Effect of Different Methods of Administration of Diltiazem on Clinical Efficacy in Patients with Acute ST-Segment Elevation Myocardial Infarction

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Background: The aim of this study was to investigate the optimal route of administration of diltiazem in emergency PCI and to provide the best clinical treatment for ASTEMI patients.

Material/Methods: A total of 90 patients with ASTEMI treated in our hospital from January 2015 to January 2016 were selected. Prior to thrombus aspiration, a thrombus aspiration catheter was used to perform diltiazem injection at the distal end of the infarct-related artery (IRA). We chose the acute ST-elevation myocardial infarction (ASTEMI) patients treated with direct PCI to compare different administration routes of diltiazem. The occurrence of major adverse cardiac events (MACEs) was closely observed during hospitalization and was obtained through outpatient visits or telephone follow-ups over the next 6 months.

Results: Intracoronary infusion of diltiazem at the distal end of the culprit vessel, compared to conventional coronary mouth and intravenous injection, was significantly improved in thrombolysis in myocardial infarction (TIMI) frame count immediately after PCI stent implantation, ST-segment drop rate after 90 min, and left ventricular ejection fraction (LVEF) after 1 week. Furthermore, the peak value of high-sensitivity cardiac troponin I (hs-Ct-I), a marker for myocardial injury, was the lowest. White blood cell count, neutrophil count, mean platelet volume (MPV), and high-sensitivity C-reactive protein (hs-CRP) were significantly lower than with the other 2 administration routes, and there was no effect on intracoronary pressure or heart rate.

Conclusions: Patients with ASTEMI who underwent emergency PCI treatment had good clinical outcomes using intracoronary diltiazem at the distal end of the culprit vessel.

MeSH Keywords: Diltiazem • Myocardial Infarction • Percutaneous Coronary Intervention

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Background

Percutaneous coronary intervention (PCI) is by far the most effective way to treat acute ST-elevation myocardial infarction (STEMI), which has been widely accepted [1]. PCI can quickly open an infarct-related artery (IRA) and restore forward blood flow of the coronary artery. However, the myocardial tissue reperfusion of nearly 40–50% of patients with acute myocardial infarction, despite opening of the IRA, is not complete, even without reperfusion [2–4], which leads to severe myocardial damage [5]. Additionally, it has become the biggest obstacle to achieving effective reperfusion. Through studying the mechanisms of no-reflow, some scientists believe that vasoconstriction is the most important factor, and, importantly, that it can be reversed [6]. For myocardial reperfusion injury in AMI-PCI, the current uses of drug or mechanical treatment after opening blood vessels are remedial. If the intervention can be applied before opening the IRA and restoring coronary flow, myocardial microcirculation in infarction-related regions can make adaptive responses to reperfusion and thus effectively reduce and prevent myocardial ischemia-reperfusion injury after IRA opening.

Clinical and basic studies have shown that calcium antagonists can attenuate coronary artery spasm (CAS) [7,8]. Calcium antagonists improve coronary blood flow through endothelium-dependent and non-endothelium-dependent relaxation. It also reduces myocardial oxygen consumption by changing inotropic effect, and then decreases free radical damage in the reperfusion. Intracoronary injection of diltiazem or verapamil, compared to nitroglycerin, is more effective in reversing no-reflow of direct PCI in patients with acute myocardial infarction [9]. Diltiazem and verapamil have similar effects except that diltiazem has greater vasodilator and weaker cardi-ac repression than verapamil [10]. Using the most appropriate route of administration is important for improving the therapeutic effect, but research on diltiazem is mostly focused on intravenous administration or simple intraoperative intracor-

Heart invasion diltiazem takes time to reach the coronary artery. In this process, the drug may be undergo metabolic inactivation, protein adsorption, and fluid dilution, resulting in decreased efficacy. With intraoperative intracoronary injection, the drug can achieve high concentrations in a short time. However, according to the guidelines, intracoronary injection is a method of administration in the coronary arteries, usually after angiography and before placing the stent. Patients can be admin-istered by a guide tube or a contrast catheter after the guide wire through the lesion or before balloon dilatation. However, at this time the level of TIMI blood flow is still 0, so the drug cannot easily directly reach the high concentration needed by the distal end of the culprit vessel. In order to achieve better reperfusion in the distal ischemic myocardium, we proposed an improved method of coronary injection. A thrombus aspi-ration catheter was used to perform diltiazem injection at the distal end of the IRA before thrombus aspiration, which maxi-mized drug entry into the small vascular bed, reduced thrombus fragments caused by PCI, and increased local drug con-centration in the microcirculation. The effect of our method was stronger and it can suppress the phenomena of no-reflow and reperfusion injury.

