# Impact of Hypoglycemia at the Time of Hospitalization for Heart Failure from Emergency Department on Major Adverse Cardiovascular Events with and without Type 2 Diabetes.

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# Abstract

**Background:** Very few studies have examined the association between hypoglycemic episodes in type 2 diabetes (T2DM) and cardiovascular outcomes at the time of hospitalization for heart failure (HF) with or without T2DM.

**Methods:** From March 2016 to June 2018, we conducted a retrospective cohort study to investigate hypoglycemia during HF hospitalization from the emergency department (ED), three-point major adverse cardiovascular events (3P-MACE) and all-cause mortality and followed up through June 2021. HF hospitalization was defined according to the American Hospital Association criteria. Hypoglycemia was defined as a glucose level <3.9 mmol/L at the time of HF hospitalization. We classified the enrolled patients according to hypoglycemia and T2DM into three groups (group 1, those without T2DM; group 2, those diagnosed with T2DM without hypoglycemia; and group 3, those with hypoglycemia and T2DM). We used Cox proportional hazard regression analysis to investigate the association between the three groups and the development of the first occurrence of 3P-MACE and all-cause mortality.

**Results:** During a median of 25 months follow-up, a total of 783 patients admitted due to HF were analyzed. In total, 159 (20.3%) cases of 3P-MACE were identified, and the mortality rate was 20.2% (n = 158). The mean age of the patients was 72.3 ± 13.8 years, and 49.0% were men. Patients with 3P-MACE had a lower body mass index (22.6 [20.4–25.1] vs. 23.8 [21.3–26.7]), higher frequency of previous history of HF (24.5% vs. 15.7%), T2DM (64.2% vs. 47.3%), higher rates of hypoglycemia at the time of HF hospitalization (19.5% vs. 7.7%), as well as lower eGFR level (61.1 [36.0–80.7] mL/min/1.73 $m^2$ vs. 69.2 [45.8–89.5] mL/min/1.73 $m^2$) than those without 3P-MACE. The multivariable adjusted HR of 3P-MACE was group 3 HR, 2.29; 95% CI, 1.04–5.06; group 2, HR: 1.42; 95% CI: 0.86–2.33; and all-cause mortality group 3; HR: 2.58; 95% CI: 1.26–5.31, group 2; HR: 1.32; 95% CI: 0.81–2.16; compared to group 1.

**Conclusions:** T2DM and hypoglycemia are independent risk factors for 3P-MACE and all-cause mortality compared to those without hypoglycemia during HF hospitalization.


# Background

In 2019, 9.3% of people aged 20–79 years had type 1 or type 2 diabetes (T2DM) worldwide [1]. In addition, there will be 578 million (10.2%) adults with diabetes by 2030. Over time, an increase in diabetes has been associated with a higher incidence of micro- and macrovascular complications [1].

Patients with poorly controlled T2DM have approximately twice the risk of developing atherosclerotic cardiovascular disease, and the risk of heart failure (HF) increases accordingly, therefore, a significant number of long-standing patients with T2DM have an increased risk of HF [2, 3].

Previous studies reported that 10 – 47% of patients with HF had T2DM, while T2DM was associated with a three-fold risk of HF compared to those without diabetes [3–5]. The Reduction of Atherothrombosis for Continued Health registry showed that type 1 or type 2 diabetes is associated with an overall 1.33-fold

greater risk of hospitalization for HF [6]. Moreover, patients with either type 1 or type 2 diabetes and HF have a 1.7-fold increased risk of myocardial infarction (MI), stroke, or cardiovascular (CV) death at 4 years compared to patients without diabetes [6].

There was a decreasing trend in major CV complications, including hospitalization due to ischemic heart disease (-29.5% vs. -14.7%), MI rate (-37.3% vs. -25.5%), and ischemic stroke rate (-37.0% vs. -28.9%) from 2006 to 2013 in Korea [7]. However, the prevalence of HF has been increasing in T2DM (men, 72–146 per 10,000 adults, women, 124–161 per 10,000 adults) from 2006 to 2015 in Korea [7]. Despite complex medical therapies addressing the underlying causes of HF, including ischemic heart disease, hyperglycemia, dyslipidemia, and hypertension, these patients had substantially higher mortality with T2DM combined with HF than without T2DM, emphasizing the need to estimate residual risk factors for mortality in T2DM and HF [7, 8].

Tight glycemic control showed beneficial effects on microvascular complications, but inconsistent results in macrovascular complications in patients with T2DM. Intensive glycemic control is inevitably associated with an increased risk of hypoglycemia and severe hypoglycemia [9]. Severe hypoglycemia is associated with unexpected and recurrent morbidity in patients with type 1 diabetes and T2DM, and is occasionally fatal [10]. Several studies and post hoc analysis of the Veterans Affairs Diabetes Trial showed that severe hypoglycemia was linked to increased CV disease [8, 11, 12].

Accordingly, current clinical guidelines emphasize that patients with T2DM should be checked for the occurrence and risk of hypoglycemia at every visit [13]. Notwithstanding, poorly controlled T2DM patients have a higher probability of using sulfonylurea or insulin therapy, which have an increased risk of hypoglycemia.

However, long-term data on the effect of hypoglycemia on adverse CV outcomes in HF hospitalization are limited. Conducting glycemic control research in patients with HF and T2DM is crucial for understanding the target blood glucose level for their treatment. Therefore, the objective of this study was to estimate the CV outcomes and all-cause mortality associated with hypoglycemia and T2DM in patients at the time of HF hospitalization.

# Methods

# Study design and oversight

A retrospective cohort study of 783 patients aged ≥ 25 years who were admitted to St. Vincent's Hospital in South Korea for HF via the emergency department (ED) between March 2016 and June 2018, consecutively followed up until June 2021 was performed. Patients with gestational diabetes, type 1 diabetes, thyroid disease, and severe illnesses, including liver cirrhosis, malignancy, or sepsis, were excluded from the current investigation. All study protocols were approved by the Institutional Review Board of the Catholic Medical Center Ethics Committee (VC20RISI0253).

# Measurements

All participants were interviewed about their medical history and performed anthropometric measurements, as described in prior publications [14]. In brief, information on medical history, medication, and current or past smoking status was obtained [14]. Fasting plasma glucose (FPG) and lipid profiles were assessed using an automated enzymatic method (736 – 40; Hitachi, Tokyo, Japan) after 8-hour fasting, and HbA1c was measured using high-performance liquid chromatography (Bio-Rad, Montreal, QC, Canada). The estimated glomerular filtration rate (eGFR) was estimated using the four-component Modification of Diet in Renal Disease equation.

