ORIGINAL RESEARCH ARTICLE

Prescription patterns of diabetes medications influencing clinical outcomes of heart failure patients with reduced ejection fraction

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Abstract

Aims   We collected the different prescription patterns of diabetes medications in a cohort of patients with heart failure with reduced ejection fraction (HFrEF) and analysed the impact of different prescription patterns on clinical outcomes.
Methods and results   Consecutive diabetic patients with HFrEF from a heart failure referral centre were retrospectively analysed between 2015 and 2016. Exclusion criteria include being lost to follow-up, not receiving diabetes medications, and having severe renal impairment with a glomerular filtration rate < 30 mL/min/1.73 m^2. Prescription of diabetes medications and the respective clinical outcomes were collected between 2016 and 2018. Among 381 patients (mean age, 64.8 ± 12.8 years; 71.9% male; mean left ventricular ejection fraction, 27.6 ± 7.0; mean body mass index, 26.1 ± 4.7 kg/m^2), the prescription rates of sodium-glucose co-transporter 2 inhibitor (SGLT2i) increased from 10.3% in 2016 to 17.6% in 2017 and 26.5% in 2018 ($P < 0.001$); the prescription rates of metformin, sulfonylurea, insulin, and dipeptidyl peptidase-4 inhibitors did not change significantly over time. The prescription rates of metformin and SGLT2i were significantly higher in patients managed by cardiologists than non-cardiologists (in 2018, 71.1% vs. 44.2% for metformin, 45.4% vs. 9.9% for SGLT2i, both $P < 0.001$). During the study period, annualized event rates of cardiovascular death or first unplanned HF hospitalization were 19.0 per 100 patient-years. After a multivariate analysis, prescriptions of metformin {odds ratio (OR): 0.49 [95% confidence interval (CI) 0.27–0.51], $P < 0.001$} and SGLT2i [OR: 0.52 (95% CI 0.28–0.98), $P = 0.042$] were independently associated with lower annualized event rates of cardiovascular death or unplanned HF hospitalization.
Conclusions   Prescription patterns of diabetes medications in diabetics with HFrEF were diverse among different specialists. Prescriptions of metformin and SGLT2i were associated with favourable clinical outcomes. Our finding indicates the importance of awareness of beneficial effect of different classes of diabetes medications and collaboration between specialists in the management of diabetic HFrEF patients.

Keywords   Heart failure; Sodium-glucose co-transporter 2 inhibitor (SGLT2i); Metformin; Diabetes mellitus

Introduction

Chronic heart failure (HF) is one of the leading causes of morbidity and mortality worldwide and a major burden on the global health care system. Owing to the rapidly aging population and prolonged survival of patients suffering from HF, the HF population is increasing rapidly worldwide.[1–3]

Diabetes mellitus (DM) is one of the most prevalent chronic diseases worldwide. Patients with DM have a 2.5-fold increased risk of developing HF. Patients with type 2 DM and poor glycaemic control and obesity are at high risk of

developing HF.[4] Diabetes patients also have increased risk of dying from HF.[5] Furthermore, in HF patients who were not treated for DM, higher haemoglobin A1c (HbA1c) was independently associated with higher risk of cardiovascular (CV) events.[6,7]

Although guideline-recommended HF therapies such as renin–angiotensin system (RAS) blockers, beta-blockers, and mineralocorticoid receptor antagonists (MRAs) work similarly well in patients with and without DM,[5] different classes of diabetes medications have different pharmacological effects on patients with HF. In particular, thiazolidinedione (TZD) causes sodium and water retention, increases risk of worsening HF and hospitalization, and is therefore contraindicated in HF patients.[8,9] In addition to TZD, other commonly used diabetes medications, such as sulfonylurea (SU) derivatives and some classes of dipeptidyl peptidase-4 inhibitor (DPP4i), possibly increase risks of CV events and worsening HF.[5,9,10] Insulin as well, which acts as a potent sodium-retaining hormone through reducing urinary sodium excretion via various sodium channels along renal tubules, exacerbates fluid retention and can therefore potentially deteriorate the congestion symptoms in HF patients.[11–14] Currently, metformin is regarded as the better treatment of choice in HF patients with DM.[15] Although there was a lack of a large-scale, randomized controlled trial confirming the beneficial effects of metformin on HF, a systemic review of nine observational studies including 34 000 subjects demonstrated no increase in adverse events among diabetic patients with HF with reduced ejection fraction (HFrEF) treated with metformin.[16] The sodium-glucose co-transporter 2 inhibitor (SGLT2i) has been demonstrated to reduce HF hospitalization in patients who had or were at risk of developing atherosclerotic CV disease and therefore has potential benefit in patients with both DM and HF.[17–19] A recent published meta-analysis of randomized, placebo-controlled, CV outcome trials of SGLT2i demonstrated that it could reduce risk of HF hospitalization by 31%.[20] Although only few patients with baseline cardiac failure of reduced left ventricular ejection fraction (LVEF) were enrolled in randomized trials of SGLT2i, the effect of SGLT2i to reduce HF hospitalization seems to be comparable and potentially superior in patients with HF than in those without HF.[17,21]

The guideline from the American Diabetes Association standard of medical care in diabetes recommends that in type 2 DM patients with CV disease, diabetic therapy should begin with lifestyle management and metformin. If HF predominates in these patients, SGLT2i with evidence of reducing HF hospitalization should be considered as the treatment strategy.[22] In patients with HFrEF, physician's adherence to treatment guideline was closely associated with clinical outcome and prognosis.[23] However, the prescription rates of various diabetes medications and treatment outcomes in real-world HF patients have not be widely reported. Therefore, the aim of our study was to analyse the physicians'

prescription pattern of diabetes medications in HF patients and to evaluate the impact of prescription pattern on clinical outcomes.