The purpose of this study was to investigate the optimal route of administration of diltiazem in emergency PCI and to pro-vide the best clinical treatment for STEMI patients. STEMI patients treated with direct PCI were selected to compare the effects of the improved intracoronary injection at the distal end of the culprit vessel, the conventional intravenous injec-tion, and to assess the effect of coronary mouth injection of diltiazem on acute PCI. We found that STEMI patients treated with the modified coronary injection method achieved good clinical results.

Material and Methods

Patients and grouping

We selected 90 patients with STEMI, including 54 males and 36 females, with an average age of 58.2±5.8 years. These patients were enrolled in our hospital from January 2015 to January 2016. This study was approved by the Ethics Committee of People’s Hospital of Hebei Province. Signed written informed consents were obtained from all participants before the study.

Inclusion criteria: In line with the diagnostic criteria of acute ST-segment elevation acute myocardial infarction in the Acute ST-Segment Elevation Myocardial Infarction Diagnosis and Treatment Guidelines developed in 2010 by the Chinese Medical Association Cardiology Branch: (1) Persistent ischemic chest pain that cannot be relieved by nitrates, with a duration of more than 30 min; (2) ST-segment elevation of 2 or more tho-racic leads adjacent (more than 0.2 mv), and/or ST-segment elevation of limb lead (more than 0.1 mv), or new complete left bundle branch conduction block, or acute myocardial in-farction hyperextension injury (ST-segment disappeared wave towering); and (3) With or without myocardial enzymes.

Exclusion criteria: (1) Cardiogenic shock, and systolic blood pressure was less than 90 mmHg and lasted more than 30 min, or need intravenous pressure drugs or intra-aortic balloon pump; (2) Severe sinus bradycardia, III degree atrioven-tricular block, and other malignant arrhythmias; (3) Renal insufficiency (creatinine >30 mg/L), and hemodialysis of chronic renal failure; (4) Recovery PCI after thrombolytic failure; (5)
Aspirin or clopidogrel contraindications; (6) Platelet count less than 100×10^10/L; (7) Bleeding history; (8) Major surgery within 6 months or easily bleeding in gastrointestinal tract, urinary tract, or reproductive tract; 9) Cerebrovascular events within 1 year; and (10) Informed consent cannot be provided.

The 90 patients were randomly divided into 3 groups, and each group contained 30 cases.

Group A (intravenous injection): Thirty minutes before surgery, diltiazem (Tianjin Tianyu Pharmaceutical Co. Tianjin, China) was continuously pumped into peripheral venous circulation at 3–5 μg/(kg-min) for 24–36 h.

Group B (coronary mouth administration): After placement of the guide catheter, intracoronary diltiazem 2 mg/4 mL was administered in a bolus dose of 500 μg per injection to a total of 2 mg, followed by intravenous infusion of 3–5 μg/(kg-min) for 24–36 h.

Group C (intraarterial administration at distal lesions): Prior to IRA (after the guide wire is passed, before the balloon is dilated, and when the anterior coronary artery has a blood flow), prophylactic IRA was bolus injections of diltiazem 2 mg/4 mL. 500 μg per injection to a total of 2 mg followed by intravenous infusion of 3–5 μg/(kg-min) for 24–36 h.

All patients were treated with radial arterial PCI before oral administration of aspirin 300 mg and clopidogrel 600 mg. After surgery, patients accepted long-term oral aspirin 100 mg, and oral clopidogrel 75 mg for at least 12 months.

