Role of Diabetes Mellitus in Acute Coronary Syndrome Patients with Heart Failure and Midrange Ejection Fraction Who Have Undergone Percutaneous Coronary Intervention: A 3-Year Case-Series Follow-Up Retrospective Study

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Background: Data are limited on the effect of diabetes mellitus (DM) on the prognosis of acute coronary syndrome (ACS) patients with heart failure with midrange ejection fraction (HFmrEF) who have undergone percutaneous coronary intervention (PCI). This study aimed to investigate the relationship between type 2 DM (T2DM) and 3-year outcomes in such a population.

Methods: A total of 377 ACS patients with HFmrEF (left ventricular EF 40%–49%) who had undergone PCI (132 diabetic and 245 nondiabetic patients) were included in the analysis. The primary outcome was a composite end point of all-cause death or HF rehospitalization. Cox proportional-hazard regression analysis and Kaplan–Meier tests were used to assess the effect of DM on the primary outcome. Sensitivity analysis was conducted with propensity score–matching analysis.

Results: During a follow-up of 3 years, diabetic patients had higher incidence of the primary outcome than nondiabetic patients (96.1 vs 44.6 per 1,000 patient-years, incidence ratio 2.301, 95% CI 1.334–3.969; P=0.002). Multivariate analysis showed that DM was associated with a significant increase in the composite outcome of all-cause death or HF rehospitalization (adjusted HR 2.080, 95% CI 1.115–3.878; P=0.021). Sensitivity analysis further confirmed that DM was an independent prognostic factor of long-term adverse outcomes for ACS patients with HFmrEF who had undergone PCI (adjusted HR 3.792, 95% CI 1.802–7.980; P<0.001).

Conclusion: Among ACS patients with HFmrEF who had undergone PCI, T2DM comorbidity was significantly associated with worse long-term outcomes.

Keywords: diabetes mellitus, acute coronary syndrome, heart failure with midrange ejection fraction, percutaneous coronary intervention, outcome

Background
Acute coronary syndrome (ACS) is the acute manifestation of ischemic heart disease. Despite optimal antithrombotic therapies and timely revascularization, ACS remains a major cause of morbidity and mortality worldwide, and can lead to the development of de novo acute heart failure (HF) or worsening of chronic HF.1 Diabetes mellitus (DM) is a complex, chronic metabolic disease, often complicated by coronary artery disease (CAD) and other atherosclerosis-related cardiovascular diseases, and is also a major risk

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factor of HF, especially for ACS patients. Epidemiological and clinical data from the last two decades have proven that DM increases the mortality of patients with HF with reduced ejection fraction (HFrEF).\(^2\) HF with midrange EF (HFmrEF), a distinct phenotype, was first defined as left ventricular EF (LVEF) of 40%–49% in the 2016 European Society of Cardiology (ESC) HF guidelines.\(^3\) Recent observational studies have focused only on description of its characteristics and prognosis of HFmrEF, and patients enrolled in these clinical trials had different HF etiology. In view this, our study concentrated on ACS patients using a 3-year retrospective analysis to investigate the role of DM in ACS patients with HFmrEF who had undergone percutaneous coronary intervention (PCI).

**Methods**

**Patient Selection**

ACS patients with HFmrEF who had undergone PCI were retrospectively (registered from January 2014 to June 2017) screened from the Coronary Angiography and Angioplasty Registry Database of Fujian Medical University Union Hospital. Inclusion criteria were hospitalization for ACS and had undergone PCI, survived to discharge following first admission, met HFmrEF diagnostic criteria according to the 2016 ESC guidelines,\(^4\) reviewed by an expert cardiologist during hospitalization, presence of symptoms and/or signs of HF, LVEF 40%–49%, BNP >35 and/or NT-proBNP >125pg/mL, objective evidence of other cardiac functional and structural alterations underlying HF, and a minimum 3-year follow-up completed. Exclusion criteria were echocardiography data or other clinical information not available, echocardiography-confirmed LVEF ≥50% or <40%, lost to follow-up, and HF due to nonischemic heart disease (such as valvular heart disease, alcoholic cardiomyopathy). Through the screening process, 377 HFmrEF patients were successfully enrolled in this analysis. This study was approved by the Ethics Committee of Fujian Medical University Union Hospital and conformed to the principles outlined in the Declaration of Helsinki (2021KY009). Informed consent was obtained from all patients. The flowchart is shown in Figure 1.

