Prognostic Implication of Admission HbA1c for All-cause Mortality in Ischemic Heart Failure Among a Chinese Population: A Prospective Cohort Study

Weida Qiu

Southern Medical University <https://orcid.org/0000-0003-2206-8439>

Sicheng Chen

Shantou University Medical College

Anping Cai

Guangdong Provincial People's Hospital: Guangdong Provincial People's Hospital

Xiaoju Xiao

Southern Medical University

Zhiping Gao

Guangdong Provincial People's Hospital: Guangdong Provincial People's Hospital

Jijin Lin

Guangdong Provincial People's Hospital: Guangdong Provincial People's Hospital

Liwen Li (✉ gdghllw@163.com)

Guangdong Cardiovascular Institute

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Abstract

Background: The impact of glycosylated hemoglobin A1c (HbA1c) on heart failure (HF) and ischemic heart disease (IHD) differs among studies, and IHD is a preponderant cause in HF. We investigated the link between admission HbA1c and all-cause mortality in a Chinese population with ischemic heart failure (IHF).

Methods: Eligible patients with IHF at the Department of Cardiology, Guangdong Provincial People's Hospital from December 2015 to June 2019 were enrolled to investigate the association between admission HbA1c and all-cause mortality of IHF with Kaplan-Meier survival analysis and Cox regression analysis.

Results: Of 1413 participants, the median age was 63.2 ± 10.9 years, 85% were men and median admission HbA1c level was 6.82%. All-cause mortality was higher in HbA1c >7% group compared with HbA1c $\leq 7\%$ group (hazard ratio (HR): 1.328, 95% confidence interval (CI): 1.016-1.735, $p = 0.037$), and sensitivity analysis appeared the consistent result. The association between HbA1c and all-cause mortality was also statistically significant in the male and younger cohorts.

Conclusions: Elevated admission HbA1c level (>7%) is an independent risk factor for all-cause mortality of IHF in the general population, and there is also a consistent trend among male and younger individuals. Further explorations are required to elucidate whether glycemic management plays a crucial role in the progression of IHF within female and elderly population.

Background

As a global epidemic, heart failure (HF) confers a rapidly escalating prevalence with aging, as well as high mortality and ominous prognosis despite humble improvement in survival over the past decades [1, 2]. Ischemic heart disease (IHD) is the most prevailing risk factor of HF in Europe and North America [1]. It's projected that 700 million and 548.4 million individuals will develop diabetes and impaired glucose tolerance (IGT) worldwide by 2045, with 50.1% being undiagnosed diabetes in 2019 [3]. Type 2 diabetes mellitus (T2DM) is enormously frequent (30–40%) in HF subjects and associated with worsening in hospitalization and readmission for HF, together with mortality, where coronary artery disease (CAD) is a major contributor to concomitant HF and T2DM [4]. Available data suggest that diabetes mellitus (DM) and IHD interact to hasten the progression of HF [5], and IHD adds further to unfavorable prognosis among HF patients with T2DM [6].

Glycosylated hemoglobin A1c (HbA1c) is the primary metric for assessing glycemic management and has been applied to date in clinical trials to determine the profit of glucose control [7]. Elevated HbA1c level is connected with excess hazard of new-onset and hospitalization for HF in patients with stable CAD [8], hospitalized and short-term mortality in acute coronary syndrome (ACS) without DM history and confirmed DM [9], all-cause mortality along with risk of myocardial infarction (MI) and HF in T2DM sufferers [10]. However, research findings at odds imply that intensive glucose control hasn't

demonstrated significant effect on peril of HF or all-cause mortality in spite of risk reduction in macrovascular or coronary incidents [11, 12]. Moreover, it seems that intensive glucose lowering modality was associated with risk increase in congestive HF and non-significant impact on MI, and HbA1c $\leq 7\%$ even significantly raised mortality of advanced systolic HF with diabetes [13, 14]. These evidences remain contradictory regarding the role of HbA1c level or glycemic administration in HF and myocardial ischemia related disorders.

In our prospective ischemic heart failure (IHF) cohort study among a Chinese population [15], we intended to identify all-cause mortality of IHF in relation to admission HbA1c level, where sex- and age- related discrepancies were additionally explored, in consideration of sex differences in coronary heart disease (CHD) [16] and HF [17], and glucose targets varying from younger to elderly individuals recommended by current diabetes guidelines [18, 19].

