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Combination of Clopidogrel and Nicorandil Improves Post-Procedure Platelet Activation and Cardiac Function Impairment in Patients with Acute Coronary Syndrome Undergoing PCI

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Abstract

Background Platelet aggregation is key to thrombosis after PCI surgery. The effects of nicorandil combined with clopidogrel on platelet activation and cardiac function injury in patients with ACS after PCI were examined.

Methods 174 patients with ACS receiving PCI were equally divided into control group (taking clopidogrel before PCI) and active group (nicorandil and clopidogrel in combination before PCI). Measurement of CD62p, CD63p and PAR was done for reflecting platelet activation, BV, PV and PSV for hemodynamics, and LVEDD, LVESD, LVEF, BNP, MMP-9 and CK-MB for cardiac function.

Results CD62p, CD63p, PAR, PV and BV levels decreased while PSV increased eminently at 24 h post-operation, whose changes in research group were greater than the control group. Postoperation, BNP and MMP-9 decreased while CK-MB increased in both groups, which were significantly lower in research group. The reduction of LVEDD and LVESD and the increase of LVEF were tested after operation, which were more prominent in research group. Patients in the nicorandil group had a better prognosis.

Conclusion Pre-procedure combined application of nicorandil and clopidogrel in patients with ACS undergoing PCI can effectively reduce the platelet activation, contributing to the recovery of patients' cardiac function after intervention.

Keywords Nicorandil, Acute coronary syndrome, PCI, Platelet activation, Cardiac function

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1 Background

Acute coronary syndrome (ACS) occurs most frequently in patients with hyperlipidemia, hypertension, diabetes and the elderly [1]. Without timely treatment, ACS patients may be complicated by arrhythmia, heart failure, shock, etc., with a high risk of death [2]. ACS is caused by the rupture of atherosclerotic plaque, which is the pathological basis of ACS [3]. Clinical improvement of platelet activation and vascular endothelial function is the key to improving the prognosis of patients with ACS [4]. Percutaneous coronary intervention (PCI) is the effective treatment of ACS to improve myocardial perfusion and relieve the condition of patients [5]. However, the procedure can increase the risk of stent thrombosis [6]. Therefore, reasonable anticoagulant drugs or endothelial protective drugs should be selected before procedure to reduce the risk of post-procedure adverse cardiovascular events. However, in terms of the use of specific drugs, there is still some controversy, especially under the background of increasing types of new drugs being developed, it is more practical to provide data support for this kind of research.

Clopidogrel is an antiplatelet drug widely used in clinical practice, it reduces the risk for cardiovascular adverse events after ACS [7]. However, clopidogrel is a prodrug requiring activation by cytochrome P450 isoenzymes, so its effect is slow [8]. Large-scale clinical trials have confirmed that the application of clopidogrel combined with aspirin before and after PCI can significantly reduce the risk of cardiovascular events and improve patient prognosis, providing a solid evidence-based medical basis for the application of clopidogrel before PCI [9]. During PCI, the vascular endothelium will be damaged to a certain extent, which will activate platelets, make them adhere to and gather at the injured site, and easily form thrombus. According to the International Consensus Statement on Platelet Function and Genetic Testing in Percutaneous Coronary Intervention (JACC: Cardiovascular Interventions 2024) [10], dual antiplatelet therapy with aspirin and $P2Y_{12}$ inhibitors after PCI is essential for the prevention of postoperative thrombotic events. A large number of clinical studies and practices have confirmed that the standardized use of aspirin and clopidogrel before PCI can inhibit platelet aggregation from different ways, significantly reduce the risk of stent thrombosis after PCI, and reduce the occurrence of cardiovascular adverse events such as myocardial infarction and stroke.

Nicorandil is a balanced vasodilator that acts as both NO donor and arterial K+ ATP channel opener. [11]. Nicorandil regulates coronary blood flow, and protects cardiomyocytes from ischemia-reperfusion injury, thereby alleviating endothelial dysfunction [12]. Crucially, nicorandil does not cause adverse reactions, such as sudden drops in blood pressure, bradycardia, and atrioventricular block [13]. Therefore, some investigators have used nicorandil in patients with PCI after the absence of reflux [13].