N-terminal-pro-B-type natriuretic peptide (NT-pro BNP) level was measured using an electrochemiluminescence sandwich immunoassay method with an Elecsys 2010 analyzer (Roche Diagnostics, Basel, Switzerland), and high-sensitivity troponin T (hsTnT) and creatinine kinase MB isoenzyme (CK-MB) were determined using the same method with an autoanalyzer (Cobas e411, Roche Diagnostics) on the day of admission.

All participants had transthoracic echocardiographic data within three days of hospital admission to assess the indices of cardiac function and structure. Transthoracic echocardiography was performed using a Vivid Seven ultrasound machine (GE Medical Systems, Horten, Norway) to estimate morphologic and hemodynamic parameters with a 2.5 MHz transducer. Standard two-dimensional measurements including left ventricular diastolic and systolic dimensions, ventricular septum and posterior wall thickness, and left atrial volume were obtained as recommended by the American Society of Echocardiography [15].

# Definition

Hypoglycemia was defined as “blood glucose < 3.9 mmol/L” and checked at the time of hospitalization for HF from ED. Accordingly, we classified the enrolled patients into three groups (group 1, those without T2DM; group 2, those diagnosed with T2DM without hypoglycemia; and group 3, those with hypoglycemia and T2DM).

HF hospitalization was defined as an event that met all of the following criteria by the American Heart Association [16]. The patient (i) was admitted to the hospital with a primary diagnosis of HF (ii) was hospitalized for at least 24 hours, (iii) exhibited documented new or worsening symptoms due to HF on presentation, (iv) had objective evidence of new or worsening HF, and (v) received or intensified at least one treatment specifically for HF [16].

The patient was considered to have T2DM if they were treated with T2DM medication or lifestyle modification at baseline, or if they had at least two FPG ≥ 7 mmol/L or HbA1c of ≥ 6.5%.

CV death includes death resulting from an acute MI within 30 days after MI, death due to HF, sudden cardiac death, death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes [16].

The term MI was used when there was evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia [16]. The diagnosis of MI required a combination of evidence of myocardial necrosis, including cardiac biomarkers and additional information from the clinical presentation, electrocardiographic changes, or the results of coronary artery imaging.

Stroke was defined as an acute episode of focal or global neurological dysfunction caused in brain as a result of hemorrhage or infarction [16]. Chronic kidney disease (CKD) was defined as at least two measures of eGFR < 60 mL/min/1.73 $m^2$ over 3 months or more [17].

# Primary and secondary outcomes

The primary outcome was the first occurrence of three-point major adverse cardiovascular events (3P-MACE), a composite of death from CV causes, nonfatal MI, or nonfatal stroke. Secondary outcomes included all-cause mortality.

If a subject experienced more than one event, the first event was considered in the analysis.

# Statistical analysis

All data are expressed as the mean ± standard deviation for normal distribution, median and interquartile range (IQR) for non-normal distribution, or frequency. Continuous symmetrical variables were tested using an independent *t*-test, and asymmetrical variables were tested using the Mann-Whitney test, and the chi-square test was used for categorical variables.

A Cox proportional hazard regression model was used for the associations between the three groups, 3P-MACE, and all-cause mortality with pre-specified covariates of age, sex, body mass index (BMI), history of cardiovascular disease (CVD), HF, etiology of HF, presence of CKD, systolic blood pressure (SBP), FPG, HbA1c, use of insulin, sulfonylurea, metformin, antihypertensive medications including angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, and diuretics including mineralocorticoid receptor antagonists, aspirin, statin, troponin-T, NT-pro BNP, C-reactive protein (CRP), and reduced ejection fraction (EF ≤ 40%). The proportional hazards assumption was estimated using a time interaction term with survival time in the regression model and log-log survival plots. There was no significant departure from proportionality to hazards over time. Potential confounders were identified *a priori*, based on a literature review. Statistical significance was evaluated using two-sided tests, with the level of significance set at 0.05. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

## Results

# Study outline

A total of 1309 subjects admitted to St. Vincent's Hospital due to HF were consecutively screened; 526 subjects were excluded: 431 patients who were misclassified, 32 excluded due to age, 5 with T1DM, and

58 with severe illness, including liver cirrhosis, malignancy, or sepsis, were excluded. Finally, 783 patients admitted for HF hospitalization from ED were recruited between March 2016 and June 2018 (Fig. 1). A total of 158 (20.2%) patients died and 159 patients (20.3%) experienced 3P-MACE during a median follow-up period (IQR, 7.0–35.0 months).

# Baseline characteristics

The mean age of the patients was 72.3 ± 13.8 years, and 49.0% were men. The mean left ventricular ejection fraction was 41.9 ± 15.4%. A total of 397 patients (50.7%) had diabetes. The etiology of HF was ischemic heart disease (29.2%) and non-ischemic heart disease (70.8%) (Table 2). The median hospital stay was 6.0 days (IQR, 4.0–10.0 days).

A total of 386 patients (49.3%) were in group 1 (HF without T2DM group), 318 (40.6%) were in group 2 (T2DM without hypoglycemia), and 79 (10.1%) in group 3 (T2DM with hypoglycemia).

Several baseline characteristics were significantly different between the groups. As shown in Table 1, FPG (5.7 ± 0.8 mmol/L, 8.5 ± 4.1, and 3.3 ± 0.7 mmol/L, $P < 0.001$ for groups 1, 2, and 3, respectively), HbA1c level (5.7 ± 0.5%, 7.3 ± 3.3%, and 7.8 ± 1.8%, $P < 0.001$), eGFR (74.8 [56.7–99.6] mL/min/1.73 $m^2$, 57.1 [36.5–83.8] mL/min/1.73 $m^2$, and 45.9 [29.4–69.2] mL/min/1.73 $m^2$, $P < 0.001$) showed significant differences between the three groups. Group 3 had a reduced left ventricular ejection fraction (38.7 ± 14.6% vs. 43.5 ± 15.0%, $P = 0.029$) compared with group 2 (Table 1).