Methods

Study design and study population

Our study aimed to evaluate different prescription patterns and effects of diabetes medications in HFrEF patients. Our study complied with the ethical principles of the Declaration of Helsinki and was approved by the institutional ethics committee of Cheng Hsin General Hospital. The definition of HF is consistent with the European Society of Cardiology (ESC) guideline: presentation of typical HF symptoms accompanied by HF signs caused by a structural and/or functional cardiac abnormality.[9] The definition of HFrEF patient is patient with New York Heart Association (NYHA) class II, III, or IV HF symptoms and with LVEF < 40%.

Between 2015 and 2016, all patients had been retrospectively and consecutively screened from the HF database in the Cheng Hsin General Hospital, which is a tertiary referral centre for HF management and cardiac transplant in Taiwan. Inclusion criteria for the current study included (i) male or female, with age $\geq$ 20 years at screening; (ii) patients with chronic HF and NYHA Functional Classification (Fc) II to IV; (iii) documented LVEF < 40% by echocardiography before screening; and (iv) DM with at least one type of oral diabetes medication and/or insulin injection. The exclusion criteria for the current study included (i) patients refused medical advice or were lost to follow-up; (ii) HF with echocardiographic LVEF $\geq$ 40%; (iii) HF primarily from right ventricular failure, pericardial disease, or congenital heart disease; (iv) severe renal impairment, defined as a glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 or requiring dialysis; and (v) patients with type 1 DM or gestational DM.

After inclusion and exclusion criteria were applied, a total of 381 eligible diabetic patients with HFrEF were enrolled (Figure 1). Baseline characteristics were recorded. The prescription patterns of diabetes medications were collected annually since the beginning of the next year after enrolment until the end of 2018. A total of 319, 340, and 324 patients had adequate data for analyses in 2016, 2017, and 2018, respectively.

Standard HF treatment of these patients, including RAS blockers, beta-blockers, MRA, diuretics, and programming of implantable cardiac device, was prescribed and performed by cardiologists. Diabetes medications were prescribed by cardiologists, endocrinologists, or internal medicine physicians. Patients could freely decide which specialists to see for diabetic control. The study protocol was approved by the institutional review board.

Figure 1 The inclusion and exclusion criteria flow chart. DM, diabetes mellitus; GFR, glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.
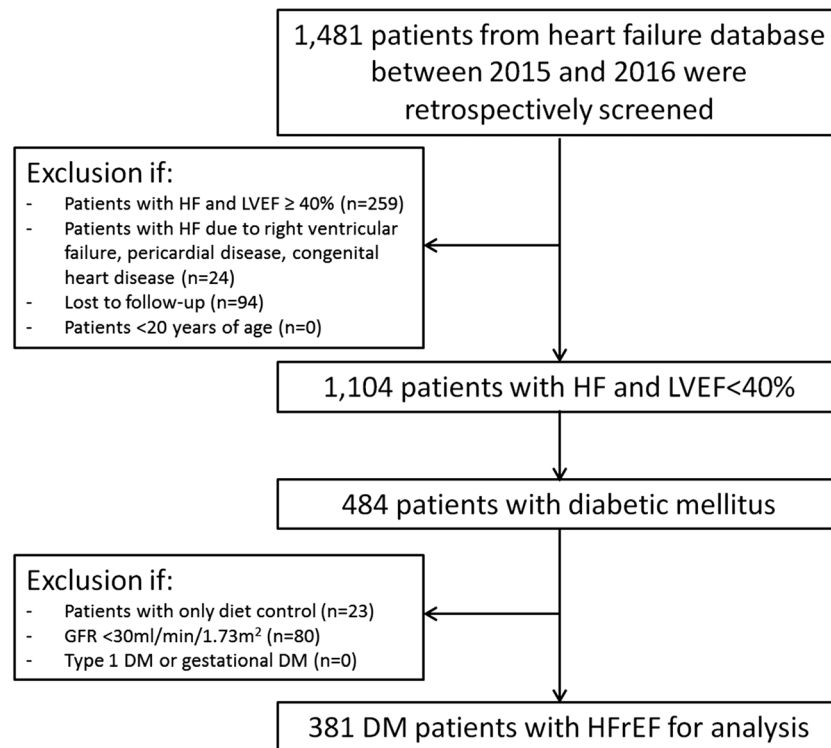
Echocardiography studies

Echocardiographic images were acquired at baseline in every patient. Left ventricular end-diastolic diameter was measured at end-diastole, and left ventricular end-systolic diameter and left atrial anteroposterior dimension were measured at end-systole on parasternal views. The LVEF was calculated using the biplane Simpson's method on apical four-chamber and two-chamber views. Continuous wave Doppler of the tricuspid regurgitation trace is used to measure and estimate pulmonary artery systolic pressure (PASP).

Prescription of diabetes medications and adherence to guideline

The classes of diabetes medications were classified as follows: metformin, SGLT2i, SU, DPP4i, alpha-glucosidase inhibitor (AGI), insulin, and TZD. Physicians prescribing diabetes medications were classified into three groups including cardiologists and endocrinologists. The data of prescriptions were collected annually in 2016, 2017, and 2018. Diabetes medications prescribed for >50% of treatment period in the particular year would be regarded as 'prescribed medications' for that year.

Prescription patterns of anti-hyperglycaemic agents were further classified as follows: Pattern A, metformin monotherapy, metformin-based therapy with SGLT2i, and SGLT2i-based therapy without metformin; Pattern B, metformin-based therapy with anti-hyperglycaemic medication other than SGLT2i; and Pattern C, anti-hyperglycaemic medication without metformin or SGLT2i.

Clinical outcomes

Death from CV causes or first unplanned hospitalization for HF was defined as the primary outcome of our study. In addition, death from CV causes alone, death from any cause, sudden cardiac death, and total incident of unplanned re-hospitalization for HF were also collected. Severe hypoglycaemia was defined as having low blood glucose levels that required hospitalization.

