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Role of Combination Therapy on no-reflow after primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction.

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ABSTRACT

Background: No-reflow is a complex process with multiple pathogenetic components that may lead to major complications and higher mortality in patients with ST-segment elevation acute myocardial infarction (STEMI) after performing percutaneous coronary intervention (PCI).This study aims to evaluate the role of combination treatment in the prevention of occurrence of no-reflow and major cardiac adverse effects in patients with STEMI undergoing primary PCI.

Subjects and methods: This is an interventional study including 100 patients with STEMI who underwent emergency primary PCI and had a high risk of no-reflow (no-flow score ≥ 8), patient were randomly divided into a controlled group (n = 50) received conventional treatment, and a combination therapy group (n = 50) received high dose 80mg atorvastatin pre-intervention, platelet membrane glycoprotein IIb/IIIa receptor antagonist (tirofiban, 10μg/kg bolus followed by 0.15 μg/kg per minute) and thrombus aspiration. Six months follow up recording of major adverse cardiac events.

Results: No-reflow was detected in3/50 cases (2.8%) in the combination therapy group versus 38/50 cases (35.2%) in the control group. TIMI grade 3 was found in 46 patients (92%) versus in 32 patients (64%) p=0.008. While MBG ≤ 1 was (14/50) 28% vs (15/50) 30% p=0.18 in the combination therapy group versus control group respectively. MACE at six months 9 events (18%) in the combination therapy group, versus 19 events (38%) in the control group p= 0.03.

Conclusion: combination therapy with thrombus aspiration, high-dose statin and platelet membrane glycoprotein IIb/IIIa receptor antagonist prior to pPCI reduces the incidence of no-reflow, and major cardiac adverse events in patients with acute ST-elevation myocardial infarction.

Key words : Combination therapy; ST-elevation myocardial infarction; No-reflow; Percutaneous coronary intervention.

INTRODUCTION

ST-segment elevation acute myocardial infarction (STEMI) is considered suggestive of ongoing coronary artery acute occlusion in the following cases: at least two contiguous leads with ST-segment elevation ≥ 2.5 mm in men < 40 years, ≥2 mm in men ≥ 40 years, or ≥ 1.5 mm in women in leads V2–V3 and/or ≥ 1 mm in the other leads [in the absence of left ventricular (LV) hypertrophy or left bundle branch block LBBB)]. In patients with inferior MI, it is recommended to record right precordial leads (V3R and V4R) seeking ST-segment elevation, to identify concomitant right ventricular (RV) infarction. Likewise, ST-segment depression in leads V1–V3 suggests myocardial ischaemia, especially when the terminal T-wave is positive (ST-segment elevation equivalent), and confirmation by concomitant ST-segment elevation ≥ 0.5 mm recorded in leads V7–V9 should be considered as a means to identify posterior MI [1].

Primary PCI is the preferred reperfusion strategy in patients with STEMI within 12 h of symptom onset, provided it can be performed expeditiously (120 min from STEMI diagnosis) by an experienced team. However, in some circumstances, primary PCI is not an immediate option and fibrinolysis could be initiated expeditiously. If the reperfusion strategy is fibrinolysis, the goal is to inject the bolus of fibrinolytics within 10 min from STEMI diagnosis. To shorten time to treatment, fibrinolysis should be administered in the pre-hospital setting if possible [2,3].Patients should be transferred to a PCI-capable facility as soon as possible after bolus of lytics administration. Rescue PCI is indicated in the case of failed fibrinolysis or in the presence of haemodynamic or electrical instability, worsening ischaemia, or persistent chest pain, while a routine early PCI strategy is indicated after successful fibrinolysis[1].

During primary PCI number of patients fail to restore optimal myocardial reperfusion and develop no-reflow phenomenon[4]. As compared to similar patients who restore adequate reflow, patients with no-reflow have a higher incidence of death, myocardial infarction and heart failure[5].