Table 1
Baseline characteristics of patients according to the presence of type 2 diabetes or hypoglycemia with heart failure hospitalization

| | Heart failure without T2 DM | Heart failure with T2DM without hypoglycemia | Heart failure with T2DM, hypoglycemia | *P* value |
|---|---|---|---|---|
| *n* | 386 (49.3) | 318 (40.6) | 79 (10.1) | |
| Age (years) | 71.6 ± 15.6 | 73.2 ± 11.3 | 72.6 ± 13.7 | 0.269 |
| Male | 196 (50.8) | 147 (46.2) | 41 (51.9) | 0.421 |
| Body mass index (kg/m$^2$) | 22.8 (20.4–26.5) | 24.0 (22.1–26.6) | 23.5 (20.8–26.3) | 0.002 |
| Smoking | | | | 0.095 |
| Current | 66 (17.1) | 48 (15.1) | 8 (10.1) | |
| Ex-smoker | 30 (7.8) | 36 (11.3) | 13 (16.4) | |
| T2DM | 0 (0.0) | 318 (100.0) | 79 (100.0) | < 0.001 |
| Duration of T2DM (years) | - | 11.2 ± 10.4 | 14.3 ± 11.7 | 0.044 |
| Hypertension | 213 (55.2) | 239 (75.2) | 62 (78.5) | < 0.001 |
| History of CHD | 45 (11.7) | 71 (22.3) | 24 (30.4) | < 0.001 |
| History of stroke | 33 (8.5) | 35 (11.0) | 9 (11.4) | 0.490 |
| Previous HF | 59 (15.3) | 58 (18.2) | 20 (25.3) | 0.092 |
| Duration of HF (years) | 3.2 ± 2.8 | 6.1 ± 5.3 | 3.8 ± 3.1 | 0.026 |
| Etiology of HF | | | | < 0.001 |

Data are number (percentage) or medians with 25th–75th percentiles, means ± SD. $P < 0.05$ was considered significant.

CHD coronary heart disease, T2DM type 2 diabetes, FPG fasting plasma glucose, eGFR estimated glomerular filtration rate, HDL high-density lipoprotein, LDL low-density lipoprotein, ACEi/ARB, ACE inhibitor/angiotensin receptor blocker, CCB, calcium channel blocker.

$^{\#}P < 0.05$ (comparison between heart failure with T2DM group and heart failure with T2DM and hypoglycemia).

| | Heart failure without T2 DM | Heart failure with T2DM without hypoglycemia | Heart failure with T2DM, hypoglycemia | *P* value |
|---|---|---|---|---|
| Ischemic cause (coronary artery disease or myocardial infarction) | 85 (22.0) | 110 (34.6) | 34 (43.0) | |
| Nonischemic cause | 301 (78.0) | 208 (65.4) | 45 (57.0) | |
| Chronic kidney disease | 107 (27.7) | 166 (52.2) | 54 (68.4) | < 0.001 |
| Systolic blood pressure (mm Hg) | 129.0 ± 26.2 | 135.0 ± 28.8 | 135.1 ± 26.4 | 0.010 |
| Diastolic blood pressure (mm Hg) | 77.9 ± 15.8 | 80.3 ± 16.7 | 77.8 ± 13.6 | 0.126 |
| Heart rate (beats per min) | 92.5 ± 23.7 | 92.8 ± 21.9 | 93.7 ± 23.3 | 0.910 |
| Left ventricular ejection fraction (%) | 41.3 ± 15.9 | 43.5 ± 15.0 | 38.7 ± 14.6 | 0.029 |
| E/e' | 19.0 ± 9.5 | 21.0 ± 10.2 | 20.9 ± 9.0 | 0.020 |
| **Laboratory variables** | | | | |
| FPG (mmol/L) | 5.7 ± 0.8 | 8.5 ± 4.1 | 3.3 ± 0.7 | < 0.001 |
| HbA1c (%) | 5.7 ± 0.5 | 7.3 ± 3.3 | 7.8 ± 1.8 | < 0.001 |
| eGFR ($mL \cdot min^{-1} \cdot 1.73m^{-2}$) | 74.8 (56.7–99.6) | 57.1 (36.5–83.8) | 45.9 (29.4–69.2) | < 0.001 |
| Total cholesterol (mmol/L) | 3.9 ± 1.0 | 3.8 ± 1.1 | 3.5 ± 1.8 | 0.072 |
| Triglyceride (mmol/L) | 0.3 (0.7–1.1) | 1.0 (0.8–1.4) | 0.8 (0.7–1.1) | < 0.001 |
| HDL-C (mmol/L) | 1.1 ± 0.3 | 1.1 ± 0.4 | 1.1 ± 0.3 | 0.140 |

Data are number (percentage) or medians with 25th–75th percentiles, means ± SD. $P < 0.05$ was considered significant.

CHD coronary heart disease, T2DM type 2 diabetes, FPG fasting plasma glucose, eGFR estimated glomerular filtration rate, HDL high-density lipoprotein, LDL low-density lipoprotein, ACEi/ARB, ACE inhibitor/angiotensin receptor blocker, CCB, calcium channel blocker.

$^{\#}P < 0.05$ (comparison between heart failure with T2DM group and heart failure with T2DM and hypoglycemia).

| | Heart failure without T2 DM | Heart failure with T2DM without hypoglycemia | Heart failure with T2DM, hypoglycemia | *P* value |
|---|---|---|---|---|
| LDL-C (mmol/L) | 2.4 ± 0.8 | 2.4 ± 0.9 | 2.2 ± 0.9 | 0.105 |
| NT-pro BNP (pg/mL) | 3900 (1707–7928) | 4250 (1828–9598) | 7485 (3266–24153) | < 0.001 |
| hsTnT (ng/L) | 25.0 (16.0–50.5) | 32.0 (18.0–75.5) | 66.0 (27.0–133.3) | < 0.001 |
| CK-MB (ng/ml) | 3.2 (2.1–5.6) | 3.1 (2.1–5.5) | 4.1 (2.4–6.3) | 0.104 |
| CPK (U/L) | 104.0 (69.0–174.5) | 103.0 (66.0–166.5) | 104.0 (62.0–164.0) | 0.722 |
| CRP (mg/dl) | 0.5 (0.2–1.7) | 0.5 (0.2–2.1) | 1.0 (0.2–3.2) | 0.132 |
| **Medication** | | | | |
| **Cardiovascular medication** | | | | |
| ACEi/ARB | 115 (29.8) | 122 (38.4) | 29 (36.7) | 0.050 |
| ß-blocker | 84 (21.8) | 98 (30.9) | 25 (31.6) | 0.013 |
| CCB | 60 (15.5) | 96 (30.4) | 28 (35.4) | < 0.001 |
| Diuretics | 148 (38.3) | 143 (45.0) | 45 (57.0) | 0.006 |
| Aspirin | 77 (19.9) | 87 (27.4) | 26 (32.9) | 0.012 |
| Statin | 68 (17.6) | 106 (33.3) | 29 (36.7) | < 0.001 |
| **Diabetes treatment** | | | | |
| Insulin | 0 (0.0) | 29 (9.1) | 11 (13.9) | 0.204 |

Data are number (percentage) or medians with 25th–75th percentiles, means ± SD. $P < 0.05$ was considered significant.