**Coronary angiography and PCI treatment**

All patients underwent coronary angiography and PCI via radial artery. Seldinger’s puncture was performed and a 5F multifunctional contrast catheter was used for angiography. The 6F or 7F catheter was used for PCI. The fractional flow reserve (FFR) was measured after PCI to evaluate myocardial microcirculation. The guide catheter delivered the pressure guide wire to the target vessel so that the pressure guide wire sensor reached the distal end of the stent at 3–4 cm, and sustained, stable, and maximum congestive state was induced by injection of adenosine 140 μg/(kg-min). Then, the distal vessel mean pressure (Pd) and aorta mean pressure (Pa) were measured by pressure guidewire sensor and coronary guide catheter, respectively. The value of Pd/Pa was FFR.

At the same time, preoperative TIMI flow classification, postoperative TIMI flow classification, corrected TIMI flowmetry frame method (CTFC), and other data were recorded, and 2 of the cardiac interventional experts, who did not know the clinical trial program of the patients, reviewed the angiographic indexes.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MBP) in the coronary arteries were measured by invasive pressure catheter.

**ECG and echocardiography**

Electrocardiogram was measured as an indirect criterion for myocardial reperfusion. We performed 18-lead electrocardiograms (ECG) immediately after admission and 90 min after surgery. The raised ST-segment back to the extent of more than 70% at 90 min after PCI was considered to be a complete fall in ST segment (STR). ECG measurements were performed by 2 physicians who did not know the patient’s clinical program. Left ventricular ejection fraction (LVEF) was measured by echocardiography at 1 week postoperatively to assess cardiac changes.

**Laboratory tests**

The myocardial infarction marker hs-cTnI was measured before and 24 h after surgery to indirectly assess myocardial infarct size. White blood cell count, neutrophil count, mean platelet volume (MPV) and high-sensitivity C-reactive protein (hs-CRP) were used indirectly for evaluation of myocardial reperfusion.

**Clinical follow-up**

The occurrence of major adverse cardiac events (MACEs) was closely observed during hospitalization, and was obtained through outpatient visits or telephone follow-ups over the next 6 months. In outpatient or telephone follow-up, MACEs were defined as: (1) cardiac death; (2) recurrence of nonfatal myocardial infarction; and (3) target vessel revascularization (TVR). Among them, nonfatal myocardial infarction was defined as: relapsed ischemic chest pain for more than 30 min with new ST-T changes lasted more than 24 h or new pathology Q wave (at least 2-lead, more than 0.04 s) and serum acid kinase increased to more than twice the normal upper limit. TVR includes PCI or CABG repeated due to recurrent myocardial ischemia or acute stent occlusion.

**Statistical analysis**

The continuous variables are expressed as mean ± standard deviation (SD), and categorical variables are expressed as rate or percentage. Continuous variables were compared between groups using a completely randomized design analysis of variance, while the percentage differences between groups was assessed using the chi-square test. When the theoretical frequency was less than 5, the Fisher test was applied. If there were significant differences between groups, retrospective analysis was performed using the SNK q test. A bilateral P value less than 0.05 was considered as statistically significant. SPSS 18.0 statistical software (SPSS Inc., Chicago, IL, USA) used for statistical analysis.
Results

Comparison of general clinical data in patients

Of 105 acute inferior wall myocardial infarction (AIMI) patients, 15 patients were excluded due to incomplete data or the need for surgical intervention. Finally, 90 patients were included in the study. These patients were divided into 3 groups – A, B, and C – and each group contained 30 patients. Group A was aged 59.8±4.8 years and included 19 males; group B was aged 58.9±5.1 years and included 17 males; and group C was aged 57.6±4.7 years and including 18 males.

There were no significant differences between the 3 groups in terms of gender, age, past medical history (hypertension, diabetes mellitus, previous angina/myocardial infarction/PCI, or smoking history), or basic medication situation (P>0.05), and so they were comparable (Table 1).

Comparison of coronary angiography and direct PCI treatment

Among the 3 groups, IRA was mainly RCA, followed by LCX. The CTFC of group C was significantly lower than that of group A and group B. The mean FFRs of the 3 groups were all greater than 0.75, among which group A was 0.79, group B was 0.84, and group C was 0.91. Group C was significantly higher than groups A and B, while groups A and B had no difference. The percentage of complete STR at 90 min postoperatively showed the highest trend in group C, but the difference was not statistically significant (P>0.05) (Table 2). In addition, there was no significant difference in the pressure and heart rate between the 3 groups before and after PCI (Table 3, P>0.05).