No-reflow is a dynamic process with multiple factors involved in its pathogenesis such as; distal atherothrombotic plaques embolization, coronary spasm, oxidative stress, and susceptibility of coronary microcirculation to ischemic injury, these factors are causing suboptimal myocardial perfusion by endothelial and tissue edema leading to the occurrence of no reflow[4,6].The process of no-reflow is multifactorial, it requires the contribution of multiple therapeutic agents rather than a single one. The administration of statins at an experimental level before reperfusion therapy has shown a decrease in the presentation of no-reflow from 20-25 percent[7,8]. Previous trials have shown that chronic and pre elective PCI statin initiation had significantly reduced myocardial infarction and improved long-term outcomes[9]. From the various lipid lowering drugs, atorvastatin is a selective and competitive HMG-CoA reductase inhibitor[10]. The main indication for its use is the primary or mixed dyslipidemia of patients that cannot be controlled through dietary, exercise, and conventional weight control measures[11]. Beyond their lipid-lowering effects, statins have favorable effects on platelet adhesion[12], thrombosis, endothelial function, plaque stability and inflammation. These pleiotropic effects could contribute to the preservation of microvascular function during ischemia and reperfusion[13].

The current study was conducted to assess the role of combination therapy (the traditional therapy + high dose atorvastatin) on prevention of occurrence of no-reflow and major cardiac adverse effects in patients with STEMI undergoing primary PCI.

PCI PROCEDURE AND MEDICATION

This is an interventional clinical trial including 100 patients with acute chest pain caused by acute ST-elevation myocardial infarction were enrolled between 1/2019 and 1/2020 at Zagazig university Hospitals, Egypt. The criteria for inclusion were patients had for the first time acute STEMI of <24hours' from the onset of symptoms and at high risk for no-reflow (no-reflow score > or = 8) and treated with pPCI[14].STEMI was defined as chest pain for at least 30 min before hospital admission suggesting presence of myocardial ischemia, with serial changes on the electrocardiogram as; ST-elevation > 2 mmin ≥ 2 precordial leads, ST-elevation > 1 mm in ≥ 2 limb leads, or a new-onset left bundle branch block. An associated increase of at least one cardiac enzyme was also a confirmation of STEMI[15].

The criteria for exclusion included a previous history of myocardial infarction, atrial fibrillation, and frequent premature beats, mechanic complications, previous coronary artery bypass grafting (CABG), or lesion needed CABG, malignant tumor. Contraindication to statins liver or muscle disease, renal failure with serum creatinine >3. patients were divided into a controlled group received conventional treatment by, thrombus aspiration or treatment of IIb/IIIa receptor antagonists were based on the decision of treating physicians and a combination therapy group received high-dose(80 mg) atorvastatin pre-treatment, platelet membrane glycoprotein IIb/IIIa receptor antagonist (tirofiban, 10 μg/kg bolus followed by0.15 μg/kg per minute), and thrombus aspiration based on the decision of treating physicians. All patients received 40 mg atorvastatin daily for seven days followed by 20 mg daily for six months at follow-up post PCI. All patients gave their written informed consent before PCI treatment. The study followed the recommendations of the Declaration of Helsinki, 2008.

PCI procedure and medication

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The patients were pre-treated at the ER before primary PCI with chewable aspirin (300 mg) and clopidogrel (600-mg loading dose). Patients received Heparin intravenously as 50−70 IU/kg bolus with subsequent boluses to achieve an activated clotting time of200−250 s. pPCI, balloon pre dilatation and stent implantation, was performed only for IRA with TIMI flow grade ≤2.

Clinical data collection

All patients were subjected to complete history taking. Clinical examination including general, local cardiac examination. Laboratory investigations including: plasma glucose, white blood cell count, creatine kinase (CK), and cardiac troponins, were required to be obtained on admission.12 ECG leads and Echocardiography were done.

Endpoints

The primary end point was the presence of no-reflow determined by a TIMI flow ≤2 in the absence of severe coronary dissection, spasm, or significant residual stenosis, as well as the level of myocardial blush grade (MBG) ≤1 in an infarct-related artery (IRA)on final angiograms obtained at the completion of PCI [16].The secondary endpoints of this study are consisted of single or combined presentation of and major adverse cardiovascularevents (MACE) occurred during six months after PCI.MACE was defined as, non-fatal MI, heart failure, arrhythmias, cardiogenic shock, ischemia driven target vessel revascularization (TVR),and cardiovascular death.