CHD coronary heart disease, T2DM type 2 diabetes, FPG fasting plasma glucose, eGFR estimated glomerular filtration rate, HDL high-density lipoprotein, LDL low-density lipoprotein, ACEi/ARB, ACE inhibitor/angiotensin receptor blocker, CCB, calcium channel blocker.

$^{\#}P < 0.05$ (comparison between heart failure with T2DM group and heart failure with T2DM and hypoglycemia).

| | Heart failure without T2 DM | Heart failure with T2DM without hypoglycemia | Heart failure with T2DM, hypoglycemia | *P* value |
|---|---|---|---|---|
| Sulfonylurea | 0 (0.0) | 59 (18.6)[#] | 30 (38.0)[#] | < 0.001 |
| Metformin | 0 (0.0) | 94 (29.6) | 26 (32.9) | 0.562 |
| DPP-4 inhibitor | 0 (0.0) | 99 (31.1) | 28 (35.4) | 0.462 |

Data are number (percentage) or medians with 25th–75th percentiles, means ± SD. $P < 0.05$ was considered significant.

CHD coronary heart disease, T2DM type 2 diabetes, FPG fasting plasma glucose, eGFR estimated glomerular filtration rate, HDL high-density lipoprotein, LDL low-density lipoprotein, ACEi/ARB, ACE inhibitor/angiotensin receptor blocker, CCB, calcium channel blocker.

[#]$P < 0.05$ (comparison between heart failure with T2DM group and heart failure with T2DM and hypoglycemia).

During a median follow-up period of 25 months, 159 patients (20.3%) developed 3P-MACE. Compared to those without 3P-MACE, patients with 3P-MACE had a lower body mass index (BMI) (22.6 [20.4–25.1] kg/m$^2$ vs. 23.8 [21.3–26.7] kg/m$^2$, $P = 0.002$), a higher frequency of history of T2DM (64.2% vs. 47.3%, $P < 0.001$), hypoglycemia at HF hospitalization (19.5% vs. 7.7%, $P < 0.001$), previous diagnosis of HF (24.5% vs. 15.7%, $P = 0.009$), CKD (49.7% vs. 39.7%, $P = 0.023$), and higher hsTnT levels (54.0 [27.0–122.8] ng/L vs. 26.0 [16.0–55.5] ng/L, $P < 0.001$), NT-pro-BNP levels (7490 [3002–19361] pg/mL vs 3825 [1603–7922] pg/mL, $P < 0.001$) than patients without 3P-MACE (Table 2).

Table 2
Baseline characteristics according to the development of three-point major adverse cardiovascular events (3P-MACE) in patients with heart failure hospitalization

| | Total (n = 783) | 3P MACE (-) (n = 624) | 3P MACE (+) (n = 159) | *P* value |
|---|---|---|---|---|
| Age (years) | 72.3 ± 13.8 | 72.4 ± 13.9 | 71.7 ± 13.8 | 0.472 |
| Male | 384 (49.0) | 297 (47.6) | 87 (54.7) | 0.109 |
| Body mass index (kg/m$^2$) | 23.5 (21.2–26.5) | 23.8 (21.3–26.7) | 22.6 (20.4–25.1) | 0.002 |
| Smoking (current) | 122 (15.6) | 95 (15.2) | 27 (17.0) | 0.390 |
| T2DM | 397 (50.7) | 295 (47.3) | 102 (64.2) | < 0.001 |
| Duration of T2DM (years) | 12.0 ± 10.8 | 12.2 ± 10.9 | 11.2 ± 10.7 | 0.484 |
| Hypertension | 514 (65.6) | 402 (64.4) | 112 (70.4) | 0.154 |
| History of CHD | 140 (17.9) | 101 (16.2) | 39 (24.5) | 0.014 |
| History of stroke | 77 (9.8) | 60 (9.6) | 17 (10.7) | 0.684 |
| History of heart failure | 137 (17.5) | 98 (15.7) | 39 (24.5) | 0.009 |
| Duration of HF (years) | 4.6 ± 4.4 | 5.3 ± 5.0 | 3.6 ± 2.9 | 0.206 |
| Etiology of heart failure | | | | 0.002 |
| Ischemic cause (coronary artery disease or myocardial infarction) | 229 (29.2) | 167 (26.8) | 62 (39.0) | |
| Nonischemic cause | 554 (70.8) | 457 (73.2) | 97 (61.0) | |
| Chronic kidney disease | 317 (41.8) | 248 (39.7) | 79 (49.7) | 0.023 |
| Systolic blood pressure (mm Hg) | 132.0 ± 27.4 | 133.1 ± 27.4 | 128.1 ± 27.5 | 0.101 |
| Diastolic blood pressure (mm Hg) | 79.0 ± 16.0 | 79.5 ± 15.9 | 76.4 ± 16.2 | 0.056 |
| Heart rate (beats per min) | 92.7 ± 23.0 | 92.6 ± 23.3 | 93.1 ± 21.8 | 0.397 |
| Left ventricular ejection fraction (%) | 41.9 ± 15.4 | 43.2 ± 15.5 | 36.8 ± 14.1 | < 0.001 |

Data are number (percentage) or medians with 25th–75th percentiles, means ± SD. $P < 0.05$ was considered significant.

CHD coronary heart disease, T2DM, type 2 diabetes, FPG fasting plasma glucose, eGFR estimated glomerular filtration rate, HDL high-density lipoprotein, LDL low-density lipoprotein, ACEi/ARB, ACE inhibitor/angiotensin receptor blocker, CCB, calcium channel blocker.