Methods

Study design and population

Design of our single-center, prospective cohort study targeting IHF patients has been published previously [15]. Patients were selected who were hospitalized in the Department of Cardiology, Guangdong Provincial People's Hospital from December 2015 to June 2019. Eligible individuals were included with: a) ≥ 18 years of age; b) left ventricular ejection fraction (LVEF) $< 45\%$ assessed by echocardiogram during hospitalization; c) IHD confirmed by coronary angiography, antecedent MI, and/or antecedent revascularization; d) available HbA1c data at admission. Patients were excluded with LVEF $< 45\%$ due to non-ischemic etiologies or without any follow-up since discharge. This cohort study was approved by the Clinical Research Ethics Committee of Guangdong Provincial People's Hospital (No. 2017128H), as well as performed in accordance with the Declaration of Helsinki. All the participants provided written informed consent before enrollment.

Data collection

Baseline data of interest, including demographics, reasons for referral, vital sign at admission, comorbidities and hypoglycemic drugs, were obtained from electronic medical records of Guangdong Provincial People's Hospital. As described already [15], venous blood at admission was drawn for evaluation of HbA1c, creatinine, high-sensitivity C-reactive protein (hs-CRP), high-sensitivity cardiac troponin-T (hs-cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations, and fasting venous blood was drawn for evaluation of fasting plasma glucose (FPG) and lipid parameters at the second day after admission. Morning urine was collected to examine urine albumin creatine ratio (UACR).

High-performance liquid chromatography (hemoglobin testing system D-10, Bio-Rad laboratories Inc, America) was utilized to test HbA1c concentration. Body mass index (BMI) was calculated as body weight in kilogram divided by height in square meter. Diabetes status was defined according to diagnostic criteria of the American Diabetes Association (ADA) guideline [20]. Confirmed diabetes was

defined as having been diagnosed diabetes priorly or two abnormal test results while in hospital (FPG ≥ 7.0 mmol/L and HbA1c $\geq 6.5\%$). Pre-diabetes was defined as FPG levels from 5.6 to 6.9 mmol/L or HbA1c levels from 5.7 to 6.4%. Excluded diabetes was defined as the absence of prior diagnosis of diabetes and normal results of blood glucose and HbA1c during the current hospital visit. Undefined status was defined as not meeting the above conditions (for example, FPG ≥ 7.0 mmol/L while HbA1c $< 5.7\%$ or FPG < 7 mmol/L while HbA1c $\geq 6.5\%$).

Follow-up and clinical endpoint

Methods of follow-up and clinical endpoint were presented previously [15]. Of note, all-cause mortality was served as clinical endpoint in the current study because of the unavailability of judgement for exact reasons of death.

Statistical analysis

Patients enrolled in the study were firstly divided into two groups based on HbA1c concentrations (HbA1c $> 7\%$ and HbA1c $\leq 7\%$). In addition, we analyzed the sex and age (age ≥ 65 years old and age < 65 years old) subgroups. Missing values of BMI, hs-CRP, hs-cTnT, NT-proBNP and UACR were filled by regression imputation. Continuous variables consistent with normal distribution were expressed as mean value $\pm$ standard deviation (SD), while the data consistent with skewed distribution expressed as median (interquartile range) and categorical variables were expressed as number and proportion. A student's t-test or Mann-Whitney U-test was used to evaluate continuous variables properly, and chi-square test or Fisher's exact test was used to compare categorical variables. Differences in baseline characteristics were examined between HbA1c $> 7\%$ vs. HbA1c $\leq 7\%$.

Univariate and multivariate logistic regression analyses were then performed to discover factors connected with HbA1c $> 7\%$. Briefly, factors with P-value < 0.1 in univariate analysis were further included in multivariate analysis with stepwise adjustment. Odds ratio (OR) and 95% confidence interval (CI) were recorded.

To determine the relationship between admission HbA1c level and all-cause mortality in IHF patients as well as in the sex and age subgroups, survival analysis with Log-Rank test and multivariate Cox proportional hazards analysis with stepwise adjustment were performed for covariates including baseline characteristics, clinical presentations, antecedent medical histories, hypoglycemic agents and medications prescribed at discharge. Due to Kaplan-Meier survival curves of HbA1c $> 7\%$ and HbA1c $\leq 7\%$ categories intersecting in the elderly subgroup, which means non-proportional risk model, time-dependent Cox regression analysis was then applied to identify the association between admission HbA1c level and all-cause mortality of IHF in the elderly subgroup.

