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THE NO-REFLOW PHENOMENON: CLINICAL AND ANGIOGRAPHIC CORRELATES

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ABBREVIATIONS AND ACRONYMS

95% CI = 95% Confidence Intervals

ACS = Acute Coronary Syndromes

CABG = Coronary Artery Bypass Graft

CAD = Coronary Artery Disease

IHD = Ischemic Heart Disease

ISACS-TC = International Survey of Acute Coronary Syndromes in Transitional Countries

IQR = Interquartile Percentile Range

LAD = Left Anterior Descending Artery

MI = Myocardial Infarction

OR = Odds Ratio

PCI = Percutaneous Coronary Intervention

RCA = Right Coronary Artery

SD = Standard Deviation

STEMI = ST- Segment Elevation Myocardial Infarction

TIMI = Thrombolyisis In Myocardial Infarction

UFH = Unfractioned Heparin

VT/VF = Ventricular Tachycardia/ Ventricular Fibrillation

ABSTRACT

No-reflow occurring during percutaneus coronary intervention (PCI) has been associated with poor outcomes. The objectives of this study were to evaluate the incidence of no-reflow as independent predictor of adverse events and to assess whether baseline pre-procedural treatment options may affect clinical outcomes. Data were derived from the International Survey of Acute Coronary Syndromes in Transitional Countries (NCT01218776) registry, a prospective survey of patients presenting with ACS over a 5-year period (January 2010 to January 2015). Data were prospectively collected from 5997 patients undergoing PCI, identifying those with no-reflow, and analyzed their treatments and clinical outcomes. No-reflow was defined as post-PCI TIMI flow grade 0-1, in the absence of post-procedural significant (≥ 25%) residual stenosis, abrupt vessel closure, dissection, perforation, thrombus of the original target lesion, or epicardial spasm. The outcome measure was in-hospital mortality. No-reflow was identified in 128 of 5997 patients who have undergone PCI (2.1%). On multivariate analysis, patients with no-reflow were more likely to be older (OR: 1.20, 95% CI: 1.01 – 1.44) and to be admitted with a diagnosis of ST-elevation myocardial infarction (OR: 2.96, 95% CI: 1.85 – 4.72). No-reflow was highly predictive of in-hospital mortality (17.2% vs. 4.2%, P <0.001) and remained a significant independent predictor of death after adjustment for demographic and clinical variables (OR: 4.60, 95% CI: 2.61 – 8.09). Multivariable regression analysis was also performed to identify independent relationship between pre-procedural treatment regimens, angiographic characteristics and no-reflow phenomenon. Administration of pre-procedural unfractioned heparin, showed a strong inverse predictive value in terms of post-PCI TIMI flow and no-reflow phenomenon (OR: 0.65, 95% CI: 0.43 – 0.99). Similarly, a 600 mg loading dose of clopidogrel showed a trend associated with a reduction in the likehood of no-reflow (OR: 0.61, 95% CI: 0.37 – 1.00). Aspirin,

enoxaparin, 300 mg loading dose of clopidogrel, did not significantly impact the occurrence of the no-reflow. Angiographic characteristics associated with no-reflow phenomenon were coronary stenosis severity ≥ 50% of the right coronary artery, presence of multivessel coronary disease and pre - procedural TIMI blood flow grade 0-1. In conclusion, no-reflow during PCI is a strong independent predictor of in-hospital mortality. Pre-procedural administration of 600 mg loading dose of clopidogrel and/or unfractioned heparin is associated with reduced incidence of no-reflow.

INTRODUCTION

Successful coronary revascularization does not always lead to coronary reperfusion. There is a group of patients who do not benefit from prompt restoration of antegrade flow, as they fail to show resolution of chest pain and electrocardiographic (ECG) changes suggestive of ischemia. These patients present an angiographic phenomenon characterized by the evidence of no-flow (Thrombolysis in Myocardial Infarction [TIMI] flow equal to or less than 1) in the affected vessel despite the absence of post-procedural significant (≥ 25%) residual stenosis, flow-limiting dissection, perforation, coronary spasm, or in-situ thrombosis [1]. No-reflow occurring during percutaneus coronary intervention (PCI) has been associated with poor prognosis [2-7].

The no-reflow phenomenon is still poorly understood. Although atherothrombotic microembolization appears to be an important contributor to no reflow, particularly in the setting of primary PCI for acute myocardial infarction [8], other explanation has been suggested including vascular dysfunction due to an over-activation of alpha-adrenergic induced vasoconstriction [9]. As a consequence selection of therapy is still under scrutiny. Therapy depends critically on an underlying model of the disease process, because only the pathophysiology of the disease may suggest a method for its treatment, and knowledge about the pathophysiology of no-reflow is still rudimentary.

