Innovative therapies for optimizing outcomes of coronary artery disease

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Chapter 3

Pre-infarction angina predicts thrombus burden in patients admitted for ST-segment elevation myocardial infarction

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ABSTRACT

Background High thrombotic burden, subsequent distal embolization and myocardial no-reflow remain a big obstacle which may negate the benefits of urgent coronary revascularization in patients with ST-elevation myocardial infarction (STEMI). We aimed at assessing the predictors of (1) thrombus grade in patients undergoing primary percutaneous coronary intervention (PPCI), and (2) infarct size, in order to optimize therapy to reduce thrombus burden.

Methods One-hundred and fifty-three consecutive patients presenting with STEMI and undergoing PPCI were included. Thrombus was evaluated on angiography and scored according to the TIMI study group score. Next, patients were categorized into two groups having either high thrombus grade (HTG; score 4-5) or low thrombus grade (LTG; score 1-3). We evaluated predictors of angiographic thrombus grade among a number of clinical, angiographic and laboratory data. We also assessed infarct size and scintigraphic left ventricular ejection fraction (LVEF) at 3 months in both patient groups.

Results Ninety-four patients (58±11 y, 75% males) presented with HTG, whereas 59 patients (58±12 y, 78% males) presented with LTG. Pre-infarction angina (PIA) was more frequently encountered in the LTG group than in the HTG group (25% vs. 10%, p=0.009). Pre-procedural TIMI flow was significantly lower in the HTG group (p<0.001), and thrombosuction was more frequently applied in the HTG group (p<0.001). Absence of PIA (OR=0.29, 95% CI=0.11-0.75, p=0.01) and proximal culprit lesion (OR=2.10, 95% CI=1.02-4.36, p=0.04) were the only independent predictors of HTG. HTG proved an independent predictor of higher peak levels of CK (p<0.001) and troponin-T (p<0.001), as well as lower LVEF (p=0.05) along with male gender and absence of prior statin therapy.

Conclusion Absence of PIA and proximal culprit lesions are associated with higher thrombus grade. Higher thrombus grade is associated with larger infarct size and slightly worse LV function. This may have clinical implications in planning strategies, particularly regarding pharmacotherapy, that aim to decrease thrombus burden prior to stent implantation.

Keywords: ST-elevation myocardial infarction, Primary percutaneous coronary intervention, Pre-infarction angina, Thrombus grade, TIMI flow, Infarct size

INTRODUCTION

Primary percutaneous coronary intervention (PPCI) for patients with ST-segment elevation myocardial infarction (STEMI) aims at early restoration of patency and adequate blood flow both in the epicardial and in the microvascular coronary circulation. However, despite adequate epicardial patency many patients fail to recover sustained myocardial perfusion due to microvascular obstruction[1, 2], which carries a prognostic indication of a poor outcome[3, 4].

A high thrombotic grade has been shown to predict distal embolization, and subsequent microvascular obstruction, thus prompting the development of strategies aimed at decreasing thrombus grade before stent deployment such as thrombus aspiration[5] and use of glycoprotein (GP) IIb/IIIa receptor antagonists[6, 7].

Pre-infarction angina (PIA) occurring shortly before the onset of acute myocardial infarction (AMI) has a cardioprotective effect by the mechanism of ischemic preconditioning[8-10], i.e. the phenomenon by which brief episodes of ischemia increase the tolerance of the heart to a subsequent major ischemic insult. Moreover, PIA has been shown to preserve microvascular function after reperfusion[11].

It has been shown that patients with AMI who have intermittent infarct-related pain or unstable angina in the seven days preceding the infarction have faster coronary artery reperfusion and smaller infarcts after thrombolytic therapy than patients without pre-infarction angina, suggesting two different types of thrombus growth and thus different responses to thrombolytic therapy[12]. During PPCI variable grades of thrombus formation are observed that can only be detected on the initial angiography. Ideally it will be possible to predict the thrombus grade clinically or through rapid laboratory investigations prior to PCI procedure. This may help to plan for an earlier and enhanced pre-hospital management using adjunctive pharmacotherapy, particularly with the newly emerging rapid-acting reversible antiplatelet agents which are currently under intense research and are expected to have higher efficacy and safety profiles than the existing treatments.