Sensitivity analysis was lastly employed to verify robustness of our results. There were 567 participants with missing values of BMI in our study owing to their serious illnesses, making them need to rest in bed and unable to measure height or weight. The remainder with BMI data were subsequently selected to

explore the relationship between HbA1c and all-cause mortality by survival analysis and multivariate Cox proportional hazards analysis. SPSS version 22.0 of Windows was utilized for all analyses, and two-sided P-value <0.05 was considered statistically significant.

Results

A total of 1520 IHF patients with LVEF <45% were included in the current cohort study. Among them, 83 patients lacked admission HbA1c data and 24 patients were lost follow-up since discharge. The final cohort consisted of 1413 participants (Figure 1). The mean age was 63.2 ± 10.9 years old and 85.0% were men. The mean HbA1c level was 6.8% and the mean FPG concentration was 6.17mmol/L. 529 patients (37.4%) were confirmed diabetes, and 497 ones (35.2%) were diagnosed pre-diabetes and 220 ones (15.6%) excluded diabetes. The most commonly used hypoglycemic agents were α -glucosidase inhibitors (16.7%), biguanides (11.7%), sulfonylureas (7.6%) and insulin (7.1%), respectively.

Baseline characteristics comparisons between HbA1c $\leq 7\%$ and HbA1c $> 7\%$

Table 1 presents baseline characteristics for all IHF individuals (n =1413), ones with HbA1c $\leq 7\%$ (n =981) and ones with HbA1c $> 7\%$ (n =432). According to Table 1, the majority of patients with HbA1c $\leq 7\%$ were men and admitted for unstable angina, with lower heart rate and triglyceride (TG). Patients with HbA1c $> 7\%$ were mainly admitted for HF, and suffered from higher FPG, hs-cTnT, NT-proBNP, UACR and larger LA diameter. Approximately 70% of subjects received coronary stenting (69.2% vs. 71.3%). More participants with HbA1c $> 7\%$ underwent intravenous diuretics and hypoglycemic agents in hospital, and were prescribed aspirin, mineralocorticoid receptor antagonists (MRA), loop diuretics and digoxin at discharge in comparison with those with HbA1c $\leq 7\%$.

Factors associated with HbA1c $> 7\%$ compared with HbA1c $\leq 7\%$

In the univariate analysis, factors associated with HbA1c $> 7\%$ comprised sex, BMI, admission for ACS and HF, heart rate, FPG, hs-cTnT, NT-proBNP, high density lipoprotein cholesterol (HDL-C), TG and UACR. Multivariate regression analysis displayed that sex, FPG, HDL-C and UACR were linked with HbA1c $> 7\%$. To be specific, per 1 mmol/L increase in FPG (OR: 2.07, 95% CI: 1.71-2.51, p =0.0001) and per log10 (UACR) mg/g Cr increase in UACR (OR: 1.86, 95% CI:1.25-2.76, p =0.002) were associated with 107% and 86% higher risks of HbA1c $> 7\%$. On the contrary, male sex (OR: 0.33, 95% CI: 0.16-0.71, p =0.004) and elevated HDL-C concentrations (OR: 0.21, 95%CI: 0.06-0.77, p =0.018) were more connected with HbA1c $\leq 7\%$ (Table 2).

Association between HbA1c and all-cause mortality in all patients

After a median follow-up time of 2.9 years, 233 patients died with an overall mortality rate of 16.5% in the study cohort. Figure 2 shows higher hazard of death among those with admission HbA1c $> 7\%$, compared to ones with HbA1c $\leq 7\%$ (Log-Rank p =0.037). Cox proportional hazards regression analysis showed that HbA1c $> 7\%$ was still associated with increased risk of all-cause mortality (HR: 1.330, 95%CI: 1.012-1.749,

p =0.041) after stepwise adjustment for baseline characteristics, clinical presentations, antecedent medical histories and medications prescribed at discharge. Other independent predictors of all-cause mortality included age, BMI, TG, LVEF, ST-segment elevation myocardial infarction (STEMI), prior stroke and tumor, aspirin therapy, beta-blockers (BB) therapy and diuretics therapy (Figure 3).

Association between HbA1c and all-cause mortality in sex and age subgroups

Figure 4a exhibits that male patients with admission HbA1c >7% had higher hazard of all-cause mortality compared to those with HbA1c ≤7% (Log-Rank p =0.016). In the female population, linkage between HbA1c and all-cause mortality didn't reach statistical difference (Figure 4b). In multivariate Cox proportional hazards regression, male participants with HbA1c >7% predicted greater risk of all-cause mortality (HR: 1.419, 95% CI: 1.047-1.922, p =0.024) in comparison to ones with HbA1c ≤7% (Figure 5a).