Thereby, this study explored the effects of nicorandil combined with clopidogrel on platelet activation and cardiac function injury in patients with ACS after PCI. The incidence of post-procedure adverse cardiovascular events was statistically analyzed.

2 Materials and Methods

2.1 Study Objects

174 patients with ACS who received PCI in Huai'an Second People's Hospital were studied. Inclusion criteria: (1) ACS was diagnosed according to American College of Cardiology (ACC)/American Heart Association (AHA) guidelines [14]; (2) Coronary angiography showed stenosis of one or more vessels; (3) PCI was performed for the first time; (4) > 18 years old; (5) No myocardial injury was found in pre-procedure examination. Exclusion criteria: (1) Patients with a history of anticoagulant or antiplatelet drug use within 7 days before this study; (2) Patients with contraindications of the use of antiplatelet drugs. Specifically, patients were assessed for clopidogrel resistance based on preoperative clopidogrel administration, and clopidogrel-resistant patients were excluded. Clopidogrel-resistant was defined as a < = 10% absolute change in 20 μmol/L ADP-induced platelet aggregation between the baseline value and at 6–8 hours after the 300 mg clopidogrel loading dose [15]; (3) Patients with dysfunction of liver, kidney and other important organs; (4) Patients with a history of using immune enhancers or hormones within 3 months prior to this study; (5) Patients with hematological diseases or malignant tumors; (6) Patients with cardiogenic shock or arrhythmia; (7) The time from onset to treatment was longer than 12 h. All patients or their families were informed and consented to the study, and the written informed consent were signed. This study was approved by the Ethics Committee of the Huai'an Second People's Hospital (IRB: HEYLL202316).

2.2 Therapeutic Schedule

According to the doctors' professional suggestions and the patients' personal wishes, 174 patients were divided into the control group and the active group with 87 cases in each group. Before PCI, all patients in both groups were routinely given aspirin (specification: 50 mg; Bayer, Germany), 75 mg once daily. Cases in the control group additionally took 75 mg clopidogrel (Sanofi, France) once daily, with the loading dose of 300 mg. In terms of the active group, the therapeutic schedule was carried out based on the treatment in control group. In addition to

clopidogrel, low molecular weight heparin was stopped 12 h before procedure and nicorandil (specification: 12 mg; Beijing Sihuan Kebao Pharmaceutical Co. Ltd, Beijing, China) was injected intravenously at a dose of 2 mg/h at 12 h before procedure. The detailed schedule was shown in Figure 1.

2.3 Elective PCI

All patients underwent coronary angiography and balloon dilatation and stenting for infarct-related vessels (IRV). A successful stent was defined as having all of the following features: significant relief or disappearance of chest pain, a fully expanded and adherent stent as revealed by angiography, less than 20% of the residual stenosis of the target vessel, no intimal tear or dissection, and a thrombolysis in myocardial infarction (TIMI) grade III flow.

2.4 Follow Up

After discharge, all patients were followed up by telephone and the outpatient review was recorded. The follow-up time was 6 months, and the occurrence of major adverse cardiovascular events was mainly recorded, including malignant arrhythmias, sudden cardiac death, acute myocardial infarction and heart failure, Target Vessel Revascularization (TVR), etc.

2.5 Detection of Platelet Activation Index and Hemodynamic Index

The levels of activation dependent granular protein P-selectin CD62p and CD63p were determined by flow cytometry. Platelet function was assessed by using the rates of adenosine diphosphate (ADP)-induced platelet aggregation rate (PAR) that measured by the Automatic Four-channel Platelet Aggregation Instrument (Beijing Precil Instrument Co., Beijing, China).

A fully automatic blood rheological instrument (Steellex, Beijing, China) was applied for the detection of whole blood viscosity (BV) and plasma viscosity (PV). Determination of peak systolic velocity (PSV) by Color Echocardiography.

