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Angiographic Stent Thrombosis After Routine Use of Drug-Eluting Stents in ST-Segment Elevation Myocardial Infarction

The Importance of Thrombus Burden

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Objectives This study sought to investigate the impact of thrombus burden on the clinical outcome and angiographic infarct-related artery stent thrombosis (IRA-ST) in patients routinely treated with drug-eluting stent (DES) implantation for ST-segment elevation myocardial infarction (STEMI).

Background There are limited data for the safety and effectiveness of DES in STEMI.

Methods We retrospectively analyzed 812 consecutive patients treated with DES implantation for STEMI. Intracoronary thrombus burden was angiographically estimated and categorized as large thrombus burden (LTB), defined as thrombus burden ≥2 vessel diameters, and small thrombus burden (STB) to predict clinical outcomes. Major adverse cardiac events (MACE) were defined as death, repeat myocardial infarction, and IRA reintervention.

Results Mean duration of follow-up was 18.2 ± 7.8 months. Large thrombus burden was an independent predictor of mortality (hazard ratio [HR] 1.76, $p = 0.023$) and MACE (HR 1.88, $p = 0.001$). The cumulative angiographic IRA-ST was 1.1% at 30 days and 3.2% at 2 years, and continued to augment beyond 2 years. It was significantly higher in the LTB compared with the STB group (8.2% vs. 1.3% at 2 years, respectively, $p < 0.001$). Significant independent predictors for IRA-ST were LTB (HR 8.73, $p < 0.001$), stent thrombosis at presentation (HR 6.24, $p = 0.001$), bifurcation stenting (HR 4.06, $p = 0.002$), age (HR 0.55, $p = 0.003$), and rheolytic thrombectomy (HR 0.11, $p = 0.03$).

Conclusions Large thrombus burden is an independent predictor of MACE and IRA-ST in patients treated with DES for STEMI. (J Am Coll Cardiol 2007;50:573–83) © 2007 by the American College of Cardiology Foundation

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Primary percutaneous coronary intervention (PCI) with bare metal stent (BMS) implantation is established as the treatment of choice for ST-segment elevation myocardial infarction (STEMI) (1,2). There are limited data regarding the use of drug-eluting stents (DES) in a STEMI setting. Initial small registries showed superiority of sirolimus-eluting stents (SES) compared with BMS up to 1 year of follow-up (3–8). Two randomized trials confirmed these results (9,10). The findings regarding paclitaxel-eluting stents (PES) are less clear with positive small single-center reports (11,12), but a negative randomized trial (13). There are no data on the routine use of DES for STEMI with midterm outcomes.

The etiology of stent thrombosis is multifactorial, involving stent thrombogenicity and procedure-, lesion-, and patient-related factors (14). Acute coronary syndromes have been recognized as a factor of increased rates of stent thrombosis both for BMS (15–17) and DES (18–20). Limited data exist regarding the incidence and predictors of DES thrombosis during STEMI (9,10,13,18).

In patients with acute coronary syndromes, angiographic presence of thrombus increases the incidence of in-hospital major adverse cardiac events (MACE) (21,22). Mechanical treatment of thrombotic lesions, by means of thrombectomy and distal protection devices, has been proposed to prevent the complications caused by thrombus and improve clinical outcomes, but randomized trials failed to show any beneficial

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Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
IRA-ST = infarct-related artery stent thrombosis
LTB = large thrombus burden
MACE = major adverse cardiac events
MI = myocardial infarction
PES = paclitaxel-eluting stents
PCI = percutaneous coronary intervention
RT = rheolytic thrombectomy
SES = sirolimus-eluting stent(s)
STB = small thrombus burden
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombosis In Myocardial Infarction
TLR = target lesion revascularization (of the infarct-related artery)
TVR = target vessel revascularization (of the infarct-related artery)

effect of routine use in "all comers" on myocardial reperfusion or clinical outcome during STEMI (23,24). There is no angiographic thrombus classification validated to predict clinical outcomes.

In a large unselected cohort of consecutive patients with STEMI treated with PCI and DES, we propose a simple angiographic thrombus classification, and we report the 2-year clinical outcome and incidence and predictors of infarct-related artery stent thrombosis (IRA-ST).

