HbA1c Level is Associated with Heart Failure with Recovered Ejection Fraction in Type 2 Diabetic Patients

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Abstract

Background:

Due to advances in medical treatments, a substantial proportion of heart failure (HF) patients with reduced left ventricular ejection fraction (EF, HFrEF) have experienced partial or complete recovery of EF, termed HFrecEF, and markedly improved clinical outcomes. In the present study, we sought to investigate the relationship between glycemic control and the incidence of HFrecEF in patients with type 2 diabetes mellitus (T2DM).

Methods:

A total of 385 T2DM patients with HFrEF were consecutively enrolled. Follow-up echocardiogram was performed after 6 to 12 months, which classified patients into HFrecEF or persistent HFrEF. Clinical outcomes of cardiovascular (CV) death and HF rehospitalization were analyzed during a mean of 3.3 years follow-up.

Results:

T2DM patients with HFrecEF had significantly lower HbA1c level than those with persistent HFrEF (6.4% [IQR 5.8%~7.1%] vs. 6.8% [IQR 6.1%~7.8%], $P=0.001$), especially in HF of ischemic etiology. After multivariate adjustment, every 1% increase in HbA1c conferred a 21.3% (OR: 0.787 [95% CI 0.658~0.933]) lower likelihood of HFrecEF. Compared to patients with good glycemic control ($\text{HbA1c} \leq 6\%$), those with poor glycemic control ($\text{HbA1c} > 8\%$) had higher risk of CV death or HF rehospitalization (HR: 2.778 [95% CI 1.470~5.251]). T2DM Patients with HFrecEF exhibited significantly better clinical outcomes than those with persistent HFrEF.

Conclusions:

This study demonstrates that T2DM patients with uncontrolled HbA1c levels were associated with compromised development of HFrecEF and worse clinical outcomes.

Background

Heart failure (HF) is a major public health burden with 5-year mortality rate as high as 53% ~ 67%[1-3]. According to the 2021 European Society of Cardiology (ESC) guideline, HF has been classified into 3 categories based on left ventricular (LV) ejection fraction (EF): HF with reduced EF (HFrEF, $\text{EF} \leq 40\%$), mildly reduced EF (HFmrEF, EF between 41% ~ 49%) and preserved EF (HFpEF, $\text{EF} \geq 50\%$)[4]. Over the past decades, a substantial proportion of HFrEF patients have experienced improved or recovery of EF attributable to advances in guideline-directed medical therapy and implantable devices. Thereafter, a new type of HF has been proposed: HF with improved or recovered EF (HFrecEF)[5]. Emerging evidence demonstrates that HFrecEF is clinically distinct from patients with HFpEF or HFrEF and is driven by

coordinated pathophysiological processes including adaptive molecular and cellular changes, improved cardiomyocyte contractility and restoration of LV chamber geometry[6-10].

Type 2 diabetes mellitus (T2DM) is an independent risk factor for the development of HF. In the Framingham Heart Study (FHS), the risk of HF was 2-fold higher in men and 5-fold higher in women with T2DM[11]. On the other hand, 12% ~ 40% of HF patients are comorbid with T2DM who suffer substantially increased risk of mortality[12-14]. Besides conventional anti-HF therapies, optimal glycemic control is generally believed to confer favorable effects on clinical outcomes in diabetic patients with HF. According to the UK Prospective Diabetes Study (UKPDS), the risk of HF was decreased by 16% for each 1% reduction in HbA1c[15]. The Heart and Soul Study showed each 1% increase in HbA1c level was related to a 36% increased risk of HF hospitalization[16]. However, few studies have focused on diabetic patients with HFrecEF so far, and whether glycemic control in T2DM is related to HFrecEF remains unknown.

In the present study, we investigated the association between glycemic control (valued by HbA1c) and the incidence of HFrecEF as well as clinical outcomes in T2DM patients with HF.

Methods

Study population

We conducted a retrospective cohort study of 539 consecutive T2DM patients with diagnosed HFrEF (EF $\leq$ 40%) on hospitalization between January 2013 and December 2019 in Shanghai Ruijin Hospital, who underwent repeat echocardiograms at least once after 6-12 months. The exclusion criteria include acute myocardial infarction, acute myocarditis, renal failure requiring hemodialysis, malignant tumor, receiving cardiac resynchronizing therapy (CRT) or heart transplantation. Eighteen patients without HbA1c at admission were also excluded. A total of 385 patients comprised the data analysis.