Statistical analysis

Quantitative data were expressed as mean ± standard deviation or as median and inter-quartile range, and categorical variables were presented as percentages. Descriptive summaries were presented for different groups of patients. The

Student *t*-test or the Mann–Whitney *U*-test was used for comparisons between continuous data, and a χ^2 test was used for comparisons between categorical data. For the clinical outcome analysis, annualized event rates were estimated using the total number of clinical outcomes during the follow-up period divided by 100 patient-years at risk. Baseline characteristics, vital signs, HbA1c, renal function, echocardiographic parameters, HF, and diabetes medications were used for a univariate analysis. A multivariate logistic regression analysis with forward selection was performed to assess the predictability of variables on the primary outcome presented as odds ratios and 95% confidence intervals (CIs) using $P < 0.1$ in univariate analyses for inclusion. A P value of <0.05 was considered to be statistically significant. All tests were two-sided. All the statistical analyses were performed using the SPSS Statistics 17.0 software (Chicago, IL, USA).

Results

General information and baseline heart failure management

Our study included 381 diabetic patients (age 64.8 ± 12.8 years, 71.9% male). The LVEF of all the patients were $<40\%$ at baseline, and the mean LVEF was 27.6 ± 7.0. The baseline characteristics are shown in *Table 1*. The prescription rates of RAS blockers, beta-blockers, and MRAs were 82.9%, 80.6%, and 63.5%, respectively. A total of 35 (9.2%) patients received cardiac resynchronization therapy and/or implantable cardioverter-defibrillator. The HF medications and cardiac implantable devices were prescribed, programmed, and monitored by cardiologists.

Prescription rates and patterns of different anti-hyperglycaemic agents

Patients in the current study received 2 ± 1 types of diabetes medications for glycaemic control. The average duration of diabetes was 9.1 ± 4.1 years. Approximately 45% of patients received diabetes medications from cardiologists. Diabetes was managed by either endocrinologists or other specialists in 30% and 25% of patients, respectively. This trend did not differ throughout the study period, as shown in *Table 2*.

Table 2 also shows the prescription rates of different diabetes medications over time. The prescription rates of SGLT2i increased significantly from 10.3% in 2016 to 17.6% in 2017 and to 26.5% in 2018 ($P < 0.001$), with an ~8% annual increment. The prescription rates of metformin were also increased from 2016 to 2018, with a 3-percentage annual increment, but this was not statistically significant ($P = 0.206$). The prescription rates of DPP4i, SU, AGI, and insulin

Table 1 Baseline characteristics of study patients

	Diabetic patients with HFrEF (*n* = 381)
Age (year)	64.8 ± 12.8
Male gender, *n* (%)	274 (71.9)
Body mass index (kg/m^2)	26.1 ± 4.7
Systolic BP (mmHg)	122.4 ± 18.7
Heart rate (b.p.m.)	82.7 ± 14.6
NYHA Fc III or IV, *n* (%)	86 (22.6)
Medical history, *n* (%)	
Non-ischaemic cardiomyopathy	166 (43.6)
Hypertension	232 (60.9)
Old myocardial infarction	157 (41.2)
Stroke/TIA	56 (14.7)
Atrial fibrillation	117 (30.7)
Previous HF hospitalization	242 (63.5)
Previous valvular surgery	31 (8.1)
Hyperlipidaemia	224 (58.8)
COPD/asthma	42 (11.0)
Chronic kidney disease	150 (39.4)
Heart failure treatment, *n* (%)	
RAS blocker	316 (82.9)
Beta-blocker	307 (80.6)
MRA	242 (63.5)
CRT/ICD	35 (9.2)
Haemoglobin A1c (%)	7.7 ± 1.8
GFR (mL/min/1.73 m^2)	67.0 ± 24.2
GFR ≥90 mL/min/1.73 m^2, *n* (%)	58 (15.2)
GFR 60–90 mL/min/1.73 m^2, *n* (%)	165 (43.3)
GFR 30–60 mL/min/1.73 m^2, *n* (%)	158 (41.5)
Echocardiographic parameters	
LVEF (%)	27.6 ± 7.0
LA diameter (mm)	48.5 ± 6.6
LVEDD (mm)	55.9 ± 8.2
LVESD (mm)	45.8 ± 9.8
PASP (mmHg)	40.5 ± 16.0
Severe mitral regurgitation, *n* (%)	94 (24.7)
Severe tricuspid regurgitation, *n* (%)	60 (15.7)

BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MRA, mineralocorticoid receptor antagonists; NYHA Fc, New York Heart Association Functional Classification; PASP, pulmonary artery systolic pressure; RAS, renin–angiotensin system; TIA, transient ischaemic attack.

did not differ significantly throughout the study period. Patients who had ever been treated with insulin therapy tend to have longer duration of diabetes than had those who did not require insulin (11 ± 4.4 vs. 8.5 ± 3.7 years, $P < 0.001$). The prescription rates of TZD were ~2% annually. None of the study patients received glucagon-like peptide-1 receptor agonist treatment.

Figure 2 demonstrates the different prescription patterns among different specialists and different years. Overall, the most commonly prescribed diabetes medication by

Table 2 Distribution of physician specialties and prescription patterns of anti-hyperglycaemic agents in study patients

Year	2016 (*n* = 319)	2017 (*n* = 340)	2018 (*n* = 324)	*P* value
Numbers of anti-hyperglycaemic agents prescribed	2.1 ± 1.0	2.1 ± 1.0	2.1 ± 1.0	0.712
Physicians who prescribe anti-hyperglycaemic agents, *n* (%)				
Cardiologists	135 (42.3)	157 (46.2)	152 (46.9)	0.778
Endocrinologists	102 (32.0)	99 (29.1)	97 (29.9)	
Others	82 (25.7)	84 (24.7)	75 (23.1)	
Prescribed anti-hyperglycaemic agents, *n* (%)				
Metformin	159 (49.8)	179 (52.6)	184 (56.8)	0.206
SGLT2i	33 (10.3)	60 (17.6)	86 (26.5)	<0.001
DPP4i	157 (49.2)	164 (48.2)	138 (42.6)	0.189
SU	156 (48.9)	158 (46.5)	142 (43.8)	0.435
AGI	71 (22.3)	66 (19.4)	62 (19.1)	0.551
Insulin	63 (19.7)	69 (20.3)	68 (21.0)	0.926
TZD	4 (1.3)	7 (2.1)	6 (1.9)	0.715

AGI, alpha-glucosidase inhibitor; DPP4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SU, sulfonyl-urea; TZD, thiazolidinedione.

cardiologists was metformin. The most commonly prescribed diabetes medication by endocrinologists was DPP4i, but endocrinologists also prescribed metformin, SU, AGI, and insulin equally in 40% of their patients. The most commonly prescribed diabetes mediation by other physicians was SU. Compared with different physicians, cardiologists preferred to prescribe metformin and SGLT2i than did other specialists.