| | Total (n = 783) | 3P MACE (-) (n = 624) | 3P MACE (+) (n = 159) | *P* value |
|---|---|---|---|---|
| E/e' | 19.9 ± 9.7 | 19.3 ± 9.2 | 23.0 ± 11.2 | < 0.001 |
| Hypoglycemia during hospitalization | 79 (10.1) | 48 (7.7) | 31 (19.5) | < 0.001 |
| **Laboratory variables** | | | | |
| FPG (mmol/L) | 6.6 ± 3.2 | 6.6 ± 3.0 | 6.9 ± 4.0 | 0.754 |
| HbA1c (%) | 6.7 ± 2.5 | 6.7 ± 2.7 | 7.0 ± 1.6 | 0.002 |
| eGFR ($mL•min^{-1}•1.73m^{-2}$) | 66.8 (45.0–87.7) | 69.2 (45.8–89.5) | 61.1 (36.0–80.7) | 0.003 |
| Total cholesterol (mmol/L) | 3.8 ± 1.1 | 3.8 ± 1.0 | 3.8 ± 1.1 | 0.916 |
| Triglyceride (mmol/L) | 0.9 (0.7–1.2) | 0.9 (0.7–1.2) | 0.9 (0.7–1.1) | 0.962 |
| HDL-C (mmol/L) | 1.1 ± 0.3 | 1.1 ± 0.3 | 1.1 ± 0.3 | 0.456 |
| LDL-C (mmol/L) | 2.4 ± 0.9 | 2.4 ± 0.8 | 2.5 ± 0.9 | 0.533 |
| NT-pro BNP (pg/mL) | 4238 (1860–9302) | 3825 (1603–7922) | 7490 (3002–19361) | < 0.001 |
| hsTnT (ng/L) | 29.0 (17.0–65.0) | 26.0 (16.0–55.5) | 54.0 (27.0–122.8) | < 0.001 |
| CK-MB (ng/ml) | 3.2 (2.1–5.6) | 3.2 (2.1–5.4) | 3.7 (2.2–6.8) | 0.044 |
| CPK (U/L) | 104.0 (68.5–170.0) | 103.0 (69.0–167.3) | 105.0 (65.0–191.0) | 0.891 |
| CRP (mg/dl) | 0.5 (0.2–2.0) | 0.5 (0.2–1.8) | 0.8 (0.3–2.9) | 0.010 |
| **Medication** | | | - | |
| **Cardiovascular medication** | | | | |
| ACEi/ARB | 266 (34.0) | 214 (34.3) | 52 (32.7) | 0.705 |

Data are number (percentage) or medians with 25th–75th percentiles, means ± SD. $P < 0.05$ was considered significant.

CHD coronary heart disease, T2DM, type 2 diabetes, FPG fasting plasma glucose, eGFR estimated glomerular filtration rate, HDL high-density lipoprotein, LDL low-density lipoprotein, ACEi/ARB, ACE inhibitor/angiotensin receptor blocker, CCB, calcium channel blocker.

| | Total (n = 783) | 3P MACE (-) (n = 624) | 3P MACE (+) (n = 159) | *P* value |
|---|---|---|---|---|
| ß-blocker | 207 (26.5) | 170 (27.3) | 37 (23.3) | 0.305 |
| CCB | 184 (23.6) | 149 (24.0) | 35 (22.0) | 0.607 |
| Diuretics | 336 (42.9) | 252 (40.4) | 84 (52.8) | 0.005 |
| Aspirin | 190 (24.3) | 148 (23.7) | 42 (26.4) | 0.479 |
| Statin | 203 (25.9) | 162 (26.0) | 41 (25.8) | 0.964 |
| **Diabetes treatment** | | | | |
| Insulin | 40 (5.1) | 32 (5.1) | 8 (5.0) | 0.961 |
| Sulfonylurea | 89 (11.4) | 63 (10.1) | 26 (16.4) | 0.027 |
| Metformin | 120 (15.3) | 88 (14.1) | 32 (20.1) | 0.060 |
| DPP-4 inhibitor | 127 (16.2) | 94 (15.1) | 33 (20.8) | 0.082 |

Data are number (percentage) or medians with 25th–75th percentiles, means ± SD. $P < 0.05$ was considered significant.

CHD coronary heart disease, T2DM, type 2 diabetes, FPG fasting plasma glucose, eGFR estimated glomerular filtration rate, HDL high-density lipoprotein, LDL low-density lipoprotein, ACEi/ARB, ACE inhibitor/angiotensin receptor blocker, CCB, calcium channel blocker.

In addition, there was higher use of sulfonylurea (16.4% vs. 10.1%) in patients with 3P-MACE than in those without 3P-MACE.

The median time from HF hospitalization to 3P-MACE was 7 months (IQR 1.0–19.0 months). Of the 159 patients who developed 3P-MACE, 31 (39.2%) were in group 3, 71 (22.3%) in group 2, and 57 (14.8%) in group 1 ($P$ for trend < 0.001).

# Relationship between type 2 diabetes, hypoglycemia and 3P-MACE, All-cause mortality

Tables 3 and S3 show that the presence of T2DM and hypoglycemia (blood glucose ≤ 3.9 mmol/L) at the time of HF hospitalization was a significant risk factor for 3P-MACE. In addition, the impact of hypoglycemia on 3P-MACE was substantially greater than that of T2DM (group 3; HR: 2.29; 95% CI: 1.04–5.06, group 2; HR: 1.42; 95% CI: 0.86–2.33) after adjusting for age, sex, BMI, diabetes duration (≥ 10 years), history of CVD, HF, etiology of HF, presence of CKD, SBP, FPG, HbA1c, use of insulin, sulfonylurea, antihypertensive medication, statin, levels of hsTnT, NT-pro BNP, and CRP, and compared to group 1 (HF without T2DM).

Table 3
Unadjusted and adjusted hazard ratios (HR) (95% CI) for adverse cardiovascular outcome and all-cause mortality in heart failure hospitalization with and without type 2 diabetes.

| | Group 1 | Group 2 | Group 3 | Model 1* | Model 2* | Model 3* |
|---|---|---|---|---|---|---|
| | Patients without T2DM | Patients with T2DM without hypoglycemia | Patients with T2DM and hypoglycemia | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| **3P-MACE** | 1.00 | 1.38 (0.97–1.96) | 2.68 (1.73–4.15) | 2.67 (1.72–4.15) | 3.53 (1.92–6.49) | 2.29 (1.04–5.06) |
| **Cardiovascular mortality** | 1.00 | 1.15 (0.73–1.82) | 3.28 (1.93–5.57) | 3.28 (1.93–5.56) | 4.95 (2.35–10.42) | 2.87 (1.17–7.05) |
| **All-cause mortality** | 1.00 | 1.45 (1.02–2.06) | 3.35 (2.17–5.16) | 3.37 (2.15–5.19) | 4.53 (2.52–8.16) | 2.58 (1.26–5.31) |
| Group 1 hospitalization for heart failure without T2DM, Group 2 hospitalization for heart failure with T2DM, Group 3 hospitalization for heart failure with T2DM and hypoglycemia, HR hazard ratio, T2DM type 2 diabetes. | | | | | | |
| *Model 1 was adjusted for age and sex. | | | | | | |
| *Model 2 additionally included body mass index, current smoking status, presence of previous coronary heart disease, stroke, heart failure, etiology of heart failure, duration of diabetes (if subjects had T2DM), systolic blood pressure, fasting plasma glucose, HbA1c ≥ 7%, and presence of chronic kidney disease (eGFR ≤ 60 mL/min/1.73 $m^2$). | | | | | | |
| *Model 3 additionally included use of antihypertensive medications, statins, insulin, sulfonylurea, hsTnT, NT-pro BNP, CRP level, and reduced EF (EF ≤ 40%). | | | | | | |

Moreover, body mass index ($P$ = 0.006), history of HF ($P$ = 0.008), SBP ($P$ = 0.001), and NT-pro BNP level ($P$ = 0.010) were also independent covariates for 3P-MACE in HF patients in this study (Table S3).

