

Late Percutaneous Coronary Intervention is Associated with Better Prognosis of Patients with Acute Myocardial Infarction

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Background: The optimal timing of invasive coronary revascularization in patients with late presentation of acute myocardial infarction (AMI) remains unclear.

Objective: This study aimed to investigate whether late percutaneous coronary intervention (PCI) is associated with the prognosis of AMI patients with HFpEF presenting >24h after symptom onset.

Methods: We enrolled 680 AMI patients with HFpEF. Patients were divided into 3 groups: early-PCI strategy (defined as the time to open IRA from symptom onset <24 h), late-PCI strategy (defined as the time of PCI-mediated reperfusion was >24 h) and non-revascularization group.

Results: A total of 144 (21.2%) experienced a MACE, including 118 (17.4%) all-cause deaths and 26 (3.8%) re-hospitalization for HF during a follow-up period of 30.20±15.62 months. After adjusting for gender, age, smoking, diabetes mellitus, NT-proBNP and eGFR, late-PCI was a significant and independent predictor of MACE (hazard ratio 0.367; 95% confidence interval 0.202–0.665; $p < 0.001$). Kaplan–Meier analysis showed that late-PCI decreased cumulative risk of MACE ($p < 0.001$).

Conclusion: Late-PCI and early-PCI strategies are associated with a reduced risk of MACE in AMI patients with HFpEF presenting >24 h after symptom onset, compared to conservative strategies.

Keywords: percutaneous coronary intervention, acute myocardial infarction, prognosis

Introduction

The non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA) are common manifestations of cardiovascular disease. Invasive strategies for NSTEMI include early coronary angiography with percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG), while noninvasive strategy is medicine therapy. PCI is the preferred reperfusion strategy in patients with acute ST segment elevation myocardial infarction (AMI).^{1,2} However, a large proportion of patients with AMI are late presenters with symptoms for more than 12 h on admission, no longer being eligible for thrombolysis.^{3,4} Therefore, the optimal timing of invasive coronary revascularization in patients with AMI presenting late remains unclear. Occluded Artery Trial (OAT) revealed no clinical benefit from routine coronary intervention in patients with persistent occlusion of the infarct-related artery (IRA).⁵ Busk et al reported that substantial myocardial salvage can be obtained beyond 12 h limit despite total infarct-artery occlusion after primary angioplasty in patients with symptoms for 12–72 h.⁶ A meta-analysis revealed that late PCI was associated with significant improvements in cardiac function and survival.⁷ Late-PCI strategy prevented LV remodeling, protected LV function, and improved clinical outcomes in AMI patients presenting >24 h after symptom onset.⁸ However, these studies

did not distinguish the impact of late-PCI strategy on the outcomes of heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF).

HFpEF is a clinical syndrome defined as heart failure symptoms with normal or near-normal ejection fraction.⁹ HFpEF accounts for approximately 50% of all cases of heart failure.¹⁰ A community surveillance study showed that the prevalence for HFpEF complicating AMI remained stable despite declining prevalence for HFrEF after AMI.¹¹ Therefore, HFpEF is associated with different phenotypes including diverse concomitant cardiovascular diseases.¹² Previous clinical studies suggested that HFpEF may be an independent predictor of major adverse cardiac events (MACE) in patients with AMI.^{13,14} However, few clinical studies have focused on the predictive factors and prognosis of AMI patients presenting with HFpEF after primary angioplasty.

Therefore, in this study we investigated whether late PCI strategy was associated with reduction in mortality and heart failure readmission in AMI patients with HFpEF presenting >24 h after symptom onset. We selected patients with NSTEMI according to the diagnostic criteria in ACC/AHA guidelines for NSTEMI/UA.

Methods

Subjects

This prospective observational study was approved by Ethics Committee of Second Hospital of Nanjing and complied with the Declaration of Helsinki. Written informed consent was obtained from all participating patients. Total 680 consecutive AMI patients with HFpEF were enrolled in this study during 2015–2016. AMI and HFpEF were diagnosed upon the admission to our Hospital. The diagnostic criteria for AMI followed the latest published guidelines.¹⁵ The diagnosis of HFpEF was made based on 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure.¹² EF was measured using common echocardiography.