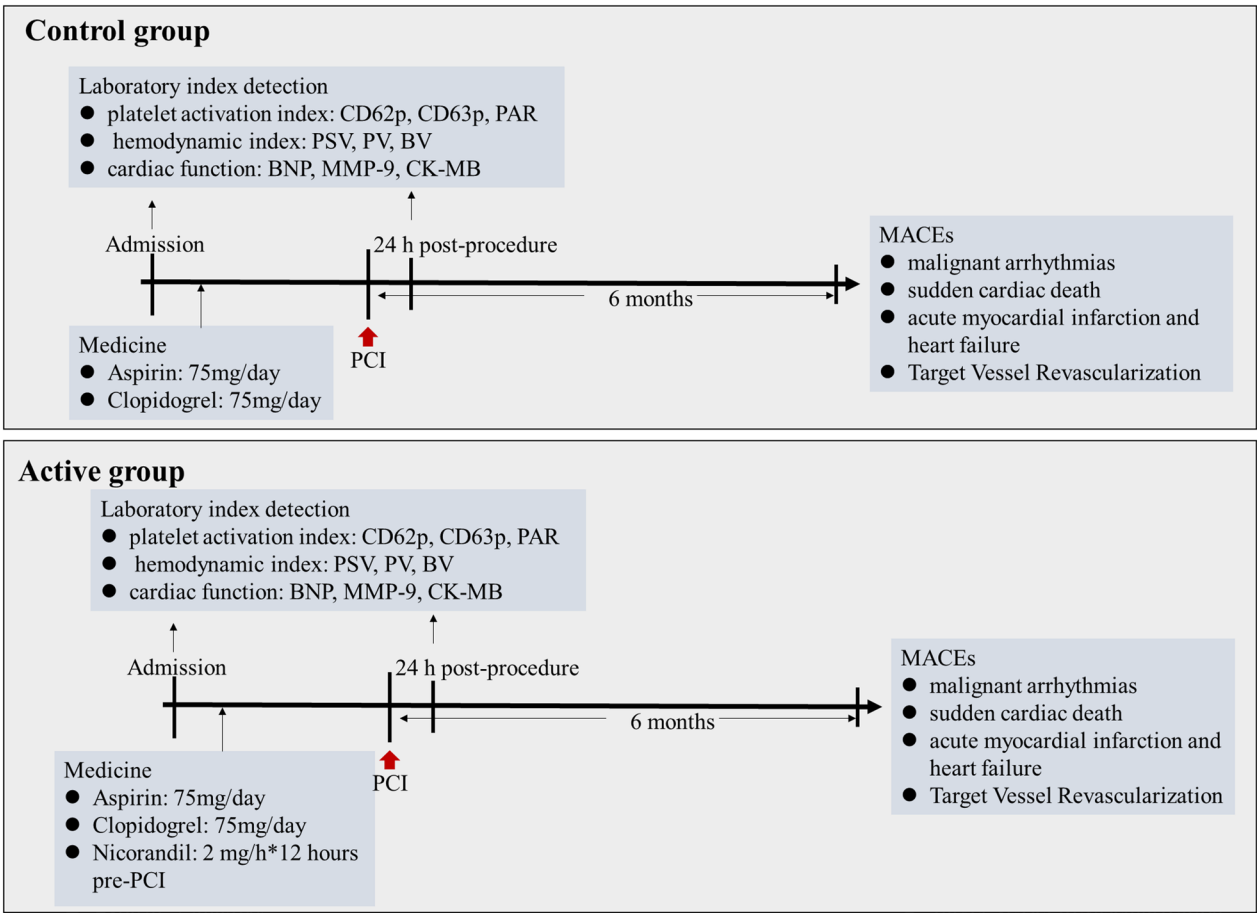

Figure 1 The detailed therapeutic schedule

2.6 Detection of Cardiac Function Index

Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD) and left ventricular ejection fraction (LVEF) were measured by using Doppler echocardiography imaging.