In this study we aimed at assessing factors predicting angiographic thrombotic grade in a consecutive series of patients presenting with STEMI treated by PPCI. In addition, the subsequent infarct size and left ventricular function were assessed among patients with different thrombus grades.

METHODS

Study population

We studied 158 consecutive patients with a diagnosis of STEMI, having clear evidence of thrombus on the initial angiography who underwent PPCI and received abciximab prior to PPCI. Patients were selected from an ongoing registry (operational since 2004) in Leiden

University Medical Center, which evaluates the effects of an all-phase integrated AMI care program (MISSION!) on short- and long-term outcomes[13,14]. Diagnosis of STEMI was made on the basis of typical electrocardiographic changes with clinical symptoms associated with elevation of cardiac biomarkers. All patients were treated according to the institutional AMI protocol (MISSION!). The MISSION! Protocol is a rather stringent, rigorously standardized protocol. It comprises a well-organized pre-hospital, in-hospital and outpatient clinical framework for decision making and treatment, so it is unlikely that procedural changes over time would have influenced the outcomes. Clinical data were prospectively entered in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center) and retrospectively analyzed[13]. The tertiary center provides a round-the-clock service of PPCI with highly experienced PCI physicians and dedicated nurses.

Medication

All patients received abciximab (Centocor B.V., Leiden, The Netherlands) as a bolus injection of 0.25 mg/ kg body weight, followed by 0.125 mcg/kg/min with a maximum of 10 mcg/min as a continuous infusion for 12 hr. Abciximab administration started before PCI according to MISSION! Protocol[13]. Furthermore all patients received an equivalent of 300 mg of acetylsalicylic acid, 600 mg clopidogrel as a loading dose before PCI and heparin given as a bolus of 5000 IU at the start of the PCI procedure. After the procedure, all patients received aspirin (75 mg/ day) indefinitely and clopidogrel (75 mg/day) for one year. Other medications, including b-blockers, ACE-inhibitors, nitrates, and statins, were prescribed according to MISSION! protocol.

Invasive procedure and angiographic evaluation

All PPCI were performed through a 6F femoral sheath. Patients underwent PPCI and stenting of the infarct-related artery according to standard techniques.

The choice of stent (bare-metal stent or drug-eluting stent) was left to the operator's discretion. Direct stenting was performed only in cases presenting clear views of the arterial lesion with adequate flow. Otherwise, the patient was subjected to balloon angioplasty and stenting was done subsequently. Thrombectomy was frequently, but not exclusively, performed when high thrombus burden was observed at the initial angiographic image of the target vessel. Thrombus score was graded as previously described by the TIMI Study Group[6, 15]. Briefly, in TIMI thrombus grade 0, no cineangiographic characteristics of thrombus are present; in TIMI thrombus grade 1, possible thrombus is present with such angiographic characteristics as reduced contrast density, haziness, irregular lesion contour, or a smooth convex "meniscus" at the site of total occlusion, suggestive but not diagnostic of thrombus; in TIMI thrombus grade 2, there is definite thrombus, with the greatest dimensions ≤ ½ the vessel diameter; in TIMI thrombus grade 3, there is definite thrombus but with greatest linear dimension > ½ but < 2 vessel diameter; in TIMI thrombus grade 4, there is definite thrombus, with the largest dimension ≥ 2 vessel diameters; and in TIMI thrombus grade 5, there is total occlusion.

We further categorized the thrombus score into two overall grades: a high thrombus grade (grades 4 and 5), and a low thrombus grade (grades 1-3) (Figure 1). We decided to use this cut-off value in line with previous studies[16-18] that showed prognostic value of this cut off. The inter-observer agreement was calculated with weighted Kappa statistics and showed good agreement (κ= 0.92, p<0.001). Coronary flow was graded according to Thrombolysis In Myocardial Infarction (TIMI) criteria[19]. TIMI flow grade was evaluated at baseline and after the PCI procedure. Procedural success was defined as residual stenosis <20% and TIMI flow grade 3. The coronary angiograms were reviewed off-line by two independent interventional cardiologists who were blinded to the clinical data.