HFpEF diagnosis was defined as the presence of symptoms and/or signs of HF, LVEF $\geq$ 50% or objective evidence of other cardiac functional and structural alterations underlying HFpEF, also referred to the Killip grade and elevated levels of NT-proBNP. Exclusion criteria were pulmonary hypertension, valvular heart disease, hypertrophic obstructive cardiomyopathy, severe inflammatory diseases, serious hepatic and renal failure, anemia with hemoglobin concentrations below 90 g/l, and cancer.

Demographic and Laboratory Characteristics

Main demographic data, cardiovascular risk factors were obtained from medical records. Smoking was defined as the current use of cigarettes and ascertained by self-report. Blood pressure and body mass index were obtained by trained staff. Blood tests were conducted early in the morning in fasted patients. The measured serum and plasma biochemical parameters included white blood cell, Neutrophil count, platelet count (PLT), lipids, serum creatinine, N-terminal pro-B-type natriuretic peptide (NT-proBNP). To limit the influence of extreme observations, NT-proBNP was natural logarithmically transformed to obtain LnNT-proBNP. Glomerular filtration rate was calculated as $(\text{mL min}^{-1} 1.73 \text{ m}^{-2}) = 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287} (\times 0.739 \text{ if female})$. Echocardiography for left ventricle function through left ventricle ejection fraction (LVEF) was performed upon the admission by experienced physicians who were blinded to patients' information. Early-PCI strategy was defined as the time to open IRA from symptom onset <24 h. Late-PCI strategy was defined as the time of PCI-mediated reperfusion from 24 h up to 15 days. The severity of coronary artery stenosis was assessed by the Gensini scores based on the results of coronary angiography.¹⁶

Outcomes and Follow-up

Major adverse cardiovascular events (MACE) included the composite of total death, hospitalization because of HF; and revascularization. All patients were followed up by interview or telephone by trained research cardiologist, and the end of follow-up was the date of the first MACE occurrence obtained by reviewing hospital records.

Statistical Analysis

All statistical analyses were performed using STATA 12.0 software (StataCorp, College Station, TX, USA). Continuous variables are shown as means $\pm$ standard deviations. Categorical variables were expressed as frequency and percentage. Statistical significance for categorical variables was tested using Chi square test, and for continuous variables the Student's *t* test was used. One-way ANOVA was used to compare multiple groups. Correlation was conducted using Spearman correlation analysis. Univariate and multivariate survival analyses involved Cox regression analysis. MACE was evaluated by Kaplan-Meier survival curves and the Log rank test was used to compare the incidence of MACE between groups. A P value of 0.05 was considered to indicate statistical significance using a two-tailed test.

Results

Baseline Characteristics of Patients

The present study included 680 consecutive patients (mean age of 60.93 ± 12.48 years), and 80.9% of them were male. Baseline characteristics are shown in Table 1. The participants were divided into three groups according to reperfusion therapy strategy: 194 early-PCI strategy, 353 late-PCI strategy and 133 non-revascularization group (mainly due to the conditions of the patients). Early-PCI group was defined as the time to open IRA from symptom onset <24 h, the median time to open IRA from symptom onset in the late-PCI group was 9 days (range, 7–15 days). There were no significant