**Definition of Type 2 Diabetes Mellitus**

Patients were considered to have type 2 DM (T2DM) if they had been previously informed of the diagnosis by a physician or were on glucose-lowering therapy, ie, insulin, oral hypoglycemic agents, diet, and exercise. Patients without previously diagnosed T2MD who required initiation of antihyperglycemic therapy during their hospital stay were also considered to have DM.\(^5\)

**Data Collection**

Patient information and coronary angiography procedural details were collected by independent trained reviewers blinded to group assignment from hospital databases and

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**Figure 1** Patient-selection flowchart.

**Abbreviations:** ACS, acute coronary syndrome; LVEF, left ventricular ejection fraction; HFmrEF, heart failure with midrange ejection fraction.

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HR analysis were age, sex, hypertension, history of myocardial infarction, Killip functional class (III–IV vs I–II), atrial fibrillation or atrial flutter, diagnosis at admission (STEMI vs NSTEMI), coronary disease status (multivessel vs single-vessel disease), complete revascularization, statins, angiotensin converting–enzyme inhibitors (ACEIs)/angiotensin-receptor blockers (ARBs), and mineralocorticoid-receptor antagonists (MRAs). Survival curves were constructed using Kaplan–Meier estimates for time to first event and compared using log-rank tests.

For sensitivity analysis, a propensity score was estimated by fitting a logistic regression model adjusted for age, sex, Killip functional class (III–IV vs I–II), hypertension, atrial flutter, coronary disease status (multivessel vs single-vessel disease), complete revascularization, ACEIs or ARBs, and calcium-channel blockers (CCBs). Pair matching (1:1) between the two groups was performed by nearest-neighbor matching without replacement. The same analysis was performed for the propensity-matched cohorts. All tests were two-tailed, and *P*<0.05 was considered statistically significant. All analyses were performed using SPSS 23.0.

### Results

#### Baseline Characteristics

In sum, 377 ACS patients with HFmrEF who had undergone PCI and survived to discharge were enrolled and divided into diabetic and nondiabetic groups. Baseline characteristics are shown in **Table 1**. Mean age was 63.2 years, and 85.9% of patients were male. Diabetic patients were older than nondiabetic patients (63.83±11.29 vs 62.89±11.07 years, *P*=0.025). Comorbidities were comparable, except for higher prevalence of hypertension (75.8% vs 54.3%, *P*<0.001) in the diabetic group. However, NT-proBNP at admission between two groups was not significantly different (959.0 [301.5–2,013.0] vs 1,133.0 [336.0–2,693.5], *P*=0.307). With regard to medication at discharge, ACEIs/ARBs and CCBs were more frequently prescribed in the nondiabetic group (57.6% vs 70.2%, *P*=0.017 and 6.1% vs 13.5%, *P*=0.036, respectively). Compared with nondiabetic patients, diabetic patients showed higher prevalence of multivessel disease (57.6% vs 47.5%, *P*=0.015) and required longer stents (43.5 [29–69.75] vs 33 [24–60] mm; *P*=0.038). However, they received less complete revascularization (47% vs 62%, *P*=0.006). There was no significant difference between the groups with respect to the proportion of
### Table 1 Baseline characteristics