Clinical knowledge about the no-reflow phenomenon has been based mainly on small cohort studies. In addition most of these studies are dated. Thus little is known about its incidence and the factors that up-to-date may predispose to its development among patients with ACS undergoing PCI. The objective of the current study was to evaluate in a large registry cohort of contemporary patients the incidence of no-reflow as independent predictor of adverse

events and to assess whether baseline pre-procedural treatment options may affect clinical outcomes.

MATERIALS AND METHODS

Data collection

Data collection and analysis for the International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC; ClinicalTrials.gov Identifier: NCT01218776) registry has been previously described [10-20]. In brief, patients were eligible for inclusion if they met the following criteria: age ≥ 18 years, symptoms consistent with acute cardiac ischemia, documented evidence of new or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block on serial electrocardiograms and/or elevated biomarkers of myocardial necrosis according to universal standardized criteria [21]. The network is constituted of 29 tertiary and 28 secondary hospitals in Eastern Europe. All hospitals had intensive coronary care units, and medical reperfusion therapy. The tertiary hospitals had cardiac catheterization facilities. The study was approved by the local research ethics committee from each participating hospital.

Participants

Six thousand six patients undergoing PCI, for ST-segment elevation myocardial infarction (STEMI) and non ST-segment elevation ACS included the ISACS-TC hospitals from January 2010 to January 2015 were analyzed, identifying those with no-reflow phenomenon, and analyzed their treatments, angiographic features and clinical outcomes. After excluding 9 patents with missing data on post-PCI TIMI blood flow grades, the final study population consisted of 5997 patients with full records on post-PCI TIMI blood flow grades.

Definitions

No-reflow phenomenon was defined as post-PCI TIMI blood flow grade 0-1 (in the absence of post-procedural residual stenosis ≥ 25%, abrupt vessel closure, dissection, perforation, thrombus of the original target lesion, or epicardial spasm) [1].

Minor bleeding was defined as any clinically sign of haemorrhage associated with a fall in haemoglobin 5 ≤ g/dl occurred during hospitalization. Major bleeding was defined as any clinically sign of haemorrhage associated with a fall in haemoglobin 5 > g/dl or ay intracranial bleeding occurred during hospitalization [22-24].

Measures of outcomes

The primary endpoint was in-hospital mortality. Secondary endpoints were to evaluate baseline clinical characteristics, pre-procedural treatment options and angiographic characteristics that may predict no-reflow phenomenon. Other outcomes of interest were the incidence of stroke, ventricular tachycardia and/or ventricular fibrillation, minor and major bleeding during hospitalization.

Statistical analysis

Baseline and angiographic characteristics of the patients were compared by *Students t-test* or Kruskal-Wallis rank-sum test for continuous variables and Pearson's χ^2 test for categorical variables, as appropriate. Results are presented as percentages for categorical variables, mean ± standard deviation (SD) or median and interquartile percentile range (IQR) for continuous variables. Kaplan - Meier curve estimates were calculated for mortality rates. Mortality rates are shown as proportion and 95% confidence intervals (95% CI). Log-rank test was used to compare event rates among the two patients groups.

Multivariable logistic regression analysis was performed in order to identify the independent predictors of in-hospital mortality in patients presenting the no-reflow phenomenon as

compared to patients without no-reflow during PCI. Another multivariable logistic regression analysis was performed to identify the independent predictors of no-reflow phenomenon. Results are presented as odds ratios (OR) and 95% CI. Constant covariates included in the analyses were: sex; age; cardiovascular risk factors: (history of hypercholesterolemia, history of diabetes, history of hypertension, smoking status); clinical history of ischemic heart disease (previous myocardial infarction, previous PCI, and previous coronary artery bypass graft) clinical history of cardiovascular disorders (previous peripheral artery disease, and previous stroke and/or previous transient ischemic attack) and severity of clinical presentation (STEMI, Killip Class ≥ 3, systolic blood pressure and heart rate). Secondary analyses were performed to identify independent relationship between pre-procedural treatment regimens, angiographic characteristics and no-reflow phenomenon. Covariates introduced in the secondary analyses, as dummy variables, were use of aspirin, clopidogrel, unfractioned heparin, enoxaparin, coronary stenosis severity ≥ 50% and baseline TIMI blood flow grade 0-1. A C-index (area under the receiver-operator characteristic curve) was generated for each regression models to measure the concordance. For all analyses, statistical significance was defined as a value of $P < 0.05$. Statistical evaluation was performed using STATA 11 (StataCorp. College Station, TX, USA).