The prescription rates of metformin by cardiologists were ~60% in 2016, and it further increased to about 70% in 2018. On the contrary, the prescription rates of metformin by non-cardiologists were ~40%, which did not increase significantly over time. The prescription rates of SGLT2i by cardiologists increased significantly from 18.3% in 2016 to 30.5% in 2017 and to 46.3% in 2018. SGLT2i was the fourth most

Figure 2 (A–F) The distribution of prescribed diabetes medications over time. Asterisk indicates *P* value < 0.05. AGI, alpha-glucosidase inhibitor; DPP4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SU, sulfonylurea.
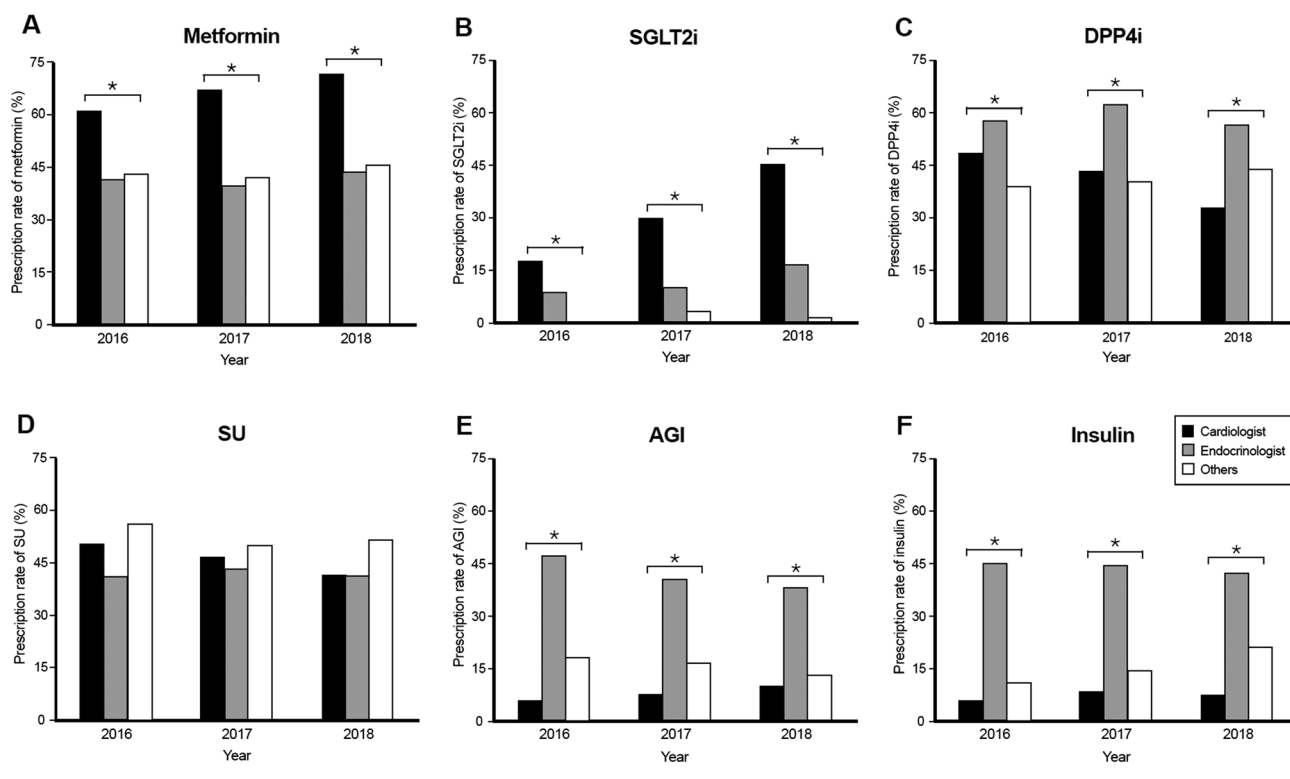
commonly prescribed diabetes medication by cardiologists in 2016 and 2017, but it became the second most commonly prescribed diabetes medication in 2018. The prescription rates of SGLT2i by endocrinologists also increased from 8.8% 2016 to 10.1% in 2017 and to 16.5% in 2018. The prescription rate of SGLT2i by other physicians was <4%. Endocrinologists were more likely to prescribe insulin, AGI, and DPP4i than were other specialists. The prescription rates of SU were similar among different specialists. These trends did not change significantly throughout the study period.

Figure 3 demonstrates the prescription patterns of diabetes medications among different specialists across different years. Pattern A increased gradually over the year [62 patients (19.4%), 92 (27.1%), and 114 (35.2%) in 2016, 2017 and 2018, respectively], and the upward trend was mainly driven by the prescription increase by cardiologists. Pattern B decreased from 103 patients (32.3%) in 2016 to 98 (28.8%) in 2017 and 86 (26.5%) in 2018, and Pattern C also decreased from 154 patients (48.3%) in 2016 to 150 (44.1%) in 2017 and 124 (38.3%) in 2018.

Clinical outcomes and predictors

Table 3 summarizes the clinical outcomes of our study. The incidence rate of death from CV causes or first unplanned hospitalization for HF was 19.0% per patient-year. The incidence rates of death from any cause, death from CV causes, and sudden cardiac death were 7.3%, 5.4%, and 3.0% per patient-year, respectively. The incidence rate of total unplanned HF hospitalization was 25.3% per patient-year.