Figure 4c shows that all-cause mortality was significantly higher in the younger patients (age <65years old) with HbA1c >7% compare to those with HbA1c ≤7% (Log-Rank p =0.002). In multivariate Cox proportional hazards regression, there was higher hazard of all-cause mortality in younger sufferers with HbA1c >7% (HR: 1.531, 95% CI: 1.014-2.312, p =0.043) in contrast to ones with HbA1c ≤7% (Figure 5b). In the elderly cohort (age ≥65years old), Kaplan-Meier survival curves of HbA1c >7% and HbA1c ≤7% intersected, meaning proportional hazards rate is violated. Hence, we implemented time-dependent Cox regression analysis instead of Cox proportional hazards model. Table 3 illustrates that in the time-dependent Cox analysis, no significant effect of HbA1c on all-cause mortality was observed in the elderly individuals.

Sensitivity analysis

In order to validate reliability of our results, we carried out sensitivity analysis in participants with available BMI data (n =846). Supplementary Table 1 presents baseline characteristics between patients with BMI data and without BMI data. Those without BMI data seemed to experience more serious illnesses during hospitalization and need to rest in bed, leading to inability to measure height and weight. The results of sensitivity analysis were similar to those from the imputed data (Supplementary Figure 1 and Supplementary Figure 2). In patients with BMI data, HbA1c >7% group suffered from greater risk of all-cause mortality compared with HbA1c ≤7% group (Log-Rank p =0.031). Multivariate Cox proportional hazards regression illustrated that HbA1c >7% remained predicting higher hazard of all-cause mortality than HbA1c ≤7% (HR: 1.552, 95% CI: 1.086-2.218, p =0.016).

Discussion

This prospective cohort study amongst a Chinese population with IHF denoted that higher level of admission HbA1c (HbA1c >7%) was significantly associated with increased all-cause mortality in general IHF sufferers, which was likewise exhibited within male and younger individuals, with the absence of such relevance in female and elderly ones on the contrary.

The present study primarily indicated that stringent glycemic administration ($\text{HbA1c} \leq 7\%$) facilitated reduction in risk of death and improved prognosis of general patients with IHF, conforming to glucose goals for a majority of DM subjects recommended by contemporary diabetes guidelines [18, 19]. Diabetes contributes to structural cardiac alterations and HF partly via myocardial ischemia or infarction, where hyperglycemia and hyperinsulinemia escalate atherosclerosis [21]. HbA1c magnitude is positively correlated with coronary and peripheral atherosclerosis in non-diabetic population [22, 23], along with severity of coronary artery stenosis in acute myocardial infarction (AMI) with DM and non-DM [24]. Meanwhile, HbA1c level is considered as one of the strongest predictors with regard to the peril of death, HF hospitalization and AMI amongst T2DM sufferers. Decreased HbA1c concentrations are linked with lower risks of these outcomes, more so of atherothrombotic incidents, even though $\text{HbA1c} \leq 7\%$ marginally shrank risk of HF hospitalization [25]. Furthermore, some of AMI patients without known diabetes history have glucose metabolic disorders, and $\text{HbA1c} \geq 39$ mmol/mol demonstrates a significant increase in risk of HF amongst those AMI subjects [26]. These findings, combined with our current study, inform detrimental effects of elevated HbA1c level or hyperglycemia on HF and myocardial ischemia related alterations, and rigorous glycemic administration to achieve low HbA1c targets predisposes patients with IHF to better outcomes.

As is known, hypoglycemia (sulfonylureas and insulin), fluid retention (thiazolidinediones), weight gain (sulfonylureas, insulin and thiazolidinediones) potentially prompt worsening in HF with certain hypoglycemic medications [7]. Intensively treated patients with poor prognosis of HF in the past studies [13, 14] are likely to encounter more adverse reactions on account of a greater amount of conventional antihyperglycemic drugs to reach lower HbA1c goals. Moreover, in the study where elevated HbA1c level ameliorated survival of advanced systolic HF with diabetes, only 123 participants were involved, and ones with $\text{HbA1c} > 7\%$ had higher ejection fraction (EF) [14], signaling the requirement of involving more subjects and comparable baseline data between HbA1c groups. The exact connection between HbA1c level and peril of IHF should be assessed by more research including randomized clinical trials.