RESULT

Among 5997 patients with ACS, 128 (2.1%) developed no-reflow phenomenon during PCI. Median hospital stay was 6 days. Overall there were 271 (4.5%) patients who died during hospitalization.

Table 1. *Baseline characteristics*

Characteristics	No-reflow phenomenon		
	Yes N=128	**No N=5869**	***P* value**
Age (years)	63.7 ± 11.6	61.2 ± 11.5	0.01
Women	32.0	29.7	0.57
History of diabetes mellitus	27.1	24.6	0.53
History of hypercholesterolemia	52.7	37.3	0.001
History of hypertension	71.1	69.1	0.62
Family history of CAD	18.1	25.4	0.07
Current smoking	44.3	40.6	0.40
History of MI	14.8	17.0	0.52
History of PCI	5.5	8.0	0.28
History of CABG	0.8	1.7	0.44
History of IHD*	17.2	20.0	0.43
History of cardiovascular disorders‡	7.8	4.3	0.05
Clinical presentation			
Systolic blood pressure at baseline (mmHg)	140.9 ± 22.9	145.3 ± 24.5	0.04
Heart rate at baseline (bpm)	82.5 ± 22.3	81.3 ± 17.9	0.48
Serum creatinine at baseline (μmol/L)	104.6 ± 6.7	93.1 ± 1.5	0.29
STEMI	75.8	53.8	<0.001
Killip class ≥ 3	5.5	2.2	0.01
Door to balloon time, min (IQR)	44.5 [28 - 75]	45 [30 - 83]	0.45
Time from symptoms onset to admission <12 hrs	74.4	77.6	0.39
Medications			
Aspirin	98.4	98.8	0.69
Clopidogrel loading dose 600 mg vs. 300 mg	65.7	75.7	0.01
UFH	59.8	73.7	<0.001
Enoxaparin	44.4	34.9	0.02
Hospital stay, days (IQR)	6 [3 - 8]	5 [3 - 7]	0.50
In-hospital mortality	17.2	4.2	<0.001

Data are presented as percentages (%), mean ± SD or median (interquartile range [IQR])
*History of IHD: history of MI and/or history of PCI and/or history of CABG
‡History of cardiovascular disorders: history of previous transient ischemic attack and/or previous stroke and/or peripheral artery disease.
CAD indicates coronary artery disease; MI, myocardial infarction; PCI, percutanous coronary intervention; CABG, coronary artery bypass graft; IHD, ischemic heart disease; STEMI, ST-segment elevation myocardial infarction; UFH, unfractioned heparin.

Patient characteristics

The baseline characteristics for the no-reflow and reflow groups are shown in **Table 1**. Patients with no-reflow were more likely to be older and to have a history of hypercholesterolemia. They were more likely to present with pulmonary oedema and/or cardiogenic shock (Killip Class ≥ 3), and to present with STEMI at index event. The rate of administration of pre-procedural antithrombotic medications, namely a loading dose of 600 mg of clopidogrel and unfractioned heparin was lower in patients presenting no-reflow. Biomarkers of myocardial necrosis that can predict infract size were significantly higher in the no-reflow group (creatine kinase - MB fraction: mean 105 versus 57.5 U/L and cardiac troponin: mean 11.1 versus 6.8 µg/L). Unadjusted in-hospital mortality rates were significantly higher for patients developing no-reflow during PCI (17.2% versus 4.2%, $P < 0.001$) (**Table 1 and Figure 1**).