| Demographics                  | Before PSM |          |          |          |          |          |          |
|-------------------------------|------------|----------|----------|----------|----------|----------|----------|
|                               | No diabetes (245) | Diabetes (132) | P        | No diabetes (130) | Diabetes (130) | P        |
| Age, years                    | 62.89±11.07 | 63.83±11.29 | 0.025    | 62.85±10.33 | 63.89±11.36 | 0.442    |
| Male                          | 217(88.6%)   | 107(81.1%)  | 0.061    | 112(86.2%)   | 107(82.3%)   | 0.496    |
| BMI, kg/m²                    | 23.91±3.16   | 24.69±3.13  | 0.439    | 24.39±2.91   | 24.68±3.14   | 0.436    |
| Smoking                       | 167(68.2%)   | 81(61.4%)   | 0.211    | 79(60.8%)    | 81(62.3%)    | 0.899    |
| Comorbidities                 |            |           |          |            |           |          |
| Hypertension                  | 133(54.3%)   | 100(75.8%)  | <0.001   | 94(72.3%)    | 98(75.4%)    | 0.672    |
| Chronic kidney disease        | 31(1.2%)     | 5(3.8%)    | 0.134    | 6(4.6%)      | 15 (11.5%)   | 0.066    |
| Hyperuricemia                 | 87(35.5%)    | 48(36.4%)   | 0.910    | 45(34.61%)   | 47(36.15%)   | 0.795    |
| Atrial fibrillation           | 22(9.0%)     | 15(11.4%)   | 0.472    | 14(10.8%)    | 15(11.5%)    | 1.00     |
| Echocardiography data         |            |           |          |            |           |          |
| LVDd, mm                      | 52.67±5.70   | 53.1±6.09  | 0.426    | 53 (50.0, 57.5) | 53 (48.95, 57.6) | 0.713    |
| LVDs, mm                      | 40.89±4.49   | 42.43±5.04 | 0.339    | 41.3(38.42,44.07) | 41.0(38.14,45.05) | 0.714    |
| LVEF, %                       | 44.96(42.10–66.65) | 44.10(42.10,46.68) | 0.290    | 44.35(42.34,46.68) | 44.10(42.15,46.60) | 0.690    |
| LVFS, %                       | 22.40(20.80–23.50) | 21.80(20.73,23.40) | 0.190    | 22.40(20.92,23.50) | 21.80(20.80,23.35) | 0.581    |
| E/e'                          | 12.40(10.10–16.70) | 13.65(11.60,18.73) | 0.009    | 13.45(10.40,17.05) | 13.60 (11.60,18.90) | 0.122    |
| 'e'                           | 0.05(0.04,0.06) | 0.05(0.04,0.06) | 0.854    | 0.05 (0.04, 0.06) | 0.05 (0.04, 0.06) | 0.840    |
| Clinical status               |            |           |          |            |           |          |
| Previous MI                   | 204(83.3%)   | 100(75.8%)  | 0.101    | 108(83.1%)   | 99(76.2%)    | 0.218    |
| Diagnosis at admission        | 0.731        | 0.599     |          | 0.015        | 0.507      |          |
| STEMI                         | 80(32.7%)    | 46(34.8%)   | 0.413    | 41(31.5%)    | 46(35.4%)    |          |
| NSTE-ACS                      | 165(67.3%)   | 86(65.2%)   | 0.610    | 84(64.6%)    | 84(64.6%)    |          |
| Killip III–VI at admission    | 9(3.7%)      | 13(9.8%)    | 0.02     | 6(4.6%)      | 13(10%)     | 0.095    |
| Coronary disease status       | 0.015        | 0.507      |          | 0.015        | 0.507      |          |
| Single vessel                 | 136(55.5%)   | 56(42.4%)   | 0.032    | 39(30.0%)    | 45(34.6%)    |          |
| Multivessel                   | 109(44.5%)   | 76(57.6%)   | 0.91     | 91(70.0%)    | 85(65.4%)    |          |
| Revascularization             | 0.006        | 0.522      |          | 0.006        | 0.522      |          |
| Incomplete                    | 93(38.0%)    | 70(53.0%)   | 0.842    | 84(64.6%)    | 78(60.0%)    |          |
| Complete                      | 152(62.0%)   | 62(47.0%)   | 0.462    | 46(35.4%)    | 52(40.0%)    |          |
| Drug-eluting stent use        | 225(91.8%)   | 125(94.7%)  | 0.304    | 127(97.7%)   | 127(97.7%)   | 1.00     |
| Type of stent                 | 0.891        | 0.511      |          | 0.891        | 0.511      |          |
| First drug-eluting            | 47(20.9%)    | 25(20.0%)   | 0.20     | 20(15.9%)    | 25(19.7%)    |          |
| Second drug-eluting           | 178(79.1%)   | 100(80.0%)  | 0.101    | 107(84.1%)   | 102(80.3%)   |          |
| PTCA                          | 10(4.0%)     | 5(3.9%)     | 0.889    | 1(0.7%)      | 0           | 0.316    |

(Continued)
drug-eluting stent use, stent number, or minimum stent diameter. Because the baseline characteristics were in dis-equilibrium, we used 1:1 propensity-score matching, after which no significant differences were observed between the groups, as also shown in Table 1.