The cohort was classified into HFrecEF and persistent HFrEF based on follow-up echocardiograms after a 6- to 12-month interval. If patients had multiple echocardiograms over time, we selected the first one done after the 6-month interval. Patients who had (1) an absolute EF improvement $\geq$ 10% and (2) a second EF $>$ 40% were classified into HFrecEF, and those who did not meet these criteria were hereafter defined as persistent HFrEF (**Figure 1**).

This study complies with the Declaration of Helsinki. The study protocol was approved by the local hospital ethics committee, and written informed consent was obtained from all participants.

Clinical and biochemical assessments

The detailed information of medical history and lifestyles including smoking habits was obtained using a standard questionnaire by trained physicians. Body mass index (BMI) was calculated as weight/height² (kilograms per square meter). Body surface area (BSA) was calculated by Stevenson's formula: $0.0061 \times$

height + 0.0128 × weight - 0.1529[17]. Blood pressure was measured on the non-dominant arm in seated position after a 10-minute rest. Three measurements were taken at 1-minute interval, and the average was used for analysis.

The diagnosis of T2DM was made according to the criteria of American Diabetes Association (symptoms of diabetes with casual plasma glucose concentration ≥ 200 mg/dL [11.1 mmol/L] or fasting plasma glucose ≥ 126 mg/dL [7.0 mmol/L], 2-hour postprandial glucose ≥ 200 mg/dL [11.1 mmol/L] during an oral glucose tolerance test, and currently or previously treated with insulin and/or oral hypoglycemic agents) [18]. Hypertension was diagnosed according to seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7)[19].

All the blood samples were drawn after an overnight fasting. Blood HbA1c was measured using ion-exchange high performance liquid chromatography with Bio-rad Variant Hemoglobin Testing System (Bio-Rad Laboratories, USA). Plasma glucose, liver and renal function, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, N-terminal pro-B-type natriuretic peptide (NT-proBNP) were assessed (HITACHI 912 Analyzer, Roche Diagnostics, Germany). The estimated glomerular filtration rate (eGFR) was computed using the Chronic Kidney Disease Epidemiology Collaboration equation[20].

Echocardiographic examination

Comprehensive transthoracic echocardiography was performed using a commercially available system (Vivid-I, GE Healthcare, Milwaukee, WI) by a single sonographer credentialed in cardiac ultrasound. Two-dimensional echocardiography and Doppler flow imaging were recorded from standard parasternal and apical transducer positions.

EF was calculated using the modified Simpson's biplane technique. The LV length was measured in an apical 4-chamber view. To facilitate application of clinical normality cut points, LV end-diastolic volume (EDV) and end-systolic volume (ESV) were indexed by BSA calculated at the study time point. LV mass was estimated from M-mode measurements by the formula: LV mass = , and was indexed by BSA, where EDD is LV end-diastolic diameter, IVST is interventricular septal thickness, PWT is LV posterior wall thickness.

Clinical endpoints

All patients were followed at Ruijin Hospital for at least every 6 months. Development of HFrecEF defined by follow-up echocardiogram after a 6- to 12-month interval was the primary endpoint. The secondary endpoints were the time-to-event endpoints documented from the date of follow-up echocardiogram to December 2020, including cardiovascular (CV) death and the composite of CV death or HF rehospitalization.