Patients and Methods

Patients and procedure. From April 2002, when DES were introduced, until December 2004, 900 consecutive patients presented with STEMI and underwent PCI (primary or rescue) within 12 h after the onset of chest pain; 37 (4.1%) were treated with balloon angioplasty, 51 (5.7%) with BMS, and 812 (90.2%) with DES. The BMS were implanted because of unavailability of all DES sizes (length or diameter) in the initial period of their approval. This analysis focuses on patients treated exclusively with DES. All patients were pretreated with 250 mg aspirin and 300 mg clopidogrel. Preprocedural intracoronary nitrates were systematically administered. A PCI was performed according to standard clinical practice. The use of rheolytic thrombectomy (RT) (Possis Medical, Inc., Minneapolis, Minnesota), the only thrombectomy or aspiration system used, and periprocedural pharmacological treatment (e.g., glycoprotein IIb/IIIa antagonists) were at the operator's discretion. All patients received dual antiplatelet therapy: aspirin 325 mg/day indefinitely and clopidogrel 75 mg/day for 3 and 6 months after SES and PES implantation, respectively.

Clinical follow-up. Information regarding baseline clinical characteristics, procedural details, and in-hospital events was obtained from electronic databases maintained at Erasmus Medical Center. Postdischarge survival status was obtained from the Municipal Civil Registry. A questionnaire was mailed to all living patients focusing on rehospitalization and MACE. Referring cardiologists, general practitioners, and patients were contacted when necessary for additional information. All patients provided written informed consent.

Angiographic analysis. Intracoronary thrombus was angiographically identified and scored in 5 grades as previously described (25). According to this classification, in thrombus grade 0 (G0), no cineangiographic characteristics of thrombus are present; in thrombus grade 1 (G1), possible thrombus is present, with such angiography 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 thrombus grade 2 (G2), there is definite thrombus, with greatest dimensions $\leq$1/2 the vessel diameter; in thrombus grade 3 (G3), there is definite thrombus but with greatest linear dimension $>$1/2 but $<$2 vessel diameters; in thrombus grade 4 (G4), there is definite thrombus, with the largest dimension $\geq$2 vessel diameters; and in thrombus grade 5 (G5), there is total occlusion (unable to assess thrombus burden due to total vessel occlusion).

In patients presenting with an open IRA, thrombus was scored in the preintervention angiographic sequence more clearly depicting its size. In patients presenting with an occluded IRA (G5; essentially no flow and not thrombus classification), thrombus was reclassified into one of the other categories after flow achievement with either guidewire crossing or a small (diameter 1.5 mm) deflated balloon passage or dilation. After reclassification of the G5 group, thrombus burden was stratified in 2 categories, scored as a small thrombus burden (STB) for thrombus $<$G4 and a large thrombus burden (LTB) for thrombus G4, based on clinical outcomes.

Thrombosis In Myocardial Infarction (TIMI) flow and myocardial blush were assessed as previously reported (26,27). No reflow was defined as reduced antegrade flow (TIMI flow grade $<$2) in the absence of occlusion at the treatment site or evidence of distal embolization. Distal embolization was defined as migration of a filling defect to distally occlude the infarct-related vessel or one of its branches, or a new abrupt cutoff of the distal vessel/branch.

Stent thrombosis was defined as a complete or partial occlusion within the stented segment with evidence of thrombus and reduced antegrade flow (TIMI flow grade $<$3) with a concurrent acute clinical ischemic event. The stent thrombosis cases were categorized according to the timing of occurrence into acute (from the end of the procedure up to 24 h), subacute (from 24 h up to 30 days), late (between 30 days and 6 months), and very late ($>$6 months).

All procedural parameters, including thrombus classification, were assessed by 2 experienced interventional cardiologists reviewing the angiograms together. Both reviewers were blinded to clinical outcomes. Consensus was achieved in all patients. Half of the films were randomly selected and reanalyzed by the same analysts for intraobserver variability, and by a third experienced interventional cardiologist for interobserver variability of the proposed LTB and STB classification.

Definitions. Repeat myocardial infarction (MI) (nonfatal) was defined as new clinical symptoms or electrocardiogram changes associated with an increase in the creatine kinase level to more than twice the upper normal limit with an increased creatine kinase-MB. In cases in which the creatine kinase level had not returned to normal values after the index event, a second peak was defined as repeat MI. Target lesion revascularization (TLR) was defined as any repeat revascularization of the IRA involving the stent and/or its 5-mm proximal or distal edges.

Target vessel revascularization (TVR) was defined as any repeat revascularization of the IRA. A MACE was defined as death, repeat MI, and TVR.