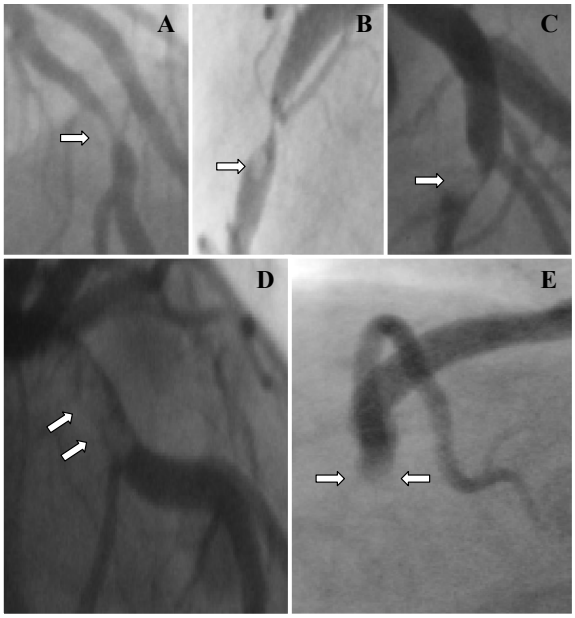

Figure 1: Thrombus (white arrows) graded according to TIMI working group classification: A: Thrombus grade 1; B: Thrombus grade 2; C: Thrombus grade 3; D: Thrombus grade 4; and E: Thrombus grade 5. We further scored the thrombus into two overall grades: a high thrombus grade (grades 4 and 5), and a low thrombus grade (grades 1-3).

Laboratory investigations

Cardiac troponin-T concentration in plasma was measured on a third generation Elecsys 2010 analyzer (Roche Diagnostics, Almere, the Netherlands). Creatine kinase (CK) activity in plasma was measured on a Roche Hitachi Modular P800 analyzer (Roche Diagnostics). According to MISSION! Protocol[13] blood samples were collected at admission and every 6 h in the first 48 h after PPCI. Subsequently these levels were determined every day up to discharge, unless clinical events prompted repeat measurements. Peak levels of CK and troponin-T in plasma were calculated as a measure of infarct size in each patient by an investigator blinded to the assigned treatment.

LVEF assessment by gated-SPECT

According to the MISSION! Protocol[13] all included patients were enrolled for a myocardial perfusion study at 90 days post-PPCI. An ECG gated-single photon emission computed tomography (SPECT) acquisition at rest using intravenous ^{99m}Technetium-Tetrofosmin (MYOVIEW, Amersham, Buckinghamshire, UK) was used to measure the left ventricular ejection fraction (LVEF) 90 days after PPCI. LVEF was calculated using an automated and validated method (QGS software, version 2.0; Cedars-Sinai Medical Center, Los Angeles, CA, USA). Detailed methods are described elsewhere[20]. In patients in whom gated-SPECT could not be performed due to technical difficulties, LVEF was estimated by echocardiographic biplane method. LVEF assessment was done by an investigator blinded to the assigned treatment.

Definition of pre-infarction angina

Pre-infarction angina (PIA) was defined as at least one episode of typical chest or left arm or jaw pain, either at rest or during exercise, less than 7 days before STEMI. The presence of PIA was diagnosed by a physician, blinded to the results of the PCI, from detailed clinical history taken before PCI.

Tested variables

We evaluated predictors of thrombus grade among different clinical, angiographic and laboratory data. Clinical data included age, gender, traditional risk factors, PIA, and symptom to balloon time. Prior pharmacotherapy at admission was also recorded including aspirin, clopidogrel, statins, β-blockers (BB), angiotensin converting enzymes inhibitors or angiotensin receptor blockers (ACEI/ARBs). Among laboratory data plasma troponin-T levels at admission were recorded. Angiographic data included the culprit artery, location of culprit lesion, and number of diseased vessels.