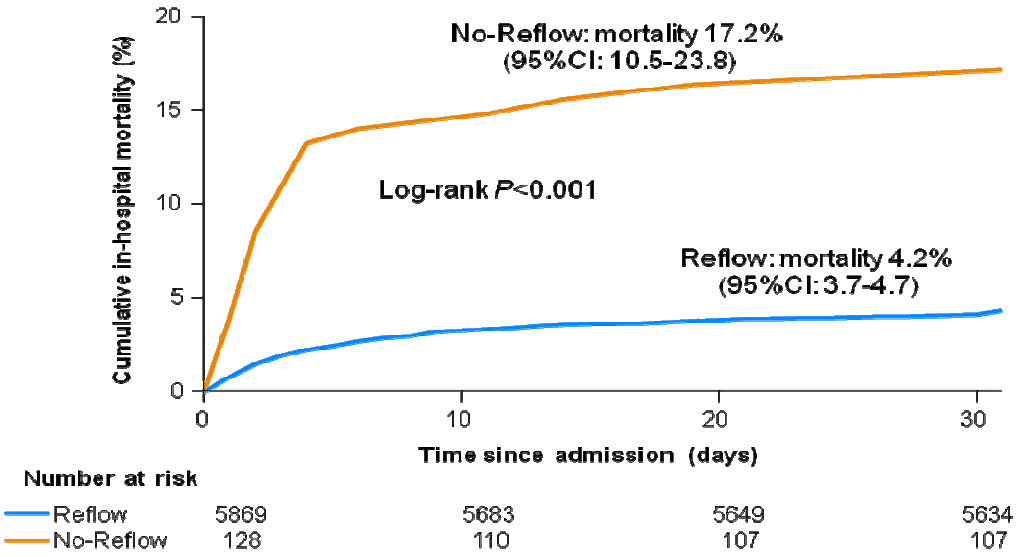

Figure 1. *Unadjusted Kaplan-Meier curves for cumulative in-hospital mortality sorted by the occurrence of no-reflow phenomenon*

Angiographic characteristics

Univariate analyses of angiographic characteristics are shown **Table 2**. Patients developing no-reflow were more likely to present with multivessel coronary disease, more severe

coronary disease of the right coronary artery and impaired baseline TIMI blood flow grade as compared to patients without no-reflow. Patients developing no-reflow were more likely to undergo PCI through the transfemoral approach. They were less likely to be stented with either bare metal stents or drug eluting stents.

Table 2. Angiographic characteristics

Characteristics	No reflow phenomenon		*P*-value
	Yes N=128	No N=5869	
Trans radial approach	37.4	72.1	<0.001
Left main stenosis ≥ 50%	5.6	6.5	0.71
LAD stenosis stenosis ≥ 50%	69.0	62.1	0.15
Circumflex artery stenosis ≥ 50%	43.2	40.1	0.66
RCA stenosis ≥ 50%	75.5	61.2	0.004
Multivessel CAD	73.0	53.8	<0.001
Bifurcation lesion	7.8	6.2	0.44
Previously treated lesion	4.7	5.4	0.73
Baseline TIMI flow grade 0-1 vs. 2-3	93.9	57.4	<0.001
Reference diameter, mm	3.2 ± 0.7	3.4 ± 5.8	0.91
Lesion length, mm	18.8 ± 11.3	19.2 ± 8.7	0.90
Stent apposition	71.0	94.6	<0.001

Data are presented as percentages (%) or mean ± SD, unless otherwise stated.
LAD indicates Left anterior descending artery; CAD, coronary artery disease; RCA, Right coronary artery TIMI, Thrombolysis In Myocardial Infarction

Factors associated with in-hospital mortality

On multivariate analysis (**Table 3**), no-reflow phenomenon, older age, history of diabetes mellitus, history of ischemic heart disease, history of cardiovascular disorders, increased heart rate at admission, STEMI as index event and Killip Class ≥ 3 were independently associated with in-hospital mortality. Conversely, a history of hypertension or hypercholesterolemia and higher systolic blood pressure levels at presentation were associated with lower adjusted mortality rates.

Table 3. *Characteristics independently associated with in-hospital mortality*

Variable	OR	95% CI	*P* Value
No-reflow phenomenon	4.60	2.61 – 8.09	<0.001
Age (per 10 years increase)	1.59	1.39 – 1.83	<0.001
Women	1.13	0.83 – 1.54	0.40
History of diabetes mellitus	1.61	1.19 – 2.19	0.002
History of hypertension	0.70	0.51 – 0.97	0.03
History of hypercholesterolemia	0.52	0.37 – 0.73	<0.001
Current smoking	1.08	0.78 – 1.49	0.63
History of IHD	1.50	1.06 – 2.12	0.02
History of cardiovascular disorders	2.24	1.35 – 3.71	0.002
Heart rate at baseline (per 1 SD increase)*	1.16	1.04 – 1.30	0.005
Systolic blood pressure at baseline (per 1 SD increase)*	0.68	0.59 – 0.77	<0.001
STEMI	1.78	1.30 – 2.43	<0.001
Killip Class ≥ 3	5.93	3.49 – 10.07	<0.001

C statistics: 0.78
Incidence of in-hospital mortality in the overall study population: n=271 (4.5%).
*SDs for heart rate and systolic blood pressure are 17.5 b.p.m and 23.1 mmHg
IHD indicates ischemic heart disease; STEMI, ST-segment elevation myocardial infarction; SD, standard deviation

In-hospital complications

With the exception of stroke and life threatening arrhythmias, which occurred more frequently in patients developing no-reflow, in-hospital complications did not differ between patient groups (**Figure 2**).