Statistical analyses

Continuous variables were presented as median (interquartile range) or mean $\pm$ standard deviation, and categorical data were summarized as frequencies (percentages). For continuous variables, normal distribution was evaluated with Kolmogorov-Smirnov test. Differences were analyzed by Student's t-test or Mann-Whitney U test when appropriate. Differences in categorical variables were analyzed by χ^2 test. Univariate logistic regression analysis was performed to identify predictors of HFrecEF. Afterwards, multivariate regression was performed by entering all the significant predictors in the univariate analysis followed by backward elimination. HbA1c was analyzed both as continuous and categorical variable in univariate and multivariate models. To evaluate for non-linear effects of HbA1c levels on HFrecEF, we used restricted cubic splines. Forest plot analysis was performed to show adjusted odds ratio (OR) of HbA1c level for the development of HFrecEF in different subgroups. Sensitivity analyses were performed to validate the association in different conditions by excluding patients with previous myocardial infarction (Model 1), having received revascularization after the index date (Model 2), with 'partial EF recovery' (with a second EF > 40% but an absolute EF improvement <10%, Model 3). The association was also tested when HFrecEF was alternatively defined by EF improvement to $\geq$ 50% (Model 4) or entering the mean HbA1c levels at baseline and throughout the echocardiogram follow-up period instead of the baseline one (Model 5). Cumulative incidence of curves for the composite endpoints and CV death were plotted and *P*-values were obtained using log-rank test. Cox proportional hazards models were used for time-to-event analyses of CV death and the composite endpoint. We considered the following covariates in adjusted models based on associations with outcomes, clinical interpretation, and previous work: age, sex, HF etiology, history of hypertension, anemia and eGFR. All statistical analyses were performed using the R statistical package v.4.0.3 (R Project for Statistical Computing, Vienna, Austria). A 2-tailed <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

A total of 385 T2DM patients with HFrEF were enrolled in this study. After 6-12 months, 167 (43.4% [95% CI 38.4%~48.3%]) patients developed HFrecEF and another 218 (56.6% [95% CI 51.7%~61.6%]) patients remained HFrEF. Compared with persistent HFrEF patients, HFrecEF patients tended to be younger and less frequently have an ischemic etiology. They also appeared to have higher blood pressure, total and LDL cholesterol levels. Other clinical characteristics including sex, history of hypertension, myocardial infarction, atrial fibrillation, smoking habits, New York Heart Association (NYHA) grades, renal function, and medication treatments were similar between the 2 groups (**Table 1**).

Changes in LV function and geometric

At baseline, T2DM patients with HFrecEF had similar LV function as persistent HFrEF patients ($33.03\% \pm 5.59\%$ vs. $33.83\% \pm 6.51\%$, $P=0.205$), but tended to have smaller LV volumes (EDV and ESV indices, all $P<0.001$). During the echocardiogram follow-up, HFrecEF patients exhibited pronounced EF

recovery ($33.03\% \pm 5.59\%$ to $52.28\% \pm 7.70\%$, $P < 0.001$) and reverse LV remodeling (Δ EDV index: -23.94 ± 23.32 mL/m², Δ ESV index: -31.75 ± 22.48 mL/m², **Supplementary Table I**).

Association between HbA1c and HFrecEF

T2DM patients with HFrecEF had significantly lower HbA1c level than those with persistent HFrEF (6.4% [IQR 5.8%~7.1%] vs. 6.8% [IQR 6.1%~7.8%], $P = 0.001$), **Figure 2A**). Lower HbA1c levels in patients with HFrecEF versus HFrEF (**Figure 2B**) were only observed in the ischemic subgroup (6.4% [IQR 5.8%~7.2%] vs. 6.9% [IQR 6.2%~8.0%], $P = 0.003$) rather than those with non-ischemic etiology (6.4% [IQR 5.8%~7.1%] vs. 6.6% [IQR 6.0%~7.4%], $P = 0.178$).

Univariate analysis (**Supplementary Table II**) revealed that predictors for HFrecEF in T2DM patients were younger age (OR: 0.758 [95% CI 0.630~0.907]), non-ischemic etiology (OR: 1.755 [95% CI 1.156~2.673]), higher diastolic blood pressure (OR: 1.153 [95% CI 1.005~1.329]), total cholesterol levels (OR: 1.323 [95% CI 1.087~1.620]) and LDL cholesterol levels (OR: 1.466 [95% CI 1.154~1.879]), as well as smaller LV volumes (OR: EDV index, 0.844 [95% CI 0.777~0.912], per 10 mL/m², ESV index, 0.904 [95% CI 0.827~0.982], per 10 mL/m²). HbA1c levels were inversely associated with HFrecEF both when treated as continuous (OR: 0.814 [95% CI 0.697~0.943]) and categorical variables (OR: 0.407 [95% CI 0.218~0.746], HbA1c > 8% vs. $\leq 6\%$).