Statistical analysis

Categorical variables were compared using the X^2 test or Fisher's exact test. Continuous normally distributed data were tested by Student's t-test or in the case of a non-Gaussian distribution by a nonparametric test for independent samples (Mann Whitney *U*-test).The inter-observer agreements were calculated using weighted Kappa statistics. Variables that at univariate analysis had a p value ≤ 0.15 were included in a multiple logistic regression model with the 2-categories thrombus grade as the outcome. Infarct size as assessed by peak CK and peak troponin-T (after logarithmic transformation), as well as 3-months LVEF were analyzed in a multivariate linear regression model among different potentially relevant variables. Correlation between the outcomes was tested using Spearman's correlation. Data were expressed as mean ± SD or as median + inter-quartile range for continuous variables according to the data distribution; categorical variables were expressed as percentages. All analyses were performed using SPSS version 17.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

Hundred and fifty-eight consecutive patients were selected for this evaluation. From this group, 5 patients were excluded due to incomplete data sets, the study population thus comprised 153 patients; 94 had high thrombus grade (HTG), and 59 had low thrombus grade (LTG). Baseline clinical and angiographic characteristics of the studied population are presented in Tables 1 and 2, respectively. The rate of PIA was significantly higher in the LTG group (25% vs. 10%, p=0.009) than in the HTG group (Figure 2). Among the angiographic characteristics, there was less initial TIMI flow grade in the HTG group (p<0.001), and higher rate of using a thrombectomy catheter in the HTG group (p<0.001) than in the LTG group. HTG tended to be more frequently encountered in proximal culprit lesions (54% vs. 39%, p=0.06).

Table 1. Baseline clinical characteristics of the study groups

	HTG N=94	LTG N=59	*p*
Age in years	58.4±11.5	57.6±12.0	0.68[a]
Male, n (%)	70(74.5)	46(78)	0.62[b]
Medical History, n (%)			
Hypertension	28(29.8)	23(39)	0.24[b]
Hyperlipidemia	21(22.3)	19(32.2)	0.17[b]
Smoking	55(58.5)	28(47.5)	0.18[b]
Family history	43(45.7)	24(40.7)	0.53[b]
Diabetes mellitus	6(6.4)	8(13.6)	0.16[b]
Previous MI	10(10.6)	5(8.5)	0.66[b]
Previous PCI	6(6.4)	5(8.5)	0.62[b]
Previous CABG	4(4.3)	1(1.7)	0.38[b]
Symptoms to balloon (min)	143(95-226)	135(88-225)	0.47[c]
Abciximab to ballon (min)	37(29-48)	36(24-60)	0.95[c]
Pre-infarction angina	9(9.6)	15(25.4)	0.009[b]
Previous aspirin	16(17)	9(15.3)	0.77[b]
Previous clopidogrel	1(1.1)	0(0)	0.42[b]
Previous statins	15(16)	9(15.3)	0.91[b]

Data are presented as mean ± standard deviation, number (%) of patients or median (Interquartile range). MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

[a] Compared using unpaired t test.

[b] Compared using Chi-square or Fisher exact test.

[c] Compared using Mann-Whitney U test.