2.7 ELISA

Serum levels of brain natriuretic peptide (BNP), matrix metalloproteinase 9 (MMP-9) and creatine kinase isoenzyme MB (CK-MB) were determined by enzyme-linked immunosorbent assay (ELISA) based on the manufacturer's instructions.

2.8 Statistical Analysis

SPSS 21.0 software was used for statistical analysis and processing. Count data were expressed as example (*n*) and percentage (%), and compared between groups via chi-square test. The differences of continuous variables between different groups were analyzed by one-way ANOVA. The K-M survival curve was plotted according to the follow-up results, and the event-free survival rate between the two groups was compared by log-rank test. The difference was considered statistically significant at the P value less than 0.05.

3 Results

3.1 Comparison of Basic Information Between the Two Study Groups

Table 1 recorded the basic information of the control group and active group. Each group consisted of 87 individuals, and their age, gender and BMI were matched ($P > 0.05$). The type of lesion and comorbidity of the study subjects were also recorded and compared, and no significant difference was tested between the two study groups ($P > 0.05$). As to routine blood parameters, there were no significant differences between two study groups ($P > 0.05$). The time of FMC-to-balloon and door to balloon were also recorded and no significant difference was detected between the two groups ($P > 0.05$). In addition, there was also no significant difference between the two groups in post-procedure medication ($P > 0.05$).

3.2 Comparison of Platelet Activation Index and Hemodynamic Index

The activation of platelet was reflected as the level changes of CD62p, CD63p and PAR. As exhibited in Figure 2A–C, CD62p, CD63p and PAR levels all decreased eminently at 24 h post-procedure relative to pre-procedure in each group ($P < 0.001$). In contrast to the control group, people in the active group had low values of CD62p, CD63p and PAR at 24 h post-procedure ($P < 0.001$).

Figure 3 exhibited the changes of hemodynamic index before and after procedure. Elevated PSV was measured in both groups at 24 h after procedure. However relative to the control group, the increase of PSV in research patients was great (Figure 3A, $P < 0.001$). Reduced PV and BV were detected in each group after procedure compared with pre-procedure in both control and active groups (Figure 3B, C, $P < 0.001$), and the search group showed a lower trend than the control group ($P < 0.001$).

3.3 Detection of Cardiac Function

According to the ELISA results, both BNP and MMP-9 levels in two groups significantly reduced at 24 h after procedure than before procedure, and active group was significantly lower than the control group (Figure 4A, B, $P < 0.001$). The post-procedure level of CK-MB in both groups was significantly higher than that before procedure, but the active group was lower than the control group (Figure 4C, $P < 0.001$).

Based on the echocardiography results, post-procedure LVEDD and LVESD levels in both groups decreased distinctly in contrast to those before procedure, and the levels in the active group were lower than those in the control group (Figure 4D, E, $P < 0.001$). Raised post-procedure LVEF was tested in each group compared to that before procedure, and the elevation was more significant in active group than that of the control group ((Figure 4F, $P < 0.001$).

3.4 Incidence of Adverse Cardiovascular Events

After follow-up, adverse cardiovascular events were recorded and analyzed in both groups within 6 months. As presented in Table 2, in the control group, 6.87% of patients (6 cases) developed malignant arrhythmia, 5.75% of patients (5 cases) developed severe heart failure, and 8.05% of patients (7 cases) developed new myocardial infarction within 6 months after PCI. However, only 8.05% (7 cases) of patients in active group developed malignant arrhythmia, 3 (3.45%) patients developed severe heart failure, and 5 (5.74%) patients with new myocardial infarction. No deaths occurred in either group. Totally, more adverse cardiovascular events occurres in the control group than the active group ($P < 0.05$).