In patients receiving metformin therapy with or without SGLT2i, the incidence of death from CV causes or first unplanned hospitalization for HF was 10.1% per patient-year, which was significantly lower than that of patients not taking metformin with or without SGLT2i therapy (30.6% per patient-year, $P < 0.001$, *Table 3A*). Incidence of death from any cause, death from CV cause, sudden cardiac death, and total numbers of unplanned re-hospitalization for HF were all significantly lower during the treatment period of metformin therapy with or without SGLT2i.

Figure 3 (A–D) The distribution of diabetes medications prescription pattern over time. Asterisk indicates statistical difference among years, *P* value < 0.05.
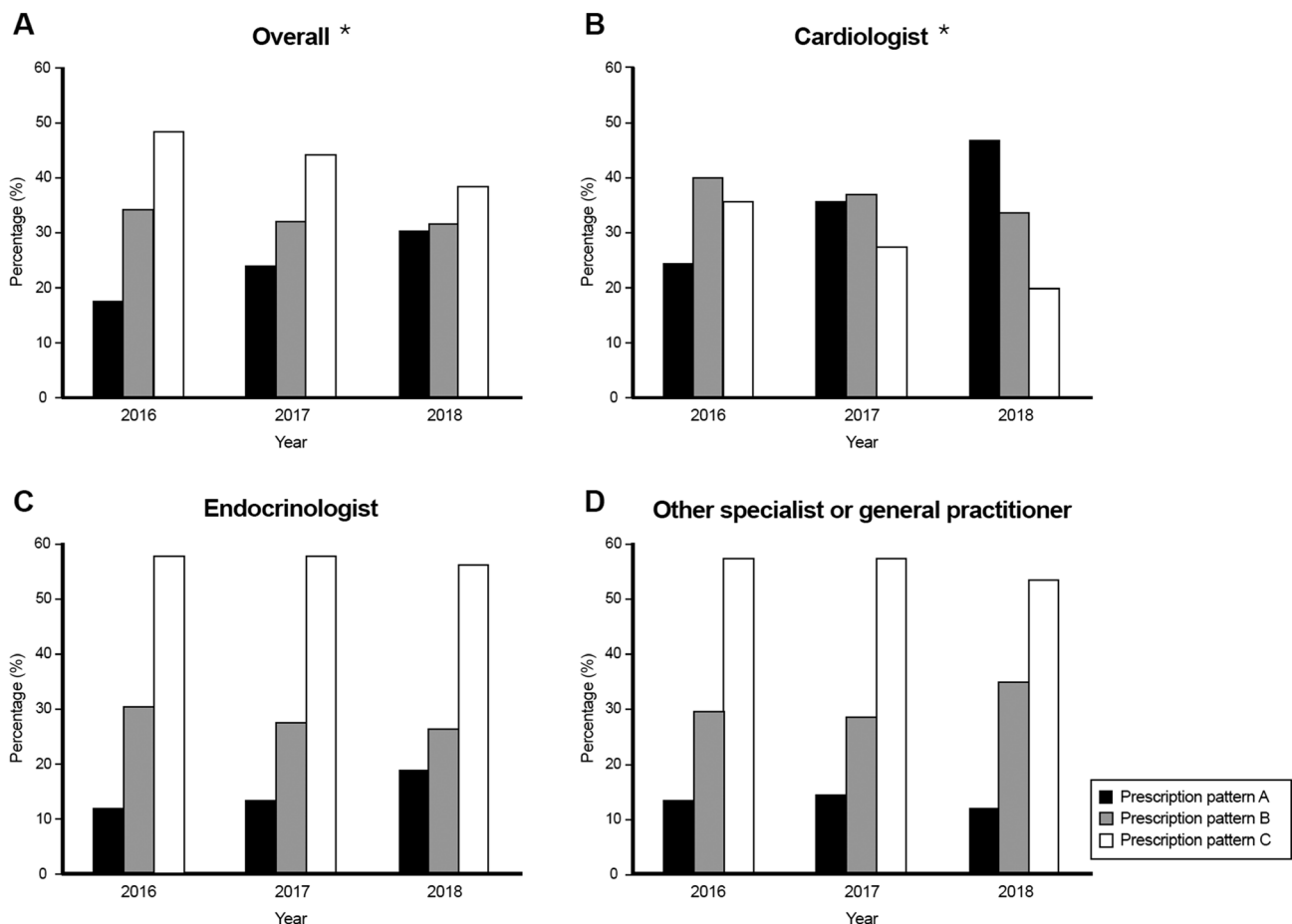
**Table 3** The cardiovascular clinical outcomes of patients

(A)

Events	Overall Incidence rate, *n* (%/patient-years)	Treated with metformin and/or SGLT2i Incidence rate, *n* (%/patient-years)	Not treated with metformin and/or SGLT2i Incidence rate, *n* (%/patient-years)	*P* value
CV death and/or 1st HFH	187 (19.0)	56 (10.1)	131 (30.6)	<0.001
All-cause mortality	72 (7.3)	20 (3.6)	52 (12.1)	<0.001
Cardiovascular death	53 (5.4)	16 (2.9)	37 (8.6)	<0.001
Total HFH	249 (25.3)	72 (13.0)	177 (41.4)	<0.001
Sudden cardiac death	29 (3.0)	10 (1.8)	19 (4.4)	0.016
Severe hypoglycaemia	5 (0.5)	1 (0.2)	4 (0.9)	0.095

(B)

Events	Pattern A Incidence rate, *n* (%/patient-years)	Pattern B Incidence rate, *n* (%/patient-years)	Pattern C Incidence rate, *n* (%/patient-years)	*P* value
CV death and/or 1st HFH	24 (9.0)	32 (11.1)	131 (30.6)	<0.001
All-cause mortality	6 (2.2)	14 (4.9)	52 (12.1)	<0.001
Cardiovascular death	5 (1.9)	11 (3.8)	37 (8.6)	<0.001
Total HFH	27 (10.1)	45 (15.7)	177 (41.4)	<0.001
Sudden cardiac death	3 (1.1)	7 (2.4)	19 (4.4)	0.035
Severe hypoglycaemia	0 (0)	1 (0.3)	4 (0.9)	0.084

Regarding different diabetes medications prescription patterns, *Table 3B* demonstrates that unfavourable clinical outcomes were least likely to occur during the treatment period of Pattern A and most likely to occur during the treatment period of Pattern C.