Statistical analysis:

Analysis of data was done using Statistical Program for Social Science version 20. Quantitative variables were distribution or Mann Whitney test as a non-parametric alternative.

Qualitative variables were described as number and percent. Qualitative variables were compared using chi-square (X2) and Fisher exact test, as indicated. When a variable was not normally distributed, a P value < 0.05 is considered significant.

presented in the form of mean and standard deviation. Continuous variables were compared using Student's T test for independent groups was used in case of normal

RESULTS:

Regarding basic characteristic of studied groups age was matched in both groups 60.6 ± 6.04 years in combination therapy group versus 59.5 ± 5.3 in control group. Male /female was (36 /14) in combination therapy group and (38/12) in control group with no significant difference. The prevalence of risk factors (smoking, diabetes mellitus, hypertension, dyslipidaemia, and positive family history) showed no significant differences between both groups p<0.05. Systolic / diastolic blood pressure and mean pulse rate showed no statistically significant difference between both groups p<0.05 (Table 1). The result showed that the Ethanolic extract of CB at dose of 100 mg/kg and 200 mg/kg has a significant reduction in the carrageenan induced paw edema (P < 0.05) in a dose dependent manner when compared to control (Table 2 & Figure 2). The standard drug, indomethacin (10 mg/kg, i.p.) was more potent than the extract. The high dose of the extract (200 mg/kg) exhibited better anti-inflammatory activity than the low dose of the extract (100 mg/kg) as shown in Figure 2.

All laboratory data (Pre-CKMB, Peak CK-MB,serum creatinine,neutrophil count, RBS, AST, and ALT) and echocardiographic parameters (LVESD and EF)did not show statistically significant difference between both groups(Tables 2,3).

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Table 1: Basic characteristics of the studied groups.

		Combination therapy group N=50		Control group N=50		t-test	P
Age/years Mean ±SD		60.6 ± 6.04		59.5 ± 5.3		1.01	0.31 NS
		N	%	N	%	X^2	P value
Gender	Male	36	72	38	76	0.21	0.65
	Female	14	28	12	24		NS
Smoking		24	48	25	50	0.04	0.48 NS
DM		18	36	17	34	0.04	0.83 NS
Hypertension		28	56	32	64	0.67	0.41 NS
Dyslipidemia		20	40	24	48	0.65	0.42 NS
+ve Family history		6	12	7	14	0.09	0.77 NS
HR	Mean ±SD	98.2 ± 20.3		92.5 ± 20.4		1.16*	0.25 NS
SBP	Mean ±SD	129.2 ± 27.3		121.8 ± 32.6		1.23*	0.22 NS
DBP	Mean ±SD	82.7 ± 15.7		76.7 ± 18.1		1.77*	0.08 NS

Table 2: laboratory data among both studied groups.

	Combination therapy group N=50	Control group N=50	t-test MW*	P value
Pre-CKMB Mean ±SD Median (range)	113.5 ± 39.8 106 (59-212)	100.1 ± 32.1 94 (55-198)	1.57*	0.12 NS
Peak CK-MB Mean ±SD Median (range)	116.9 ± 50.3 102 (49 – 243)	107.8 ± 36.99 100 (49 – 273)	0.24*	0.81 NS
Serum Creatinine Mean ±SD Median (range)	1.19 ± 0.37 1.1 (0.5 – 2.1)	1.19 ± 0.41 1.1 (0.5 - 2.2)	0.09*	0.93 NS
Neutrophil count Mean ± SD Median (range)	7.57 ± 2.29 6.85 (3.7 – 12)	8.01 ± 2.12 8.5 (3.3–12)	1.001	0.319 NS
RBS Mean ± SD Median (range)	237.97 ± 57.4 300 (100 – 331)	252.9 ± 64.9 245 (107 – 405)	1.22	0.22 NS
AST Mean ± SD Median (range)	26.2 ± 7.4 23 (12 – 42)	28.6 ± 9.03 29 (10 – 49)	1.44	0.15 NS
ALT Mean ± SD Median (range)	22.5 ± 6.44 23 (12 – 37)	25.6 ± 10.14 28 (9-46)	1.71*	0.09 NS

NS: P-value>0.05 is not significant S: P-value<0.05 is significant *Mann-whitny test of non-parametric data

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Table 3: Echo-cardio graphic after 72 parameters among both studied groups.