Multivariate analysis (**Table 2**) showed that age, non-ischemic etiology, LDL cholesterol levels, baseline EDV index and HbA1c levels were associated with the development of HFrecEF. When treated as categorical variables, patients with HbA1c > 8.0% corresponded to a 57.5% (OR: 0.425 [95% CI 0.205~0.863]) decreased likelihood of HFrecEF as compared to those with $\leq 6\%$. Restricted cubic spline analysis showed consistently decreased incidence of HFrecEF with elevated HbA1c levels peaked at 8.2% (**Supplementary Figure I**).

Subgroup analyses demonstrated that T2DM patients who were male, younger, with ischemic etiology, smoking habits, history of hypertension, lower BMI and poorer renal function were more likely to be affected by HbA1c than respective counterparts in the development of HFrecEF. The association between HbA1c and HFrecEF was affected by smoking habits (P for interaction = 0.018) and history of hypertension (P for interaction = 0.038, **Figure 3**).

All the sensitivity analyses are presented in **Table 3**. After multivariate adjustment, the association between HbA1c levels and HFrecEF persisted after exclusion of patients with previous myocardial infarction (Model 1), receiving coronary revascularization (Model 2) or with 'partial EF recovery' (a second EF > 40% but an absolute EF improvement < 10%, Model 3). The association remained significant when HFrecEF was alternatively defined by EF recovery to $\geq 50\%$ (Model 4). When entering the mean HbA1c level of all the available tests at baseline and throughout the echocardiogram follow-up instead of the one obtained at admission, it remained inversely associated with the development of HFrecEF (Model 5).

Glycemic control and HF prognosis

The cohort was followed-up for 3.3 ± 1.7 years, with a total of 1261.1 patient-years. Patients with poor glycemic control were more likely to experience CV death or HF rehospitalization ($P=0.026$, **Table 4** and **Figure 4A**). In fully adjusted models, patients with HbA1c $>8\%$ had a 2.8-fold increased risk of the composite end point (HR: 2.778 [95% CI 1.470~5.251], $P=0.002$) compared to those with HbA1c $\leq 6\%$ (**Table 4**).

CV death occurred in 17.1% (66 of 385) of the cohort. Age- and sex-adjusted 5-year CV mortality was 10.8%, 19.0%, 19.0% and 34.7% in patients with HbA1c $\leq 6\%$, $6\% \sim 7\%$, $7 \sim 8\%$ and $>8\%$, respectively. There was no significant difference in CV mortality between patients with different glycemic control levels ($P=0.097$, **Figure 4B**).

Of note, T2DM with HFrecEF had substantially lower risk of the composite endpoint (HR: 0.341 [95% CI 0.199~0.584], **Figure 4C**) and CV death (HR: 0.406 [95% CI 0.210~0.785]) compared to those with persistent HFrecEF (**Figure 4D**).

Discussion

The major findings of the present study are that T2DM patients with uncontrolled HbA1c levels are less likely to develop HFrecEF. The risk of CV death or HF rehospitalization increases by 2.8-fold in patients with poor glycemic control (HbA1c $>8\%$) than those with good glycemic control (HbA1c $\leq 6\%$). However, CV mortality does not significantly differ between patients with different glycemic control levels.

Data from existing cohort studies suggest that HFrecEF is more likely to occur in patients who are of younger age, female sex, with nonischemic etiology, and fewer comorbidities such as diabetes[7, 9, 21]. However, given the high prevalence of diabetes in HF population, which is further compounded by hypoglycemic agents and coexisting comorbidities, characterization of predisposing factors for HFrecEF in the setting of diabetes is of particular importance.

This study for the first time described predisposing factors for HFrecEF in T2DM with HF cohorts. In the univariate analysis, we showed that younger age, non-ischemic etiology, higher diastolic blood pressure, elevated cholesterol levels and less LV forward remodeling were associated with the development of HFrecEF, which were in line with previous findings in the general population from Val-HeFT trial and cohort data[22, 23]. In addition, we provided evidence that lower HbA1c levels were also related to the incidence of HFrecEF in diabetic patients, suggesting that the development of HFrecEF in T2DM was both affected by traditional influencing factors in the general population as well as glycemic control levels.