Table 2. Angiographic and peri-procedural characteristics of the study groups

	HTG N=94	LTG N=59	*p*
Infarct related artery, n (%)			0.1[b]
Left main artery	3(3.2)	0(0)	
Left anterior descending artery	33(35.1)	24(40.7)	
Circumflex artery	9(9.6)	12(20.3)	
Right coronary artery	49(52.1)	23(39)	
Diseased vessels, n (%)			0.18[b]
1-vessel	57(60.6)	31(52.5)	
2-vessel	33(35.1)	21(35.6)	
3-vessel	4(4.3)	7(11.9)	
Proximal culprit lesion, n (%)	51(54.3)	23(39)	0.06[b]
Abciximab	94(100)	58(98.3)	0.9[b]
Initial TIMI flow grade, n (%)			<0.001[b]
0	61(64.9)	16(27.1)	
1	16(17)	12(20.3)	
2	14(14.9)	16(27.1)	
3	3(3.2)	15(25.4)	
Final TIMI flow grade, n (%)			0.16[b]
1	2(2.1)	0(0)	
2	18(19.1)	6(10.2)	
3	74(78.7)	53(89.8)	
Aspiration thrombectomy	65(69.1)	13(22)	<0.001[b]
Drug eluting stents, n (%)	45(57)	52(70)	0.1[b]
Stent number, n (%)			0.25[b]
0	4(4.2)	0(0)	
1	59(62.8)	37(62.7)	
>1	31(33)	22(37.3)	
Predilatation, n (%)	66(70.2)	46(78)	0.29[b]

Data are presented as mean ± standard deviation, number (%) of patients.
TIMI, Thrombolysis In Myocardial Infarction.
[a] Compared using unpaired t test.
[b] Compared using Chi-square or Fisher exact test.

Predictors of high thrombus grade (HTG)

Univariate and multivariate logistic regression analyses with thrombus grade as outcome revealed that only absence of PIA (OR=0.29, 95% CI=0.11-0.75, p=0.01) and presence of a proximal culprit lesion (OR=2.10, 95% CI=1.02-4.36, p=0.04) were independent predictors of HTG (Table 3).

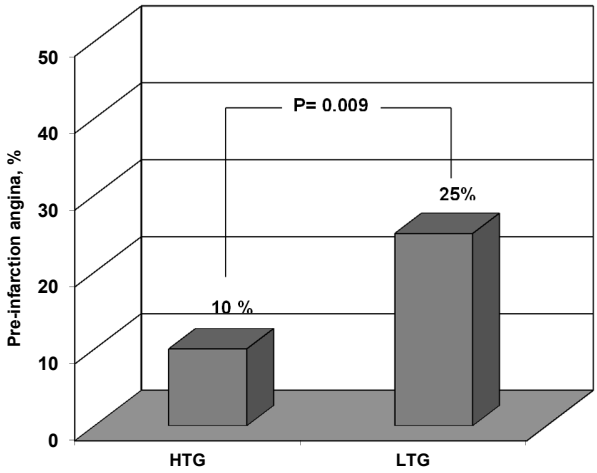

Figure 2: Rate of pre-infarction angina among the two categories of thrombus grade. HTG, high thrombus grade; LTG, low thrombus grade.

Infarct size

Peak levels of CK and troponin-T in plasma were significantly higher in the HTG group than in the LTG group (p<0.001 for both) (Table 4). Among the potentially relevant variables including age, sex, symptom to balloon time, hypertension, current smoking, hypercholesterolemia, diabetes mellitus, PIA, prior drug therapy, number of vessels diseased, culprit artery, proximal culprit lesion, thrombus grade and use of thrombosuction, HTG predicted high peak levels of CK (*B*= -1.0, 95% CI= -1.4 – -0.6, p<0.001) and troponin-T (*B*= -1.1, 95% CI= -1.6 – -0.6, p<0.001).

Scintigraphic LVEF at 3 months

LVEF was not significantly different between both groups of thrombus grade (Table 4). However, when corrected for the aforementioned factors in a multivariate linear regression model, it was found that HTG predicted a slightly worse LVEF (*B*=4.9, 95% CI= -0.06 – 10, p=0.05), along with male gender and absence of prior statin therapy. The outcomes were moderately correlated (r= -0.45, p<0.0001 for LVEF and peak CK, and r= -0.5, p<0.0001 for LVEF and peak TnT)

DISCUSSION

Key findings of the present study were: 1) the absence of PIA and a proximal location of the culprit lesion independently predicted higher angiographic thrombus grade, 2) Higher thrombus grade was associated with significantly higher infarct size as assessed by peak CK

Table 3. Univariate and multivariate logistic regression analyses with thrombus grade as end-point