### Comparison of 3-Year Outcomes Between Diabetic and Nondiabetic Patients

During a follow-up of 3 years, incidence of the primary outcome was higher in diabetic patients than nondiabetic patients (33 [25.5%] vs 31 [12.6%], \( P = 0.002 \)). Incidence of the composite outcome of all-cause death/HF rehospitalization, composite outcome of cardiovascular death/HF rehospitalization, all-cause death, cardiovascular death, HF rehospitalization, and unplanned revascularization per 1,000 patient-years were 96.1 vs 44.6, 88.6 vs 41.6, 49.5 vs 20.8, 43.7 vs 14.9, 82.4 vs 35.7, and 92.9 vs 48.4 for the diabetic and nondiabetic groups, respectively (Table 2). Incidence ORs were 2.301 (95% CI 1.334–3.969, \( P = 0.002 \)), 2.055 (95% CI 1.291–3.272, \( P = 0.003 \)), 2.254 (95% CI 1.148–4.260, \( P = 0.019 \)), 2.784 (95% CI 1.287–6.023, \( P = 0.009 \)), 2.320 (95% CI 1.417–3.800, \( P = 0.001 \)) and 2.056 (95% CI 1.196–3.532, \( P = 0.010 \)) for each outcome (Table 2).

Univariate analysis of the composite of all-cause death or HF rehospitalization using Cox regression demonstrated that DM, age, sex, Killip functional class III–IV at admission, complete revascularization, and atrial fibrillation were significantly associated with the primary outcome. Multivariate analysis of these factors showed that DM (adjusted HR 2.080, 95% CI 1.115–3.878; \( P = 0.021 \)), age (adjusted HR 1.038, 95% CI 1.007–1.069; \( P = 0.015 \)), Killip III–VI at admission (adjusted HR 1.268, 95% CI 1.006–2.213; \( P = 0.032 \)), multivessel disease (adjusted HR 3.146, 95% CI 1.210–8.185; \( P = 0.019 \)), complete revascularization (adjusted HR 0.149, 95% CI 0.057–0.391; \( P < 0.001 \)), and atrial fibrillation (adjusted HR 3.411, 95% CI 1.510–7.702; \( P = 0.003 \)) were associated with worse prognosis (Table 3). After propensity-score matching, DM (adjusted HR 3.792, 95% CI 1.802–7.980; \( P < 0.001 \)) was still significantly associated with the primary outcome on multivariate analysis (Table 4).

Figure 2 shows survival curves constructed using Kaplan–Meier estimates for time to first event and the cumulative incidence of each outcome. Cumulative incidence of the composite of all-cause death/HF rehospitalization

### Table 1 (Continued).

| Demographics          | Before PSM | After PSM |
|-----------------------|------------|-----------|
|                      | No diabetes (245) | Diabetes (132) | \( P \) | No diabetes (130) | Diabetes (130) | \( P \) |
| Stent number          | 1(1–2)     | 2(1–3)    | 0.133 | 2(1.2)         | 2(1.2)       | 0.393 |
| Total stent length (mm)| 33(24.0,60.0) | 43.5(29.0,69.75) | 0.038 | 38(24,62.5)    | 43.5(27.75,70.25) | 0.623 |
| Minimum stent diameter (mm) | 2.75(2.5,3.0) | 2.75(2.5,3.0) | 0.505 | 2.75(2.5,3.0)  | 2.75(2.5,3)   | 0.176 |
| Medication at discharge |            |           |       |               |              |       |
| Antplatelets          | 237(96.71%) | 128(97.0%) | 1.000 | 127(97.7%)     | 129(99.2%)   | 0.622 |
| Statins               | 227(92.7%) | 119(90.2%) | 0.434 | 119 (91.5%)    | 115 (88.5%)  | 0.536 |
| ACEIs or ARBs         | 172(70.2%) | 76(57.6%)  | 0.017 | 86 (66.2%)     | 81(62.3)     | 0.605 |
| β-blockers            | 188(76.7%) | 106(80.3%) | 0.515 | 98 (75.4%)     | 103 (79.2%)  | 0.554 |
| MRAs                  | 96(39.2%)  | 64(48.5%)  | 0.101 | 57 (43.8%)     | 62 (47.7%)   | 0.619 |
| CCBs                  | 33(13.5%)  | 8(6.1%)    | 0.036 | 14 (10.8%)     | 11 (8.5%)    | 0.675 |
| Diuretics             | 72(29.4%)  | 40(30.3%)  | 0.906 | 33 (25.4%)     | 47 (36.2%)   | 0.080 |
| Anticoagulants        | 10(4.1%)   | 8(6.1%)    | 0.450 | 9(6.9%)        | 8(6.1%)      | 0.801 |
| Nitrate               | 12(4.9%)   | 3(2.3%)    | 0.276 | 8(6.15%)       | 3(2.3)       | 0.123 |