With respect to sex-related disparities in linkage between death risk of IHF and HbA1c, our research implicated that HbA1c showed positive relationship with all-cause mortality of IHF among male sufferers, while there was no significant difference for female ones. IHF subjects involved in our investigation were recognized with $\text{LVEF} < 45\%$, which was defined as HF with reduced ejection fraction (HFrEF). Previous study found higher lifetime risk of HFrEF in men than women, and it might be attributed to men encountering heavier load and prior episode of CHD compared with women [27]. In addition, it's thought that HFrEF is predominantly a disease of men, where macrovascular lesions (e.g. CAD and MI) have been postulated to play a critical role, and conversely, women preponderate in HF with preserved ejection fraction (HFpEF), attributable to their susceptibility to coronary microvascular dysfunction and endothelial inflammation [17], although other research has demonstrated that lifetime risk of HFpEF was almost on a par between both sexes [27]. It can therefore be assumed that male individuals with HFrEF benefit more from strict glucose conduct in the setting of ischemic cardiomyopathy, whilst female ones

fail to display the connection due to their predisposition to HFpEF and a paucity of adequate female participants (25% in our study).

Another notable indication in our results was that elevated level of HbA1c was linked with poor survival of IHF in the younger category (age <65 years old) rather than in the elderly category (age $\geq$ 65 years old). It has previously been observed that risks of HF hospitalization, AMI and death related with diabetes illustrated a stepwise decline from younger to older age groups in the context of HbA1c beyond target range, and also of note, hazard of hospitalization for HF was not expected to shrink with HbA1c not outside target range [25], which is not congruous with our outcome. What's more, preceding evidence suggests that younger sufferers aged <55 years with T2DM are susceptible to excessive risk of HF, of which excess risk declines with advancing age [28]. Intensive glucose lowering therapy significantly raises risk of hypoglycemia [11, 13], and diverse studies appear a consistently U shaped relationship between HbA1c and risk of death amongst HF subjects, with moderate HbA1c level (7% to 8%) conferring the lowest mortality [21]. Accordingly, up-to-date diabetes guidelines have recommended that more lenient HbA1c goals may be suitable for individuals with limited life expectancy and severe comorbidities [18, 19]. A plausible explanation for the results and evidence might be that there are greater potential benefits from more aggressive treatment on blood glucose for younger patients with IHF, whereas probable gains from lower admission HbA1c level ($\leq$ 7%) across elderly ones are offset by deleterious impact of hypoglycemia.

Our observational investigation has several strengths and also some noteworthy limitations. Patients with HFrEF caused by ischemic cardiomyopathy or IHD in China were included. The positive association between admission HbA1c magnitude and peril of IHF in the majority of population was substantiated. Nevertheless, this is a single center based and observational cohort study. More female participants are supposed to be incorporated to disclose the power of glucose control over prognosis of IHF in women. There was a comparatively small portion of application in novel glucose-lowering drugs in our participants, containing glucagon-like peptide-1 receptor agonists (GLP-1 RA), dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, signaling the need for more employment of these new therapies to recognize how drop in HbA1c contributed by them affects hazard of IHF.

In conclusion, elevated admission HbA1c level (>7%) is an important indicator of increased all-cause mortality of IHF among general patients, and so for male and younger individuals. Further explorations are required to elucidate whether glycemic management plays a crucial role in the progression of IHF within female and elderly population.

Abbreviations

HbA1c, hemoglobin A1c; HF, heart failure; IHD, ischemic heart disease; IHF, ischemic heart failure; HR, hazard ratio; CI, confidence interval; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus; DM, diabetes mellitus; CAD, coronary artery disease; ACS, acute coronary syndrome; MI, myocardial infarction;

CHD, coronary heart disease; LVEF, left ventricular ejection fraction; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin-T; NT-proBNP, N-terminal pro-brain natriuretic peptide; FPG, fasting plasma glucose; UACR, urine albumin creatine ratio; BMI, body mass index; ADA, American Diabetes Association; SD, standard deviation; OR, odds ratio; TG, triglyceride; MRA, mineralocorticoid receptor antagonists; HDL-C, high density lipoprotein cholesterol; STEMI, ST-segment elevation myocardial infarction; BB, beta-blockers; AMI, acute myocardial infarction; EF, ejection fraction; HFrEF, HF with reduced ejection fraction; HFpEF, HF with preserved ejection fraction; GLP1 RA, glucagon-like peptide-1 receptor agonists; DPP-4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter-2.

Declarations

Ethics approval and consent to participate

The Clinical Research Ethics Committee of Guangdong Provincial People's Hospital approved the study protocol (No. 2017128H) in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants.

Consent for publication

The manuscript was approved by all authors for publication.

