Glycemic Control is Associated with Heart Failure with Recovered Ejection Fraction in Diabetic Patients

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Original investigation

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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 (LVEF, HFrEF) have experienced partial or complete recovery of LVEF, 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 310 age- and sex-matched T2DM patients with HFrecEF and persistent HFrEF were retrospectively enrolled based on 12-month repeat echocardiograms. HFrecEF was defined as follow-up LVEF > 40% and absolute LVEF improvement ≥ 10% compared to the baseline. The relationship between HFrecEF and HbA1c levels was analyzed.

Results:

During the 12-month follow-up, LVEF recovered from 35.93% ± 5.62% to 51.11% ± 8.53% in the HFrecEF group (P<0.001), while remained reduced (33.08% ± 6.40% to 33.63% ± 6.10%, P=0.238) in the HFrEF group. 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 6.3%~7.4%], P<0.001), irrespective of HF etiology. After multivariate adjustment, every 1% increase in HbA1c conferred a 20.8% [OR: 0.792, 95% CI 0.642~0.967] lower likelihood of HFrecEF. When dividing HbA1c into tertiles, patients with HbA1c ≥ 7.1% corresponded to a 60.9% [OR: 0.391, 95% CI 0.201~0.750] decreased likelihood of HFrecEF as compared to those with HbA1c < 6.2%.

Conclusions:

This study demonstrates that HFrEF patients with T2DM are more likely to develop HFrecEF under optimal glycemic control valued by lower HbA1c level.

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 (LVEF): HF with reduced LVEF (HFrEF, LVEF ≤ 40%), mildly reduced LVEF (HFmrEF, LVEF between 41% ~ 49%) and preserved EF (HFpEF, LVEF ≥ 50%) [4]. Over the past decades, a substantial proportion of HFrEF patients have experienced improved or recovery of LVEF attributable to advances in guideline-directed medical therapy (GDMT), development of new pharmacotherapies such as sodium-glucose cotransporter 2 inhibitors and implantable devices. Thereafter, a new type of HF has been proposed: HF with improved or recovered LVEF (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, 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 focus 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 LVEF trajectory in T2DM patients with HF by repeat echocardiogram assessments during 12-month follow-up and analyzed the association between glycemic control (valued by HbA1c) and the incidence of HFrecEF.

Methods

Study population

We retrospectively screened T2DM patients aged 40 to 75 years with diagnosis of HFrEF (LVEF ≤ 40%) on hospitalization between September 2014 and May 2019 in Shanghai Ruijin Hospital, who underwent r-epeat echocardiograms at around 12-month follow-up. The exclusion criteria include: congenital heart disease, primary valvular disease, specific cardiomyopathy (e.g., hypertrophic, infiltrative, restrictive or right-ventricular cardiomyopathy), patients receiving implantable devices, mechanical circulatory support or heart transplantation. Based on initial and follow-up echocardiograms, patients were classified into HFrecEF (follow-up LVEF > 40% and absolute LVEF improvement ≥ 10%), and otherwise persistent HFrEF. Finally, 155 pairs of age- and sex-matched patients with HFrecEF and persistent HFrEF were enrolled in the final analysis.

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/height^2 (kilograms per square meter). Body surface area (BSA) was calculated by Stevenson's formula: 0.0061 × 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, serum insulin, creatinine, 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). Serum levels of high-sensitivity C-reactive protein (hsCRP) were determined by ELISA (Biocheck Laboratories, Toledo, OH, USA). The estimated glomerular filtration rate (eGFR) was computed using the Chronic Kidney Disease Epidemiology Collaboration equation[20].

Echocardiographic examination

Comprehensive transthoracic echocardiography was performed on the time of hospitalization and at 12-month follow-up, 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.

LVEF was calculated using the modified Simpson's biplane technique. The LV length was measured in the apical 4-chamber view. To facilitate application of clinical normality cut points, LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were indexed by BSA calculated at each study time point. LV mass was estimated from M-mode measurements by the formula: LV mass = $0.8 \times 1.04 \times \left[(LVEDD + IVST + LVPWT)^3 - LVEDD^3 \right] + 0.6$, and was indexed by BSA, where LVEDD is LV end-diastolic diameter, IVST is interventricular septal thickness, LVPWT is LV posterior wall thickness.

Statistical analyses

Continuous variables were presented as median (interquartile range) or mean ± standard deviation, and categorical data were summarized as frequencies (percentages). For continuous variables, normal distribution was evaluated with Kolmogorov-Smirnov test. For non-normally distributed continuous variables, differences were analyzed by Mann-Whitney U test. Differences among groups were analyzed

by Student's t-test or one-way analysis of variance (ANOVA) followed by post hoc Bonferroni correction. Differences in categorical variables were analyzed by χ^2 test. Univariate logistic regression analysis was performed to identify univariate predictors of HFrecEF. Afterwards, multivariate regression was performed by entering all the conventional risk factors and significant predictors in the univariate analysis after backward elimination. HbA1c was analyzed both as continuous and categorical variable in univariate and multivariate models. Restricted cubic splines were further used to evaluate the relationship between HbA1c and HFrecEF in the multivariate logistic regression model. Forest plot analysis was performed to show adjusted odds ratio (OR) of HbA1c level in association with HFrecEF in different subgroups. 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

Compared with T2DM patients with persistent HFrEF, those with HFrecEF tended to have higher systolic blood pressure and cholesterol levels. There was no significant difference in duration of diabetes, history of hypertension, previous myocardial infarction, atrial fibrillation, smoking habits, etiology of HF, coronary revascularization and New York Heart Association (NYHA) functional classification between the 2 groups. Levels of fasting glucose, insulin, triglyceride, renal function, hsCRP and NT-proBNP were also similar. Medication treatments were comparable except for beta-blockers which were more frequently used in HFrecEF patients (Table 1).