Table 1 Baseline Characteristics of AMI Patients with HFpEF

Variables*	Early-PCI Group (n=194)	Late-PCI Group (n=353)	Non-Revascularization Group (n=133)	P value
Gender (male)	166 (85.6)	289 (81.9)	95 (71.4)	0.005
Age (year)	58.83 ± 12.60	59.46 ± 11.60	67.90 ± 12.21	<0.001
BMI (kg/m ²)	24.25 ± 2.62	23.81 ± 2.99	23.25 ± 2.18	0.005
Heart rate (bpm)	74.69 ± 14.32	73.49 ± 14.15	80.86 ± 22.63	<0.001
SBP (mmHg)	124.76 ± 21.71	123.80 ± 20.79	118.65 ± 22.21	0.026
DBP (mmHg)	77.86 ± 14.09	76.25 ± 12.07	73.62 ± 13.80	0.015
Current smoking	132 (68.0)	214 (60.6)	62 (46.6)	<0.001
Hypertension	85 (43.8)	151 (42.8)	53 (39.8)	0.767
Diabetes	27 (13.9)	44 (12.5)	29 (21.8)	0.033
Prior MI	8 (4.1)	24 (6.8)	12 (9.0)	0.196
Anterior wall infarct	95 (49.0)	184 (52.1)	77 (57.9)	0.281
WBC count (10 ⁹ /L)	9.84 ± 3.44	8.23 ± 3.79	11.44 ± 6.73	<0.001
Neutrophil count (10 ⁹ /L)	74.64 ± 18.02	66.81 ± 14.43	68.83 ± 25.69	<0.001
PLT count (10 ⁹ /L)	182.59 ± 88.57	194.78 ± 74.31	176.08 ± 68.59	0.035
TC (mmol/L)	4.25 ± 1.32	4.02 ± 1.05	4.08 ± 1.06	0.074
TG (mmol/L)	1.62 ± 0.95	1.71 ± 0.90	1.57 ± 0.99	0.278
LnNT-proBNP	2.81 ± 0.37	2.88 ± 0.43	3.18 ± 0.69	<0.001
eGFR	126.72 ± 11.43	113.18 ± 15.08	146.23 ± 11.75	<0.001
Gensini Score	73.8 ± 40.10	61.68 ± 37.23	65.98 ± 38.67	<0.001
Current medication				
Statins	175 (95.6)	336 (96.3)	77 (97.5)	0.771
Aspirin	180 (98.4)	347 (99.4)	76 (96.2)	0.067
P2Y12 inhibitor	183 (100.0)	347 (99.4)	77 (97.5)	0.063
ACEI/ARB	161 (88.0)	312 (89.4)	63 (79.7)	0.061
β -blockers	165 (90.2)	301 (86.2)	52 (65.8)	<0.001

Notes: *Data were at admission. The P values of variables with significant differences were in bold.

Abbreviations: AMI, acute myocardial infarction; HFpEF, heart failure with preserved ejection fraction; BMI, body mass index; Prior MI, prior myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglycerides; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PLT, platelets; WBC, white blood cell count; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

differences among the three groups with respect to hypertension, history of MI, and anterior wall infarct. However, an intergroup comparison revealed that patients in the non-revascularization group were older and more often female; and had higher heart rate, NT-proBNP, eGFR.

Clinical Characteristics of Patients with and without MACE

Among the 680 patients, 144 (21.2%) experienced a MACE, including 118 (17.4%) all-cause deaths and 26 (3.8%) rehospitalization for HF during a follow-up period of 30.20 ± 15.62 months. Table 2 shows the baseline characteristics of patients with and without MACE. Patients with MACE were significantly older, more often female, had higher BMI and faster heart rate compared with patients without MACE. The prevalence of diabetes mellitus and smoking was significantly higher in the MACE group ($P < 0.009$ and $P < 0.001$, respectively, Table 2). Patients with MACE had markedly increased levels of WBCs, neutrophils, NT-proBNP, and lower eGFR than those without MACE. Angiographic findings, such as Gensini scores and anterior wall infarct did not differ between the two groups. Early-PCI and late-PCI strategy decreased the risks for MACE compared with non-revascularization patients.