Availability of data and materials

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

Competing interests

All authors declare that they have no competing interests.

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Authors' contributions

QWD contributed to the data collection, analysis and drafted the manuscript. CSC drafted the manuscript. CAP critically revised the manuscript. XXJ contributed to the data collection. GZP, LJJ and LLW contributed to the conception and design of the work. All authors read and approved the final manuscript.

Corresponding author

Correspondence to Jijin Lin and Liwen Li.

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Tables

Table 1. Baseline Characteristics Comparisons between $HbA1c \leq 7.0\%$ and $HbA1c > 7.0\%$.

Variables	Overall (n=1413)	HbA1c≤7.0% (n=981)	HbA1c>7.0% (n=432)	P- value
Age(years)	63.2±10.9	63.5±11.3	62.6±10.0	0.123
Male, n (%)	1201 (85.0)	852 (86.9)	349 (80.8)	0.003
BMI (kg/m2)	23.6±3.3	23.5±3.4	23.9±3.1	0.058
Reasons for referral				
STEMI, n (%)	230 (16.3)	162 (16.5)	68 (15.7)	0.717
Non-STEMI, n (%)	112 (7.9)	72 (7.3)	40 (9.3)	0.218
Unstable angina, n (%)	633 (44.8)	468 (47.7)	165 (38.2)	0.001
Heart failure, n (%)	407 (28.8)	255 (26.0)	152 (35.2)	<0.001
Others, n (%)	31 (2.2)	24 (2.4)	7 (1.6)	0.431
Vital sign at admission				
SBP (mmHg)	125±20	125±20	126±20	0.594
DBP (mmHg)	75±12	75±13	75±12	0.798
HR (bpm)	80±15	79±15	83±15	<0.001
Diabetic status				
Confirmed diabetes, n (%)	529 (37.4)	159 (16.2)	370 (85.6)	<0.001
Pre-diabetes, n (%)	497 (35.2)	497 (50.7)	0 (0)	<0.001
Excluded diabetes, n (%)	220 (15.6)	220 (22.4)	0 (0)	<0.001
Undefined, n (%)	167 (11.8)	105 (10.7)	62 (14.4)	<0.001
Comorbid conditions				
Smoking, n (%)	343 (24.2)	252 (25.7)	91 (21.1)	0.062
Obesity, n (%)	63 (4.5)	39 (4.0)	24 (5.6)	0.185
Hypertension, n (%)	729 (51.6)	504 (51.4)	225 (52.1)	0.806
Dyslipidemia, n (%)	888 (62.8)	611 (62.3)	277 (64.1)	0.510
Atrial fibrillation, n (%)	90 (6.4)	62 (6.3)	28 (6.5)	0.909
Prior stroke/TIA, n (%)	110 (7.8)	79 (8.1)	31 (7.2)	0.571
COPD, n (%)	107 (7.6)	77 (7.8)	30 (6.9)	0.554
Prior tumor, n (%)	19 (1.3)	18 (1.8)	1 (0.2)	0.002

Prior MI, n (%)	498 (35.2)	351 (35.8)	147 (34.0)	0.525
Prior PCI, n (%)	818 (57.9)	559 (57.0)	259 (60.0)	0.297
Prior CABG, n (%)	26 (1.8)	15 (1.5)	11 (2.5)	0.201
Laboratory				
HbA1C (%)	6.82±1.64	5.94±0.56	8.84±1.47	<0.001
FPG (mmol/L)	6.17±2.54	5.29±1.31	8.22±3.41	<0.001
Hemoglobin (mg/dL)	131.8±19.1	132.3±18.7	130.6±19.9	0.126
Creatinine (μmol/L)	105.1±74.3	105.3±73.8	104.8±75.5	0.917
eGFR (ml/min/1.73m ²)	72.93±22.35	72.82±21.77	73.19±23.64	0.778
Hs-CRP (mg/L) *	5.06 (1.41-15.25)	5.06 (1.33-16.38)	5.19 (1.53-14.40)	0.735
Hs-cTnT (pg/mL) *	36.82 (18-229.3)	32.2 (17.0-186.8)	47.4 (21.8-310.4)	<0.001
NT-proBNP (pg/mL) *	1608 (648-3606)	1492 (593-3206)	1834 (777-4447)	<0.001
TC (mmol/L)	4.39±1.32	4.42±1.32	4.35±1.31	0.369
LDL-C (mmol/L)	2.88±1.01	2.89±1.03	2.86±0.97	0.510
HDL-C (mmol/L)	0.94±0.24	0.95±0.24	0.91±0.24	0.004
TG (mmol/L) *	1.30 (0.99-1.78)	1.24 (0.98-1.71)	1.46 (1.05-1.98)	<0.001
UACR (mg/g Cr) *	8.85 (3.93-45.04)	6.16 (3.32-29.01)	21.93 (7.12-108.04)	<0.001
Echocardiographic indices				
LVEF (%)	35.00±6.90	35.17±6.90	34.62±6.90	0.167
LVEF ≤ 40%, n (%)	1069 (75.7)	568 (74.6)	501 (76.8)	0.336
In-hospital treatment				
Coronary stenting, n (%)	987 (69.9)	679 (69.2)	308 (71.3)	0.432
IV inotrope, n (%)	173 (12.2)	112 (11.4)	61 (14.1)	0.153
IV diuretics, n (%)	508 (36.0)	323 (32.9)	185 (42.8)	<0.001
Hypoglycemic agents				
Sulfonylureas, n (%)	108 (7.6)	38 (3.9)	70 (16.2)	<0.001
Biguanides, n (%)	166 (11.7)	39 (4.0)	127 (29.4)	<0.001