Changes in LV function and geometric

Compared with T2DM patients with persistent HFrEF, HFrecEF patients tended to have better LV function (P<0.001) and smaller LV volumes (LV end-diastolic and end-systolic volumes, all P<0.001) at baseline. During the 12-month follow-up, LVEF recovered from 35.93% ± 5.62% to 51.11% ± 8.53% in the HFrecEF group (P<0.001), while remained reduced (33.08% ± 6.40% to 33.63% ± 6.10%, P=0.238) in the HFrEF group. In accordance, reverse LV remodeling was more prominent in HFrecEF versus HFrEF patients (ΔLVEDV index: -21.78 ± 25.66 vs. -1.81±19.37 mL/m^2, P<0.001; ΔLVESV index: -28.77 ± 24.35 vs. -2.45 ± 17.69 mL/m^2, P<0.001; Table 2).

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 6.3%~7.4%], P<0.001), Figure 1A). The difference remained consistent irrespective of HF etiology with lower HbA1c levels in HFrecEF than HFrEF patients (non-ischemia : 6.4%

[IQR 5.7%~6.9%] vs. 6.7% [IQR 6.1%~7.4%], *P*=0.013; ischemia: 6.4% [IQR 5.9%~7.3%] vs. 7.0% [IQR 6.4%~7.8%], *P*<0.001; Figure 1B).

Univariate analysis (Table 3) revealed that predictors for HFrecEF in T2DM patients were higher systolic blood pressure (OR: 1.246 [95% CI 1.107~1.412], per 10 mmHg), total cholesterol and lipoprotein levels (OR of total cholesterol: 1.266 [95% CI 1.034~1.562], HDL cholesterol: 3.478 [95% CI 1.359~9.255], LDL cholesterol: 1.417 [95% CI 1.094~1.858]), and medication use of beta-blockers (OR: 1.980 [95% CI 1.069~3.768]). Meanwhile, better LV function (LVEF, OR: 2.223 [95% CI 1.509~3.348], per 10%) and smaller LV volumes (OR of LVEDV index: 0.766 [95% CI 0.694~0.837, per 10 mL/m^2; LVESV index: 0.749 [95% CI 0.667~0.832], per 10 mL/m^2) were also associated with subsequent development of HFrecEF. HbA1c levels were inversely associated with HFrecEF both when treated as continuous (OR: 0.775 [95% CI 0.639~0.929]) and categorical variables (OR: 0.349 [95% CI 0.196~0.614], HbA1c ≥ 7.1 mmol/L vs. < 6.2 mmol/L).

Multivariate analysis (Table 4) showed that decreased HbA1c, higher HDL cholesterol levels, lower baseline LVEDV index and use of beta-blockers (borderline significant) were associated with the development of HFrecEF. After multivariate adjustment, every 1% increase in HbA1c conferred a 20.8% [OR: 0.792, 95% CI 0.642~0.967] lower likelihood of HFrecEF. Restricted cubic spline analysis further revealed a consistent decrease in the likelihood of HFrecEF in patients with higher HbA1c control level peaked at 8.4% (Figure 2). When dividing HbA1c into tertiles, patients with HbA1c ≥ 7.1% corresponded to a 60.9% [OR: 0.391, 95% CI 0.201~0.750] decreased likelihood of HFrecEF as compared to those with HbA1c < 6.2%.

In addition, subgroup analyses demonstrated that HbA1c level was significantly associated with development of HFrecEF irrespective of HF etiology and renal function after covariate adjustment. However, T2DM patients who had history of hypertension, lower BMI or LVEF were more likely to be affected by HbA1c level than respective counterparts with regard to the development of HFrecEF (Figure 3).

Discussion

The major findings of the present study are that T2DM patients with HFrecEF tend to have lower HbA1c level than those with persistent HFrEF. Poor glycemic control is independently associated with decreased likelihood of HFrecEF after multivariate adjustment. The association between glycemic control and the development of HFrecEF is irrespective of HF etiology and is more prominent in patients with poorer LV function.

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

and renal dysfunction, characterization of predisposing factors for HFrecEF in the setting of diabetes is of importance and cannot be simply inferred from existing knowledge of the general population.