Late-PCI Strategy as an Independent Predictor of MACE Occurrence in AMI Patients with HFpEF

The results of univariate Cox analysis of the factors predicting MACE in AMI patients with HFpEF are shown in Table 3. Significant predictors of a MACE were age, gender, heart rate, diabetes mellitus, smoking, WBCs, neutrophils, NT-proBNP, eGFR, early-PCI and late-PCI strategy. The factors with significance in univariate analysis were chosen for multivariate analysis. After adjusting for gender, age, smoking, diabetes mellitus, NT-proBNP and eGFR, multivariate Cox analysis showed that late-PCI strategy was a significant and independent predictor of MACE [hazard ratio (HR) 0.367; 95% confidence interval (95% CI) 0.202–0.665; $P < 0.001$] (Table 4). Kaplan-Meier analysis showed that late-PCI

Table 2 Clinical Characteristics of AMI Patients with HFpEF with or without MACE

Variables	MACE (n=144)	Without MACE (n=536)	P value
Gender (male)	99 (68.8)	451 (84.1)	<0.001
Age (year)	69.82 ± 10.791	58.54 ± 11.812	<0.001
BMI (kg/m^2)	23.4348 ± 2.46399	23.93 ± 2.83205	0.039
Heart rate (bpm)	83.71 ± 21.352	73.01 ± 13.995	<0.001
SBP (mmHg)	120.82 ± 23.276	123.67 ± 20.876	0.157
DBP (mmHg)	75.15 ± 13.741	76.48 ± 12.89	0.279
Smoking	77 (53.5)	195 (38.4)	<0.001
Hypertension	76 (52.5)	315 (58.8)	0.197
Diabetes	31 (21.5)	69 (12.9)	0.009
Prior MI	12 (8.3)	32 (6.0)	0.306
PCI			<0.001
<24 hours	16 (11.1)	178 (33.2)	
>24 hours	42 (29.2)	311 (58.0)	
Anterior wall infarct	81 (56.3)	275 (51.3)	0.292
WBC count ($10^9/\text{L}$)	11.3959 ± 5.09385	8.7587 ± 4.30287	<0.001
Neutrophile count ($10^9/\text{L}$)	74.8838 ± 18.50085	67.9771 ± 18.16235	<0.001
PLT count ($10^9/\text{L}$)	189.44 ± 91.574	187.16 ± 73.872	0.753
TC (mmol/L)	4.0978 ± 1.09996	4.0955 ± 1.1456	0.983
TG (mmol/L)	1.6344 ± 1.01586	1.664 ± 0.91049	0.736
LnNT-proBNP	3.1650 ± 0.57266	2.8530 ± 0.43135	<0.001
eGFR	144.5814 ± 110.09220	117.8452 ± 36.35052	<0.001
Gensini Score	73.27 ± 38.092	65.11 ± 38.686	0.129

Abbreviation: MACE, major adverse cardiac event.

Table 3 Univariate Cox Analysis of the Factors Predicting MACE in AMI Patients with HFpEF

Variables	HR	95% CI	P value
Gender (vs female)	2.155	1.515–3.066	<0.001
Age (per 1 year)	1.080	1.063–1.097	<0.001
BMI (per 1 kg/m ²)	0.943	0.888–1.000	0.051
Heart rate (per 1 bpm)	1.032	1.024–1.041	<0.001
SBP (per 1 mmHg)	0.992	0.984–1.001	0.069
DBP (per 1 mmHg)	0.991	0.978–1.004	0.184
Smoking	1.915	1.379–2.660	<0.001
Hypertension	1.277	0.921–1.772	0.143
Diabetes	1.741	1.170–2.591	0.006
Prior MI	1.359	0.753–2.455	0.309
PCI			
<24 hours	0.082	0.048–0.140	<0.001
>24 hours	0.112	0.077–0.162	<0.001
Anterior wall infarct	1.189	0.855–1.653	0.304
WBC count (10 ⁹ /L)	1.060	1.042–1.077	<0.001
Neutrophil count (10 ⁹ /L)	1.027	1.014–1.040	<0.001
PLT count (10 ⁹ /L)	1.000	0.998–1.002	0.928
TC (mmol/L)	0.988	0.855–1.141	0.867
TG (mmol/L)	0.954	0.794–1.147	0.619
LnNT-proBNP	4.845	2.654–8.843	<0.001
eGFR (mL · min ⁻¹ · 1.73 m ⁻²)	1.005	1.004–1.007	<0.001
Gensini Score	1.006	1.000–1.012	0.059