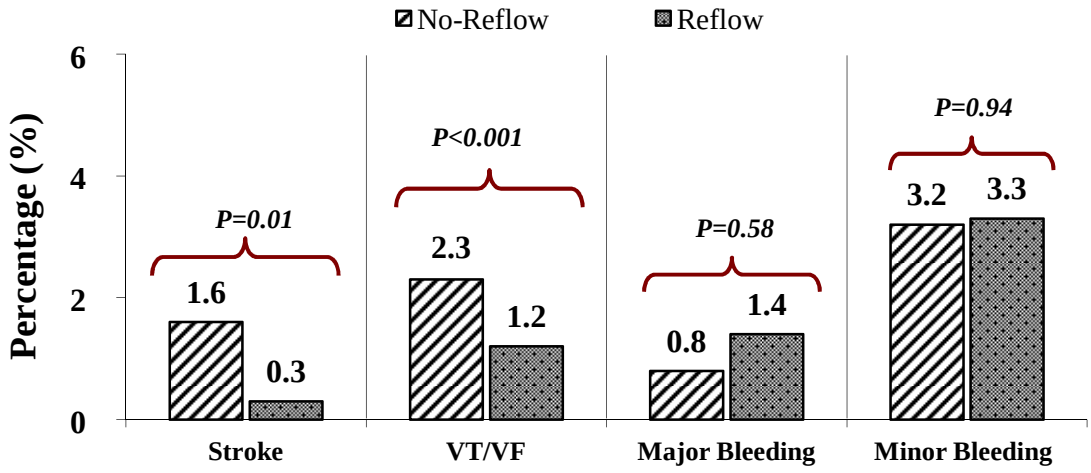

Figure 2. *In-hospital complications*
Data are percentages. VT/VF, indicates ventricular tachycardia /ventricular fibrillation

Factors associated with no-reflow phenomenon

Predictors of no-reflow phenomenon are shown in **Table 4**. Older age, history of hypercholesterolemia and STEMI at presentation were independently associated with the development of no-reflow phenomenon during PCI.

Table 4. *Predictors of No-Reflow Phenomenon*

Variable	OR	95% CI	*P* Value
Age (per 10 years increase)	1.20	1.01 – 1.44	0.04
Women	1.15	0.75 – 1.75	0.50
History of diabetes mellitus	1.06	0.68 – 1.66	0.78
History of hypertension	0.98	0.63 – 1.54	0.95
History of hypercholesterolemia	1.95	1.31 – 2.91	0.001
Current smoking	1.11	0.73 – 1.68	1.68
History of IHD	0.72	0.42 – 1.25	0.25
History of cardiovascular disorders	1.81	0.88 – 3.73	0.10
Heart rate at baseline (per 1 SD increase)*	0.97	0.81 – 1.16	0.76
Systolic blood pressure at baseline (per 1 SD increase)*	0.88	0.74 – 1.05	0.76
STEMI	2.96	1.85 – 4.72	<0.001
Killip Class ≥ 3	1.73	0.59 – 5.05	0.31

C statistics: 0.70

*SDs for heart rate and systolic blood pressure are 17.5 b.p.m and 23.1 mmHg

IHD indicates ischemic heart disease; STEMI, ST-segment elevation myocardial infarction; SD, standard deviation

Impact of oncurrent preprocedural treatments and angiographic characteristics

On secondary analyses (**Table 5**), administration of pre-procedural unfractioned heparin, showed a strong inverse predictive value in terms of post-PCI TIMI flow and no-reflow phenomenon. Similarly, a 600 mg loading dose of clopidogrel showed a trend associated with a reduction in the likehood of no-reflow. The presence of a mutivessel coronary disease, stenosis ≥ 50% of the right coronary artery and impaired pre-procedural TIMI blood flow

grade predicted the development of no-reflow phenomenon. The areas under the under the receiver-operator characteristic curves for the models ranged from 0.70 to 0.79 indicating good discriminatory powers (**Table 5**).