HbA1c, reflecting ambient glucose levels over the preceding 2 to 3 months, is well-recognized to affect HF prognosis. However, the specific pattern of the relationship has been inconsistent. Candesartan Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study showed a linear relationship between HbA1c and risk of all-cause mortality as well as HF hospitalization[24]. An analysis of the Metabolic Exercise Cardiac Kidney Index (MECKI) score database revealed a worse prognosis in HFrecEF patients with HbA1c $> 8\%$ after adjustment for confounding factors[25]. In contrast, more contemporary

data on cohort of HF populations pointed to a U-shaped relationship between HbA1c control level and HF prognosis. [26-28].

Nevertheless, our study clearly demonstrated an inverse association between HbA1c level and HFrecEF after adjustment for confounding factors. Every 1% increase in HbA1c corresponded to a 21.3% decreased likelihood of HFrecEF. Restricted cubic spline also showed a consistent decrease in the likelihood of HFrecEF in patients with higher HbA1c control level peaked at 8.2%. In accordance, patients with poor glycemic control were more likely to experience CV death or HF rehospitalization during a mean of a 3.3-year follow-up. Interestingly, although CV mortality in HFrecEF was significantly lower compared to persistent HFrEF, it did not significantly differ between patients with different HbA1c levels. Taken together, these data imply that relatively low glycemic control level in essence is in favor of myocardial recovery and improved prognosis in diabetic conditions. Under intensive glycemic control, however, adverse cardiovascular effects of certain glucose-lowering therapy and attendant hypoglycemic events may counteract the beneficial effects of LV function recovery, thereby leading to a compromised prognosis[29].

Our findings should be interpreted in the context of following limitations. First, this study is a retrospective, observational study in nature from a single center, and the result is potentially subject to survival bias. Second, although the sensitivity analysis that used the mean HbA1c levels during follow-up pointed to consistent results, most of the analyses were performed by using HbA1c levels at baseline. Changes in HbA1c were shown to be associated with increased hospitalization and mortality in HF patients with T2DM. We previously also showed that glycemic variability was associated with adverse LV remodeling after myocardial infarction[30]. Assessments of HbA1c at different timepoints should provide more insights into the impact of glycemic control on the development of HFrecEF. Finally, prospective studies are warranted to analyze the causal link between glycemic control and occurrence of HFrecEF and clinical outcomes.

Conclusions

In conclusion, our findings suggest that uncontrolled HbA1c levels are associated with compromised development of HFrecEF in T2DM and higher risk for CV death or HF rehospitalization. An optimal glycemic control is desirable for myocardial recovery in diabetic patients with HF.

Abbreviations

BMI: body mass index, BSA: body surface area, CV: cardiovascular, CRT: cardiac resynchronizing therapy, EDV: end-diastolic volume, EF: ejection fraction, eGFR: estimated glomerular filtration rate, ESC: European Society of Cardiology, ESV: end-systolic volume, HDL: high-density lipoprotein, HF: heart failure, HFmrEF: heart failure with mildly reduced ejection fraction, HFpEF: heart failure with preserved ejection fraction, HFrecEF: heart failure with recovered ejection fraction, HFrEF: heart failure with reduced ejection fraction,

LDL: low-density lipoprotein, LV: left ventricle, NT-proBNP: N-terminal pro-B-type natriuretic peptide, NYHA: New York Heart Association, OR: odds ratio, T2DM: type 2 diabetes mellitus.