Figure 4 demonstrates the differences of annual incidence rate of death from CV causes or first unplanned hospitalization for HF, stratified according to prescriber (*Figure 3A*) and baseline renal function (*Figure 3B*). The incidence of CV death or first unplanned hospitalization for HF was significantly lower among patients receiving metformin and/or SGLT2i than among those who did not receive these medications, regardless of the prescriber. Similar statistical differences were also observed in the patients with GFR of 30–89 mL/min/1.73 m^2.

Figure 4 Annual incidence of death from cardiovascular causes or first unplanned hospitalization for heart failure in diabetic HFrEF patients, stratified according to diabetes medication prescriber (A) and baseline renal function (B). Asterisk indicates *P* value < 0.05. CV, cardiovascular; HFrEF, heart failure with reduced ejection fraction; SGLT2i, sodium-glucose co-transporter 2 inhibitor.
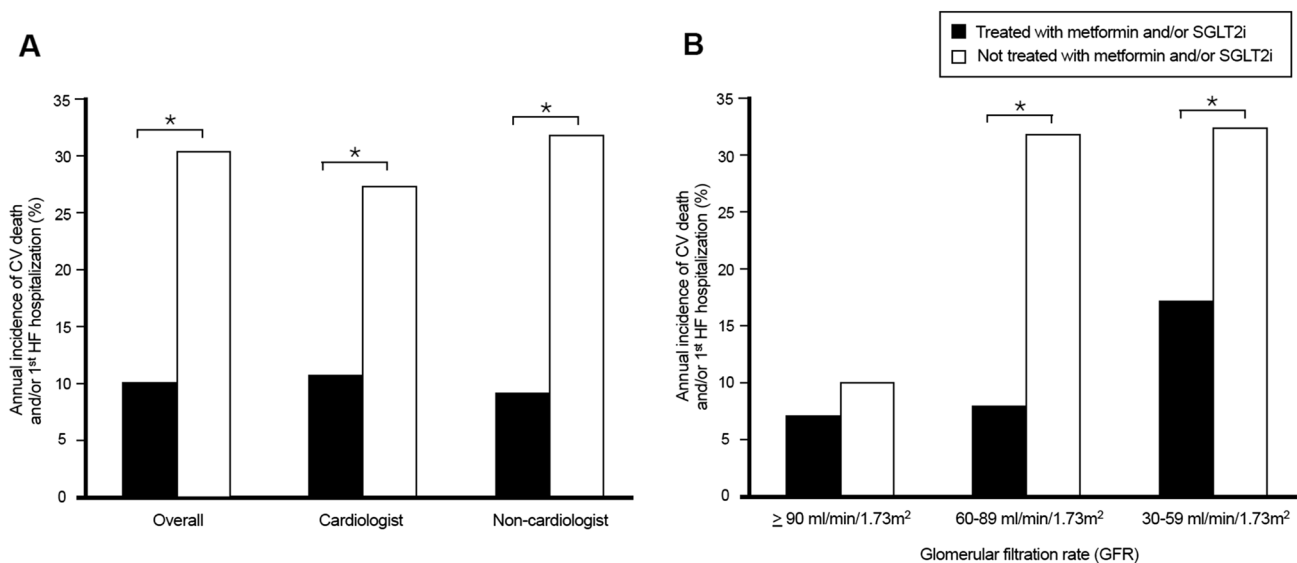
However, the event rates were low and did not differ significantly in patients with GFR $\geq$ 90 mL/min/1.73 m^2.

After adjustment for baseline characteristics, echocardiographic parameters, HF medications, diabetes medications, and physicians, the multivariate logistic regression analysis showed that the incidence of CV death or first unplanned hospitalization for HF was associated with history of chronic obstructive pulmonary disease, stroke or transient ischaemic attack, severe HF symptoms, worse LVEF, and higher baseline PASP. On the contrary, the prescriptions of RAS blocker, beta-blocker, metformin, and SGLT2i were all independently associated with favourable outcomes (*Table 4*, Model 1). In Model 2, diabetes medication prescription pattern was again demonstrated as an independent predictor of favourable clinical outcomes.

The incidence of severe hypoglycaemia was 0.5 per 100 patient-years. Severe hypoglycaemic event did not occur during the treatment period of Pattern A. There was numerically higher incidence of hypoglycaemia during the treatment period of Patterns B and C (0.3 and 0.9 per 100 patient-years, respectively, P = 0.084).

Discussion

The prescribing trend of diabetes medications

The prescription rates of SGLT2i were significantly increased across the study period, reflecting the impact of

Table 4 Multivariate analysis for risk factors associated with cardiovascular death or first unplanned hospitalization for heart failure