Table 5. *Therapeutic and angiographic factors associated with no-reflow phenomenon in multivariate analysis*

Variable	OR (95% CI)	*P* Value	*C* statistics
Model 1			
Aspirin	0.83 (0.11 – 6.25)	0.82	0.70
Model 2			
Clopidogrel 600 mg vs. 300 mg	0.61 (0.37 – 1.00)	0.05	0.72
Model 3			
UFH	0.65 (0.43 – 0.99)	0.04	0.70
Model 4			
Enoxaparin	1.47 (0.98 – 2.20)	0.06	0.70
Model 5			
Mutivessel disease	2.13 (1.29 – 3.50)	0.003	0.74
Model 6			
LAD stenosis ≥ 50%	1.21 (0.76 – 1.93)	0.40	0.72
Model 7			
RCA stenosis ≥ 50%	1.81 (1.08 – 3.01)	0.02	0.73
Model 8			
Baseline TIMI flow grade 0-1 vs. 2-3	7.67 (3.30 – 17.81)	<0.001	0.79

LAD indicates left descending artery; RCA, right coronary artery, TIMI, Thrombolysis In Myocardial Infarction; UFH, unfractioned heparin.

The following covariates are sequentially included in the adjusted models as dummy variables*:* Model 1 as in Table 4 with the inclusion of aspirin. Model 2 as in Table 4 with the inclusion of clopidogrel. Model 3 as in Table 4 with the inclusion of UFH. Model 4 as in Table 4 with the inclusion of enoxaparin. Model 5 as in Table 4 with the inclusion of multivessel coronary disease. Model 6 and 7 as in Table 4 with the inclusion of coronary stenosis severity. Model 8 as in Table 4 with the inclusion of baseline TIMI flow grade 0-1.

DISCUSSION

In the present study patients developing no-reflow during PCI in the clinical setting of ACS had over four-fold higher risk of in-hospital mortality as compared with those in which patency and flow was restored successfully. These results did not change after adjusting for baseline characteristic and clinical presentation. No-reflow phenomenon occurred more frequently in patients presenting with STEMI as index event, and in patients with multivessel coronary artery disease. Yet, the major strength of the study is its therapeutic findings: pre-procedural administration of unfractioned heparin and/or a 600 mg loading dose of clopidogrel was associated with approximately 35% reduction in the incidence of no-reflow.

Previous studies on the incidence of no-reflow phenomenon

In the present study the incidence of no-reflow was 2.1%. The reported incidence of no-reflow varies across studies ranging from 0.6% to 42% [2-7]. Possible reasons might be that the incidence of no-reflow depends on the clinical setting and the definitions used. No-reflow is more common in patients presenting with myocardial infarction. Among 291,380 acute MI patients undergoing PCI, enrolled in the National Cardiovascular Data Registry (NCDR), the incidence of no-reflow, defined as TIMI blood flow grade 0-1 was 2.8% [3]. However, the definition of no-reflow in this study included also those patients having mechanical complications of PCI, which makes difficult a comparison with our findings. Other observations have shown that no-reflow is more common in STEMI patients undergoing primary PCI than in those performing elective PCI. In a large study among 1,406 STEMI patients undergoing primary PCI, no-reflow was identified in 29% of these patients [4]. In a subgroup post-hoc analysis of the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, no-reflow occurred in 10.2% of patients [5].

The current study analyzed all ACS patients undergoing PCI regardless of timing of procedure and clinical presentation. A similar study reported an incidence of no-reflow of 3.1% [6]. The higher incidence of no-reflow in previous observations as compared with our findings (3.1% versus 2.1%) could be explained by the elapsed time between the two studies, over a decade. Prior studies could not account for large improvements in adjunctive therapies and catheter based interventions.

Impact of no-reflow phenomenon on prognosis

In the present study the risk of short-term mortality was 4.6-fold higher in patients who developed no-reflow phenomenon during PCI. Similarly, more than 3-fold increase in the risk of in-hospital mortality was reported in the NCDR registry. In the current study older age, diabetes, STEMI and higher Killip Classes had the strongest associations with mortality by multivariate analysis. All of these factors have been recognized as determinants of poor outcome in patients with ACS. Elderly, diabetic and STEMI patients have a greater atherosclerotic plaque burden, which makes them at greater risk of adverse events [25, 26]. In acute heart failure patients' reduced myocardial contractility may result in reduced cardiac output, which in turn may further impair coronary blood flow [27, 28]. Several studies have shown that no-reflow during PCI impacts significantly also long term prognosis [5, 29]. In one small study mortality rates in no-reflow patients increased progressively over a 6-month follow-up period [29]. Other studies have reported more than two-fold increase for cardiovascular mortality in no-reflow patients at 5-year follow-up [5]. This matter is of concern considering that no-reflow consists in an acute and transient reduction of coronary flow. Previous studies have shown strong associations of no-reflow with considerable decrease of myocardial salvage, larger infarct size and reduced left ventricular function [30].

In the present study infarct size as measured by creatine kinase - MB fraction or troponin levels was higher in patients who developed no-reflow.