Predictors	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Male gender	0.82	0.38- 1.78	0.62			
Age	1.01	0.97-1.03	0.68			
Symptom to balloon time	1.00	0.99- 1.00	0.72			
Hypertension	1.51	0.76- 2.99	0.24			
Hypercholesterolemia	1.65	0.79- 3.43	0.17			
Current smoking	0.64	0.33- 1.23	0.18			
Family history	0.81	0.42- 1.57	0.54			
Diabetes Mellitus	2.30	0.76- 7.00	0.14	2.61	0.81-8.39	0.11
Pre-infarction angina	0.31	0.13- 0.77	0.01	0.29	0.11-0.75	0.01
Prior aspirin therapy	0.87	0.36- 2.14	0.77			
Prior statin therapy	0.95	0.39- 2.33	0.91			
Prior β-blocker therapy	1.29	0.33- 5.02	0.71			
Prior ACEI/ARB therapy	1.54	0.70- 3.39	0.28			
Infarct related artery † :			0.12			0.17
LAD (including LM)	0.70	0.34-1.44	0.34	0.62	0.29-1.34	0.22
CX	0.35	0.13-0.95	0.04	0.39	0.14-1.11	0.08
Number of diseased vessels *:			0.21			
2-vessel disease	0.85	0.42-1.72	0.66			
3-vessel disease	0.31	0.08-1.14	0.08			
Proximal culprit lesion	1.86	0.96- 3.60	0.06	2.10	1.02- 4.36	0.04
Admission troponin-T	1.15	0.59- 2.24	0.67			

ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; LAD, left anterior descending; CX, circumflex.
† Right coronary artery (RCA) as reference.
* 1-vessel disease as reference

Table 4. Peak CK and troponin-T levels and 3-months LVEF in the study groups.

	HTG N=94	LTG N=59	*p*
Peak CK (U/L)	2435±218	1527±234	<0.001[a]
Peak troponin-T (μg/L)	6.5±0.7	3.8±0.7	<0.001[a]
LVEF at 3 months*	52±13	54±12	P=0.4[b]

Data are presented as mean ± standard deviation.
CK, creatine kinase; LVEF, left ventricular ejection fraction;
HTG, high thrombus grade; LTG, low thrombus grade.
[a] Compared using Mann-Whitney *U* test.
[b] Compared using unpaired *t*-test.
* Computed By Myoview, except in 11% of the patients,where 2-D echocardiographic biplane method was utilized.

and troponin-T levels in plasma, as well as lower LVEF at 3 months along with male gender and absence of prior statin therapy.

The issue of identifying predictors of thrombus grade has gained wide interest from the time PPCI was established as the gold standard reperfusion strategy for STEMI. The presence of large thrombus burden has been found to be an independent predictor of major adverse cardiac events (MACE) and infarct-related artery stent thrombosis in patients treated with drug-eluting stents for STEMI[21, 22].

Cardioprotective effect of PIA

PIA is associated with improved prognosis after AMI[9, 12, 23, 24]. Several mechanisms may explain this protective effect of PIA on myocardial reperfusion, such as myocardial ischemic preconditioning[9, 24, 25], enhanced collateral circulation towards the ischemic myocardium[26], and increased sensitivity to thrombolysis[12].

Recently, a new cardioprotective mechanism of PIA was proposed, which is the inhibition of microvascular obstruction phenomenon[27-29]. This was supported by a study conducted by Jesel *et al.*[30], who showed that absence of PIA was the only independent predictor of MRI-detected microvascular obstruction. This provides a new hypothetical mechanism for the clinical benefit of PIA, suggesting that PIA attenuates the development of the no-reflow phenomenon, not only through microvascular ischemic preconditioning[31], but also through limiting the extent of microvascular obstruction induced by distal embolization from large thrombus burden. This has to be further elucidated in larger studies reinforced by IVUS or OCT on one hand, and MRI or myocardial contrast echocardiography on the other for relating the culprit plaque morphology and microvascular obstruction extent respectively with PIA.