	Combination therapy group N=50	Control group N=50	t-test\ MW*	P value
LVESD Mean ±SD Range	 56.6 ± 5.11 45 – 65	 57.4 ± 5.11 47 – 67	0.81	0.422 NS
EF \% Mean ± SD Range	 46.2 ± 6.25 30 – 59	 44.02 ± 7.49 28 – 62	1.59	0.11 NS

NS: P-value>0.05 is not significant S: P-value<0.05 is significant

The patients were enrolled in this study have been chosen according no-reflow score which was almost equally in both groups 8.56 ± 0.95 vs 8.57 ± 1.04p=0.96. Procedural findings showed no significant differences regarding the artery related to the infarction and number of vessels affected. There were also no significant differences between both groups regarding stenting diameter, length, number and type92 % of combination therapy group and 82% were treated with stents with mean stent diameter 3.17 ± 0.28 vs 3.23 ± 0.35mm P=0.39**(Tables 4,5).**

Table 4: Procedural data among both studied groups.

	Combination therapy group N=50	Control group N=50	X^2 t-test*	P value
Stent diameter Mean ±SD Median (Range)	 3.17 ± 0.28 3 (2.75 – 4)	 3.23 ± 0.35 3 (2.75 – 3.5)	0.86*	0.39 NS
Total stent length Mean ±SD Median (Range)	 34.98 ± 8.04 36 (18 - 48)	 32.2 ± 6.53 33 (18 – 48)	1.39*	0.07 NS
Infarct related artery LAD RCA LCX LM	 32 (64%) 16 (32%) 1 (2%) 1 (2%)	 34 (68%) 16 (32%) 0 (0.0%) 0 (0.0%)	2.06	0.56 NS
PTCA	0 (0.0%)	1 (2%)	Fisher	0.315 NS
Pre-stent	33 (66%)	26 (52%)	2.03	0.16 NS
Direct stenting	14 (28%)	15 (30%)	0.05	0.83 NS

HS: P-value<0.001 is high significant

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Table 5: Clinical data among both studied groups.

	Combination therapy group N=50	Control group N=50	X^2 MW*	P value
NF score Mean ±SD Median (Range)	 8.56 ± 0.95 8 (8 - 12)	 8.57 ± 1.04 8 (8 – 12)	t-test 0.06	 0.96 NS
Multiple vessel disease Single vessel disease	32 (64%) 18 (36%)	27 (54%) 23 (46%)	1.03	0.31 NS
Killip class n (%) 1 2 3 4	 28 (58.3%) 10 (20%) 3 (6.2%) 9 (18.8%)	 30 (60%) 8 (16%) 2 (4%) 10 (20%)	0.54	0.909 NS
TIMI after PCI 0 1 2 3	 0 (0.0%) 1 (2%) 3 (6%) 46 (92%)	 2 (4%) 3 (6%) 13 (26%) 32 (64%)	11.76	0.008 S
MBG 0 1 2 3	 8 (16%) 6 (12%) 13 (26%) 23 (46%)	 6 (12%) 9 (18%) 21 (42%) 14 (28%)	4.96	0.18 NS
Thrombus aspiration device	25 (50%)	13 (26%)	6.11	0.01 S
Tirofiban	30(60%)	12(24%)	13.3	<0.001 HS

HS: P-value<0.001 is high significant

concomitant treatment during interventional procedure showed statistically significant differences between groups as the use of glycoproteins IIb/IIIa inhibitors were in 30 patients(60%) in combination therapy group and 12 (24%) in the control group, p<0.001, thrombus aspiration devise used in 25 patients (50%) in combination group and 13 patients (26%) in control group p=0.01**(Table5)**.Primary endpoints TIMI flow score was significantly different between both groups TIMI grade 3 was found in 46 patients (92%) of combination therapy group and in 32 patients (64%) in standard therapy group p=0.008. While MBG showed no significant difference between groups p=0.18**(Table 5**).

Secondary endpoints MACE presentation at six months. There were 9 (18%) events in combination therapy group, which was significantly lower than 19 (38%) events in controlgroup p= 0.03; there were no deaths in both groups at six months follow up **(Table 6)**.