Impact of in-hospital complications

Life threatening ventricular arrhythmias such as ventricular tachycardia and/or ventricular fibrillation occurred more frequently in patients who developed no-reflow (2.3% versus 1.2%), which is in keeping with the observation that higher rates of reperfusion arrhythmias are related to continuing ischemia due to microvascular damage [31, 32]. Previous studies have also shown that coronary patency is associated with an increase on the incidence of accelerated idioventricular rhythm and ventricular tachycardia and have reported a positive correlation between frequency of ventricular arrhythmias and biomarkers of necrosis [33, 34]. Although, infrequent, stroke is a critical complication of ACS, that occurs in 0.7 - 2.5% of patients [35, 36]. In the current study the overall rates of stroke were 0.3%. This lower incidence in our cohort could be explained by the fact that most of the previous studies have assessed the incidence of stroke in combination with fibrinolytic or antithrombotic therapy, which is a well-recognized cause of stroke. Interestingly, in the current study the rates of stroke following PCI were higher in no-reflow patients group, which may be associated with the fact that the rates of thrombus aspiration were relatively low in our cohort (3.4%). In addition, PCI with thrombus aspiration was performed more frequently in the no-reflow group, which is concordant with recent data from the Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL) Trial. The trial reported two fold increase in the rates of stroke within 30 days follow up in the routine thrombectomy arm [37].

Main predictors of no-reflow

In the ISACS – TC clinical and demographic predictors of no –reflow were older age STEMI as index event and hypercholesterolemia. Elderly, and STEMI patients carries a greater

thrombus and atherosclerotic plaque burden. Indeed, patients in the ISACS – TC, in whom occurred no-reflow had lower degrees of pre-procedural TIMI blood flow grade (93.9% versus 57.4%). On multivariate analysis, no-reflow phenomenon was more than 7 – fold higher in patients who had a baseline TIMI blood flow grade 0 - 1. This finding could be related to higher rates of STEMI as index event, high-burden thrombus formation and greater lesion complexity. Several reports have shown that the incidence of distal embolization is higher in patients with greater thrombus burden. Thrombus features related to no - reflow have been documented to be, large thrombus with cut-off pattern occlusion pattern, presence of accumulated thrombus or floating thrombus proximal to occlusion [38]. Other studies have reported that high risk coronary lesions (American Heart Association/American College of Cardiology class C lesions), longer lesions and bifurcated lesions are associated with no-reflow phenomenon [3]. In the current cohort, there were no differences with respect to mean lesion length or bifurcated lesions, however presence of multivessel coronary disease was a predictor of no reflow. A recent study linked no-reflow phenomenon with higher SYNTAX scores. Although in this study multivessel coronary disease was not directly associated with no-reflow phenomenon, it should be noted that patients having higher SYNTAX scores had higher also rates of multivessel coronary disease [39]. Multivessel coronary disease is incorporated in the SYNTAX score [40] and therefore may have a role in the prediction of no-reflow phenomenon.

Hypercholesterolemia is well recognized risk factors for microvascular dysfunction. It may contribute, at least partially, in the pathogenesis of no-reflow. Hypercholesterolemia has been found to be associated with reperfusion injury oxidative stress and consequent no-reflow in rabbits [41]. Our observations are in agreement. Hypercholesterolemia therefore may mediate no-reflow through systemic inflammatory response, platelet/endothelial activation, micro-

vascular vasoconstriction, myocardial oedema, oxygen-derived free radicals and calcium overload.

Benefits of unfractioned heparin

Lack of randomized controlled clinical trials remains a limitation to give specific guidelines. No-reflow can still occur even under the best provided care, which emphasizes the need for more specific medical treatments. In the current study pre-procedural administration of unfractioned heparin was associated with a 35% decrease in the incidence of no-reflow during PCI. Because platelet thrombin and fibrin plugging is an important contributor to the pathogenesis of the no-reflow phenomenon, unfractioned heparin may be beneficial in the prevention of the no-reflow phenomenon during percutaneous coronary intervention. Studies have shown that unfractioned heparin is beneficial in reducing the dynamic process of thrombus formation and propagation. Many of patients experiencing no reflow presented late from symptom onset. For late treated patients more thrombin-specific agents are needed, as fresh thrombi have the highest proportion of platelets, while the proportion of fibrin fibbers increases over time, as the level of thrombin increases [42]. Under these circumstances, unfractioned heparin is particularly beneficial as it is effective in modulating the contact activation pathway by inactivating thrombin, through an antithrombin-dependent mechanism [43]. Unfractioned heparin also inhibits thrombin-induced activation of platelets and the resulting formation of an insoluble fibrin network [43]. Accordingly our data have showed that enoxaparin is not effective in preventing the no reflow. The shorter chain length of this drug enoxaparin is unable to block the contact activation pathway and, therefore, has a reduced ability to inhibit thrombin. Low-molecular-weight fractions of heparin react less with platelets than high-molecular-weight fractions [42]. Few controlled studies have confirmed the beneficial effects of unfractioned heparin in the setting of no reflow. However, these