Declarations

Ethics approval and consent to participate

The study was approved by the Hospital Ethics Committee, and written informed consent was obtained from all patients.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CY and XW performed study design, data analysis and data interpretation. CY, MA and XW performed manuscript writing. CY, MA, JQ, JC, XS and XW performed data collection. FD, WS, LL, RZ, WP and XW performed manuscript revision. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline demographic and clinical characteristics

	HFrEF	HFrecEF	<i>P-value</i>
n	218	167	
<i>Demographic characteristics and clinical assessments</i>			
Male sex	181 (83.0)	140 (83.8)	0.943
Age, years	63.22±10.49	59.68±12.22	0.002
Duration of diabetes, years	8.86±7.06	9.58±6.24	0.521
Hypertension	142 (65.1)	95 (56.9)	0.123
Previous myocardial infarction	21 (9.6)	10 (6.0)	0.265
Atrial fibrillation	21 (9.6)	17 (10.2)	0.995
Smoking habits	105 (48.2)	71 (42.5)	0.317
BMI, kg/m ²	24.63±3.29	25.30±4.51	0.102
Systolic blood pressure, mmHg	124.69±18.89	128.20±25.72	0.134
Diastolic blood pressure, mmHg	74.17±12.92	77.41±17.59	0.043
Ischemic etiology	150 (68.8)	93 (55.7)	0.011
NYHA grades (II/III/IV)	37 (17.0) / 154 (70.6) / 27 (12.4)	29 (17.4) / 111 (66.5) / 27 (16.2)	0.545
<i>Laboratory measurements</i>			
HbA1c, %	6.8 (6.1~7.8)	6.4 (5.8~7.1)	0.001
Fasting glucose, mmol/L	6.23 (5.03~7.48)	5.89 (5.03~7.29)	0.386
Triglyceride, mmol/L	1.28 (0.95~1.82)	1.37 (1.03~1.73)	0.337
Total cholesterol, mmol/L	3.80±1.02	4.12±1.12	0.005
HDL cholesterol, mmol/L	1.02±0.27	1.03±0.26	0.803
LDL cholesterol, mmol/L	2.25±0.82	2.55±0.94	0.002
eGFR, mL/min/1.732m ²	86.44±21.53	88.94±19.92	0.244
NT-proBNP, pg/mL	1932.50 (865.18~4017.25)	1967.50 (778.85~4865.50)	0.653
<i>Medication</i>			
Aspirin	142 (65.1)	97 (58.1)	0.191

P2Y12 inhibitors	123 (56.4)	80 (47.9)	0.120
Beta-blockers	183 (83.9)	148 (88.6)	0.245
ACEI/ARB/ARNI	168 (77.1)	133 (79.6)	0.630
Calcium channel blockers	20 (9.2)	27 (16.2)	0.055
Spironolactones	168 (77.1)	128 (76.6)	1.000
Diuretics	161 (73.9)	115 (68.9)	0.335
Statins	113 (51.8)	73 (43.7)	0.139
OHA	140 (64.2)	116 (69.5)	0.332
Biguanides	49 (22.5)	37 (22.2)	1.000
Sulfonylureas	23 (10.6)	15 (9.0)	0.735
Meglitinides	5 (2.3)	5 (3.0)	0.916
Glucosidase inhibitors	105 (48.2)	88 (52.7)	0.437
SGLT2 inhibitors	21 (9.6)	26 (15.6)	0.108
Insulin	33 (15.1)	16 (9.6)	0.142

ACEI, angiotensin-converting enzyme inhibitors, ARB, angiotensin receptor blockers, ARNI, angiotensin-receptor neprilysin inhibitors, BMI, body mass index, eGFR, estimated glomerular filtration rate, HDL, high-density lipoprotein, HFrecEF, heart failure with recovered ejection fraction, HFrEF, heart failure with reduced ejection fraction, LDL, low-density lipoprotein, NT-proBNP, N-terminal pro-B-type natriuretic peptide, NYHA, New York Heart Association, OHA, oral hypoglycemic agents, SGLT2, sodium-glucose cotransporter 2.

Table 2. Multivariate analysis for development of HFrecEF

Covariates	Model 1		Model 2	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age, per 10 years	0.762 (0.611~0.945)	0.014	0.755 (0.603~0.938)	0.012
Non-ischemic etiology	1.707 (1.038~2.819)	0.035	1.748 (1.057~2.900)	0.030
LDL cholesterol	1.305 (1.008~1.698)	0.045	1.301 (1.004~1.699)	0.049
EDVI, per 10 mL/m ²	0.830 (0.757~0.903)	<0.001	0.833 (0.759~0.907)	<0.001
HbA1c, per 1%	0.787 (0.658~0.933)	0.007		
HbA1c categories	-	-		
≤ 6%	-	-	Reference	-
6% ~ 7%	-	-	0.618 (0.356~1.066)	0.085
7%~8%	-	-	0.300 (0.142~0.612)	0.001
>8%			0.425 (0.205~0.863)	0.019

CI, confidence interval, EDVI, end-diastolic volume index, HFrecEF, heart failure with recovered ejection fraction, LDL, low-density lipoprotein, OR, odds ratio.