According to the results of 6-month follow-up, K-M curve was drawn to analyze the predictive value of nicorandil for adverse cardiovascular events after PCI procedure in AMI patients. As displayed in Figure 5, patients in the nicorandil group had a better prognosis while those in the control group had a worse prognosis, and the difference between the two groups was statistically significant (log Rank $P < 0.01$). The findings indicated that pre-procedure administration of nicorandil can reduce the

Table 1 Basic information statistics of subjects

Item	Control group (*n*=87)	Active group (*n*=87)	*P*
Age (year)	54.39±5.25	55.53±5.35	0.159
Gender (n/%)			0.879
Male	44(50.57)	43(49.43)	
Female	43(49.43)	44(50.57)	
BMI (kg/m^2)	25.06±2.03	24.87±1.74	0.551
Type of lesion (n/%)			0.376
Instability	59(67.82)	56(64.37)	
Non-st-segment elevation	20(22.99)	17(19.54)	
St-segment elevation	8(9.19)	14(16.09)	
Comorbidity (n/%)			0.935
Hypertension	28(32.18)	26(29.89)	
Diabetes	10(11.49)	11(12.64)	
Hyperlipidemias	39(44.83)	40(45.98)	
SBP (mmHg)	122.52±26.28	127.44±27.29	0.227
DBP (mmHg)	62.60±15.73	66.45±13.73	0.087
TG (mmol/L)	1.12±0.26	1.19±0.25	0.089
TC (mmol/L)	5.79±1.60	5.87±1.66	0.735
HDL-C (mmol/L)	1.39±0.46	1.31±0.31	0.171
LDL-C (mmol/L)	2.78±1.12	2.94±1.09	0.345
FBG (mmol/L)	6.36±2.74	6.97±2.64	0.142
Uric acid (μmol/L)	375.39±101.14	385.65±106.46	0.515
Hemoglobin (g/L)	130.63±21.23	129.61±20.61	0.749
Albumin (g/L)	38.17±1.89	38.03±2.19	0.679
Procedural characteristics			
FMC-to-balloon	153.74±51.05	160.99±48.32	0.337
Door-to-balloon	123.98±42.77	134.33±40.67	0.103
Medications			
Beta-blocker	18(20.69)	16(18.39)	0.702
Calcium-blocker	7(8.04)	10(11.49)	0.444
Aspirin	87(100)	87(100)	–
Clopidogrel	87(100)	87(100)	–
ACEI/ARB	25(28.74)	23(26.43)	0.734

All data in the table were presented as mean ± standard deviation or *n*/%

BMI Body Mass Index, *FBG* fasting blood glucose, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *FMC* first medical contact

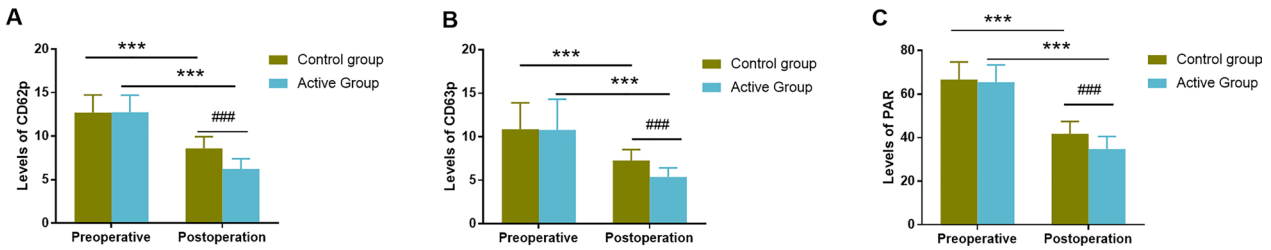

Figure 2 Levels of platelet activation index in the two study groups before or after PCI procedure. People in the active group had low values of CD62p (**A**), CD63p (**B**) and PAR (**C**) at 24 h post-procedure. *** indicates $P < 0.001$; ### indicates $P < 0.001$ relative to control group post-procedure