This study for the first time described predisposing factors for HFrecEF in T2DM with HF cohorts. In the univariate analysis, we showed that higher systolic blood pressure, cholesterol levels, use of beta-blockers, better LV function and less LV forward remodeling were associated with the development of HFrecEF. Due to an age- and sex-matched case-control design, the contribution of age and sex in HFrecEF cannot be determined. The associations of blood pressure, use of beta-blockers, less LV remodeling with HFrecEF were in line with previous findings in the general population from Val-HeFT trial and cohort data[22, 23]. Likewise, the positive relationship between cholesterol levels, especially HDL cholesterol, and HFrecEF was part in congruent with previous data that low serum cholesterol was associated with a worse prognosis in HF patients and the protective role of HDL in the development of HF[24–26]. Interestingly, there was no significant association between ischemic etiology and HFrecEF in our study. A plausible explanation is that diabetes *per se* is independently associated with micro- and macrovascular complications even when no severe coronary artery occlusion is detected, as well as with the pathogenesis of non-ischemic cardiomyopathy[27]. Hence, the development of HFrecEF might be more dependent on diabetes status than the specific HF etiology.

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[28]. An analysis of the Metabolic Exercise Cardiac Kidney Index (MECKI) score database revealed a worse prognosis in HFrEF patients with HbA1c > 8% after adjustment for confounding factors[29]. In contrast, more contemporary data on cohort of HF populations pointed to a U-shaped relationship between HbA1c control level and HF prognosis. A hospital-based cohort study found that individuals with established HF and diabetes had the lowest mortality with modest glycemic control ($7.1\% < \text{HbA1c} \leq 7.8\%$)[30]. Another study of 123 diabetic patients with advanced systolic HF discovered that $\text{HbA1c} \leq 7\%$ was associated with an increased risk of death as compared with HbA1c > 7%[31]. A large cohort study of the general HF population also supported a U-shaped relationship between HbA1c level and all-cause first hospitalization and mortality[32].

Nevertheless, our study clearly demonstrated an inverse and unidirectional association between HbA1c level and HFrecEF after adjustment for confounding factors. Compared to patients with HbA1c < 6.2%, those with $\text{HbA1c} \geq 7.1\%$ had a 60.9% decreased likelihood of HFrecEF. Restricted cubic spline analysis also showed a consistent decrease in the likelihood of HFrecEF in patients with higher HbA1c control level peaked at 8.4%. Taken together, these data imply that low glycemic control level in essence is in favor of myocardial recovery 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 unexpected poor HF outcomes[33].

Our findings should be interpreted in the context of following limitations. First, this study is a retrospective, observational case-control study in nature with relatively small sample size from a single center, and the result is potentially subject to survival bias. Second, HbA1c level was only assessed 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[34]. 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, as well as the prognostic value of HbA1c for hard cardiovascular events in T2DM subjects with HFrecEF.

Conclusions

In conclusion, our findings suggest that relatively lower HbA1c is associated with higher likelihood of HFrecEF in T2DM. An optimal glycemic control is desirable for myocardial recovery in diabetic patients with HF.

Abbreviations

ANOVA, one-way analysis of variance; BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; 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; hs-CRP, high-sensitivity C-reactive protein; IVST, interventricular septal thickness; LDL, low-density lipoprotein; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVPWT, left ventricular posterior wall thickness; 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, data interpretation, and manuscript writing. CY, MA, LL, FD and XW performed data collection. ZY, JH, RZ, WS and XW performed manuscript revision. All authors read and approved the final manuscript.

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References

1. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation. 1993;88(1):107–15.
2. Murad K, Goff DC Jr, Morgan TM, Burke GL, Bartz TM, Kizer JR, Chaudhry SI, Gottdiener JS, Kitzman DW. Burden of Comorbidities and Functional and Cognitive Impairments in Elderly Patients at the Initial Diagnosis of Heart Failure and Their Impact on Total Mortality: The Cardiovascular Health Study. JACC Heart Fail. 2015;3(7):542–50.

3. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355(3):251–9.
4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–726.
5. Punnoose LR, Givertz MM, Lewis EF, Pratibhu P, Stevenson LW, Desai AS. Heart failure with recovered ejection fraction: a distinct clinical entity. J Card Fail. 2011;17(7):527–32.
6. Wilcox JE, Fang JC, Margulies KB, Mann DL. Heart Failure With Recovered Left Ventricular Ejection Fraction: JACC Scientific Expert Panel. J Am Coll Cardiol. 2020;76(6):719–34.
7. Agra Bermejo R, Gonzalez Babarro E, Lopez Canoa JN, Varela Roman A, Gomez Otero I, Oro Ayude M, Parada Vazquez P, Gomez Rodriguez I, Diaz Castro O, Gonzalez Juanatey JR. Heart failure with recovered ejection fraction: Clinical characteristics, determinants and prognosis. CARDIOCHUS-CHOP registry. Cardiol J. 2018;25(3):353–62.
8. Basuray A, French B, Ky B, Vorovich E, Olt C, Sweitzer NK, Cappola TP, Fang JC. Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. Circulation. 2014;129(23):2380–7.
9. Kalogeropoulos AP, Fonarow GC, Georgiopoulou V, Burkman G, Siwamogsatham S, Patel A, Li S, Papadimitriou L, Butler J. Characteristics and Outcomes of Adult Outpatients With Heart Failure and Improved or Recovered Ejection Fraction. JAMA Cardiol. 2016;1(5):510–8.
10. Nijst P, Martens P, Mullens W. Heart Failure with Myocardial Recovery - The Patient Whose Heart Failure Has Improved: What Next? Prog Cardiovasc Dis. 2017;60(2):226–36.
11. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol. 1974;34(1):29–34.
12. Dei Cas A, Khan SS, Butler J, Mentz RJ, Bonow RO, Avogaro A, Tschoepe D, Doehner W, Greene SJ, Senni M, et al. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. JACC Heart Fail. 2015;3(2):136–45.
13. Thrainsdottir IS, Aspelund T, Thorgeirsson G, Gudnason V, Hardarson T, Malmberg K, Sigurdsson G, Ryden L. The association between glucose abnormalities and heart failure in the population-based Reykjavik study. Diabetes Care. 2005;28(3):612–6.
14. From AM, Leibson CL, Bursi F, Redfield MM, Weston SA, Jacobsen SJ, Rodeheffer RJ, Roger VL. Diabetes in heart failure: prevalence and impact on outcome in the population. Am J Med. 2006;119(7):591–9.
15. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405–12.
16. van Melle JP, Bot M, de Jonge P, de Boer RA, van Veldhuisen DJ, Whooley MA. Diabetes, glycemic control, and new-onset heart failure in patients with stable coronary artery disease: data from the heart and soul study. Diabetes Care. 2010;33(9):2084–9.

17. Stevenson P. Height. weight. surface formula for the estimation of surface area in Chinese subjects. Chin J Physiol. 1937;12:327–30.
18. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15(7):539–53.
19. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT, Jr. et al: **Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure**. *Hypertension* 2003, **42**(6):1206-1252.
20. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
21. Lupon J, Diez-Lopez C, de Antonio M, Domingo M, Zamora E, Moliner P, Gonzalez B, Santesmases J, Troya MI, Bayes-Genis A. Recovered heart failure with reduced ejection fraction and outcomes: a prospective study. Eur J Heart Fail. 2017;19(12):1615–23.
22. Florea VG, Rector TS, Anand IS, Cohn JN. **Heart Failure With Improved Ejection Fraction: Clinical Characteristics, Correlates of Recovery, and Survival: Results From the Valsartan Heart Failure Trial**. *Circ Heart Fail* 2016, 9(7).
23. Ghimire A, Fine N, Ezekowitz JA, Howlett J, Youngson E, McAlister FA. Frequency, predictors, and prognosis of ejection fraction improvement in heart failure: an echocardiogram-based registry study. Eur Heart J. 2019;40(26):2110–7.
24. Rauchhaus M, Clark AL, Doehner W, Davos C, Bolger A, Sharma R, Coats AJ, Anker SD. The relationship between cholesterol and survival in patients with chronic heart failure. J Am Coll Cardiol. 2003;42(11):1933–40.
25. Sirtori CR, Ruscica M, Calabresi L, Chiesa G, Giovannoni R, Badimon JJ. HDL therapy today: from atherosclerosis, to stent compatibility to heart failure. Ann Med. 2019;51(7-8):345–59.
26. Li C, Chen JW, Ding FH, Shen Y, Liu ZH, Wang F, Zhang RY, Shen WF, Lu L, Wang XQ. Relationship of High-Density Lipoprotein-Associated Arylesterase Activity to Systolic Heart Failure in Patients with and without Type 2 Diabetes. Sci Rep. 2019;9(1):5979.
27. Bertoni AG, Tsai A, Kasper EK, Brancati FL. Diabetes and idiopathic cardiomyopathy: a nationwide case-control study. Diabetes Care. 2003;26(10):2791–5.
28. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur Heart J. 2008;29(11):1377–85.
29. Paolillo S, Salvioni E, Perrone Filardi P, Bonomi A, Sinagra G, Gentile P, Gargiulo P, Scoccia A, Cosentino N, Gugliandolo P, et al. Long-term prognostic role of diabetes mellitus and glycemic control in heart failure patients with reduced ejection fraction: Insights from the MECKI Score database. Int J Cardiol. 2020;317:103–10.

30. Aguilar D, Bozkurt B, Ramasubbu K, Deswal A. Relationship of hemoglobin A1C and mortality in heart failure patients with diabetes. J Am Coll Cardiol. 2009;54(5):422–8.
31. Eshaghian S, Horwich TB, Fonarow GC. An unexpected inverse relationship between HbA1c levels and mortality in patients with diabetes and advanced systolic heart failure. Am Heart J. 2006;151(1):91.
32. Lawson CA, Jones PW, Teece L, Dunbar SB, Seferovic PM, Khunti K, Mamas M, Kadam UT. Association Between Type 2 Diabetes and All-Cause Hospitalization and Mortality in the UK General Heart Failure Population: Stratification by Diabetic Glycemic Control and Medication Intensification. JACC Heart Fail. 2018;6(1):18–26.
33. Gilbert RE, Krum H. Heart failure in diabetes: effects of anti-hyperglycaemic drug therapy. Lancet. 2015;385(9982):2107–17.
34. Yang CD, Shen Y, Ding FH, Yang ZK, Hu J, Shen WF, Zhang RY, Lu L, Wang XQ. Visit-to-visit fasting plasma glucose variability is associated with left ventricular adverse remodeling in diabetic patients with STEMI. Cardiovasc Diabetol. 2020;19(1):131.

