European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 08, Issue 03, 2021

Role of Combination therapy on no-reflow after primarypercutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction

Kamal S. Mansor, Tarek A. Naguib, Tamer M. Mostafa, Mohamed M. Moukhtar

Department of Cardiology, Faculty of Medicine, Zagazig University

Abstract

Background: Primary percutaneous coronary intervention (PCI) has been shown to be the most effective reperfusion strategy in the treatment of acute myocardial infarction (AMI).

Aim of the Work:To investigate the association the effectiveness of a combination therapy (pretreatment with high dose atorvastatin and Intra Coronary tirofiban) for the prevention of no-reflow in patient with acute STEMI will undergo primary PCI.

Patients and Methods: This study enrolled 100 patients admitted with first acute STEMI and at high clinical risk for no Reflow. High risk patients (no-reflow score ≥ 8) were randomly divided into a controlled group A (50 patients) received conventional treatment and a combination therapy group B(50 patients) received combination treatment (atorvastatin 80 mg and IC tirofiban).The patient was considered to exhibit a no-reflow phenomenon if blood flow in the IRA was a TIMI≤2 flow despite successful dilatation and absence of mechanical complications such as dissection, spasm or angiographically evident distal embolization after completion of the procedure.

Results: The rate of no-reflow was significantly lower in combination therapy group (10 %) compared to control group (36%).Regarding Indirect perfusion outcome: We found that percent of ST resolution and peak CKMB were significantly higher in combination therapy compared to control group (P value = 0.013 – 0.001 respectively).Ejection fraction tend to be higher in the combination therapy group but not statistically significant (P>0.05).Regarding in hospital complication and 30 days MACE; we found that heart failure symptoms were significantly lower in combination group therapy during in hospital stay and at 30 days follow up (3% and 2% respectively). The composite end point of 30 days MACE occur only in 3% in combination therapy group while 10 % in control group (P =0.033). using Kaplan Meier curve for free survival MACE at 30 days there were also significant different regarding free event rate for MACE, log rank =4.737, P =0.030. We also observed that high thrombotic burden (thrombus grade ≥ 4) was independent predictor for angiographic no reflow (p =0.012), and the use of combination therapy were strongly independent predictors for prevention of no reflow (p =0.002) with relative Risk reduction 72.2% and absolute risk reduction = 26%.

Conclusion: Combination of pre-procedure high dose atorvastatin and IC bolus tirofiban can effectively reduce the incidence of no-reflow after primary PCI in patients with acute myocardial infarction who are at high risk of no-reflow.Large thrombus load is independent predictor of angiographic no reflow after primary PCI. However, this combination therapy is strong independent predictors for prevention of angiographic no-reflow.

Key words: Combination therapy, no-reflow primary percutaneous coronary intervention, acute ST-segment elevation myocardial infarction

Introduction

Primary percutaneous coronary intervention (PCI) has been shown to be the most effective reperfusion strategy in the treatment of acute myocardial infarction (AMI) **(1).**Brisk Thrombolysis in Myocardial Infarction (TIMI) grade-3 flow immediately after PCI in AMI is related to improved clinical outcomes **(2).**

However, a sizable number of patients fail to restore optimal myocardial reperfusion, mostly because of no-reflow (NRF) phenomenon **(3).**

No-reflow phenomenon is defined as suboptimal myocardial perfusion through a part of coronary circulation without angiographic evidence of mechanical vessel obstruction, and also considered a dynamic process characterized by multiple pathogenetic components including distal atherothrombotic embolization, ischemic injury, reperfusion injury, and susceptibility of coronary microcirculation to injury, and current ways of treatment are limited**(4).**

This phenomenon has been documented in more than 30% of AMI patients after thrombolysis or primary mechanical intervention **(5).**

Also, in patients with ST-segment elevation myocardial infarction (STEMI) treated by primary PCI, the NRF phenomenon is a strong predictor of both short-term and long-term mortality **(6).** Compared with those with adequate reflow, patients with NRF phenomenon tend to have higher incidences of death, myocardial infarction, and heart failure **(7).**

To date, no medication has been shown to reverse established no reflow. Thus, prevention strategies of no-reflow used before reperfusion may berather important **(8).** Clinical prediction models have been extensively used in clinical practice to identify patients at high risk who may benefit from specific interventions **(9-10).**

Depending on risk prediction scoremodel of no-reflow in previous studies in which we were able to find out patient at high risk for no reflow **(11).**

We aimed at this work to investigate the effectiveness of a combination therapy (pretreatment with high dose statins and IC tirofiban) for the prevention of no-reflow in patient presented with acute STEMI who will undergo primary PCI.

Patients and Methods

Study population:

This study was carried out in cardiology department,Zagazig University and National heart institute from May 2018 to December 2019. During this period, emergency cardiac catheterization was performed to 100patientsadmitted with first acute STEMI and are at high clinical risk for no Reflow. Informed consent was obtained from every patient on participation in the study.

The study included patients who had for the first time acute STEMI of < 24hours' from onset of chest pain and at high risk for no reflow (no reflow score ≥8 according toclinical prediction score, and treated with primary PCI.

STEMI was defined as chest pain suggestive of myocardial ischemia for at least 30 min before hospital admission, with a new, or presumed new ST segment elevation in 2 or more contiguous leads of at least 2mm at the J point in leads V2-V3 or 1mm in all other leads, or those with new or presumably new LBBB.