Angiographic thrombus burden

In 2010, Sianos et al[18] published a score for stratifying thrombus burden in STEMI patients. It was actually a modification from the established TIMI study group score[6], where they reclassified patients with Thrombus grade 5 into the other categories. They did that either after crossing with a wire or predilating with a balloon. In our study we adopted the original TIMI classification based on the fact that wire crossing and balloon inflation may alter thrombus grade, by inducing distal embolization. TIMI study group was precise in defining thrombus grade 5 not only on basis of total occlusion, but also based on the shape of this total occlusion, which ended abruptly, with a squared-off or an upstream convex termination, creating a stump or arterial cul-de-sac from which dye washout was delayed.

PIA and thrombus burden

Our study is the first to address the relation between PIA and thrombus grade in patients with STEMI. Previous studies have shown the benefits of PIA on surrogate markers of reperfusion[29], as well as on clinical outcomes[32].

Using IVUS, Higashikuni *et al.*[33] found that the culprit plaques of patients without PIA contained larger amount of necrotic core component than patients with PIA, whereas the plaques of patients with PIA consisted of larger amounts of the fibrofatty component than the plaques of patients without PIA. Moreover, they found more plaque rupture among patients without PIA than in those with PIA. This difference may explain the difference in thrombus burden and consequently the difference in clinical outcomes between both groups of patients. The necrotic core component was shown to be the most thrombogenic component in human atherosclerotic plaques[34, 35]. Exposure of the necrotic core component (plaque rupture) leads to exposure of Tissue Factor, thereby increasing thrombogenicity and abrupt thrombus formation. Thus, necrotic core-rich plaques may produce large thrombus burden, which may often result in sudden onset of AMI without PIA. Previously, Kojima *et al.*[36] demonstrated that patients with PIA were more likely to have plaque erosion as a substrate rather than plaque rupture, with subsequent exposure of the proteoglycan-rich matrix without a large lipid core; this has less potent thrombogenicity than plaques with lipid-rich core and consequently leads to less thrombus burden. In a study by Capone *et al.*[37], the incidence of thrombus by angiographic analysis was higher in patients with recent onset of rest angina than in those with slowly progressive PIA.

Proximal location of culprit lesion and thrombus burden

The present study revealed proximal location of the culprit artery as an independent predictor of HTG. To our knowledge, there was one previous study which has addressed this issue[16], revealing no predictive role for the location of the culprit lesion on the thrombus grade. However, in their study they analyzed the thrombus in the majority of the cases after the insertion of a 6F perfusion catheter, in contrast to our study in which the thrombus was analyzed and graded on the initial angiogram.

The PAMI study[38] showed that patients with proximal culprits had worse angiographic features with higher rates of initial TIMI 0-1 flow, and consequently worse in-hospital clinical outcomes despite rapid and successful reperfusion in the vast majority, thus arguing for the inclusion of proximal culprit lesion in the angiographic prognostication of AMI patients.

Coronary thromboses leading to AMI are distributed in a nonuniform manner. They tend to cluster within the proximal one-third of the coronary arteries and the likelihood of clinically significant plaque rupture decreases by 13–30% for each 10 mm distally from the coronary artery ostia[39, 40].

Thrombus burden and infarct size

Our study showed that HTG was a predictor of larger infarct size and when corrected for other relevant risk factors, HTG was associated with a lower LVEF.

Although no previous study has related thrombus grade to infarct size or LVEF, previous studies have shown that distal embolization and the subsequent no-reflow, which is partly

related to higher thrombus burden, were associated with larger infarct size, LV remodeling, and depressed LV function[41, 42].

PIA: a predictor of infarct size?

Although the myocardial protective benefits of PIA have been established in previous studies[10, 11, 43], we could not reproduce this finding. A possible explanation is that a study with a relatively small sample size (only 24 patients had PIA) lacks statistical power. In a previous study[44], it has been concluded that the protective effect of PIA in AMI is overwhelmed by the protective effects of complete revascularization provided by PPCI.