There were no significant interactions between the effect of hypoglycemia and BMI ($P$-interaction = 0.866), SBP ($P$-interaction = 0.243), and NT-pro BNP ($P$-interaction = 0.810) on the risk of 3P-MACE. A significant interaction of the effect of hypoglycemia and previous HF with the risk of 3P MACE was observed in this study ($P$ for interaction = 0.036).

The cumulative hazard rate (HR) of the development of 3P MACE and all-cause mortality according to T2DM or hypoglycemia is shown in Fig. 2. The highest rate of all-cause mortality was noted in group 3. Thirty-three patients (42.3%) in group 3 and 70 patients (21.9%) in group 2, and 55 patients (14.2%) in group 1 died, and the HR of group 3 for all-cause mortality was 2.58 (95% CI: 1.26–5.31) ($P$ for trend = 0.002).

Mortality rate at 1 year was 12.7% in all patients with HF; 10.1% in group 1, 11.0% in group 2, and 32.9% in group 3. Mortality rate at 2 years was 17.6% (138) in patients with HF, 13.5% in group 1, 17.0% in group 2, 40.5% in group 3.

Older age ($P = 0.022$), lower body mass index ($P < 0.001$), history of HF ($P = 0.023$), SBP ($P = 0.012$), hsTnT ($P = 0.025$), and NT-proBNP ($P = 0.002$) were also significant predictors of all-cause mortality. However, there were no significant interactions between the effects of hypoglycemia and age ($P$-interaction = 0.810), BMI ($P$-interaction = 0.387), SBP ($P$-interaction = 0.703), hsTnT ($P$-interaction = 0.423), and NT-pro BNP ($P$-interaction = 0.685) on the risk of all-cause mortality.

A similar result was found for CV mortality (Table 3): Group 3 was a significant predictor of CV mortality (group 3; HR: 2.88; 95% CI: 1.17–7.05, group 2; HR: 1.12; 95% CI: 0.61–2.07) compared to group 1.

## Discussion

This study found that hypoglycemia and T2DM were associated with increased overall mortality and adverse CV outcomes compared to patients without T2DM during HF hospitalization from ED, even after adjusting for multiple covariates. Covariates for CV outcome and all-cause mortality included age, sex, body mass index, diabetes duration, smoking status, history of CVD, history and etiology of HF, SBP, FPG, HbA1c, CKD (eGFR $\leq$ 60 mL/min/1.73 $m^2$), presence of systolic HF (EF $\leq$ 40%), use of antihypertensive drugs, insulin, sulfonylurea, statin, hsTnT, NT-pro BNP, and CRP levels. Among the components of 3P-MACE, the presence of T2DM and hypoglycemia has a greater association with the development of CV mortality and nonfatal MI. To our knowledge, this study is one of the first to investigate the effect of hypoglycemia in HF hospitalization on 3P-MACE and all-cause mortality.

# Type 2 DM in heart failure

Previous studies have shown that chronic hyperglycemia is associated with the risk of HF in T2DM, with a 1.15-fold risk for HF proportional to an increase of 1% of HbA1c [18]. HF is related to increased mortality and CV mortality; in particular, the clinical outcome appears worse in T2DM, and even in prediabetes [19]. T2DM is related to significant changes in myocardial structure and function via overt myocardial ischemia, and increased risk of HF, the so-called cardiovascular disease continuum [20–22]. T2DM is also associated with higher levels of atherogenic dyslipidemia which leads to thrombosis, inflammation, plaque ulceration, accumulation of advanced glycation end-products that cross-link extracellular matrix proteins and transduce fibrogenic signals, endothelial dysfunction, and oxidative stress [3, 23].

# Hypoglycemia in heart disease, heart failure

The combination of hypoglycemia and T2DM had a stronger negative impact on 3P-MACE, and all-cause mortality among HF hospitalizations than T2DM without hypoglycemia in this study. Aguilar et al. showed that the association between baseline HbA1c in T2DM and HF and all-cause mortality appears U-

shaped, with the lowest risk of all-cause mortality at HbA1c of 7.1–7.8% [24]. A similar result was shown in a general HF population in a UK study [25]. In addition, an observational cohort study showed a U-shaped relationship between time-weighted mean HbA1c and mortality, which showed the lowest risk in patients with HbA1c of 7.1–8.0% and the U-shape is present in drug-treated but not in diet-treated T2DM [26]. This result corresponds to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials, which revealed increased mortality in the intensive treatment group, indicating the potential role of treatment-associated hypoglycemia on adverse cardiovascular outcomes in the T2DM population [27]. Severe hypoglycemia is also known to increase CV risk in the Atherosclerosis Risk in Communities study, which showed a two-fold risk of incident or recurrent CVD, and a 1.7-fold risk of all-cause mortality [11].

We hypothesized that hypoglycemic events in patients with T2DM might have clinical and prognostic implications in patients hospitalized for HF from the ED. Thus, we compared the adverse cardiovascular outcomes and all-cause mortality according to the presence of T2DM and hypoglycemia (group 1: HF without T2DM, group 2: HF with T2DM, group 3: HF with T2DM, and hypoglycemia) at the time of HF hospitalization and follow-up. In this study, subjects with group 3 had higher HbA1c levels than group 2 (7.8 ± 1.8% vs. 7.3 ± 3.3%, p = 0.004) suggesting group 3 patients might have a higher risk of hypoglycemia with intensified T2DM treatment, which corresponds to ACCORD, and the Outcome Reduction With Initial Glargine Intervention trial which showed severe hypoglycemia in the standard therapy group who experienced a higher relative risk of all-cause mortality [28, 29].

Subjects included in group 3 might be in a high-risk state because of the reduced ejection fraction and increased NT-pro BNP and hsTnT levels, followed by a high rate of 3P-MACE and increased mortality in HF hospitalization. However, significant associations of hypoglycemic events in HF hospitalization persisted after adjustment for multiple covariates including SBP, glycemic status, reduced EF, biomarkers, and traditional CV risk factors. Thus, clinicians should pay more attention to avoiding hypoglycemia during HF hospitalization to reduce the risk of increased mortality and adverse CV outcomes.