α -glucosidase inhibitors, n (%)	236 (16.7)	72 (7.3)	164 (38.0)	<0.001
Thiazolidinediones, n (%)	6 (0.4)	4 (0.4)	2 (0.5)	1.00
Glinides, n (%)	32 (2.3)	10 (1.0)	22 (5.1)	<0.001
GLP-1 receptor agonists, n (%)	2 (0.1)	0 (0)	2 (0.5)	0.093
DPP-4 enzyme inhibitors, n (%)	30 (2.1)	5 (0.5)	25 (5.8)	<0.001
SGLT2i, n (%)	2 (0.1)	0 (0)	2 (0.5)	0.093
Insulin, n (%)	100 (7.1)	13 (1.3)	88 (20.4)	<0.001
Medications prescribed at discharge				
Aspirin, n (%)	1263 (89.4)	866 (88.3)	397 (91.9)	0.042
Clopidogrel, n (%)	1053 (74.5)	726 (74.0)	327 (75.7)	0.502
Ticagrelor, n (%)	182 (12.9)	123 (12.5)	59 (13.7)	0.563
Statins, n (%)	1341 (94.9)	933 (95.1)	408 (94.4)	0.602
RASi, n (%)	1001 (70.8)	694 (70.7)	307 (71.1)	0.903
ARNI, n (%)	39 (2.8)	25 (2.5)	14 (3.2)	0.483
MRA, n (%)	720 (51.0)	466 (47.5)	254 (58.8)	<0.001
CCB, n (%)	137 (9.7)	100 (10.2)	37 (8.6)	0.340
Betablocker, n (%)	1199 (84.9)	829 (84.5)	370 (85.6)	0.581
Diuretics, n (%)	680 (48.1)	441 (45.0)	239 (55.3)	<0.001
Digoxin, n (%)	102 (7.2)	61 (6.2)	41 (9.5)	0.029
Oral anticoagulants, n (%)	98 (6.9)	68 (6.9)	30 (6.9)	0.993

HbA1c, hemoglobin A1c; BMI, body Mass Index; STENI, ST-segment elevation myocardial infarction; Non-STEMI, Non-ST-segment elevation myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beat per minute; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; Hs-CRP, high sensitivity C reactive protein; Hs-cTnT, high sensitivity cardiac troponin-T; NT-proBNP, N-terminal pro B-type natriuretic peptide; TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; UACR, urine albumin creatine ratio; LVEF, left ventricular ejection fraction; IV, intravenous; GLP-1, Glucagon-likepeptide-1; DPP-4, dipeptidyl peptidase-4; SGLT2i, sodium-dependent glucose transporters 2 inhibitor; RASi, renin-angiotensin-system inhibitor; ARNI,

angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; CCB, calcium channel blocker.

Table 2 Factors associated with HbA1C $\geq$ 7.0% compared to HbA1C $\leq$ 7.0%.