Patients with previous history of myocardial infarction, previous PCI, previous coronary artery bypass grafting (CABG) or lesion needed CABG, malignant tumour, contraindication to statins (liver or muscle disease), renal failure (serum creatinine > 3 mg/dl), low risk prediction score for no reflow and patients with contraindication toThienopyridines and acetylsalicylic acid were excluded from the study.

Study protocol

Before PCI procedure, study patients were assessed for their clinical risk of no-reflow by using a **Wang et al., 2013 prediction model**. High risk patients (no-reflow score ≥ 8) were randomly divided into a controlled group**A** and a combination therapy group **B**.

Group A:included 50 patient whoreceived conventional treatment.Using ofthrombus aspiration or/and treatment by intracoronary (tirofiban, 25 μg/kg bolus followed by 0.15 μg/kg per minute)were be left for the treating physicians' decision.

Group B:included 50 patientswhoreceivedhigh-dose (80 mg) atorvastatinpre-treatment on admission at the emergency department, intracoronary tirofiban (25μg/kg bolus followed by 0.15 μg/kg per minute). Using thrombus aspiration will be based on the treating physicians' decision.

All patients were subjected to all of the following:

A) Full history taking:

- **Evaluation of the patients for the following risk factors:**

Sex, age, hypertension, diabetes mellitus, dyslipidemia, smoking status, positive family history, drug intake history specially beta blockers, and onset of chest pain to hospital admission

B) Clinical Examination

- Blood pressure.
- Heartrate andrhythm
- Chest examination
- cardiac examination

- Patients who had developed heart failure were classified regarding KILLIP class as: (**Nesković et al.(5**)
  - **Class I:** Absence of rales over the lung fields and absence of S3.
  - **Class II:** Rales over 50% or less of the lung fields or the presence of an S3.
  - **Class III:** Rales over more than 50% of the lung fields (pulmonary edema).
  - **Class IV:** Carcinogenic shock or hypotension (systolic blood pressure < 90 mmHg), and evidence of low cardiac output(oliguria, sweating or impaired mental status).

C) Electrocardiogram:

- A 12-lead ECG was performed at ER before the intervention, 1 h post-intervention at a paper speed of 25 mm/second and amplification of 10 mm/mv, then daily during the hospital stay and whenever indicated

- ECG was analyzed for: ST segment elevation, number of leads with ST elevation and sum of ST segment elevation. Development of tachyarrhythmia or bradyarrhythmiaduring course of admission was reported for every patient

- STEMI was diagnosed according to the following: New ST segment elevation at J-point in ≥ 2 contiguous leads of≥ 1 mm in leads V2 andV3 and ≥ 1 mm in all other leads. ST-segment depression ≥ 1mm in leads V1 to V3, consistent with a posterior STEMI, was considered as ST-segment elevation. **(12)**,sum of ST segment elevation, measured 20 ms after the J point. The height (in mm) of ST segment elevations was measured in leads I, aVL, and V1 through V6 for anterior infarction; leads II, III, aVF for inferior infarction and leads V5 to V6 for lateral**(13).**

ST-segment resolution (STR): ST-segment resolution was calculated as the sum of ST-segment elevation on the initial ECG minus the sum ofST-segment elevation on the ECG at 60 min post-PCI, divided by the sum of ST-segment elevation on the initial ECG and expressed as a percentage **(13).**

- ST-segment resolution was classified as complete (if the resolution was more than 70%), partial (if the resolution was between 30% and 70%), or absent (if the resolution was less than 30%) **(13).**

5- Echocardiography:

- LVEF was measured using modified Simpson's method.
- Recordings and calculations of different parameters were performed according to the recommendations of the American Society of Echocardiography **(14)**
- Examinations were done with the patient in left lateral position; utilizing left parasternal long axis, short axis, apical 4, apical 5 and apical 2 chamber views. The main outcome was calculation of ejection fraction (EF) using 2D measurements of volumes, the biplane Simpson's method. Both left ventricle end diastolic (LVED) and end systolic (LVES) volumes in apical four chamber (A4C) and apical two chamber (A2C) views were measured. End-systole was defined as the frame with the smallest cavity area and end diastole as the frame with the largest LV cavity area (Figure 15) The EF was then calculated using the following formula for each view:

  EF (%) = [(EDV - ESV) / EDV] x 100 **(14)**

- The mean of the two readings (the biplane) ejection fraction was then taken. The cutoff point of 50% was chosen before the analysis; 50% represents a clinically meaningful delineation between LV dysfunction (or normal LV function). (**15)**

E) Laboratory investigations:

- **Routine Labs:** Complete blood count with defferential, random blood sugar, urea, creatinine and liver enzymes were withdrawn on admission. Kidney function test (urea,creatinine) were daily withdrawn during admission.
- **Serial cardiac enzymes:** Creatine phosphokinase (CPK) and CKMB Cardiac enzymes were withdrawn on presentation

- (CKMB) level was checked every 8 h for 48 h after primary PCI, Peak CKMB was defined as the highest serum concentration with in the first 48 h. Considered elevated if more than 25ng/ml **(16).**