**Abbreviations:** PSM, propensity-score matching; BMI, body-mass index; LVFS, left ventricular fractional shortening; E/e, mitral valve E velocity divided by mitral annular e’ velocity; PTCA, percutaneous transluminal coronary angioplasty.
(P=0.0023, Figure 2A), composite of cardiovascular death/ HF rehospitalization (P=0.0028, Figure 2B), all-cause death (P=0.0163, Figure 2C), cardiovascular death (P=0.0071, Figure 2D), HF hospitalization (P=0.0006, Figure 2E), and unplanned revascularization (P=0.0081, Figure 2F) were significantly higher in the diabetic patients. After adjustment by propensity-score matching, DM still increased the cumulative incidence of the composite of all-cause death/HF rehospitalization (P=0.0001, Figure 3A), composite of cardiovascular death/HF rehospitalization (P=0.0004, Figure 3B), all-cause death (P=0.0004, Figure 3C), cardiovascular death (P=0.0004, Figure 3D), and HF rehospitalization (P=0.0003, Figure 3E), but no significant association was found between DM and cumulative incidence of unplanned revascularization (P=0.1189, Figure 3F).

**Subgroup Analysis**
To confirm the association between DM and the composite of all-cause death/HF rehospitalization across various subgroups, we performed post hoc subgroup analyses. As Figure 4 shows, despite complete revascularization having been done, DM patients still suffered a higher risk of the primary outcome (OR 0.24, 95% CI 0.10–0.59; P<0.05). No difference between groups was found for patients with incomplete revascularization. DM also increased the risk of adverse outcomes in patients with multivessel disease (OR 0.45, 95% CI 0.22–0.94; P<0.05), hypertension (OR 0.45, 95% CI 0.23–0.87; P<0.05), or left anterior descending artery as target vessel (OR 0.42, 95% CI 0.22–0.80; P<0.05), but not among patients with single-vessel disease or right coronary/left circumflex artery as target vessel (all P≥0.05). The effect of DM on ACS patients with HFmrEF who had undergone PCI was not related to age or creatinine-clearance rate on subgroup analysis (all P≥0.05). Similar results were found in propensity score–matched cohorts, except for the fact that regardless of revascularization having been performed or not, DM still increased the risk of the composite endpoint (as shown in Figure 5).

To further study the effect of glycemic control status on prognosis, we divided diabetic patients into two groups: well controlled (HbA1c <7.5%) and poorly controlled (HbA1c ≥7.5%), according to the level of glycosylated hemoglobin tested at baseline and at the end of 1-year follow-up. As the survival curves show in Figure 6, compared with well-controlled diabetic patients, cumulative incidence of the composite of all-cause death/HF rehospitalization was significantly higher in poorly controlled diabetic patients (all P<0.05).

**Discussion**
HF with LVEF of 40%–49% is a gray area existing between HFrEF and HFpEF that the 2016 ESC HF guidelines termed HFmrEF. In view of the fact that previous studies had focused only on describing its characteristics with no focus on etiology, our study concentrated on ACS patients in a 3-year retrospective analysis to further investigate the relationship between DM and long-term outcomes in the ACS patients with HFmrEF after PCI.
The major finding of the present study was that DM significantly increased the risk of the composite of all-cause death/HF rehospitalization in this population, especially in ACS patients with poorly controlled glycemic status. This is an another in-depth report to identify such a relationship between DM and ACS patients with HFmrEF who have undergone PCI.

There is a consensus that patients with HF often have higher DM prevalence. The proportion of T2DM in chronic HF patients is about 30%, irrespective of HF phenotype (i.e., HFrEF and HFpEF), and 30%–40% in clinical trials on acute HF. We found similar results: approximately 35% of our HFmrEF patients had DM. Although a majority of data in the past suggested that DM significantly increased the risk of HF secondary to CAD, most of those data were limited to patients with HF whose EF was reduced or preserved. Maybe our research has provided some data to fill the lack of knowledge on HFmrEF and furthers exploration of the pathophysiological mechanisms of DM increasing the risk of adverse prognoses for HFmrEF patients.

