did not meet either set of criteria (among the 166 patients in the cohort who initiated treatment with SGLT2i, 54 [32.5%] met one or the other set of criteria). The 5-year cumulative incidence of admission for HF among the patients who met the EMPA-REG-like criteria or the DECLARE-like criteria was 5.7% or 2.8%, respectively (Figure 6), resulting in an estimated number of cumulative events of 37.3 and 75.4 events. When we combined the patients who met either of the two sets of criteria (after we categorized those with overlapping indications in the EMPA-REG-like criterion group),

the estimated event count was 97.1 over the 5 years (Table 3). Based on the risk reduction estimates from the two clinical trials, if 75% of those meeting either set of criteria were treated with SGLT2i, the event count was estimated to be 75.6, constituting a reduction of 21.5 events within 5 years among this cohort of 6,192 patients who initiated antidiabetic drug treatment.

DISCUSSION

In the present study, we assessed the incidence of admissions for HF among type 2 diabetes mellitus patients and the potential reduction in this incidence with the further introduction of SGLT2i. Notably, among the patients who initiated treatment with an oral antidiabetic drug, the 5-year cumulative incidence of hospitalization for HF was 5.4%, equivalent to the incidence of CV outcomes, such as stroke (6.1%). A significant portion of patients in our cohort met EMPA-REG-like (10.5%) and DECLARE-like criteria (43.3%), and the estimated reduction in the 5-year cumulative incidence of HF admissions among these patients was substantial.

The patients in the present study population were more likely to be older, female, with lower BMI and lower HbA1c than the patients in the representative large-scale randomized clinical trials^{2–4}. When we compared our population with the other national diabetes registry, it was slightly older, but had similar CV disease profiles^{8–10}. In terms of the treatment pattern, the use of metformin was lower, and the use of DPP4i was higher in the present study than in other studies^{2–4,8,9}. This finding probably stems from the unique characteristics of the Japanese medical system, which focuses on the safety profile rather than the efficacy or cost of medications¹¹. However, the use of SGLT2i increased over the study period, even in the Shizuoka Kokuho database, suggesting that the results of the representative trials have had a definite impact, and that a paradigm shift has occurred in the management of patients with type 2 diabetes mellitus and established CV diseases, shifting the aim from lowering HbA1c alone to a broader focus on reducing CV outcomes.

The event rate of hospitalization for HF in the present study was 10.4/1,000 person-years. The corresponding rates in the placebo arms of the EMPA-REG OUTCOME, Canagliflozin Cardiovascular Assessment Study (CANVAS) and DECLARE-TIMI 58 trials were 14.5, 8.7 and 8.5/1,000 person-years, respectively, so our results are comparable to the results of those studies. Age has been reported as one of the strongest predictors of HF hospitalizations among type 2 diabetes mellitus patients^{12–14}, and was consistent in the present study. The disease burden on society from HF hospitalizations among type 2 diabetes mellitus patients seems particularly grave for nations with a rapidly increasing number of older adults, such as Japan. Recent studies have shown that SGLT2i consistently reduce the risk of HF hospitalization across a broader spectrum of patients with type 2 diabetes mellitus^{5,15}, suggesting that

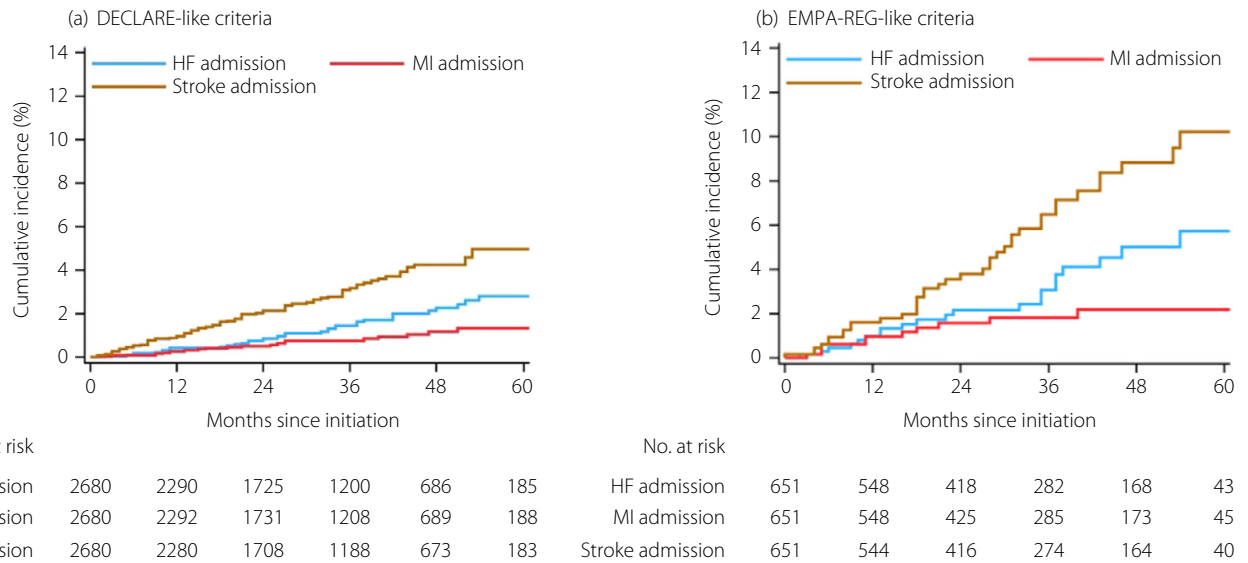


Figure 6 | Five-year cumulative incidence of admission for heart failure (HF), myocardial infarction (MI) and stroke among patients who met the (a) DECLARE-like or (b) EMPA-REG-like criteria. DECLARE, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58); EMPA-REG, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME).