In this study, a lower body mass index was also associated with an increase in 3P-MACE and all-cause mortality, indicating poor prognosis in HF, which may be associated with poor nutrition or a general unhealthy state that results in weight loss [30].

As in this study, prior studies reported that lower SBPs with SBP < 100 mm Hg continued to be associated with higher mortality and CV mortality in systolic HF patients [31, 32]. Hypertension often precedes the development of HF, and causes mortality in HF. The lower BP in patients with HF may be due to antihypertensive drugs or a state of more advanced HF and low cardiac output [32].

# Potential mechanism of hypoglycemia and T2DM in HF patients

The association between hypoglycemia and T2DM in HF hospitalization may be supported by a potential mechanism. Hypoglycemia is linked to coronary artery calcification in T2DM after modifying glycemic control status, which might be associated with profound surges in the sympathoadrenal system as a

counter-regulatory mechanism, leading to increased cardiac workload and transient ischemia or cardiac failure. Hypoglycemia is also associated with an increase in proinflammatory markers and cytokines related to endothelial dysfunction, which contributes to atherosclerosis [33, 34].

Hypoglycemia can induce increased myocardial electrical vulnerability and vascular thrombosis [34]. Suggested mechanisms include cardiac arrhythmia, prolongation of cardiac repolarization, and hypoglycemia-associated autonomic failure may be associated with lethal ventricular arrhythmia. The association between baseline QTc and CV mortality has been reported in patients with T2DM [35]. Insulin-induced hypoglycemia, which causes catecholamine, including epinephrine, release and increases the QTc interval [36].

In addition, increased high-sensitivity troponins and natriuretic peptides including NT-pro BNP are well-known, substantial prognostic biomarkers for acute HF, reflecting subclinical myocardial structural changes, thus providing useful information about underlying disease progression [37]. Group 3 subjects were in acute HF and showed increased hsTnT and NT-pro BNP levels compared with groups 1 or 2, thus indicating poor prognosis for cardiovascular outcomes and all-cause mortality. Thus, hypoglycemia and T2DM are associated with all, or a combination, of these mechanisms and could be related to increased mortality and adverse CV outcomes at HF hospitalization.

# Limitations

This study has several limitations. First, this was a retrospective, observational design with a small number of participants. Thus, we could not control for all confounding factors influencing CV outcomes and mortality, though we tried to minimize this effect by adjusting for multiple conventional risk factors. Further prospective studies are needed to confirm the causal relationship between hypoglycemia and adverse CV outcomes in patients with HF.

Second, we only have data on Korean population.

# Conclusion

This study suggests that hypoglycemia in T2DM is an independent risk factor for 3P-MACE and all-cause mortality compared to those without hypoglycemia in HF hospitalization from ED. The relationship between hypoglycemia in T2DM and cardiovascular outcome was independent of traditional CV risk factors and the value of several biomarkers, including hsTnT, NT-pro BNP, and CRP. Clinicians should pay more attention to preventing and reducing the risk of hypoglycemia in hospitalized patients with HF. Further studies are needed to investigate the pathogenic mechanism of hypoglycemia for adverse CV outcomes and increased mortality in HF patients.

# Abbreviations

***T2DM:*** Type 2 diabetes

***HF:*** Heart failure

***MI:*** Myocardial infarction

***CV:*** Cardiovascular

***ED:*** Emergency department

***FPG:*** Fasting plasma glucose

***eGFR:*** Estimated glomerular filtration rate

***NT-pro BNP:*** N-terminal-pro-B-type natriuretic peptide

***hsTnT:*** High-sensitivity troponin T

***CK-MB:*** Creatinine kinase MB isoenzyme

***CKD:*** Chronic kidney disease

***3P-MACE:*** Three-point major adverse cardiovascular events

***IQR:*** Interquartile range

***BMI:*** Body mass index

***CVD:*** Cardiovascular disease

***SBP:*** Systolic blood pressure

***CRP:*** C-reactive protein

***ACCORD:*** Action to Control Cardiovascular Risk in Diabetes

# Declarations

***Ethics approval and consent to participate:*** This study protocol was approved by the Institutional Review Board of the Catholic Medical Center Ethics Committee in accordance with the ethical principles described in the latest version of the Declaration of Helsinki.

***Consent for publication:*** All the authors listed have approved the manuscript for publication.

***Funding:*** Not applicable.

***Availability of data and materials:*** The data of this study may be available on reasonable request to the corresponding author.

***Competing interests:*** The authors declare that they have no competing interests.

***Acknowledgements:*** Not applicable.

***Authors' contributions:*** SAC analyzed data and wrote the manuscript. JSY acquired and researched data and reviewed and edited the manuscript. GHK reviewed and edited the manuscript. YBA designed the study and the guarantor of this work. All authors have read and approved the final manuscript.