Future clinical implications

The present study argues for the consideration of PIA as a clinical predictor of thrombus burden in STEMI patients, thus setting the basis for implementing strategies aiming to decrease thrombus grade before stent implantation such as thrombus aspiration and the use of platelet glycoprotein IIb/IIIa antagonists in selected patients. Earlier administration of Gp IIb/IIIa antagonists results in higher pre-interventional TIMI flow with subsequently improved perfusion post-PCI[45-47], which in turn reflects less thrombus burden. Earlier Gp IIb/IIIa antagonists administration requires treatment in the pre-hospital setting, which for many dedicated primary PCI centers may pose substantial logistical obstacles. Therefore, the early administration of Gp IIb/IIIa antagonists could be limited to patients in whom high thrombus burden is predicted.

This may set a strategy for pre-hospital triage of STEMI patients receiving early pre-hospital antithrombotic treatment. Since high-dose clopidogrel administration takes 3–4 h to reach the top of inhibition of platelet aggregation[48], Gp IIb-IIIa inhibitors are considered to rapidly inhibit platelet aggregation, with subsequent benefits in mortality according to the risk profile. The use of risk scores, such as the TIMI Risk Score[49], should be strongly encouraged to identify a high risk population with thrombotic complications that largely outweigh the risk of bleeding complications, and in whom a selective strategy of pre-hospital/pre-PCI aggressive anti-thrombotic therapy is to be adopted.

Recently, a great deal of research has focused on development of new antiplatelet agents that could be administered orally or intravenously and, unlike the currently applied thienopyridines, could provide direct-acting reversible inhibition of the platelet P2Y12 receptor. New agents as "Cangrelor"[50-53] and "Elinogrel"[54, 55] are characterized by a rapid onset of action, more effective platelet inhibition, and favorable safety profile with rapid reversal of its antiplatelet effect post-infusion, thus allowing for surgery without a significant delay. Furthermore, "Vorapaxar" (SCH 530348)[56, 57] and "Atopaxar" (E5555)[58, 59] are orally administered agents that reversibly inhibit platelet protease activated receptor (PAR)-1, through which thrombin induces its effect on platelet aggregation, and thus, thrombus formation. This concept of rapidly acting and rapid reversibility of platelet inhibition could fuel further research about

the triage of pre-hospital treatment among STEMI patients with suspected high thrombotic burden.
We believe that the next step towards further optimization of care among STEMI patients is to improve pre-hospital triage, not only by diagnosing STEMI patients in the ambulance, but also starting early pre-hospital pharmacotherapy which necessitates the implementation of a risk/benefit scoring system. This scoring system should take in consideration clinical (as PIA) as well as rapid bed-side laboratory data (cardiac biomarkers), among others, to identify patients who would benefit most from early pre-hospital treatment.

LIMITATIONS

The study may have been limited by its observational design, and the relatively small sample size which may hinder the prognostic power. However, implementation of a stringent protocol for the study population (MISSION! protocol)[13] reinforces our results. No long-term clinical follow-up was performed. Therefore, a correlation between thrombus burden and clinical outcomes is lacking.
Owing to the small number of included population, and the retrospective nature of the study, we could not perform reliable testing of each single thrombus subgroup. However, Sianos et al[18] validated this categorization in a large cohort of 900 STEMI patients, and found that large thrombus (≥ twice the vessel diameter) independently predicted mortality and MACE.
Many factors can influence the angiographic assessment of thrombus burden (such as the TIMI flow, vessel size, culprit complex lesions with ulcers or intra-plaque dissections) that can confuse the analyst. More reliable methods to assess thrombus burden should be considered such as; the amount of aspirated thrombus, or thrombus assessed by optical coherence tomography.

CONCLUSION

PIA is associated with a decreased angiographic thrombus grade, whereas proximal culprit lesions are associated with higher thrombus grade. Higher thrombus grade was in turn associated with larger infarct size as well as slightly worse LV function. This may have clinical implications in planning strategies, particularly regarding pharmacotherapy, that aim to decrease thrombus burden prior to stent implantation, particularly in high risk patients without PIA.

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