	Univariate analysis			Multivariate analysis	
	Event (+)	Event (−)	P value	OR (95% CI)	P value
Model 1 including different anti-hyperglycaemic agents					
Age (years)	66.7 ± 12.7	64.8 ± 12.2	0.036	—	NS
Stroke/TIA	21.4%	13.8%	0.009	1.72 (1.09–2.71)	0.019
Atrial fibrillation	37.4%	30.2%	0.049	—	NS
Previous HF hospitalization	78.1%	59.0%	<0.001	—	NS
COPD/asthma	19.3%	8.3%	<0.001	2.16 (1.30–3.59)	0.003
NYHA Fc III or IV	46.5%	13.6%	<0.001	3.93 (2.67–5.79)	<0.001
Systolic BP (mmHg)	119.0 ± 19.4	123.9 ± 18.2	<0.001	—	NS
LVEF (%)	26.2 ± 7.2	28.3 ± 6.9	<0.001	0.96 (0.94–0.99)	0.007
LA diameter (mm)	50.4 ± 5.9	47.9 ± 6.6	<0.001	—	NS
PASP (mmHg)	45.6 ± 17.0	38.1 ± 15.3	<0.001	1.02 (1.01–1.03)	0.001
GFR (mL/min/1.73 m^2)	57.6 ± 17.7	70.0 ± 25.2	<0.001	—	NS
Heart failure medication					
Prescription of RAS blocker	74.3%	87.1%	<0.001	0.49 (0.31–0.76)	0.002
Prescription of beta-blocker	71.7%	83.2%	<0.001	0.65 (0.43–0.99)	0.049
Diabetes mellitus medication					
Prescription of metformin	26.7%	59.3%	<0.001	0.40 (0.27–0.59)	<0.001
Prescription of SGLT2i	8.0%	20.6%	<0.001	0.52 (0.28–0.98)	0.042
Prescription of DPP4i	55.1%	44.7%	0.011	—	NS
Prescription of insulin	28.9%	18.3%	0.001	—	NS
Prescribed by cardiologist	36.4%	47.2%	0.007	—	NS
Model 2 including different prescription patterns					
Age (years)	66.7 ± 12.7	64.8 ± 12.2	0.036	—	NS
Stroke/TIA	21.4%	13.8%	0.009	1.74 (1.11–2.74)	0.017
Atrial fibrillation	37.4%	30.2%	0.049	—	NS
Previous HF hospitalization	78.1%	59.0%	<0.001	—	NS
COPD/asthma	19.3%	8.3%	<0.001	2.36 (1.41–3.96)	0.002
NYHA Fc III or IV	46.5%	13.6%	<0.001	4.24 (2.88–6.25)	<0.001
LVEF (%)	26.2 ± 7.2	28.3 ± 6.9	<0.001	0.96 (0.94–0.99)	0.006
LA diameter (mm)	50.4 ± 5.9	47.9 ± 6.6	<0.001	—	NS
PASP (mmHg)	45.6 ± 17.0	38.1 ± 15.3	<0.001	1.02 (1.01–1.03)	0.001
GFR (mL/min/1.73 m^2)	57.6 ± 17.7	70.0 ± 25.2	<0.001	—	NS
Heart failure medication					
Prescription of RAS blocker	74.3%	87.1%	<0.001	0.47 (0.30–0.73)	0.001
Prescription of beta-blocker	71.7%	83.2%	<0.001	0.64 (0.42–0.97)	0.038
Diabetes mellitus prescription pattern			<0.001	2.05 (1.57–2.68)	<0.001
Pattern A	12.8%	30.7%			
Pattern B	17.1%	32.0%			
Pattern C	70.1%	37.3%			
Diabetes medications prescribed by cardiologist	36.4%	47.2%	0.007	—	NS

BP, blood pressure; COPD, chronic obstructive pulmonary disease; DPP4i, dipeptidyl peptidase-4 inhibitors; GFR, glomerular filtration rate; HF, heart failure; LA, left atrial; LVEF, left ventricular ejection fraction; NYHA Fc, New York Heart Association Functional Classification; PASP, pulmonary artery systolic pressure; RAS, renin–angiotensin system; SGLT2i, sodium-glucose co-transporter 2 inhibitor; TIA, transient ischaemic attack.

growing evidence on HF reduction by SGLT2i. However, SGLT2i was only the fourth most commonly prescribed diabetes medications among the seven classes of drugs in 2018, after metformin (56.8%), DPP4i (43.8%), and SU (42.6%).

Metformin treatment was recommended as the first-line medication in the current guideline, and therefore, it was naturally the most prescribed anti-hyperglycaemic drug, although its gastrointestinal side effects were common and might restrict its usage.[22] In the DAPA-HF trial, which evaluated the effect of dapagliflozin in HFrEF patients, the most commonly prescribed baseline diabetes medication was metformin (50.8%).[24] The ASIAN-HF registry enrolled 5276 HFrEF patients from Northeast Asia, South Asia, and Southeast Asia between October 2012 and December 2015, which demonstrated that the most commonly prescribed diabetes medications were metformin (54%).[25] The prescription rates of metformin in both studies were similar to those in our study.

The current study showed that SU and DPP4i were respectively the second and third most commonly prescribed medications between 2016 and 2018. In the ASIAN-HF registry, SU was also the second most commonly prescribed diabetes medication (53%), and the prescription rates of insulin were the lowest in Taiwan and South Korea, whereas the prescription rates of DPP4i were the highest in Taiwan and Japan. The reasons for the heterogeneity of prescription pattern were not addressed, but the relatively high prescription rate of DPP4i was also shown in our study.[25]

Role of Dipeptidyl Peptidase-4 Inhibitors on cardiovascular system

Previously, the SAVOR TIMI-53 trial demonstrated that the saxagliptin group showed a significantly higher incidence of HF hospitalization than did the control group.[26] In the EX-AMINE study, patients with recent acute myocardial infarction treated with alogliptin also showed a trend of slight increase in admission to hospital for HF, although not statistically significant [hazard ratio (HR) 1.19, 95% CI 0.89–1.58, P = 0.22].[27] On the contrary, the VIVIDD study, which evaluated the effect of vildagliptin on ventricular function in HFrEF diabetic patients with NYHA Fc I to III and LVEF < 40%, demonstrated that although change of LVEF was not significant between vildagliptin and control groups, the left ventricular end-diastolic volume was significantly increased in the vildagliptin group than in the control group after 52 weeks of follow-up (P = 0.007).[28] As for another commonly prescribed DPP4i, linagliptin, the recently published CARMELINA trial, enrolling subjects with DM, high CV risk, and high renal risk, showed that adding linagliptin to usual care, when compared with placebo, resulted in a non-inferior risk of a

composite CV outcome.[29] Despite the slight incoherent results between different classes of DPP4i, the prescription rate of DPP4i remained high not only in our study group but also in the larger-scaled, aforementioned ASIAN-HF registry.[25] Based on our analysis, DPP4i is associated with a higher rate of CV death or unplanned hospitalization for HF in the univariate analysis, but not after multivariate adjustment.