1. Primary Percutanous Coronary Intervention Procedureandmedication

All patients transferred directly to cath lab on emergency basis in accordance with guidelines. Coronary angiography was done after local infiltration anesthesia by lignocaine, the common femoral artery or the radial artery was punctured using seldinger's technique. A 6-F right and leftJudkin diagnostic catheterswereused for diagnosisandaccording to the angiographic findings, guiding catheters were chosenfor the primary PCI procedure

- All patients were loaded at the ER before primary PCI with aspirin (300 mg) and clopidogrel (600-mg loading dose).
- Pretreatment with high dose atorvastatin 80 mg was administrated early on admission at emergency department for the combination therapy group (B). Then given as 40 mg for all patients in the study after Primary PCI.
- Heparin was adjusted as follows:IVbolus of 70-100 IU/kg (maximum 10,000 U), while patient assigned to tirofiban received 50 to 70 IU/kg (maximum 7,000 U).
- Intracoronary Glycoprotein IIB/IIIA inhibitors, tirofiban, 25 μg/kg bolus followed by 0.15 μg/kg per minute for 18 h is given for all patients in combination therapy group and Bailout in control group.
- Using Thrombus aspiration device was based on the treating physicians' decision.
- The operator determined the size and length of the stent. Drug eluting stents were used in all patients.

The angiographic analysis include: identification of the Infract Related Artery (IRA), initial and final TIMI flow grades, door to balloon time, thrombus burden grade, number of stents used,total stent length and diameter were recorded.

The patient was considered to exhibit a no-reflow phenomenon if blood flow in the IRA was a TIMI≤2 flow despite successful dilatation and absence of mechanical complications such as dissection, spasm or angiographically evident distal embolization after completion of the procedure. **(17)**Visual assessmentof no-reflow was made by two experienced interventional cardiologists blinded to the randomization.

Follow up:

Follow up of the patients was done during the hospital stay and 30 days after discharge for the following:

A) During the hospital stay:

- In hospital mortality
- Heart failure (HF): Based on symptoms and signs of heart failure detected during clinical examination of the patients
- Arrhythmia:fatal ventricular arrhythmia (VT & VF) and Brady-arrhythmia (high grade AV nodal block)

- Re-infarction: should be considered when ST elevation ≥0.1 mV recurs, or new pathognomonic Q waves appear, in at least two contiguous leads, particularly when associated with ischemic symptoms for 20 min or longer**(20)**and re-elevation of creatine kinase or creatine kinase-MB by at least 50% above the trough level after documentation that the level was decreasing prior to this re-elevation**(21)**
- Stroke
- Target lesion revascularization
- Major and minor bleeding: Major bleeding was defined as an intracranial bleeding or clinically significant overt signs of hemorrhage associated with a decrease of more than 5 g/dL in Hemoglobin or, when hemoglobin was not available, an absolute decrease of at least 15% in hematocrit. **(22)**

B) Follow up after 30 days:

Follow up for each patient was done 30 days after hospital discharge for detection of:

- Heart failure
- myocardial infarction
- Death
- Target lesion revascularization

Major adverse cardiac event (MACE); was defined as cardiac death, MI, development HF and target lesion revascularization (TLR).

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 25.0 for windows (SPSS Inc., Chicago, IL, USA) and NCSS 12.0 for windows (NCSS LCC., Kaysville, UT, USA).

Quantitative data of normal distribution were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

Results

The current study involved 100 patients, 74 % were male and 26 % were female. The mean age of the study population was 60.1 ± 5.7. 60% of study population were hypertensive, 50 % were diabetic, 49 % were smoker, 44% had history of dyslipidemia and 13 % had positive family history for coronary artery disease. 30 % of the patients were on regular statins, 35% on ACEI or ARBs, 66% on aspirin and 20 % on previous BB.**(Table 1).**

In our study population, 23 patient (23%) developed angiographic no-reflow. The incidence of no-reflow was significant lower in combination therapy (group B) compared with control group A, (5 patients, 10% in group B vs. 18 patients, 36% in group A with P value = 0.002) **(Figure 1).**

73 % of the study population showed complete STR > 70%, the percentage of STR in combination group B (42 patients, 84%) was significant higher than control group A (31 patients, 62%) and p value =0.013, Mean and SD of peak CK- MB in combination therapy group was (133.4 ± 61.3) and significant higher than control (101.0 ± 25.2) with p value = 0.001 **(Table 2).**

Myocardial function was assessed by transthoracic echocardiography day 3 post infarction. Mean LVEF in combination therapy group B was (44.2± 6.2) while in control group A was (43.9 ± 7.4), Ejection fraction tend to be higher in the combination therapy group but not statistically significant (P>0.05). There was no significant difference regarding end diastolic and end systolic volume **(Table 3).**