Table 3 | Estimated number of admissions for heart failure by the sodium–glucose cotransporter 2 inhibitors eligibility criteria and percentage of patients put on sodium–glucose cotransporter 2 inhibitors treatment

	SGLT2i eligibility criteria		
	Total <i>n</i> = 2,849	EMPA-REG-like <i>n</i> = 651	DECLARE-like <i>n</i> = 2,680
Proportion of SGLT2i initiators			
Estimated cumulative incidence of HF admission	97.1	37.3	75.4
Estimated number of HF admissions within 5 years if 25–75% of those who met the criteria were treated with SGLT2i			
75%	75.6	27.6	60.6
50%	82.8	30.9	65.5
25%	89.9	34.1	70.5

DECLARE, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58); EMPA-REG, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME); HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitors.

SGLT2i should be considered for patients with type 2 diabetes mellitus regardless of age, a history of HF or CV risk.

Before 2015, in general, none of the landmark trials in patients with type 2 diabetes mellitus showed that reduced CVD or mortality rates were better achieved with intensive glycemic control than with conventional glycemic control¹⁶. However, in the past 5 years, several major trials showed improved CV outcomes with SGLT2i in patients with type 2 diabetes mellitus, either with or without established CVD. Given the magnitude of the CV benefits observed in these clinical trials, it is important to understand the proportion of patients potentially eligible for these trials in real-world

clinical practice and the current patterns of use of these medications in potentially eligible patients^{2–4}. Among the 6,192 patients with overt type 2 diabetes mellitus in our cohort, 651 (10.5%) and 2,680 (43.3%) were identified as potentially eligible for the EMPA-REG OUTCOME and DECLARE-TIMI 58 trials, respectively, which are similar to other registry data in the USA and Europe^{8,9}. Furthermore, the use of SGLT2i in potentially trial-eligible patients was low, with 1.9% of potentially eligible patients receiving SGLT2i. This finding is consistent with those of a previous study in which 5.2% of the potentially eligible patients in a large USA diabetes outpatient registry received SGLT2i⁸.

The patient characteristics and outcomes of Asians with type 2 diabetes mellitus differ considerably from those of patients in Western countries¹⁷. The Asia-Pacific Cohort Studies Collaboration pooled retrospective studies from the region and confirmed that type 2 diabetes mellitus was associated with a twofold increase in the risk of CVD among Asians, with even greater hazard ratios in younger compared with older people¹⁸. Previously, we have also evaluated the impact of diabetes in two large-scale coronary artery disease registries from Japan and the USA. Although the prevalence of type 2 diabetes mellitus was greater in the Japanese patients, the long-term mortality rate was significantly lower in the Japanese type 2 diabetes mellitus patients than the USA patients¹⁷. Therefore, the outcomes of type 2 diabetes mellitus patients in relation to novel drug treatments, such as SGLT2i in regions outside of North America and Europe, including CV events, might also differ, albeit reassuringly, the Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium–Glucose Cotransporter 2 Inhibitors (CVD-REAL 2) study showed that commencing treatment with an SGLT2i was associated with a significantly lower risk of CV events than commencing treatment with other glucose-lowering drugs, even in Asian–Pacific countries¹⁹. These findings underscore the importance of better understanding the underlying ethnicity-specific mechanisms of poor outcomes for type 2 diabetes mellitus, and of aggressive ethnicity-tailored strategies to prevent type 2 diabetes mellitus and its complications. Here, we have shown the potential number of events that could be avoided in a contemporary Asian type 2 diabetes mellitus population. In this way, the present findings contribute to the growing body of literature on improved outcomes for Asian type 2 diabetes mellitus-affected populations.

The present study should be interpreted in the context of the following potential limitations. First, because Japanese clinical guidelines leave treatment selection to the physician's discretion, with consideration of the patient's characteristics and the pathophysiology of the disease, Japanese physicians often favor DPP4i and prescribe metformin to ~50% of patients^{11,20,21}. Therefore, it might be difficult to extrapolate the present results to Western patients, because the patient characteristics, prescribing practices and the management of type 2 diabetes mellitus differ. Second, like other studies involving secondary use of claims databases for clinical research, the outcomes were defined with ICD-10 codes in the present study. We chose a conservative definition, using only hospitalized cases for the outcomes, but the validity of these codes has not been fully tested in our study population, leaving room for the over- or underestimation of the disease incidence rates. Third, we assumed that the treatment effect of SGLT2i was the same as that in the randomized controlled trial cohorts and was uniform across patients. The treatment effect of SGLT2i in our cohort might have differed from that reported in the randomized controlled trials cited, especially if the treatment effects are not homogenous across the patients.