Role of insulin on cardiovascular system

The interaction between insulin signalling pathway and HF is complicated. Various studies demonstrated that insulin resistance and hyperinsulinaemia are associated with cardiomyocyte mitochondrial dysfunction, LV remodelling with hypertrophy, and subsequent HF, likely through the regulation of insulin receptor substrate, PI-3K, Akt kinase, and Foxo-1.[30] Moreover, Defronzo *et al*. had described the anti-natriuretic effect of insulin.[13] Therefore, insulin could worsen fluid retention, and this raises the concern of exacerbation of HF symptoms.

Some observational studies had shown worse prognosis in patients treated with insulin.[31,32] However, in the ORIGIN trial, among patients with CV risk with diabetes or pre-diabetes, insulin glargine was not related to the increase in composite primary outcome of non-fatal myocardial infarction, non-fatal stroke, or death from CV causes as well as revascularization or hospitalization for HF.[33]

In our study cohort, the insulin-treated group had a higher event rate only after the univariate analysis, but the difference became insignificant after the multivariate analysis.

Benefit of sodium-glucose co-transporter 2 inhibitor and metformin in heart failure patients

The 2016 ESC Guideline of HF indicated that empagliflozin should be considered in diabetic patients to prevent or delay the onset of HF.[9] According to the recently published 2019 ESC expert consensus, the ability of all SGLT2i's to prevent the hospitalizations for HF in patients with DM is regarded as a class effect.[34] However, this consensus also emphasized that no specific recommendations for the use of SGLT2i in patients with established HF can be concluded owing to a lack of definite evidence. The upcoming randomized controlled trials such as DAPA-HF[24] and EMPEROR[35] could help to address this question.

The limitations of previous SGLT2i CV outcome trials were that the diagnosis, phenotype, and severity of HF had not been well characterized in general. In our current study exclusively enrolling DM patients with HFrEF, we found that patients who received metformin-based therapy

alone or with SGLT2i had significantly lower risk of all-cause mortality (3.6 vs. 12.1 per 100 patient-years, $P < 0.001$), death from CV causes (2.9 vs. 8.6 per 100 patient-years, $P < 0.001$), sudden cardiac death (1.8 vs. 4.4 per 100 patient-years, $P = 0.016$), and re-hospitalizations for HF (13.0 vs. 41.4 per 100 patient-years, $P < 0.001$) than had those without the therapy. The result basically echoes our current concept that SGLT2i is one of the most beneficial medications for decreasing HF and death. In the subgroup analysis of DECLARE-TIMI 58 trial, dapagliflozin reduced the risk of CV death or HF hospitalizations, CV death alone, HF hospitalizations alone, and all-cause mortality in patients with HFrEF. The benefit of dapagliflozin in patients with HFrEF occurred soon after drug initiation; in contrast, the benefit in HF patients with preserved LVEF was observed only after 1 year of administration of dapagliflozin.[21] This result echoed our study finding that early intervention with SGLT2i could allow early improvement of the clinical outcomes within a year.

The role of metformin on the CV system is less well established. Metformin acts through decreasing hepatic glucose production. It also functions as insulin sensitizer to enhance peripheral glucose uptake and utilization. To date, there has not been any large, randomized, controlled study focusing on the safety or efficacy of metformin in those with HF. However, Eurich et al. have conducted a systemic review of nine observational studies, including 34 000 patients with both DM and HF, to evaluate the association of metformin use on all-cause mortality and all-cause hospitalization. According to their analysis, metformin was associated with a small reduction in all-cause hospitalizations. Besides, metformin was not associated with increased risk of lactic acidosis. Therefore, the author concluded that metformin is at least as safe as other glucose-lowering agents in the population.[16] Chia et al. demonstrated that only metformin therapy was associated with reduced risk of the 1 year all-cause mortality or HF hospitalization in the ASIAN-HF registry after propensity score adjustment and that no significant risk reduction was found with other diabetes medications.[25]

In line with the aforementioned studies, our study also demonstrated a reduced risk of CV death and all-cause mortality, and hospitalization for HF in patients treated with metformin and SGLT2i. The DPP4i, along with 'insulin provision therapies', including insulin itself and SU, was negatively associated with CV events.

It is worth noting that the benefits of metformin-based therapy alone or with SGLT2i in current study were noted in patients with GFR of 30 to 90 mL/min/1.73 m^2 but not in patients with GFR $\geq$ 90 mL/min/1.73 m^2. Baseline risks among these patients with preserved renal function were relatively low, and hence, it was difficult to demonstrate the benefit of drug effects with a smaller sample size. Interestingly, GFR of 30 to 90 mL/min/1.73 m^2 was also the inclusion criterion of the CREDENCE trial, which enrolled patients at high risk of CV disease and demonstrated that canagliflozin could reduce HF hospitalization by 39% and CV death by 22%.[36] This finding further emphasizes the importance of optimal diabetes treatment for high-risk HFrEF patients with mild-to-moderate chronic kidney disease.

Study limitations

There were several limitations in the present study. First, in this observational, retrospective study, despite covariate adjustment, other unmeasured confounding factors might affect clinical outcomes. For example, N-terminal pro-BNP level is a useful tool to predict prognosis, but it was not extensively studied in our patients. Second, the reasons for not initiating metformin or SGLT2i treatment were not obtained; therefore, we could not provide a detailed explanation on not prescribing these medications. However, some patients could have discontinued these medications because of acute illness and worsening renal function, which could possibly correlate with subsequent CV events. Third, we did not measure the baseline insulin level and C-peptide level, and we did not regularly examine the change of echocardiography after the adjustment of diabetes medications.

Conclusions

The prescription patterns of diabetes medications in diabetics patients with HFrEF were diverse among different specialists. The treatment with metformin and SGLT2i was associated with better clinical outcomes. Establishing educational programme for physicians to increase awareness of the evidence-based diabetes medications in treating HFrEF patients is important to improve clinical outcome.

Conflict of interest

None declared.

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