	Univariate		Multivariable	
Variables	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (per 1-year increase)	0.99(0.98-1.00)	0.141	N/A	
Men vs women	0.64(0.47-0.86)	0.003	0.33(0.16-0.71)	0.004
BMI (per 1-kg/m ² increase)	1.04(1.00-1.09)	0.058	0.97(0.89-1.06)	0.547
ACS vs non-ACS	0.68(0.54-0.87)	0.002	0.17(0.03-1.11)	0.064
HF vs non-HF	1.55(1.21-1.97)	<0.0001	0.22(0.03-1.58)	0.132
SBP (per 1-mmHg increase)	1.00(1.00-1.01)	0.593	N/A	
DBP (per 1-mmHg increase)	1.00(0.99-1.01)	0.798	N/A	
Heart rate (per 1-bpm increase)	1.02(1.01-1.03)	<0.0001	1.00(0.98-1.02)	0.879
Smoking vs non-smoking	1.09(0.72-1.64)	0.683	N/A	
Hypertension vs non-hypertension	1.03(0.82-1.29)	0.806	N/A	
Dyslipidemia vs non-dyslipidemia	1.08(0.86-1.37)	0.510	N/A	
COPD vs non-COPD	0.88(0.57-1.36)	0.554	N/A	
AF vs non-AF	1.03(0.65-1.63)	0.909	N/A	
Prior stroke/TIA vs non- prior stroke/TIA	0.88(0.57-1.36)	0.571	N/A	
Prior MI vs non-prior MI	0.93(0.73-1.18)	0.525	N/A	
Prior PCI vs non-prior PCI	1.13(0.90-1.42)	0.297	N/A	
Prior CABG vs non-prior CABG	1.68(0.77-3.69)	0.195	N/A	
Hemoglobin (per 1-mg/dL increase)	1.00(0.99-1.00)	0.126	N/A	

FPG (per 1-mmol/L increase)	1.96(1.78-2.15)	<0.0001	2.07(1.71-2.51)	<0.0001
TC (per 1-mmol/L increase)	0.96(0.88-1.05)	0.369	N/A	
LDL-C (per 1-mmol/L increase)	0.96(0.86-1.08)	0.510	N/A	
HDL-C (per 1-mmol/L increase)	0.49(0.30-0.80)	0.004	0.21(0.06-0.77)	0.018
TG (per 1-mmol/L increase)	1.23(1.10-1.38)	<0.0001	1.06(0.85-1.33)	0.589
eGFR (per 1-ml/min/1.73m ² increase)	1.00(1.00-1.01)	0.771	N/A	
Hs-CRP (per log10(hs-CRP) mg/L increase)	1.04(0.84-1.27)	0.733	N/A	
Hs-cTNT (per log10(hs-cTNT) pg/mL increase)	1.19(1.04-1.38)	0.014	1.19(0.78-1.83)	0.416
NT-proBNP (per log10(NT-proBNP) pg/mL increase)	1.52(1.23-1.89)	<0.0001	0.73(0.37-1.46)	0.377
UACR (per log10(UACR) mg/g Cr increase)	2.16(1.74-2.69)	<0.0001	1.86(1.25-2.76)	0.002

HbA1C, hemoglobin A1c; BMI, body Mass Index; ACS, acute coronary syndrome; HF, heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beat per minute; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; TIA, transient ischemic attack; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; FPG, fasting plasma glucose; TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate; Hs-CRP, high sensitivity C reactive protein; Hs-cTnT, high sensitivity cardiac troponin-T; NT-proBNP, N-terminal pro B-type natriuretic peptide; UACR, urine albumin creatine ratio.

Table 3. Time-dependent Cox's regression analysis in elderly cohort.

	Wald	HR	95%CI	p-value
HbA1C (>7% VS ≤7%)	1.199	1.330	0.798, 2.217	0.273
Time-covariate	166.817	0.143	0.106, 0.192	<0.001

Figures

Figure 1

Study flowchart IHF, ischemic heart failure; LVEF, left ventricular ejection fraction; HbA1C, hemoglobin A1c.

Figure 2

Kaplan-Meier survival curves of patients with HbA1c≤7% versus HbA1c>7%.

Figure 3

Adjusted multivariate Cox proportional-hazard model for all-cause mortality in the overall population. HR, hazard ratio; CI: confidence interval; BB, beta blocker; TG, triglycerides; LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction; BMI, body mass index; HbA1c, hemoglobin A1c.

Figure 4

Kaplan-Meier survival curves of gender (a and b) and age (c) subgroup patients with $\text{HbA1c} \leq 7\%$ versus $\text{HbA1c} > 7\%$.

(a) multivariable Cox proportional hazard analysis in male population

(b) multivariable Cox proportional hazard analysis in young population

Figure 5

Adjusted multivariate Cox proportional-hazards model for all-cause mortality in the male population (a) and in the younger population (b). HR: hazard ratio; CI: confidence interval; HDL-C, high density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction; BMI, body Mass Index; HbA1c, hemoglobin A1c

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