The incidence of HF among Japanese type 2 diabetes mellitus patients is high and is almost equivalent to that of major vascular events, such as stroke. The increased prevalence of SGLT2i use among patients with a high CV risk might significantly reduce the disease burden associated with HF.

ACKNOWLEDGMENTS

The Research Support Center in Shizuoka General Hospital conducts contract research projects for public health in Shizuoka Prefecture, including this study.

DISCLOSURE

Dr Kohsaka reports investigator-initiated grant funding from Bayer and Daiichi Sankyo. Dr Kumamaru has received consultation fees from Mitsubishi Tanabe Pharma and speaker fees from Pfizer Japan Inc. Dr Yamamoto has received consultation fees from Mitsubishi Tanabe Pharma, speaker fees from Chugai Pharmaceutical Co., Ltd. and Ono Pharmaceutical Co., Ltd., and payment for a manuscript from Astellas Pharma Inc. Dr Miyata has received a research grant from AstraZeneca K.K. for an independent research project through PeoPLe consortium at Keio University. Dr Kohsaka, Dr Kumamaru, Dr Nishimura, Dr Shoji, Dr Ichihara, Dr Yamamoto and Dr Miyata are affiliated with the Department of Healthcare Quality Assessment at the University of Tokyo. The department is a social collaboration department supported by National Clinical Database, Johnson & Johnson K.K. and Nipro Corporation. The other authors declare no conflict of interest.

REFERENCES

1. American Diabetes Association. Cardiovascular disease and risk management: standards of medical care in diabetes-2020. *Diabetes Care* 2020; 43: S111–S134.
2. Zinman B, Wanner C, Lachin JM, *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128.
3. Neal B, Perkovic V, Mahaffey KW, *et al.* Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 644–657.
4. Wiviott SD, Raz I, Bonaca MP, *et al.* Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; 380: 347–357.
5. Zelniker TA, Wiviott SD, Raz I, *et al.* SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019; 393: 31–39.
6. Cosentino F, Grant PJ, Aboyans V, *et al.* 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020; 41: 255–323.
7. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet* 2005; 365: 82–93.

8. Arnold SV, Inzucchi SE, Tang F, *et al.* Real-world use and modeled impact of glucose-lowering therapies evaluated in recent cardiovascular outcomes trials: an NCDR® Research to Practice project. *Eur J Prev Cardiol* 2017; 24: 1637–1645.
9. Birkeland KI, Bodegard J, Norhammar A, *et al.* How representative of a general type 2 diabetes population are patients included in cardiovascular outcome trials with SGLT2 inhibitors? A large European observational study. *Diabetes Obes Metab* 2019; 21: 968–974.
10. Giorgino F, Vora J, Fenici P, *et al.* Cardiovascular protection with SGLT2 inhibitors in type 2 diabetes mellitus: does it apply to all patients? *Diabetes Obes Metab* 2020; 22: 1–15.
11. Nishimura R, Kato H, Kisanuki K, *et al.* Treatment patterns, persistence and adherence rates in patients with type 2 diabetes mellitus in Japan: a claims-based cohort study. *BMJ Open* 2019; 9: e025806.
12. Nichols GA, Gullion CM, Koro CE, *et al.* The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004; 27: 1879–1884.
13. Chen HF, Ho CA, Li CY. Risk of heart failure in a population with type 2 diabetes versus a population without diabetes with and without coronary heart disease. *Diabetes Obes Metab* 2019; 21: 112–119.
14. Dunlay SM, Givertz MM, Aguilar D, *et al.* Type 2 diabetes mellitus and heart failure: a scientific statement from the American Heart Association and the Heart Failure Society of America: this statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. *Circulation* 2019; 140: E294–E324.
15. Fitchett D, Butler J, Van De Borne P, *et al.* Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOMEVR trial. *Eur Heart J* 2018; 39: 363–370.
16. Boineau R, Domanski M, Troutman C, *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358: 2545–2559.
17. Kohsaka S, Komeda M, Goto M, *et al.* Impact of diabetes among revascularized patients in Japan and the U.S. *Diabetes Care* 2012; 35: 654–659.
18. Asia Pacific Cohort Studies Collaboration (APCSC). The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. *Diabetes Care* 2003; 26: 360–366.
19. Kosiborod M, Lam CSP, Kohsaka S, *et al.* Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. *J Am Coll Cardiol* 2018; 71: 2628–2639.
20. Haneda M, Noda M, Origasa H, *et al.* Japanese clinical practice guideline for diabetes 2016. *J Diabetes Investig* 2018; 9: 657–697.
21. Morita Y, Murayama H, Odawara M, *et al.* Treatment patterns of drug-naïve patients with type 2 diabetes mellitus: a retrospective cohort study using a Japanese hospital database. *Diabetol Metab Syndr* 2019; 11: 1–10.

SUPPORTING INFORMATION

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

Figure S1 | Age group and sex-specific 5-year cumulative incidence of admissions of heart failure, myocardial infarction and stroke.