Comparison of hs-cTnI and echocardiography

The levels of hs-cTnI peak and inflammatory cytokines (neutrophil percentage, neutrophil percentage, MPV, and hs-CRP) in group C were the lowest. LVEF in group C was the highest at 1 week after PCI. For hs-cTnI peak, inflammatory cytokines, and LVEF, there were significant difference between group C and groups A or B group (both P<0.05, Table 4).

Major cardiac adverse events (MACEs) occurrences

No MACEs were reported during hospitalization for any patients. However, at 6 months after discharge, MACEs were reported in each group, but there were no significant differences among the groups (P>0.05, Table 5).

Table 1. Comparison of the general data of the three groups.

|                | Group A (n=30) | Group B (n=30) | Group C (n=30) | F/x² | P(C/A) | P(C/B) | P(B/A) |
|----------------|---------------|---------------|---------------|------|--------|--------|--------|
| Age            | 59.8±4.8      | 58.9±5.1      | 57.6±4.7      | 2.971| 0.059  | 0.148  | 0.322  |
| Male           | 19 (63.3%)    | 17 (56.7%)    | 18 (60%)      | 0.135| 0.305  | 0.101  | 0.462  |
| BMI (kg/m²)    | 20.5±2.6      | 21.2±2.5      | 20.9±2.0      | 0.872| 0.078  | 0.061  | 0.200  |
| Hypertension   | 14 (46.7%)    | 16 (53.3%)    | 12 (40%)      | 0.526| 0.508  | 0.066  | 0.134  |
| Diabetes       | 9 (30%)       | 8 (26.7%)     | 6 (20%)       | 0.458| 0.472  | 0.723  | 0.493  |
| History of smoking | 18 (60%)  | 17 (56.6%)    | 16 (53.3%)    | 0.132| 0.592  | 0.458  | 0.831  |
| Family history | 7 (23.3%)     | 9 (30%)       | 6 (20%)       | 0.413| 0.633  | 0.118  | 0.174  |
| Past angina pectoris | 6 (20%)  | 5 (16.7%)     | 9 (30%)       | 0.823| 0.245  | 0.206  | 0.636  |
| Past MI        | 4 (13.3%)     | 4 (13.3%)     | 5 (16.7%)     | 0.092| 0.837  | 0.893  | 0.901  |
| Past PCI       | 3 (10%)       | 1 (3.3%)      | 3 (10%)       | 0.611| 0.501  | 0.079  | 0.263  |

Drugs

- **Aspirin**: 30 (100%) 30 (100%) 30 (100%)
- **Clopidogrel**: 30 (100%) 30 (100%) 30 (100%)
- **Statins**: 30 (100%) 30 (100%) 30 (100%)
- **ACEI/ARB**: 19 (63.3%) 21 (70%) 21 (70%)
- **Betaloc Zok**: 8 (26.7%) 9 (30%) 9 (30%)
- **Tirofiban**: 3 (10%) 5 (16.7%) 3 (10%)

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### Table 2. Comparison of three groups of coronary angiography and direct PCI treatment.

| Group | A (n=30) | B (n=30) | C (n=30) | F/x² | P(C/A) | P(C/B) | P(B/A) |
|-------|----------|----------|----------|------|--------|--------|--------|
| Time from Incidence to Intervention (h) | 6.8±1.5 | 7.2±1.6 | 7.3±1.5 | 2.781 | 0.209 | 0.807 | 0.330 |
| Doorball time (min) | 65.6±17.4 | 71.2±18.8 | 69.1±18.2 | 6.554 | 0.457 | 0.667 | 0.244 |
| IRA | | | | | | | |
| RCA | 21 (70%) | 18 (60%) | 19 (63.3%) | 0.332 | 0.583 | 0.791 | 0.417 |
| LCX | 9 (30%) | 11 (36.7%) | 11 (36.7%) | 0.192 | 0.584 | 1 | 0.584 |
| LAD | 0 (0%) | 1 (33.3%) | 0 (0%) | 1.000 | 1 | 0.313 | 0.313 |
| Number of implanted stents | 1.5±0.9 | 1.7±0.6 | 1.6±0.8 | 1.625 | 0.656 | 0.592 | 0.324 |
| TIMI3 level | 23 (76.7%) | 25 (83.3%) | 27 (90%) | 0.954 | 0.166 | 0.448 | 0.519 |
| CTFC | 29.5±3.8 | 28.4±3.6 | 24.9±2.8 | 2.984 | 0.000* | 0.000 | 0.262 |
| FFR | 0.79 | 0.84 | 0.91 | 3.248 | 0.000* | 0.000 | 0.067 |
| STR | 23 (76.7%) | 24 (80%) | 27 (90%) | 0.981 | 0.166 | 0.278 | 0.754 |

* Statistically significant differences between group C and group A or group B.