Tables

Table 1

Baseline demographic and clinical characteristics

	HFrEF	HFrecEF	*P-value*
n	155	155	
Demographic characteristics and clinical assessments			
Male sex	126 (81.3)	126 (81.3)	1.000
Age, years	61.70±7.54	61.75±7.62	0.958
Duration of diabetes, years	8.66±5.86	9.67±7.33	0.404
Hypertension	83 (53.5)	97 (62.6)	0.135
Previous myocardial infarction	8 (5.2)	14 (9.0)	0.269
Atrial fibrillation	19 (12.3)	13 (8.4)	0.351
Smoking habits	56 (36.1)	72 (46.5)	0.084
BMI, kg/m^2	24.64±3.30	24.60±3.60	0.929
Systolic BP, mmHg	118.82±17.30	127.44±22.34	<0.001
Diastolic BP, mmHg	73.78±13.60	76.01±14.17	0.163
Ischemic etiology	82 (52.9)	89 (57.4)	0.493
PCI or CABG (% in IHD)	36 (43.9)	33 (37.1)	0.452
NYHA classification (II/III/IV)	26 (16.8) / 102 (65.8) / 27 (17.4)	26 (16.8) / 106 (68.4) / 23 (14.8)	0.820
Laboratory measurements			
Fasting glucose, mmol/L	6.14 (5.08~7.35)	6.06 (5.16~7.58)	0.610
Fasting insulin, μU/L	7.87 (5.05~14.09)	8.11 (5.16~12.34)	0.908
Triglyceride, mmol/L	1.37 (0.95~1.91)	1.37 (1.01~1.89)	0.796
Total cholesterol, mmol/L	3.88±1.20	4.18±1.06	0.023
HDL cholesterol, mmol/L	0.98±0.26	1.06±0.23	0.009
LDL cholesterol, mmol/L	2.30±0.89	2.57±0.89	0.008
Serum creatine μmol/L	122.26±135.00	109.30±105.83	0.348
Blood urea nitrogen, mmol/L	9.04±4.35	8.20±5.11	0.125
eGFR, $mL/min/1.732m^2$	87.93±25.98	89.02±19.12	0.674

hsCRP, mg/L	2.60 (0.79~7.09)	2.05 (0.75~4.42)	0.174
NT-proBNP, pg/mL	2238.50 (785.55~4940.00)	1832.00 (705.35~4299.50)	0.343
Medication			
Aspirin	83 (53.5)	98 (63.2)	0.107
P2Y12 inhibitors	66 (42.6)	74 (47.7)	0.424
Beta-blockers	123 (79.4)	137 (88.4)	0.045
ACEI/ARB/ARNI	123 (79.4)	124 (80.0)	1.000
Calcium channel blockers	8 (5.2)	12 (7.7)	0.488
Spironolactones	113 (72.9)	116 (74.8)	0.796
Diuretics	112 (72.3)	107 (69.0)	0.618
Statins	71 (45.8)	70 (45.2)	1.000
OHA	99 (63.9)	104 (67.1)	0.633
Biguanides	35 (22.6)	26 (16.8)	0.253
Sulfonylureas	16 (10.3)	13 (8.4)	0.696
Meglitinides	4 (2.6)	4 (2.6)	1.000
Glucosidase inhibitors	70 (45.2)	80 (51.6)	0.306
SGLT2 inhibitors	17 (11.0)	28 (18.1)	0.107
Insulin	23 (14.8)	18 (11.6)	0.502

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin-receptor neprilysin inhibitors; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HFrecEF, heart failure with recovered ejection fraction; HFrEF, heart failure with reduced ejection fraction; hsCRP, high-sensitivity C-reactive protein; IHD, ischemic heart disease; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OHA, oral hypoglycemic agents; PCI, percutaneous coronary intervention; SGLT2, sodium-glucose cotransporter 2.