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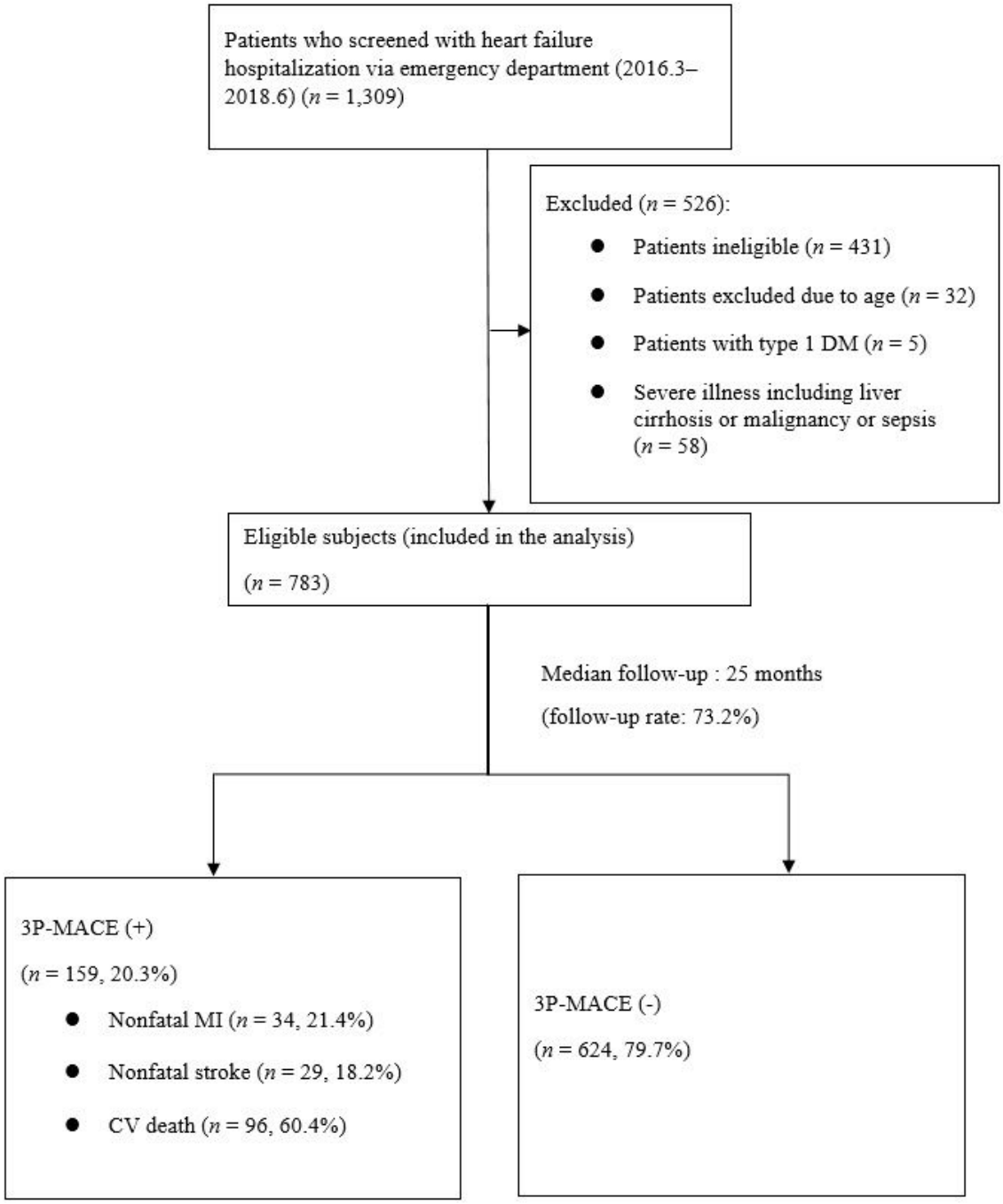
# Figures




## Figure 1

## Study outline

3P-MACE three-point major adverse cardiovascular events

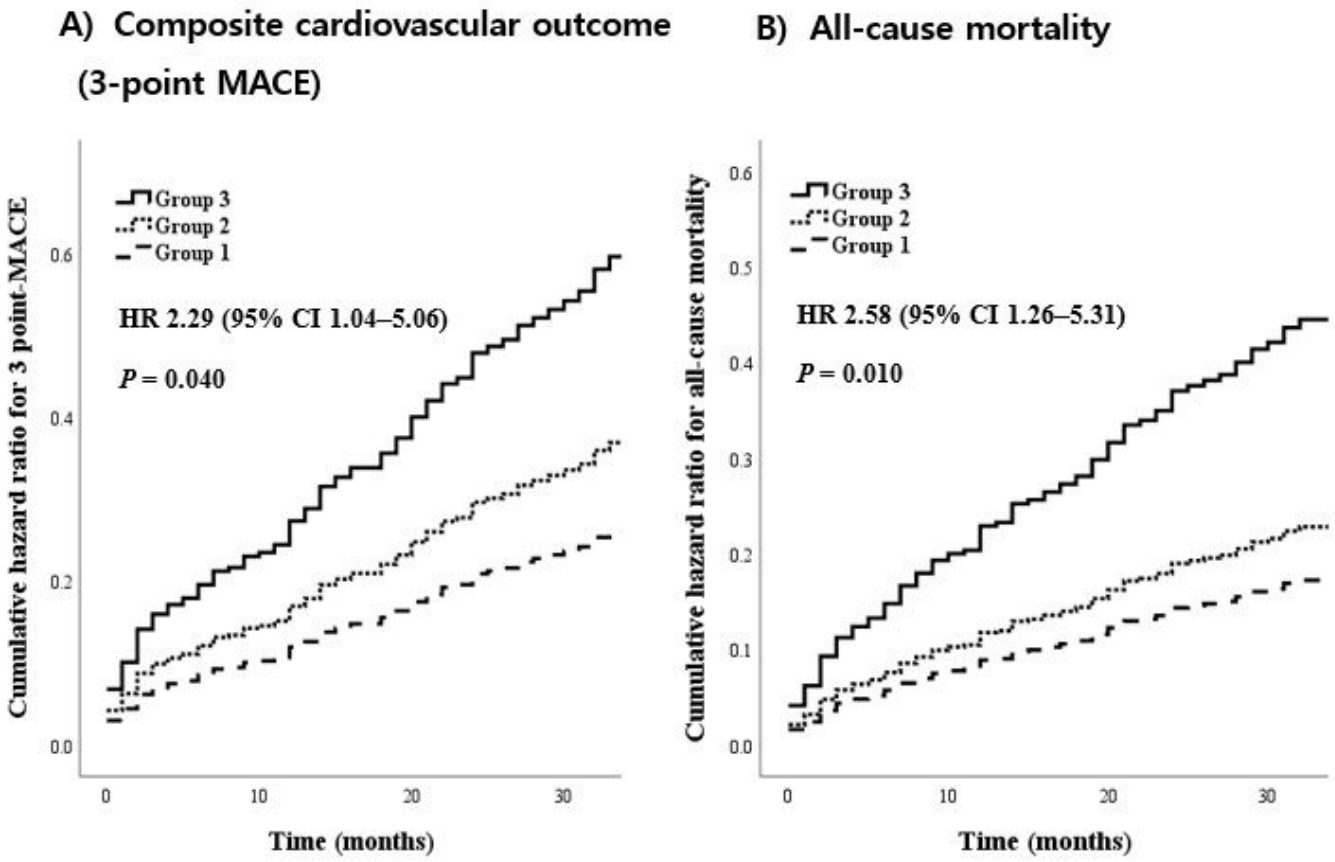



Figure 2

**Cumulative hazard rate of the development of cardiovascular outcome and all-cause mortality according to presence of T2DM and hypoglycemia in patients with heart failure hospitalization by emergency department.**

3P-MACE three-point major adverse cardiovascular events, Group 1 hospitalization for heart failure without T2DM, Group 2 hospitalization for heart failure with T2DM, Group 3 hospitalization for heart failure with T2DM and hypoglycemia, HR hazard ratio, T2DM type 2 diabetes.

# Supplementary Files

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- Supplementaryinformation.docx