Knowledge about pathophysiological aspects of myocardial dysfunction in T2DM has increased enormously in recent years. Widely accepted is the fact that DM patients

### Table 3 Unadjusted and adjusted HRs for primary outcome

|                               | Univariate analysis |                     | Multivariate analysis |                     |
|-------------------------------|---------------------|---------------------|-----------------------|---------------------|
|                               | HR                  | 95% CI              | P                     | HR                  | 95% CI              | P     |
| Diabetes mellitus             | 2.666               | 1.618,4.390        | <0.001                | 2.080               | 1.115,3.878        | 0.021 |
| Age                           | 1.045               | 1.017,1.073        | 0.001                 | 1.038               | 1.007,1.069        | 0.015 |
| Male                          | 1.050               | 1.023,1.078        | <0.001                | 0.943               | 0.416,2.140        | 0.889 |
| Previous MI                   | 1.034               | 0.952,1.122        | 0.432                 |                     |                     |       |
| Killip III–VI at admission    | 2.824               | 1.428,5.5844       | 0.003                 | 1.268               | 1.006,2.213        | 0.032 |
| Smoking                       | 0.907               | 0.545,1.507        | 0.706                 |                     |                     |       |
| LVDd, mm                      | 1.023               | 0.980,1.068        | 0.292                 |                     |                     |       |
| LVDs, mm                      | 1.036               | 0.982,1.094        | 0.196                 | 1.201               | 0.879,1.640        | 0.250 |
| Hypertension                  | 1.589               | 0.917,2.755        | 0.099                 | 1.391               | 0.712,2.721        | 0.334 |
| Chronic kidney disease        | 1.378               | 0.334,5.679        | 0.657                 |                     |                     |       |
| Hyperuricemia                 | 1.173               | 0.919,1.497        | 0.201                 |                     |                     |       |
| STEMI vs NSTEMI               | 0.902               | 0.622,1.060        | 0.514                 | 0.899               | 0.696,1.160        | 0.414 |
| Multi- vs single-vessel       | 1.528               | 0.887,2.631        | 0.126                 | 3.146               | 1.210,8.185        | 0.019 |
| Complete vs incomplete revascularization | 0.208 | 0.093,0.465 | <0.001 | 0.149 | 0.057,0.391 | <0.001 |
| Atrial fibrillation           | 3.138               | 1.753,5.618        | <0.001                | 3.411               | 1.510,7.702        | 0.003 |
| Antiplatelet                  | 0.991               | 0.599,1.637        | 0.971                 |                     |                     |       |
| Statins                       | 0.534               | 0.254,1.126        | 0.099                 | 1.327               | 0.434,4.060        | 0.620 |
| ACEIs or ARBs                | 1.176               | 0.685,2.02         | 0.556                 | 1.002               | 0.524,1.917        | 0.995 |
| β-blocker                     | 0.945               | 0.519,1.722        | 0.854                 | 0.648               | 0.321,1.309        | 0.226 |
| CCBs                          | 0.706               | 0.283,1.761        | 0.455                 |                     |                     |       |
| Loop diuretics               | 0.783               | 0.448,1.366        | 0.389                 |                     |                     |       |
| MRAs                          | 0.932               | 0.563,1.542        | 0.784                 | 1.709               | 0.927,3.148        | 0.086 |

**Abbreviations:** LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; CCBs, calcium-channel blockers.
Develop CAD more easily and suffer more diffuse coronary disease. As shown in Table 1, the prevalence of multivessel disease in the diabetic group was higher and stents longer, demonstrating that T2DM causes accelerated atherosclerosis and more diffuse atherosclerosis in the coronary arteries, which may partly explain why DM is associated with adverse prognoses. Complete revascularization in diabetic patients was proportionally lower (47% vs 62%, \( P < 0.05 \)), which suggests that complete revascularization may help to protect HF patients from adverse events. Evidence-based data on the importance of complete revascularization in HF cases are limited, but randomized data provide evidence suggesting CAD patients with HF may benefit from complete revascularization (SYNTAX and FAME trials). However, the worse prognosis of diabetic patients did not change in the propensity score–matched cohort after differences in complete revascularization had been balanced. Subgroup analyses also demonstrated that whether revascularized or not, DM patients still suffered a higher risk of adverse outcomes (Figures 4 and 5), suggesting that revascularization alone is not enough to change the prognosis of diabetic patients.