Regarding inhospital complication :Re- infarction was reported in 1% of all patients (2% versus 0% of group A, B respectively, P=1.000)**Brady-arrhythmia** (high grade AV nodal block) was evident in 3 % in all patients (0 % versus 6 % of group A, B respectively, P=0.242), also ventricular arrhythmia was reported in 3% of all patients (4% versus 2% in group A, B respectively, P=1.000), **Minor bleeding** occurred in 6 % of all patients (4% versus 8% in group A, B respectively, P=0.678)**Major** bleeding occurred in 2 % of all patients (2 % versus 2% in group A, B respectively, P=1.000). **Heart failure** occurred in 13% of all patients and with significant lower incidence of HF in combination therapy group (20 % versus 6 % in group A, B respectively, P=0.037). **Urgent target lesion revascularization** was reported in 1 % of all patients (2% versus 0% of group A, B respectively, P=1.000)**Incidence of death** was 3% of all patients (4% versus 2% in group A, B respectively, P=1.000). **Stroke** was no occurred in both groups. These results were shown in **table 4 Regarding 30 days MACE**of 97 patient of all study population,**Re-infarction**: occurred in 2 patients of the study population (2.1 %), (2 patients 4.2 % in group A and 0 % in group B and no statistical significance, P 0.242). **Heart Failure:** occurred in 10 patients of the study population (10.3 %), (8 patients, 16.7% in group A and 2 patients, 4.1 % in group B and statistical significance, P 0.042. **Target lesion Revascularization (TLR):** one patients of whole study population (1 patient, 2.1 % in group A and 0 % in group B with no statistical significance, P = 0.495.**Death:** total mortality was 2.1 % (1 patient, 2.1 % in group A and 1 patient, 2.0 % in group B with no statistical significance, P = 1.000 **Stroke:** no stroke cases presented in all patients. **Composite endpoint**: total composite endpoint of MACE occurred in 13 patients of all patients, 13.4 % (10 patients, 20.8 % in group A and 3 patients, 6.1 % in group B with statistical significance P= 0.033. **Figure (2)**

Table (1): Demographic data of the whole study population.

Demographic data	All patients
Count (%)	100 (100%)
Age (years)	
Mean ± SD	60.1 ± 5.7
Risk factors	
Male gender	74 (74%)
HTN	60 (60%)
DM	50 (50%)
Smoking	49 (49%)
Dyslipidemia	44 (44%)
Family history	13 (13%)
Drug history	
Statins	30 (30%)
ACEIs	35 (35%)
Aspirin	66 (66%)
Beta blockers	20 (20%)

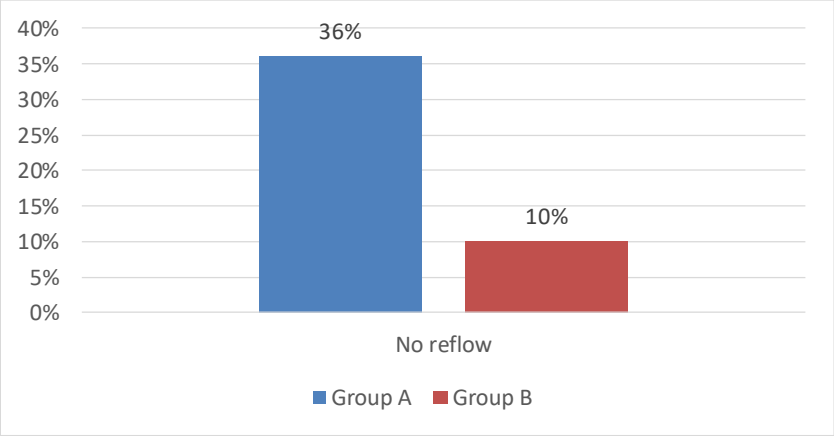

Figure (1): Incidence of No reflew in both groups

Table (2): Comparison of STR in the study population and CKMB

ECG outcome	Total	Group A	Group B	P-value (Sig.)
Count	100	50	50	
ST resolution > 70 %	73 (73%)	31 (62%)	42 (84%)	0.013(S)

Peak CK-MB	Total	Group A	Group B	P-value (Sig.)
Count	100	50	50	
Mean ± SD	117.2 ± 49.4	101.0 ± 25.2	133.4 ± 61.3	0.001(S)

Table (3): Comparison between the studied groups regarding the echocardiographic data.

Echocardiographic data	Group A	Group B	P-value (Sig.)
Count	50	50	
EDV (mL)			
Mean ± SD	115.5 ± 17.5	109.3 ± 14.2	0.063(NS)
ESV (mL)			
Mean ± SD	64.8 ± 13.3	60.7 ± 11.7	0.106(NS)
EF (%)			
Mean ± SD	43.9 ± 7.4	44.2 ± 6.2	0.526(NS)

Table (4): Comparison between the studied groups regarding in-hospital complication.

in hospital complication	All patients	Group A	Group B	P-value (Sig.)
Count	100	50	50	
In hospital complication				
Re-infarction	1 (1%)	1 (2%)	0 (0%)	1.000 (NS)
Brady-arrhythmia	3 (3%)	0 (0%)	3 (6%)	0.242 (NS)
Ventricular Arrhythmia	3 (3%)	2 (4%)	1 (2%)	1.000 (NS)
Major bleeding	2 (2%)	1 (2%)	1 (2%)	1.000 (NS)
Minor bleeding	6 (6%)	2 (4%)	4 (8%)	0.678 (NS)
HF	13 (13%)	10 (20%)	3 (6%)	0.037 (S)
Urgent	1 (1%)	1 (2%)	0 (0%)	1.000 (NS)

Revascularization				
Death	3 (3%)	2 (4%)	1 (2%)	1.000 (NS)
Stroke	0	0 (0%)	0 (0%)	1.000 (NS)