considerations are also, supported by recent findings from randomized trials that confirmed that unfractioned heparin is at least as effective and safe as enoxaparin in primary PCI for STEMI [44].

Benefits of clopidogrel

As previously mentioned, platelet and fibrin plugging is an important contributor to the pathogenesis of the no-reflow phenomenon. Clopidogrel may be, therefore, beneficial in the prevention of the no-reflow phenomenon during percutaneous coronary intervention as well. In our study, patients receiving 600-mg loading dose of clopidogrel showed a significantly lower incidence of no reflow compared to those treated with 300-mg. Improved 30-day clinical outcomes have been recently shown with clopidogrel 600 mg in a small, nonrandomized study of patients with STEMI who underwent primary PCI compared to a 300-mg dose [45]. These data are concordant with previous observations on the effects of a glycoprotein IIb/IIIa blocker (abciximab) on angiographic no-reflow phenomenon [46] Patients who received abciximab before coronary intervention had significantly more TIMI blood flow grade 3 compared with patients who received placebo. It is therefore suggested that antiplatelet therapy not only result in better epicardial blood flow but also lead to less no-reflow phenomenon and better flow of the coronary microcirculation.

Bleeding

Although the present study supports the concept of the pre-procedural administration of UFH and 600 mg loading of clopidogrel in patients with ACS undergoing PCI is beneficial in terms of reduction of incidence of no-reflow, concerns about bleeding with antithrombotic therapy are still relevant to clinical practice. In the current study, risk of major bleeding was insignificant and did not differ between patients groups (no-reflow: 0.8% versus 1.4%, P=0.58).

Strengths of the study

This study has several strengths. First, patients having mechanical complications, such abrupt vessel closure, dissection, perforation, thrombus of the original target lesion, or epicardial spasm during PCI were not included in the no-reflow group. Also patients in whom the procedural success was not achieved were excluded from the no-reflow definition. Second, the definition of no-reflow varies considerably across studies. Many studies defined no-reflow phenomenon as post-procedural TIMI blood flow grade ≤ 2. The present study defined no-reflow as post-procedural TIMI blood flow grade 0 – 1 and not included in the no-reflow group patients with post-procedural TIMI blood flow grade 2, an angiographic condition generally referred to as coronary slow-flow. Third, in the current study the independent relationships between medications and the incidence of no-reflow were estimated introducing in the models pre-procedural medications such as unfractioned heparin and clopidogrel. Glycoprotein IIb/IIIa inhibitors may have been selectively administered during PCI and therefore were not included in the models. Finally, patient groups were comparable with respect to the majority of demographic, baseline and angiographic characteristics enabling to control the incidence of no-reflow for pre-procedural medications, clinical and angiographic severity of illness, which may be persistent important confounders.

Study limitations

There are several limitations. First, although patient groups were comparable, bias may still be present. The present study cannot rule out that unmeasured confounders may have affected the results. Second, information about intracoronary vasodilators such as adenosine, nitroglycerin, sodium nitroprusside, verapamil, dialtiazem or nicoradil, which have been shown to be effective in the treatment of no-reflow was not available. Third, relatively few patients had information on whether they had distal embolization and therefore were not

excluded from the study. However, there is strong evidence that distal embolization of the plaque/thrombus following balloon inflation is an important factor in the development of no-reflow [8, 47]. Moreover angiographically evident distal embolization occurs in approximately 15% of patients [48]. Thus the choice was not to exclude patients with full records on distal embolization as this would have underrepresent the incidence of no-reflow. Finally, the observational nature of this study do not control for unmeasured confounders. However, results of a registry are valuable as they allow studying real-world practice patterns.

CONCLUSIONS

No-reflow during PCI is a strong independent predictor of in-hospital mortality. Pre-procedural administration of 600 mg loading dose of clopidogrel and unfractioned heparin in this study is associated with reduced incidence of no-reflow. Aggressive antithrombotic strategies could be considered in order to reduce the no-reflow incidence and improve outcomes. Despite these observations, further prospective larger studies remain necessary to confirm the results.

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