Table 2

Changes in left ventricular volumes and ejection fraction during follow-up

		HFrEF	HFrecEF	*P-value*
LVEDV index, mL/m^2	B	135.76±34.72	112.41±26.95	<0.001
	F	133.95±35.35	90.63±19.99	<0.001
	Δ	-1.81±19.37	-21.78±25.66	<0.001
LVESV index, mL/m^2	B	91.54±28.97	73.84±23.51	<0.001
	F	89.09±29.28	45.07±15.49	<0.001
	Δ	-2.45±17.69	-28.77±24.35	<0.001
LVEDD, mm	B	67.49±7.60	62.33±6.94	<0.001
	F	67.12±7.40	56.54±5.99	<0.001
	Δ	-0.37±3.98	-5.79±6.06	<0.001
LVESD, mm	B	56.55±7.75	51.30±6.42	<0.001
	F	56.06±7.47	41.43±6.59	<0.001
	Δ	-0.48±4.43	-9.87±6.82	<0.001
IVST, mm	B	9.01±1.31	9.75±1.51	<0.001
	F	9.12±1.28	10.08±1.43	<0.001
	Δ	0.11±1.15	0.33±1.16	0.097
LVPWT, mm	B	8.70±1.08	9.19±1.35	<0.001
	F	8.83±1.11	9.43±1.30	<0.001
	Δ	0.12±1.18	0.24±1.19	0.388
LV Mass index, g/m^2	B	148.38±33.78	140.29±34.53	0.040
	F	148.75±34.83	123.13±28.57	<0.001
	Δ	0.37±25.53	-17.15±29.83	<0.001
LVEF, %	B	33.08±6.40	35.93±5.62	<0.001
	F	33.63±6.10	51.11±8.53	<0.001
	Δ	0.54±5.70	15.18±9.58	<0.001

B, baseline; F, follow-up; Δ, changes in corresponding parameters; HFrecEF, heart failure with recovered ejection fraction; HFrEF, heart failure with reduced ejection fraction; IVST, interventricular septal thickness; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; LVPWT, left ventricular posterior wall thickness.

Table 3

Univariate analysis

Variate	OR (95% CI)	*P*-value
Ischemic etiology	1.200 (0.767~1.882)	0.424
Duration of diabetes, per 10 years	1.046 (0.773~1.416)	0.771
Hypertension	1.451 (0.923~2.288)	0.108
Previous myocardial infarction	1.824 (0.758~4.692)	0.190
Atrial fibrillation	0.655 (0.305~1.368)	0.265
Smoking habits	1.519 (0.922~2.515)	0.102
Body mass index	0.997 (0.934~1.065)	0.929
Systolic BP, per 10 mmHg	1.246 (1.107~1.412)	**<0.001**
Diastolic BP, per 10 mmHg	1.124 (0.955~1.328)	0.164
Fasting glucose, per mmol/L	1.009 (0.923~1.104)	0.844
Fasting insulin, per μU/L	1.004 (0.991~1.025)	0.562
Triglyceride, per mmol/L	0.976 (0.802~1.185)	0.806
Total cholesterol, per mmol/L	1.266 (1.034~1.562)	**0.025**
HDL cholesterol, per mmol/L	3.478 (1.359~9.255)	**0.011**
LDL cholesterol, per mmol/L	1.417 (1.094~1.858)	**0.010**
eGFR, per 10 mL/min/1.732m^2	1.021 (0.926~1.129)	0.673
NT-proBNP, per SD	0.944 (0.742~1.197)	0.629
hsCRP, per SD	0.780 (0.475~1.087)	0.235
Beta-blockers	1.980 (1.069~3.768)	**0.033**
ACEI/ARB/ARNI	1.041 (0.598~1.814)	0.888
Calcium channel blockers	1.542 (0.619~4.041)	0.358
Statins	0.974 (0.623~1.524)	0.909
OHA	1.153 (0.722~1.846)	0.550
Insulin	0.754 (0.385~1.457)	0.403
LVEF, per 10%	2.223 (1.509~3.348)	**<0.001**
LVEDV index, per 10 mL/m^2	0.766 (0.694~0.837)	**<0.001**
LVESV index, per 10 mL/m^2	0.749 (0.667~0.832)	**<0.001**
HbA1c, per 1%	0.775 (0.639~0.929)	**0.007**

HbA1c tertiles		**<0.001***
<6.2 mmol/L	Reference	**-**
6.2 ~ 7.1 mmol/L	0.535 (0.307~0.923)	**0.025**
≥ 7.1 mmol/L	0.349 (0.196~0.614)	**<0.001**

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin-receptor neprilysin inhibitors; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OHA, oral hypoglycemic agents; OR, odds ratio; SD, standard deviation.

Table 4

Multivariate analysis

Covariate	**Model I**		**Model II**	
	95% CI	***P*-value**	**95% CI**	***P*-value**
Systolic BP, per 10 mmHg	1.121 (0.982~1.286)	0.097	1.115 (0.976~1.281)	0.114
HDL cholesterol, mmol/L	3.730 (1.261~11.435)	0.019	3.235 (1.084~9.974)	0.037
Beta-blockers	2.091 (0.995~4.488)	0.054	2.198 (1.041~4.745)	0.041
LVEDV index, per 10 mL/m^2	0.756 (0.679~0.832)	<0.001	0.754 (0.678~0.831)	<0.001
HbA1c level				
per mmol/L	0.792 (0.642~0.967)	0.025	-	-
Tertiles	-	-	-	<0.001
<6.2 mmol/L	-	-	Reference	-
6.2 ~ 7.1 mmol/L	-	-	0.605 (0.326~1.116)	0.109
≥7.1 mmol/L	-	-	0.391 (0.201~0.750)	0.005

BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; LVEDV, left ventricular end-diastolic volume.