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

Table 4 Multiple Cox Analysis of the Factors Predicting MACE in AMI Patients with HFpEF

Variables	HR	95% CI	P value
Age (per 1 year)	1.061	1.034–1.088	<0.001
PCI			
<24 hours	0.133	0.052–0.341	<0.001
>24 hours	0.367	0.202–0.665	<0.001
LnNT-proBNP	1.872	1.035–3.387	0.038
eGFR	1.006	1.001–1.011	0.033

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

strategy decreased the cumulative risk of MACE ($P < 0.001$). These data indicated that late-PCI strategy was an independent predictor of MACE in AMI patients with HFpEF.

Discussion

The results of the present study demonstrated that early-PCI and late-PCI strategy was significantly associated with reduced risk of MACE in AMI patients with HFpEF presenting >24 h after symptom onset, compared to non-revascularization group. Additionally, older age, NT-proBNP, and eGFR were important independent predictors of the HFpEF course in AMI patients.

The presence of HFpEF may indicate poor prognosis in AMI patients, and the risk of adverse events increases due to therapy limitations.^{13,14} A community study showed that declines in HF were observed for HFrEF but not for HFpEF, indicating a change in the case mix of HF after MI that requires new prevention strategies.¹¹ Identification of AMI patients who are at risk of suffering from HFpEF could be beneficial for the management and prognosis of the disease.

Consistent with the results of previous studies, our findings showed that older age, worsening renal function, elevated NT-proBNP level could independently predict adverse outcomes in AMI patients with HFpEF.^{17,18} These findings help clinicians perform prevention treatments for AMI patients who have preserved LVEF.

Primary PCI is recommended in all patients who present within 12 h of symptom onset.¹ Our findings support that reducing time to reperfusion therapy is pivotal because “time is muscle”. However, the relationship between the probability of death and duration of ischemia from symptoms onset to reperfusion therapy is controversial.¹⁹ In addition, a high proportion of AMI patients present beyond this time limit due to patients or treatment delay in the real world and the relative benefits of reperfusion therapy after 12 h from symptom onset is controversial. Whereas the Occluded Artery Trial (OAT) revealed no clinical benefit of from late recanalization performed 3–28 days (median 8 days) after AMI, BRAVE-2 Trial demonstrated that primary PCI improved myocardial salvage and 4-year survival compared with conservative medical treatment in AMI patients with symptoms for 12–48 h on admission.^{20–23} Primary PCI between 12 hours to 28 days was more effective than conservative therapy in real-world AMI patients.²⁴ The influence of late-PCI strategy on adverse outcomes in AMI patients with HFpEF presenting >24 hours has not been examined. Our findings revealed that PCI strategy was associated with a reduced risk of MACE compared with conservative strategies in AMI patients with HFpEF presenting >24 hours from the onset of symptoms. Our study is the first to evaluate the prognostic value of late-PCI strategy and provides supporting evidence for the application of reperfusion treatment in late presenters of AMI with HFpEF. Individual variations such as intermittent or partial coronary occlusion, the chance of an existing coronary collateral circulation, degree of ischemic preconditioning, and the metabolic status within the ischemic myocardium may explain why myocardial salvage can be achieved even beyond the 12 h limit.²⁵

Our study has several limitations. First, because the number of patients in the study was relatively small, these findings need to be verified by multicenter and large-scale studies. Second, residual and uncontrolled confounding might still be present because this was an observational study. In addition, we could not report the details of the coronary artery lesions of non-revascularization patients due to the lack of coronary angiographic characteristics.

In conclusion, our results suggest that late-PCI and early-PCI are associated with low risk of MACE in AMI patients with HFpEF presenting more than 24 h after the onset of symptom, compared with conservative strategies.

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Disclosure

The authors declare no competing interests.

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