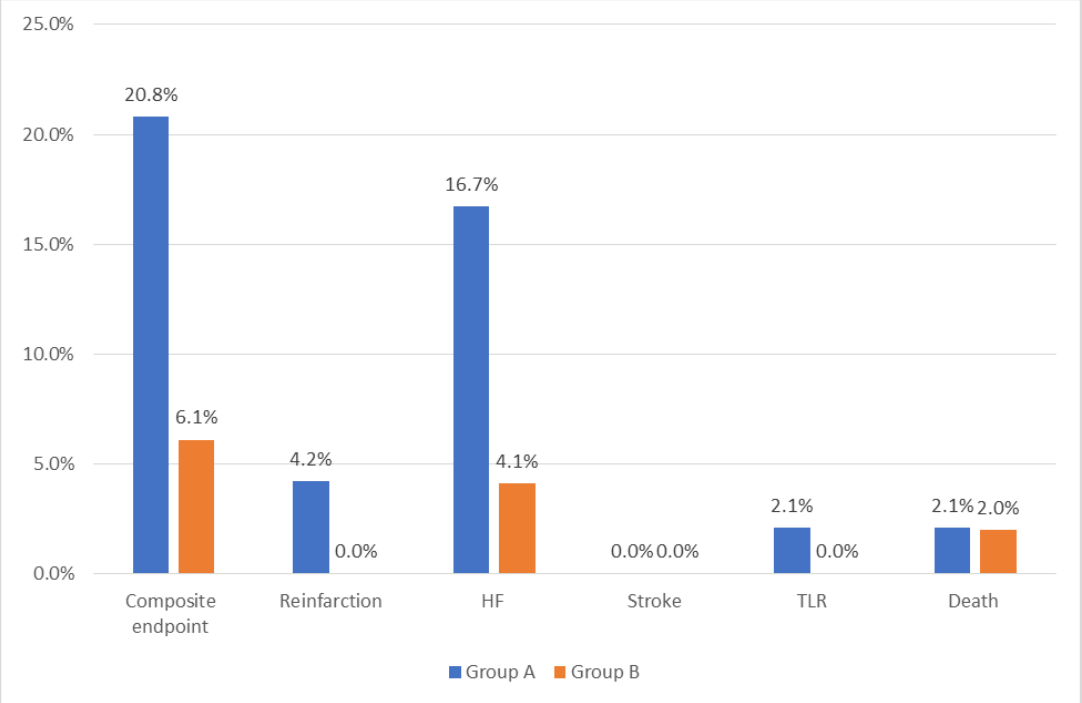

Figure (2): Comparison between the studied groups regarding 30 days MACE

Univariate regression analysis was done in order to identify factors correlated with incidence of no-reflow in our study population.Thrombus burden ≥ 4, thrombus aspiration and combination therapy (atorvastatin 80 mg and IC high dose tirofiban) were significantly associated with the incidence of no-reflow.

- **High thrombus burden** (grade ≥ 4): significantly associated with increased incidence of no reflow: odds ratio (OR): 3.770, 95% confidence interval (CI): 1.7- 6.1 and P= 0.041
- **Thrombus aspiration device:** significantly associated with lower incidence of no re-flow: odds ratio (OR): 0.415, 95% confidence interval (CI): 0.16- 0.85 and P = 0.034
- **Combination therapy:** significantlyassociated with lower incidence of no re-flow:odds ratio (OR): 0.19, 95% confidence interval (CI): 0.06- 0.58 and P = 0.004**(Table 5)**

Multivariate regression analysis: was done to identify independent predictors of no re-flow in our study.**High thrombus load ≥ grade4** was independent predictor for increased incidence of no-re-flow (odds ratio (OR): 2.67, 95% confidence interval (CI): 1.6- 8.9 and P = 0.014) while **combined therapy of (high dose statins and IC Tirofiban)**is independent predictors for prevention of no-reflow (odds ratio (OR): 0.17, 95% confidence interval (CI): 0.05- 0.53 and P = 0.002) **(Table 6)**

The combination therapy when added to conventional primary PCI associated with **Relative risk Reduction** of 72.2 % for angiographic no-reflow in respect to conventional PCI alone as in control group A and **absolute Risk Reduction** 26 % for angiographic no-reflow. **Risk Ratio** was 3.6, which mean 4 patient treatment with combination therapy proposed to prevent one case of angiographic no-reflow

Table (5): Univariate regression analysis for incidence of no reflow.

Variable	95% Confidence Interval for OR			P-value (Sig.)
	Unadjusted OR	Lower Bound	Upper Bound	
Age	0.986	0.907	1.071	0.733
Male gender	0.749	0.268	2.094	0.581
HTN	1.714	0.633	4.643	0.289
DM	1.405	0.550	3.590	0.477
Smoking	0.941	0.370	2.390	0.898
Dyslipidemia	0.607	0.231	1.599	0.313
Family history	0.246	0.030	2.004	0.190
Chest pain duration (hour)	1.205	1.205	1.205	0.803
Sum of ST segment elevation	1.038	0.945	1.141	0.432
Killip class > 1	2.152	0.837	5.533	0.112
RBG (mg/dL)	1.003	0.997	1.010	0.356
Neutrophil count (*1000/mm^3)	0.830	0.675	1.021	0.782
MVD	0.440	0.171	1.132	0.089
Initial TIMI (0, 1)	1.859	0.212	16.289	0.575
DTB time (min)	1.013	0.989	1.037	0.287
More than one stent	0.091	0.008	1.077	0.057
Total stent length (mm)	0.986	0.943	1.031	0.532
Thrombus grade ≥ 4	3.770	1.722	6.109	0.041
Thrombus aspiration	0.415	0.161	0.855	0.034
Pre-dilatation	1.962	0.733	5.253	0.180
Combination therapy	0.198	0.066	0.587	0.004

Table (6): Multivariate regression analysis:independent predictors of no-reflow.