Figures

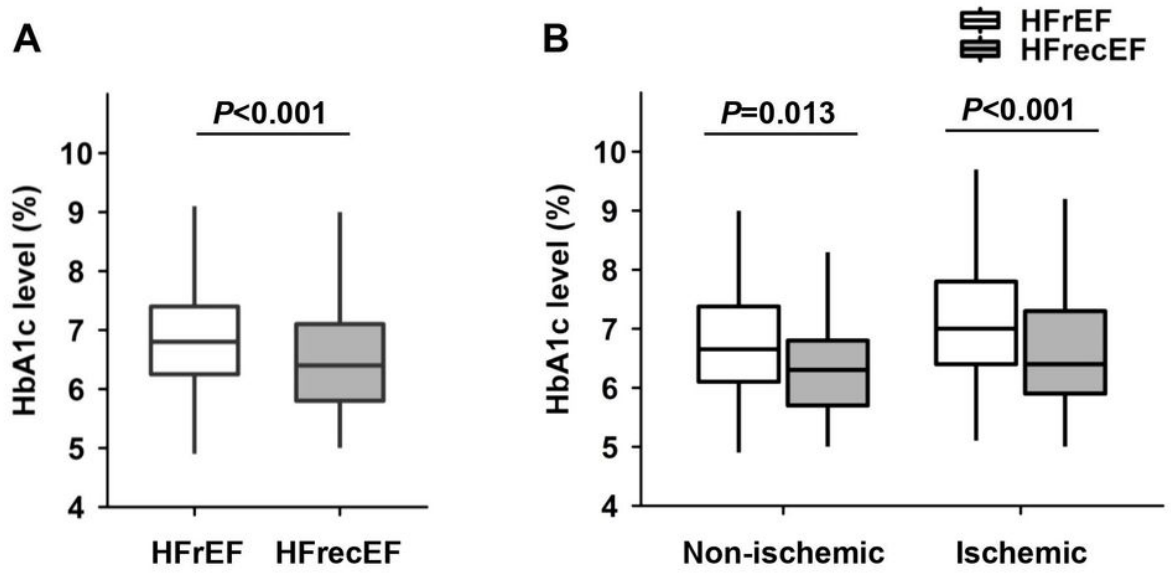

Figure 1

HbA1c levels in T2DM patients with heart failure. Shown are HbA1c levels in T2DM patients with HFrecEF and persistently HFrEF in the overall study population (A) or subgroups according to whether the presence of ischemic etiology (B). Horizontal lines in the box: upper, 25% percentile; middle, median; lower, 75% 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.