**Table 4** Unadjusted and adjusted HRs for primary outcome in propensity score–matched cohorts

|                      | Univariate analysis |          |          | Multivariate analysis |          |          |
|----------------------|---------------------|----------|----------|-----------------------|----------|----------|
|                      | HR                  | 95% CI   | P        | HR                    | 95% CI   | P        |
| Diabetes mellitus    | 4.481               | 2.047, 9.810 | <0.001  | 3.792                 | 1.802, 7.980 | <0.001  |
| Age                  | 1.054               | 1.019,1.091 | 0.003   | 1.039                 | 1.007,1.073 | 0.016   |
| Male                 | 1.244               | 0.531,2.912 | 0.615   |                       |          |          |
| Previous MI          | 0.943               | 0.421,2.112 | 0.886   |                       |          |          |
| Killip III–VI at admission | 2.710         | 1.480,4.960 | 0.001   | 1.878                 | 0.963,3.659 | 0.064   |
| Smoking              | 0.654               | 0.336,1.270 | 0.21    |                       |          |          |
| Alcohol              | 1.225               | 0.333,4.500 | 0.76    |                       |          |          |
| LVDd, mm             | 1.024               | 0.969,1.082 | 0.406   |                       |          |          |
| LVDs, mm             | 1.043               | 0.973,1.118 | 0.233   |                       |          |          |
| Hypertension         | 1.918               | 0.809,4.549 | 0.139   |                       |          |          |
| Chronic kidney disease | 1.764            | 0.179,17.381 | 0.627   |                       |          |          |
| Hyperuricemia        | 1.088               | 0.809,1.890 | 0.130   |                       |          |          |
| STEMI vs NSTE-ACS    | 0.702               | 0.523,1.256 | 0.654   |                       |          |          |
| Multi- vs single-vessel | 1.300            | 0.389,4.344 | 0.670   |                       |          |          |
| Complete vs incomplete revascularization | 1.235 | 0.395,3.855 | 0.717   |                       |          |          |
| Atrial fibrillation  | 3.306               | 1.411,7.748 | 0.006   | 2.988                 | 1.432,6.236 | 0.004   |
| Antiplatelets        | 1.046               | 0.739,1.480 | 0.801   |                       |          |          |
| Statins              | 0.864               | 0.309,2.417 | 0.781   |                       |          |          |
| ACEIs or ARBs        | 0.808               | 0.411,1.587 | 0.536   |                       |          |          |
| β-blockers           | 0.543               | 0.265,1.114 | 0.096   | 0.613                 | 0.306,1.231 | 0.613   |
| CCBs                 | 0.692               | 0.198,2.427 | 0.566   |                       |          |          |
| Diuretics            | 1.002               | 0.491,2.046 | 0.996   |                       |          |          |
| MRAs                 | 1.111               | 0.574,2.152 | 0.755   |                       |          |          |

**Abbreviations:** LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter.
Figure 2 Comparison of estimated event rates: (A) all-cause death and heart-failure hospitalization; (B) CV death and heart-failure hospitalization; (C) all-cause death; (D) CV death; (E) heart-failure hospitalization; (F) unplanned revascularization between diabetes group (red dotted line) and nondiabetes group (solid blue line) after PCI.
Figure 3 Comparison of estimated event rates: (A) all-cause death and heart-failure hospitalization; (B) CV death and heart-failure hospitalization; (C) all-cause death; (D) CV death; (E) heart-failure rehospitalization; (F) unplanned revascularization between diabetes group (dotted red line) and nondiabetes group (solid blue line) after PCI in propensity score–matched cohorts.
Neurohormonal antagonists (ACEIs, MRAs, and β-blockers) are recommended and have been shown to improve survival in patients with HF. However, few differences were observed between the diabetic and nondiabetic groups in respect of medication at discharge (MRAs and β-blockers, but not ACEIs/ARBs) for HF in this study, especially in propensity score–matched cohorts. In other words, HF patients with DM had not received individualized or optimal treatment different from those without DM, which may be one of the reasons for the worse prognosis for these patients. Thus far, there have been no clinical trials of HF treatment to include only patients with T2DM, so the evidence available is from subgroup analyses of mixed populations. The embarrassing situation of there being no specific recommendations on HF treatment in T2DM patients needs solving urgently.