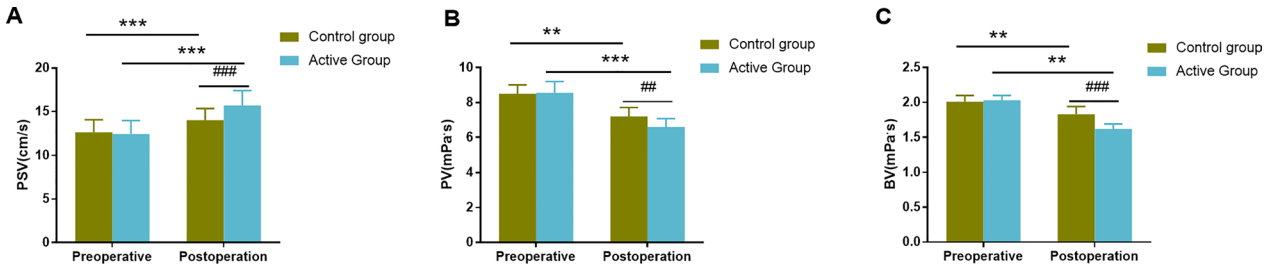

Figure 3 Levels of hemodynamic index in the two study groups before or after PCI procedure. Post-procedure, PSV levels (**A**) were significantly higher in active group relative to the control group, while PV (**B**) and BV (**C**) levels decreased. *** indicates $P < 0.001$; ### indicates $P < 0.001$ relative to control group post-procedure

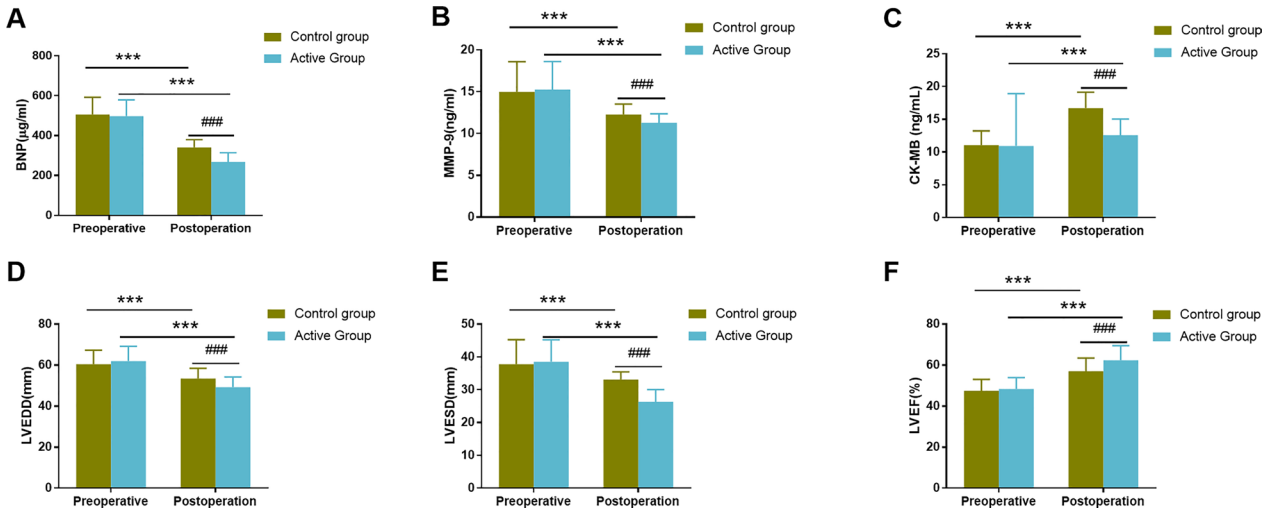

Figure 4 Levels of cardiac function index in the two study groups before or after PCI procedure. The post-procedure level of BNP (**A**) and MMP-9 (**B**) decreased while CK-MB (**C**) increased compared with pre-procedure in both groups, which were all significantly lower in active group than the control group. The echocardiography determined the reduce of LVEDD (**D**) and LVESD (**E**) and the increase of LVEF (**F**) in both groups after procedure, while the changes were more prominent in the active group than in the control group. *** indicates $P < 0.001$; ### indicates $P < 0.001$ relative to control group post-procedure

Table 2 Comparison of adverse cardiovascular events between the two groups, n (%)

Group	Malignant arrhythmia	Severe heart failure	New myocardial infarction	Total
Control group	6 (6.87)	14 (16.09)	7 (8.05)	27 (31.03)
Active group	5 (5.75)	3 (3.45)	5 (5.74)	13 (14.94)
X^2				6.363
P				0.012

occurrence of adverse cardiovascular events in patients after PCI, which was beneficial to prognosis.