Variable	Adjusted OR	95% Confidence Interval for OR		P-value (Sig.)
		Lower Bound	Upper Bound	
Thrombus grade ≥ 4	2.675	1.658	8.941	0.014
Thrombus aspiration	0.769	0.595	2.263	0.305
Combination therapy	0.173	0.056	0.534	0.002

Kaplan Meier curve in relation to the free event survival rate for MACE to 30 days. Combination treatment when added to conventional PCI, there were significant different regarding free event rate for MACE compared with conventional PCI alone, log rank =4.737, P =0.03 **(Figure 3)**

In subgroup analysis according to the use of thrombus aspiration in each group, we found that thrombus aspiration was not associated with further impact on incidence of no-reflow, in hospital outcome and short term MACE when added to combination therapy and conventional therapy patients.

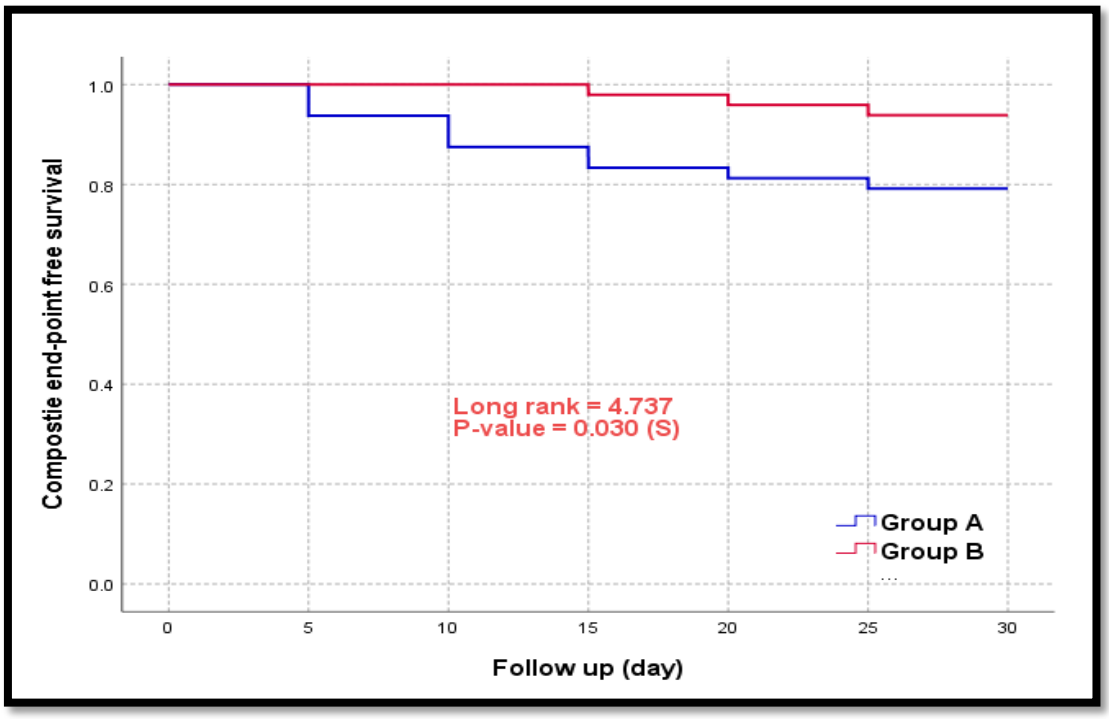

Figure (3):Kaplan Meier MACE free survival curve at 30 days

Discussion

Immediately after PCI in AMI is related to improved clinical outcomes.However, a sizable number of patients fail to restore optimal myocardial reperfusion, mostly because of no-reflow (NRF) phenomenon **(1)**.

No-reflow phenomenon is defined as sub-optimal myocardial reperfusion through a part of coronary circulation without angiographic evidence of mechanical vessel obstruction. This phenomenon has been documented in >30% of AMI patients after thrombolysis or primary mechanical intervention. **(23)**

Also, in patients with ST-segment elevation myocardial infarction (STEMI) treated by primary PCI, the NRF phenomenon is a strong predictor of both short-term and long-term mortality **(24)**

Compared with those with adequate reflow, patients with NRF phenomenon tend to have higher incidences of death, myocardial infarction, and heart failure. **(24)**

The etiology of NRF is not yet fully understood, but it is assumed to be of multifactorial origin. Previous studies have identified several factors associated with NRF phenomenon, including plasma glucose, age, and pre-PCI thrombus burden. **(25)**