### Table 3. Comparison of intracoronary pressure and heart rate before and after PCI treatment.

| Group | A (n=30) | B (n=30) | C (n=30) | F/x² | P(C/A) | P(C/B) | P(B/A) |
|-------|----------|----------|----------|------|--------|--------|--------|
| SBP (mmHg) | 108.5±11.2 | 110.2±13.5 | 106.9±12.4 | 3.685 | 0.608 | 0.336 | 0.604 |
| DBP (mmHg) | 61.4±8.2 | 63.5±7.1 | 64.1±6.9 | 2.664 | 0.103 | 0.481 | 0.301 |
| MBP (mmHg) | 78.9±6.8 | 79.1±7.3 | 77.6±9.0 | 1.732 | 0.537 | 0.489 | 0.914 |
| HR (bpm) | 56.8±6.9 | 59.3±7.8 | 57.2±8.1 | 0.687 | 0.840 | 0.319 | 0.201 |

### Table 4. Comparison of the laboratory parameters and echocardiography between the three groups.

| Group | A (n=30) | B (n=30) | C (n=30) | F/x² | P(C/A) | P(C/B) |
|-------|----------|----------|----------|------|--------|--------|
| hs-cTnI (ng/mL) | 61.2±20.1 | 58.3±15.3 | 50.1±14.5 | 4.276 | 0.019* | 0.041* |
| LVEF (%) | 51.2±3.2 | 54.8±4.1 | 58.5±3.6 | 8.732 | 0.000* | 0.001* |
| hs-CRP (mg/L) | 27.4±8.2 | 24.5±5.5 | 21.3±6.8 | 1.218 | 0.003* | 0.048* |
| WBC(×10⁹/L) | 11.8±3.2 | 10.4±3.1 | 8.7±3.2 | 4.773 | 0.000* | 0.04* |
| Neutrophil percentage | 75.8% | 71.5% | 62.9% | 2.434 | 0.000* | 0.016* |
| Mean platelet volume (fl) | 11.2±1.7 | 10.5±0.9 | 9.1±1.1 | 25.63 | 0.000* | 0.000* |

* Statistically significant differences between group C and group A or group B.†
Table 5. MACEs occur within 6 months after discharge between the three groups.

| Group       | A (n=30) | B (n=30) | C (n=30) | F/x²  | P(C/A) | P(C/B) | P(B/A) |
|-------------|----------|----------|----------|-------|--------|--------|--------|
| Total       | 3 (10%)  | 2 (6.7%) | 1 (3.3%) | 0.52  | 0.300  | 0.554  | 0.640  |
| Death       | 1 (3.3%) | 0 (0.0%) | 0 (0.0%) |       |        |        |        |
| Recurrent MI| 1 (3.3%) | 1 (3.3%) | 1 (3.3%) |       |        |        |        |
| TVR         | 1 (3.3%) | 1 (3.3%) | 0 (0.0%) |       |        |        |        |

Discussion

Direct PCI treatment can open the infarct-related artery earlier, restore effective myocardial reperfusion, and reduce mortality. It is internationally recognized as the most effective way to treat AMI [11,12]. However, even with the coronary artery on heart-surface full reperfusion, myocardial microvascular damage is still possible with no re-flow phenomenon, which causes serious damage to the heart, affects ventricular remodeling, and eventually leads to ventricular dilatation and heart failure [13,14]. The incidence of no-reflow phenomenon in emergency PCI is significantly higher than that in elective PCI, by up to 25–40% [15]. The re-flow can seriously affect the treatment outcome of patients with AMI. Resnic et al. [16] show that mortality in AMI patients with no-reflow phenomenon was significantly higher than that of those with normal blood flow, which was also reported by Ito et al. [17]. Therefore, how to reduce the incidence of no-reflow in the emergency PCI treatment has become an important topic.