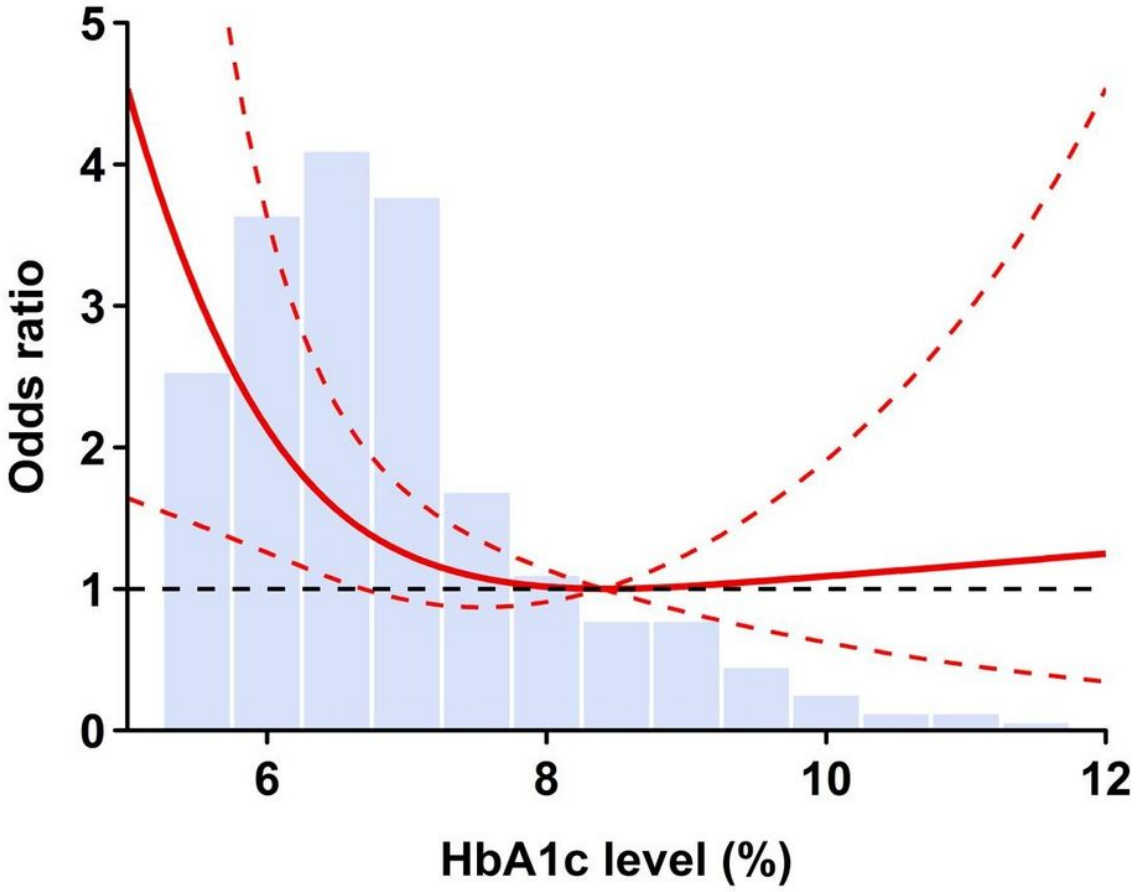

Figure 2

Restricted cubic spline plots for the likelihood of HFrecEF by HbA1c levels after covariate adjustment. The central solid line represents the adjusted odds ratio, and the dashed lines denote 95% confidence interval. The background histograms represent the distribution of HbA1c in the study population. HFrecEF, heart failure with recovered ejection fraction.

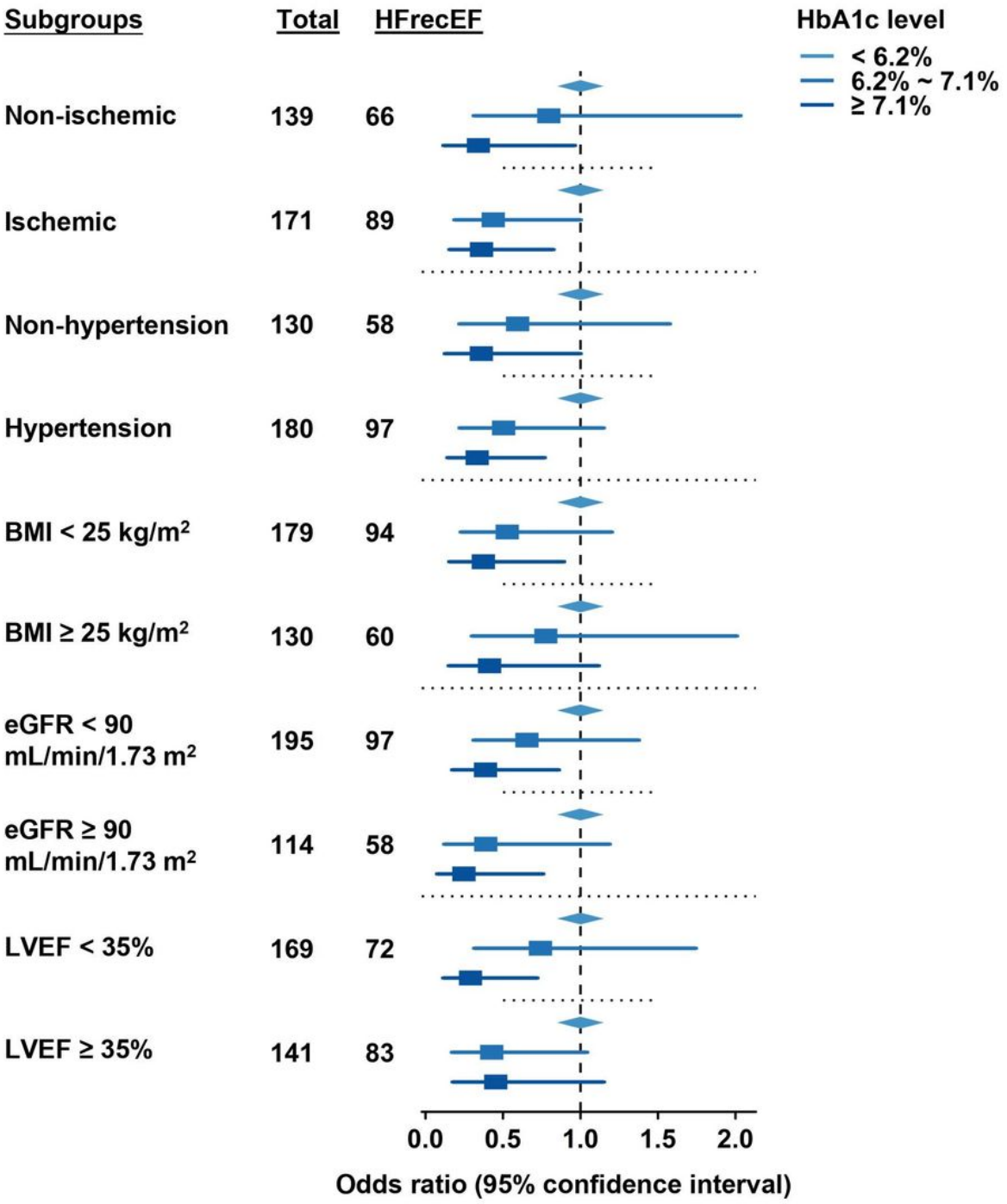

Figure 3

Forest plot for the likelihood of HFrecEF in different subgroups. The first tertile of HbA1c level (<6.2 mmol/L) was set as reference. Odds ratios and their corresponding confidence intervals after covariate adjustment were shown. BMI, body mass index; eGFR, estimated glomerular filtration rate; HFrecEF, heart failure with recovered ejection fraction; LVEF, left ventricular ejection fraction.