Currently, there still lack of effective methods that can classify the no-reflow patients and give a targeted therapy to those ones highly affected by no-reflow.Howeverin our studywe depend on a fast and simple clinical risk scoreby recently published by **Wang et al** for prediction of no reflow and classify well between patients who were at high risk of developing no-reflow and those who were not. **(11)**

The pathogenesis of no-reflow is complex. Severalknownmechanismincluding distal embolization, ischemia-reperfusion injury, and individual predisposition of coronary microcirculation to injury are

variable in different patients.Because Multi mechanisms are involved, several therapeutic strategies have been tested for the prevention and treatment of no-reflow with inconsistent results.**(4)**Current several mono therapies are reported to have certain effects, but not satisfactory at all.**(11)**

To Date no enough published data to study the effectiveness of combined different therapy in reducing the incidence of no-reflow. So the current study was conducted to examine the effectiveness of combination therapy (pretreatment with high dose atorvastatin 80 mg and high bolus IC tirofiban) on the reducing incidence of angiographic no reflow, in hospital and short term MACE.

In our study we enrolled 100 patients with STEMI who at high clinical risk for no reflow. Patients were randomly divided into two groups' combination therapy group and conventional therapy group.

There were no significant differences between both groups regarding demographic, laboratory, clinical data, angiographic and reperfusion technique. However sum of ST segment was significantly higher in combination group, (P =0.003).

The overall Incidence of no-reflow after primary was 23 % which is consistentto previously publishedno reflow rates**(26).**Incidence of no-reflow was significantly lower in combination group (10 %) compared to control group (36 %).

These result was similar to recently study published by **Zhou et al** in which compared conventional PCI and combination therapy (IC adenosine, IC tirofiban, pretreatment atorvastatin 80 mg and thrombus aspiration) in Acute high risk STEMIfor no reflow**(27).** The high risk Patients were selected according to Wang et al clinical score.**(11)**They found that incidence of no reflowin combination group highly significant lower compared to control high risk patients(2.8 %and 35.2 %respectively, p =0.001).

We found that percent of ST resolution and peak CKMB were significantly higher in combination therapy compared to control group (P value =0.013 – 0.001 respectively).How ever there was no significant impact on in hospital LVEF.

Zouh et al also used myocardial contrast echocardiography for farther assessment myocardial perfusion72 h post primary PCI, and he suggested higher myocardial perfusion values in combination therapy group. **(27)**

In our study we used simple 12 ECG leads and peak CK MB to evaluate indirect perfusion outcome. Previously described by **Santoro et al**thatST-segment resolutionis a helpful and inexpensive method to evaluate myocardial reperfusion after primary PCI.They studied the relationship between ST-segment changes and myocardial perfusion evaluated by myocardial contrast echocardiography in patients with acute myocardial infarction treated with primary PCI. A rapid ST-segment decrease was highly specific (91%) for myocardial reperfusion (or the absence of no-reflow on myocardial contrast echocardiography) although less sensitive (77%)**(28)**Recently reported by **Niccoli et al,** that incomplete ST resolution strongly related to Micro vascular obstruction(MVO) detected by cardiac MRI.**(29)**

In**Zouh et al**study, The mean EF of combination group after 3 months follow up was significant higher(53 ± 8) than control high risk group (44± 6), $P < 0.05$**(27)**

Lack of significant improvement of systolic function in our study in combination therapygroup may be attributed to the phenomenon of "Myocardial stunning " which can show later recovery over a variable period of time following reperfusion

We found heart failure symptoms were significantly lower in combination group therapy during in hospital stay and 30 days follow up.(3% and 2% respectively).The composite end point of30 days MACE occur only in 3% in combination therapy group while 10 % in control group (P =0.033). using Kaplan Meier curve for free survival MACE at 30 days there werealso significant different regarding free event rate for MACE, log rank =4.737, P =0.030.

In concordant to our results, Zhou et al reportedsignificant lower ischemia driventotal MACE during in hospital stay compared to high risk control group.Also after Six months clinical follow-up, There were 6 (6.3%) events (one death, two non-fatal MIs and three revascularizations) in combination therapy group, significantly lower than 12 (13.2%) events (four deaths, three non-fatal MIs and five revascularizations) in controlled group **(27)**

We found high thrombotic burden (thrombus grade ≥ 4) was independent predictor for angiographic no reflow (p =0.012), and the use of combination therapy (high dose statins and high dose IC tirofiban) were strongly independent predictors for prevention of no reflow (p =0.002) withrelative Risk reduction 72.2% and absolute risk reduction = 26%.

Similarly, many previous studies concluded certain clinical and procedural independent predictors of no-reflow phenomenon after primary PCI.**Wang et al. (24)**found that thrombus burden > 2 and recently **Mazaheret al.(30)** alsofound thrombus load ≥ 4 was independent predictors for angiographic no reflow.

Conclusion

Combination of pre-procedurehigh dose atorvastatin and IC bolus tirofiban can effectively reduce the incidence of no-reflow after primary PCI in patients with acute myocardial infarction who are at high risk of no-reflow.Large thrombus load is independent predictor of angiographic no reflow after primary PCI. However, this combination therapy is strong independent predictors for prevention of angiographic no-reflow.

Conflict of interest:

No Conflict of Interest for any contributed author of this work.