4 Discussion

ACS, as a class of acute cardiac ischemia syndrome, is associated with atherosclerotic plaque rupture, coronary endothelial injury and thrombosis [16]. According to relevant reports, abnormal platelet activation occurs in patients with ACS, and thrombosis caused by it is the main pathogenesis of ACS [17]. Moreover, platelet aggregation is the key to thrombosis after procedure [18]. Effective anti-platelet aggregation therapy can largely prevent the occurrence of multiple complications [19]. In view of the slow efficacy of clopidogrel, it can not meet clinical needs [20]. The combination of clopidogrel and nicorandil was applied in the present study. The present clinical results illustrated that the addition of nicorandil before procedure reduced

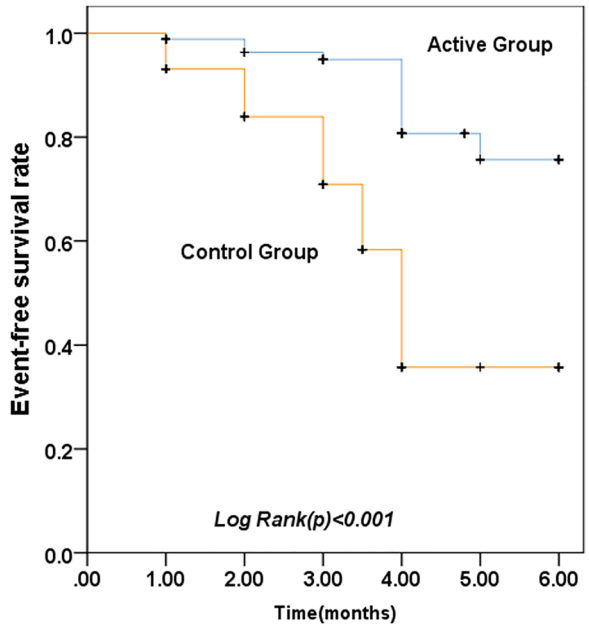

Figure 5 K-M curve based on the 6-month follow-up results. Patients in the nicorandil group had a better prognosis while those in the control group had a worse prognosis

platelet activation and improved the post-procedure cardiac function of ACS cases.

Platelets have the physiological function of clotting and stopping bleeding in the body [21]. Platelet activation can promote the release of a large number of local bioactive substances and accelerate the formation of thrombus, resulting in myocardial insufficiency or even ACS [22]. CD62p and CD63p are membrane glycoproteins of platelets, and their increased expression is an important marker of platelet activation [23]. Platelet activation is accompanied by exposure of CD62p and CD63p, which promotes the release of vasoactive substances and activation of neutrophils, contributing to thrombosis [24]. In this study, post-procedure CD62p, CD63p, PAR, PV and BV levels in both groups were decreased compared with those before procedure, while PSV levels were increased. However, in the active group, the range of changes in various indexes was more significant. The results suggested that nicorandil combined with clopidogrel can effectively reduce the platelet activation status of patients with ACS after PCI and improve the hemodynamics of the body. The reason may be related to nicorandil-mediated dilation of blood vessels and the opening of K^+ channels [25]. After nicorandil treatment, the blood flow state and thrombosis of the body can be effectively improved, accompanied by the weakening of platelet activation.