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Table 6: Complications among studied groups:

Complications	Combination therapy group N=50 N (%)	Control group N=50 N (%)	X^2	P
No complications	41 (82%)	31 (62%)	4.96	0.03 S
Ischemia driven MACE	1 (2%)	4 (8%)	Fisher	0.169 NS
Ischemia driven TVR	0 (0.0%)	1 (2%)	Fisher	0.32 NS
Major bleeding	1 (2%)	1 (2%)	------	------
Minor bleeding	3 (6%)	2 (4%)	Fisher	0.65 NS
Arrhythmia	2 (4%)	3 (6%)	Fisher	0.65 (NS)
Acute heart failure	2 (4%)	6 (12%)	Fisher	0.04 S
Urgent revascularization	0 (0.0)	1 (2%)	Fisher	0.32 NS
Recurrent angina	0 (0.0%)	1 (2%)	Fisher	0.32 NS
Mortality	0 (0%)	0 (0%)	---	---

DISCUSSION

No-reflow mainly refers to the event in which blood supply of the cardiac tissues cannot be normally restored after PCI despite coronary vessels recanaliza¬tion[17,18].

The pathogenetic mechanisms for its occurrence are still not clarified entirely, and currently, it is believed that no-reflow after PCI is related to micro-distal vascular embolization, ischemic injury and susceptibility to reperfusion injury. The no-reflow incidence is high, and for high risk patients is estimated as high as 40% or higher, which has serious impacts on patients' prognosis and life quality [19]. To avoids no-reflow after PCI, the treatment in the latest guidelines with the use of intracoronary injection of adenosine, sodium nitroprusside or other vasodilators during the PCI has currently a class IIb indication[20].

In the present study, we tested the effectiveness of combined therapy of thrombus aspiration, high-dose statin, and platelet membrane glycoprotein IIb/IIIa receptor antagonists in reducing the incidence of no-reflow after PCI and further reducing the incidence of MACE. There were no significant differences between study groups regarding the basic characteristics of participants such as; age, sex, risk factors, and clinical examination findings. These findings came in agreement with Garcia-Mendez et al.[17]; Kim et al.[21]; and Liu et al. [22]. Also, Zhou et al.[23]study characteristics were comparable in between groups except for DM which was more prevalent in combination therapy group. There was a male predominance (74%) in our study with respect to the whole study population in contrast to Liu et al. [22]who reported equal distribution of sex in the whole study population (50% each).

In our study, there were no statistically significant differences regarding all laboratory parameters in agreement with Garcia-Mendez et al.[17]. While in the study of Zhou et al.[23]there was a significant difference between combined therapy group and control group regarding serum glucose level and neutrophil count $p<0.05$.

Our study shows that there was no statistically significant difference among both studied groups regarding echocardiographic parameters (LVESD and EF)72 hours after pPCI. This was in agreement with Liu et al. [22] who reported that the left ventricular end-systolic diameter (LVESD) and LVEF were increased for the patients in the three groups after the treatment. However, the differences were not statistically significant among the groups. In contrast Zhou et al.[23] showed that significant improvement of LVEF three days after pPCI from 44 ± 6 % to 53 ± 8% $p<0.05$ also Zhou et al used Myocardial contrast echocardiography (MCE) was done 72 h after PCI in order to assess the myocardial perfusion which demonstrated better perfusion and heart function after treatment in combination therapy group than that of high risk control group.

The study included 621 patients with STEMI who underwent emergency pPCI. Patients with high risk of no-reflow were randomly divided into a controlled group (n = 108) and a combination therapy group (n = 108).Study results showed that the incidence of no-reflow was 38 cases (35.2%) of controlled group and 3 cases (2.8%) of combination therapy group. This is similar to the results of our study regarding the primary endpoint shown the incidence of no-reflow was significantly lower 4 cases (8%) in combination therapy group as compared with control group 18 cases (36%). TIMI flow grade 3 was 92% in combination therapy versus 64% in control group. While rate myocardial blush grade ≤ 1was matched in both groups. In addition Garcia-Mendez et al.[17] studied the effect of administration of a loading dose of 80 mg atorvastatin before