References

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003; 361: 13−20.
2. Gibson CM, Cannon CP, Murphy SA, et al. TIMI Study Group. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary

intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. Circulation. 2002; 105:1909–1913.

3. Rezkalla SH, Kloner RA. Coronary no-reflow phenomenon: from the experimental laboratory to the cardiac catheterization laboratory. Catheter Cardiovasc Interv. 2008; 72:950–957.
4. Niccoli G, Burzotta F, Galiuto L, et al. Myocardial no-reflow in humans. J Am Coll Cardiol 2009; 54:281–92.
5. Piana RN, Paik GY, Moscucci M, et al. Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. Circulation. 1994; 89:2514–2518.
6. Brosh D, Assali AR, Mager A, et al. Effect of no-reflow during primary percutaneous coronary intervention for acute myocardial infarction on six-month mortality. Am J Cardiol. 2007; 99: 442–445.
7. Bolognese L, Carrabba N, Parodi G, et al. Impact of microvascular dysfunction on left ventricular remodeling and long-term clinical outcome after primary coronary angioplasty for acute myocardial infarction. Circulation 2004; 109: 1121−1126.
8. Niccoli G, Kharbanda RK, Crea F, et al. No-reflow: again prevention is better than treatment. Eur Heart 2010; 31: 2449–2455.
9. Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet 2009; 373: 739–745.
10. Gray A, Goodacre S, Nicholl J, et al. The development of a simple risk score to predict early outcome in severe acute acidotic cardiogenic pulmonary edema: the 3CPO score. Circ Heart Fail 2010; 3: 111–117.
11. Wang JW, Chen YD, Wang CH, et al. Development and validation of a clinical risk score p redicting the no-reflow phenomenon in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Cardiology 2013; 124: 153−160
12. Bhave PD, Hoffmayer KS, Armstrong EJ, Garg S, et al. Predictors of depressed left ventricular function in patients presenting with ST-elevation myocardial infarction, The American journal of cardiology 2012; 109, 327–331.7.
13. Schröder R. Prognostic impact of early ST-segment resolution in acute ST-elevation myocardial infarction. Circulation 2004; 110:e506 –10.
14. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction With the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005; 18:1440–1463
15. Bhave PD, Hoffmayer KS, Armstrong EJ, Garg S, et al. Predictors of depressed left ventricular function in patients presenting with ST-elevation myocardial infarction, The American journal of cardiology 2012; 109, 327–331.7.
16. Mair J, Artner E, Dworzak,et al. Early detection of acute myocardial infarction by measurement of mass concentration of creatine kinase-MB: The American Journal of Cardiology. Dec:17(68), P 1545-1550

17. Niccoli G, Cosentino N, Spaziani C, et al. No-reflow: incidence and detection in the cath-lab. Curr Pharm Des. 2013; 19:4564–75.

18. TIMI Study Group : The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. New England Journal of Medicine 1985; 312:932-936.

19. Gibson CM, de Lemos JA, Murphy SA et al. Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: a TIMI 14 substudy. Circulation. 2001; 103(21), 2550–2554.

20. Mendis S, Thygesen K, Kuulasmaa K, et al. Writing group on behalf of the participating experts of the WHO consultation for revision of WHO definition of myocardial infarction. World Health Organization definition of myocardial infarction: 2008–09 revision. Int J Epidemiol 2011; 40:139–146.

21. Schömig A, Mehilli J, Antoniucci D, et al. Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptoms onset.JAMA 2005; 293 (23):2865-2872

22. Thrombolysis in Myocardial Infarction (TIMI). Definitionsused in TIMI trials. Available at: http://www .timi.org. Accessed February 5, 2005

23. Reffelmann T., Kloner R.A. The no-reflow phenomenon: basic science and clinical correlates. Heart. 2002; 87:162–168.

24. Wang JW, Zhoud ZQ, Chen YD, et al. A risk score for no reflow in patients with ST-segment elevation myocardial infarction after percutaneous coronary intervention. Clin Cardiol. 2015; 38(4):208–215.

25. Henriques JP, Zijlstra F, van't Hof AW, et al. Angiographic assessment of reperfusion in acute myocardial infarction by myocardial blush grade. Circulation 2003; 107: 2115−2119.

26. Harrison GW, Aggarwal A, Ou FS, et al. American college of cardiology national cardiovascular data registry. Incidence and outcome of no reflow during percutaneous coronary intervention among patient with acute myocardial infarction, Am J cardiol 2013 ; 111: 178- 84.

27. Zhou S, Tian F, Chen YD, et al. Combination therapy reduces the incidence of no-reflow after primary per-cutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction, Geriatr Cardiol. 2015 ; 12 (2): 135–142.

28. Santoro GM, Valenti R, Buonamici P, et al. Relation between STsegment changes and myocardial perfusion evaluated by myocardial contrast echocardiography in patients with acute myocardial infarction treated with direct angioplasty. Am J Cardiol, 1998;82:932-7.

29. Niccoli G, Scalone G, Lerman A, et al. Coronary microvascular obstruction in acute myocardial infarction. Eur Heart J. 2016; 37:1024-1033.

30. Mazhar J., Mashicharana M., Farshid A. Predictors and outcome of no-reflow post primary percutaneouscoronary intervention for ST elevation myocardial infarction. IJC Heart Vasc. 2016; 10:8–12.