BNP is mainly secreted by the ventricle, with diuretic, sodium and diastolic blood vessels and other physiological functions [26]. Relevant studies have found that frequent myocardial ischemia can lead to hemodynamic changes in the body, accompanied by massive secretion of BNP [27]. Recent clinical studies have found that the expression level of MMP-9 can be elevated in patients with a variety of cardiovascular diseases such as ACS, heart failure and hypertension [28]. It is believed that MMP-9 can affect the structural stability of atherosclerotic plaque, and accelerate the rupture of the fiber cap, contributing to the formation of acute thrombosis [28]. In this study, the post-procedure levels of BNP, MMP-9, LVEDD and LVESD were decreased in both groups, while the levels of CK-MB and LVEF were increased. Except for CK-MB, the changes of other indexes in the active group were greater than those in the control group, suggesting that nicorandil combined with clopidogrel can effectively reduce myocardial injury, increase the stability of atherosclerotic plaque, thus contributing to the improvement of post-procedure cardiac function in patients. Nicorandil can increase potassium outflow, and reduce vasospasm, thereby promoting vascular smooth muscle relaxation [29]. Based on the vascular relaxation effects, nicorandil can effectively reduce systemic blood flow resistance, ensure improvement of myocardial ischemia and inhibit vascular inflammation. These influences can significantly improve myocardial injury and promote post-procedure cardiac function recovery in patients with ACS after PCI. Interestingly, a latest study by Zhong et al. has reported the clinical efficacy of nicorandil-clopidogrel combination therapy in patients with coronary heart disease (CHD) [9]. Both the report and our current results affirm the positive effects of the combination of nicorandil and clopidogrel in patients with ACS. It provides strong evidence support for clinical treatment, indicating that the combination of nicorandil and clopidogrel is an effective treatment strategy. The difference is that Zhong et al. 's study highlights the significant clinical efficacy of the combination in the entire CHD patient population. Our study focused on patients with ACS who underwent PCI, highlighting the importance and advantages of preoperative combination therapy for this specific surgical population. In general, the conclusions of these two studies complement each other, providing more comprehensive evidence for the combination of nicorandil and clopidogrel in the treatment of coronary heart disease, and providing a richer reference for clinicians to formulate treatment plans for patients with coronary heart disease under different conditions.

Furthermore, the adverse cardiovascular events were also recorded after six-month follow-up. It was found that malignant arrhythmia and severe heart failure are common events after PCI. It was observed that patients

had good values of LVEF on the first day after PCI, indicating that the patients had comparable cardiac function prior to PCI. However, a certain percentage of cases suffered from malignant arrhythmias during the 6-month follow-up. These observations indicate that the cardiac function may be severely impaired following selective PCI for those patients. In addition, we observed that longer time of FMC-to-balloon and Door-to-balloon also might be the reason for the high occurrence of malignant arrhythmias after PCI [30, 31]. It was concluded that nicorandil combined with clopidogrel can effectively improve the prognosis of patients after PCI, which is consistent with the above functional discoveries. Bleeding is an important consideration for PCI patients [32]. However, this study has a distinct limitation in that no assessment of bleeding was carried out among the acute coronary syndrome patients who underwent PCI. This study focuses on the major adverse cardiovascular events in 6-month follow-up. In future studies, it is essential to include bleeding measurement to obtain a more accurate and complete view of the treatment outcomes for the patients' population in a more long-term follow-up.

5 Conclusion

In conclusion, pre-procedure combined application of nicorandil and clopidogrel in patients with ACS undergoing PCI can effectively reduce the platelet activation, contributing to the recovery of patients' cardiac function after interaction. The findings provide a certain clinical evidence support for the combined application of nicorandil and clopidogrel before PCI procedure.

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Author Contributions
All authors designed the research study. Z.H. C, J. Z, X. Z, C.P. Z and W. Z performed the research and analyzed the data. X. Z and C.P. Z wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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

Declarations

Conflict of Interest
The authors declare no competing interests.

Ethics Approval and Consent to Participate
The study protocol was approved by The Ethics Committee of Huai'an Second People's Hospital (IRB: HEYLL202316). All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki Declaration and later versions. In addition, for investigations involving human subjects, written informed consent has been obtained from the participants involved.

Consent for Publication
Not applicable.

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