Table 3. Sensitivity analysis

Models	OR (95% CI)	P-value
Model 1	0.723 (0.586~0.879)	0.002
Model 2	0.705 (0.553~0.880)	0.003
Model 3	0.785 (0.642~0.951)	0.015
Model 4	0.901 (0.821~0.975)	0.017
Model 5	0.807 (0.653~0.982)	0.039

Model 1, excluded patients with previous myocardial infarction

Model 2, excluded patients who received coronary revascularization after the index date

Model 3, excluded patients with a second EF > 40% but an absolute EF improvement <10%

Model 4, by defining HFrecEF as EF recovery to ≥ 50%

Model 5, by entering the mean HbA1c level of all the available tests at baseline and throughout the echocardiogram follow-up period into the model instead of the one obtained at admission

CI, confidence interval, EF, ejection fraction, HFrecEF, heart failure with recovered ejection fraction, OR, odds ratio.

Table 4. Cox proportional hazards regression analysis for the composite endpoint of CV death or HF rehospitalization by HbA1c levels

	Model 1		Model 2		Model 3	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
≤ 6%	Reference	-	Reference	-	Reference	-
6% ~ 7%	1.324 (0.751~2.331)	0.332	1.371 (0.778~2.416)	0.275	1.438 (0.779~2.656)	0.246
7%~8%	1.589 (0.854~2.958)	0.144	1.733 (0.928~3.235)	0.084	1.857 (0.962~3.584)	0.065
>8%	2.268 (1.288~3.995)	0.005	2.458 (1.390~4.346)	0.002	2.778 (1.470~5.251)	0.002

Model 1, univariate analysis,

Model 2, adjusted for age and sex,

Model 3, adjusted for age, sex, HF etiology, history of hypertension, anemia and eGFR.

CI, confidence interval, CV, cardiovascular, eGFR, estimated glomerular filtration rate, HF, heart failure, HR, hazard ratio.

Figures

Figure 1

Flowchart of patient enrollment.

Figure 2

HbA1c levels were lower in patients with HFrecEF than those with persistent HFrEF.

Shown are HbA1c levels in T2DM patients with HFrecEF and persistently HFrEF in the overall study population (A) or subgroups according to the presence of ischemic etiology (B). Horizontal lines in the box: upper, 75% percentile; middle, median; lower, 25% percentile. Upper whisker, 95% percentile; lower whisker, 5% percentile. HFrecEF, heart failure with recovered ejection fraction; HFrEF, heart failure with reduced ejection fraction; T2DM, type 2 diabetes mellitus.

Figure 3

Forest plot for the likelihood of HFrecEF in different subgroups after multivariate adjustment.

Shown are odds ratios and corresponding confidence intervals for HFrecEF in different subgroups after multivariate adjustment. BMI, body mass index, eGFR, estimated glomerular filtration rate, HFrecEF, heart failure with recovered ejection fraction.

Figure 4

Kaplan-Meier curves, adjusted for age and sex, across patients with different HbA1c control levels or the presence of HFrecEF.

(A and B) The composite endpoint of CV death or HF rehospitalization (A, log-rank $\chi^2=9.231$, $P=0.026$) and CV death (B, log-rank $\chi^2=6.316$, $P=0.097$) after adjustment for age and sex across patients with different HbA1c control levels. (C and D) The composite endpoint (C, log-rank $\chi^2=22.702$, $P<0.001$) and CV death (D, log-rank $\chi^2=14.470$, $P<0.001$) across patients with HFrecEF or persistent HFrEF. CV, cardiovascular, HF, heart failure, HFrecEF, heart failure with recovered ejection fraction, HFrEF, heart failure with reduced ejection fraction.

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