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primary PCI, and the results revealed Angiographic no-reflow was reported in 34 (63%) patients in standard treatment group and 13 (27%) patients in the group treated with high dose atorvastatin plus standard therapy prior to PCI. Liu et al. [22] study included 138 patients with STEMI randomly divided into 3 groups of 46 individuals each: control group in which patients were not treated with atorvastatin before PCI; a conventional dose atorvastatin treatment group in which patients received a single dose of 20 mg at bedtime one day prior to PCI; and a high-dose atorvastatin treatment group in which patients were treated with 40 mg divided in two doses the day before PCI. The results showed that the primary endpoint (TIMI grade ≤2, and MBG grade ≤1levels) were signifi¬cantly lower in combination therapy group than those in the conventional treatment group (P=0.01).they attributed these results due to the improvement of lipid levels in the patients and to the reduction in the VLDL after the operation, which can effectively prevent thrombosis under microcirculation after STEMI[22].

In 2013 a meta-analysis was done by Li et al.[24]to assess the effect of pre-procedural statin therapy on myocardial no-reflow following percutaneous coronary intervention. The analysis included 7 studies with 3086 patients, 1404 cases, and 1682 controls all trials defined no-reflow as TIMI flow grade ≤2. The meta-analysis demonstrated mean 4.2% absolute reduction of risk of no-reflow after PCI in all patients, including 3.3% in STEMI cases, 5.0% in non-STEMI cases, and 5.9% in patients treated with intensive statin. The study concluded that treatment with intensive statin prior to PCI results in significant reduction of the risk of post-intervention no-reflow phenomenon and the routine administration of statins before PCI should be recommended[24].

In our study six months follow up showed a marked significant reduction of incidence of MACE in the combination therapy group (18%) than the standard control group (38%) this rate was higher than results reported by Zhou et al.[23]Six months clinical follow-up was obtained in 552 patients, there were 6(6.3%) events (one death, two non-fatal MIs and three revascularizations)in the combination therapy group, significantly lower than 12 (13.2%) events (four deaths, three non-fatal MIs and five revascularizations) in the control group.

Liu et al. [22] showed that during the one-year follow-up the complications and adverse outcomes, such as; death, occurrence of re-stenosis, , non fatal myocardial infarction, and cardiogenic shock in the high-dose atorvastatin (80mg) group were significantly lower compared with those in the conventional-dose atorvastatin or the control group. Results of the ARMYDA- RECAPTURE trial revealed that early pre-procedural treatment with high-dose atorvastatin load has a good outcome in patients already onchronic statin therapy. Particularly, results showed that giving a bolus of 80mg atorvastatin 12 hs before PCI and followed by an extra 40 mg pre-procedural dose was associated with a reduction of 50% of the relative risk of MACE at 30 days versus placebo[25].

In the present study, thrombus aspiration was an important part of interventions during PCI. It was used in 25 patients (50%) of the combination therapy group and 13 patients (26%) in the control group. The role of a simple manual aspiration was assessed by the REMEDIA trial,[26]which was a randomized trial to compare thrombectomy, with conventional pPCI. The results of this trial showed that manual thrombectomy was safe and more efficient in restoration of myocardial perfusion as compared with standard pPCI. Furthermore, a sub-study of the same trial demonstrated reduction of incidence of no-reflow in the MCE after intervention[27].

platelet membrane glycoprotein IIb/IIIa receptor antagonists use in the setting of STEMIis a Class II indication in the current 2011 PCI guidelines[28].In our trial glycoprotein IIb/IIIa receptor antagonist was used in 30(60%) of patients in the combined therapy group while it was administered to 12 patients (24%) in the control group. Large scaled clinical researches have proven the preventive effects of platelet membrane glycoprotein IIb/IIIa receptor antagonists on the no-reflow events after AMI[29].

CONCLUSION:

This study suggests that combination therapy with of thrombus aspiration, high-dose statin, and platelet membrane glycoprotein IIb/IIIa receptor antagonist prior to pPCI reduces the incidence of no-reflow and major cardiac adverse events in patients with acute ST-elevation myocardial infarction with a high risk of no-reflow after pPCI.

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