The mechanism of no-reflow is not clear. Many studies suggest that microvascular spasm caused by ischemia and reperfusion is the core cause of no-reflow. Ischemia and reperfusion injury directly promote endothelial cells to reduce NO and vasodilation, and enhances the vasoconstriction effect, and ATP-sensitive potassium channels (KATP) are inhibited by coronary artery spasm. Ischemia and reperfusion injury also can promote cardiac sympathetic nervous excitation, causing coronary artery microcirculation spasm. PCI causes thrombotic fragmentation, platelet degranulation, and the release of serotonin and thromboxane A2 and other vasoconstrictor factors, which lead to microvascular spasm. Additionally, inflammatory medium white blood cells, neutrophils, platelets, and high-sensitivity C-reactive protein [18] are immersed in the coronary microcirculation, releasing oxygen free radicals and many factors, and promoting microvascular sustained strong contraction, and finally result in no-reflow.

Diltiazem is a benzothiazole-like calcium antagonist that acts by inhibiting myocardial calcium influx, thereby inhibiting myocardial contractility and conduction and vascular smooth muscle contraction. Thus, the effect of calcium antagonists on no-reflow is to reduce microvascular resistance and improve the forward blood flow, as well as reducing the flow of calcium and reducing myocardial reperfusion injury.

This study used myocardial blood FFR as an important indicator of myocardial microcirculation during acute myocardial infarction PCI. FFR has been used in recent years to assess whether patients with coronary artery lesions need to be implanted, and its determination requires vasoactive drugs to achieve maximum myocardial perfusion state. The pressure in the distal end of the lesion (which in turn reflects the narrow distal resistance) is measured by the pressure guide, and the pressure in the aorta is measured by the guide catheter (which is actually equal to the perfusion available after opening the blood vessel). The ratio of these is the FFR, which is 1 under normal conditions. Studies [19] have suggested FFR less than 0.75 as a standard for myocardial ischemia, with 88% sensitivity and 100% specificity. Additionally, FFR is not affected by myocardial contractility, heart rate, blood pressure, or other changes in hemodynamic parameters. In this study, patients in the 3 groups were assessed immediately for FFR after direct PCI; their values were all greater than 0.75 and had completed myocardial reperfusion. However, the degree of myocardial reperfusion was different, with the best in group C. The best average FFR in C group was 0.91 and was significantly different from the other 2 groups (both P<0.05).

In this study, we found that the effect of intracoronary infusion of diltiazem at the distal end of the culprit vessel was significantly higher than that with conventional coronary arterial administration and intravenous injection. The number of TIMI frames immediately after PCI stent implantation, 90-min ST-segment drop rate, and LVEF after 1 week were significantly improved. In addition, the peak value of hs-cTnI was the lowest, and the white blood cell count, neutrophil count, MPV, and hs-CRP were significantly lower than those of the other 2 groups. There was no significant effect on intracoronary pressure or heart rate. We confirmed that the infusion of diltiazem at the distal end of the culprit vessel can move faster into the coronary microcirculation, and can relieve microcirculation spasm, dilate microcirculation, increase the blood flow of ischemic myocardium, and achieve effective reperfusion. Its effects were better than intravenous injection and...
coronary mouth administration. One of the possible reasons was that the drug was injected at the distal end of the culprit vessel, which increased the drug concentration in the area of myocardial reperfusion injury, allowed the drug to maximize the effect on the lesion area, and also could reduce the effects of drugs on other areas. Administration was started after the passage of the guide wire, before the balloon dilatation, and the coronary artery had a forward blood flow. Compared with the other 2 modes of administration, the improved method relieved coronary microcirculation spasm earlier, thus ensuring the drug effect on the lesion area.

There are some limitations of this study. First, this was a small and short study, so a multi-center, large-scale, and long-course follow-up is needed to observe the difference between complete

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STR and MACES. Further research is needed to determine the best method of modified coronary arterial injection of diltiazem in the perioperative period, as well as the most effective and safest dose of the drug.

Conclusions

Our study showed that patients with ASTEMI who underwent emergency PCI treatment had a good clinical outcome by using intracoronary diltiazem at the distal end of the culprit vessel.

Conflict of interest

None.