Many clinical trials have observed that T2DM-related processes can cause myocardial dysfunction in certain diabetic patients, but in the absence of CAD. Rubler et al came up with a new theory named “diabetic cardiomyopathy” to explain such a phenomenon.19 Hyperglycemia and insulin resistance are the two major consequences of DM responsible for cardiovascular disorders in patients with DM.20 Their detrimental effects interact with each other and exert a potentiating effect, leading to several maladaptive responses and resulting in myocyte alteration, a common element in these chains being that ROS production increases diabetic cardiomyocytes. Hyperglycemia and insulin resistance affect myocardial function by breaking the balance of ROS production in cardiomyocytes, leading to impaired cellular function and cardiovascular pathology.21 Subgroup analysis revealed that DM was associated with adverse outcomes independently of age, sex, and hypertension (Figures 4 and 5). Figure 6 shows that compared with diabetic patients with well-controlled glycemic status (HbA1c <7.5%), diabetic patients with poorly controlled glycemic status (HbA1c ≥7.5%) were more at risk of composite end-point events, demonstrating that hyperglycemia itself has an important impact on the prognosis of HF patients with DM, indirectly indicating that optimized antidiabetic treatment and strict blood-glucose control is of great significance in improving the prognosis. However, old antidiabetic drugs used widely, such as insulin and sulfonlureas, have not been proved safe in HF patients with T2DM,22,23 and some drugs have even been shown to increase the risk of HF hospitalization (ie, rosiglitazone, pioglitazone, and saxagliptin).24–27 Inappropriate antidiabetic treatment not only fails to benefit patients but may also lead to adverse outcomes. Fortunately, some new antidiabetic drugs, such as GLP1-receptor agonists and DPP4 inhibitors, have no impact on the risk of HF hospitalization.28–32 In addition, SGLT2 inhibitors (eg, empagliflozin and canagliflozin) have demonstrated a significant reduction in the risk of HF hospitalization in patients with T2DM, and are currently being investigated as a potential addition to the
optimal medical treatment of HF, especially in patients with T2DM. Therefore, we speculate that combined use of optimized hypoglycemic drugs and anti-HF drugs may bring the greatest improvement to HF patients with DM in prognosis.

**Limitations**

Several limitations of this study should be acknowledged. Firstly, this was a single-center, retrospective, observational study, the sample was limited, and the number of subjects with DM modest (132), but it still provides meaningful evidence for clinical practice. Secondly, we attempted to explore the impact of complete revascularization on the prognosis of ACS patients with HFmrEF, and found that it may be one of the factors affecting prognosis, but not the only one. In view of this, we tried to study whether optimization of drug treatment, including anti-HF and antidiabetic drugs, may be more important for the prognosis of such a population, but the limited data are not enough to support our conjecture. More large-scale randomized controlled trials are required to verify such
a conjecture. Thirdly, the details of antidiabetic therapy were not collected, so the effects of such therapy on the prognosis of HFmrEF complicated with DM was not completed.

**Conclusion**

Taken together, our data suggested that T2DM was associated with adverse outcomes in ACS patients with HFmrEF who had undergone PCI and significantly increased the risk of mortality and HF rehospitalization compared to HF patients without T2DM. For management of this population, in addition to effective revascularization, optimal medication including the optimization of hypoglycemic therapy and anti-HF therapy was probably more significant.

**Abbreviations**

T2DM, type 2 diabetes mellitus; ACS, acute coronary syndrome; HFmrEF, heart failure with midrange ejection fraction; HFrEF, HF with reduced EF; HfP EF, HF with preserved EF; LVEF, left ventricular EF; PCI, percutaneous coronary intervention; CAD, coronary artery disease; MI, myocardial infarction; STEMI, ST-elevation MI; NSTEMI, non–ST segment elevation; ACEI, angiotensin converting–enzyme inhibitor; ARB, angiotensin-receptor blocker; CCB, calcium-channel blocker; MRA, mineralocorticoid-receptor antagonist.

**Data Sharing**

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

**Ethics and Consent**

The study (2021KY009) was approved by the Clinical Research Ethics Committee of Union Hospital, Fujian Medical University, Fuzhou, Fujian, China.

**Author Contributions**

All authors made a significant contribution to the work reported, whether in conception, design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

**Funding**

This work was supported by a grant from the Natural Science Foundation of Fujian Province (2020J011028) and partially sponsored by the Fujian Provincial Health Technology Project (2020CXB015).

**Disclosure**

The authors declare that they have no competing interests.

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