Statistics. Categorical variables (presented as counts and percentages) were compared using the chi-square test or Fisher exact test where the expected value in any cell was <5. The unpaired *t* test was used for comparing continuous variables (presented as the mean ± SD). Cumulative event rates were estimated using the Kaplan-Meier method, and differences between groups were assessed by the log-rank test of significance. Variables associated with event rates on univariate analysis at a level of $p \leq 0.2$ were entered in a multivariate Cox model with a stepping algorithm, and then the variables referring to thrombus burden and RT were forced into the model to estimate their independent effect along with the other predictors of clinical outcome (mortality, MACE, stent thrombosis). In-hospital events were included in the survival analysis. All tests were 2-tailed, and a value of $p < 0.05$ was considered significant. The SPSS statistical software package (version 12.0 for Windows, SPSS Inc. Chicago, Illinois) was used for the analysis.

Table 1 Baseline Clinical, Angiographic, and Procedural Characteristics

Characteristic	Total Population (n = 792)	STB (n = 567)	LTB (n = 225)	p Value*
Age (yrs)	59.4 ± 11.5	59.6 ± 11.6	58.8 ± 11.1	0.38
Female	166 (21%)	122 (21.5%)	44 (19.6%)	0.54
Diabetes	80 (10.1%)	50 (8.8%)	30 (13.3%)	0.057
Hypertension	215 (27.1%)	148 (26.1%)	67 (29.8%)	0.294
Hypercholesterolemia	240 (30.3%)	177 (31.2%)	63 (28.0%)	0.374
Smoking	299 (37.8%)	223 (39.3%)	76 (33.8%)	0.146
Family history of CAD	207 (26.1%)	144 (25.4%)	63 (28.0%)	0.452
Previous MI	80 (10.1%)	54 (9.5%)	26 (11.6%)	0.392
Previous PCI	46 (5.8%)	24 (4.2%)	22 (9.8%)	0.003
MI presentation				
Infarct duration (h)†	4.5 ± 11.3	4.3 ± 8.5	4.9 ± 14.9	0.659
Peak CK-MB (IU/l)	314.5 ± 303.6	305.3 ± 292.4	335.9 ± 328.2	0.699
Primary PCI	712 (89.9%)	503 (88.7%)	209 (92.9%)	0.079
Rescue PCI	80 (10.1%)	64 (11.3%)	16 (7.1%)	0.079
Cardiogenic shock	76 (9.6%)	50 (8.8%)	26 (11.6%)	0.238
Stent thrombosis	22 (2.8%)	6 (1.1%)	16 (7.1%)	<0.001
Prehospital resuscitation	21 (2.7%)	15 (2.6%)	6 (2.7%)	0.987
Multivessel disease	309 (39.0%)	229 (40.4%)	80 (35.6%)	0.209
Infarct-related artery				0.007
Left main stem	11 (1.4%)	10 (1.8%)	1 (0.4%)	
Left anterior descending	404 (51%)	299 (52.7%)	105 (46.7%)	
Right coronary artery	297 (37.5%)	199 (35.1%)	98 (43.6%)	
Circumflex coronary artery	75 (9.5%)	58 (10.2%)	17 (7.6%)	
Vein or IMA graft	5 (0.6%)	1 (0.2%)	4 (1.8%)	
Multivessel PCI	85 (10.7%)	69 (12.2%)	16 (7.1%)	0.038
Pacemaker	107 (13.5%)	46 (8.1%)	61 (27.1%)	<0.001
IABP	91 (11.5%)	57 (10.1%)	34 (15.1%)	0.044
Inotropes	90 (11.4%)	59 (10.4%)	31 (13.8%)	0.177
Glycoprotein IIb/IIIa antagonists	401 (50.6%)	251 (44.3%)	150 (66.7%)	<0.001
Distal protection device	15 (1.9%)	2 (0.4%)	13 (5.8%)	<0.001
Drug-eluting stent type				0.004
Sirolimus-eluting stent	200 (25.3%)	159 (28.0%)	41 (18.2%)	
Paclitaxel-eluting stent	592 (74.7%)	408 (72.0%)	184 (81.8%)	
Bifurcational stenting	51 (6.4%)	33 (5.8%)	18 (8.0%)	0.26
Direct stenting	442 (55.8%)	321 (56.6%)	121 (53.8%)	0.469
Rheolytic thrombectomy	63 (8.0%)	4 (0.7%)	59 (26.2%)	<0.001

*STB versus LTB group. †Infarct duration was available in 531 patients (361 in the STB and 170 in the LTB group).

CAD = coronary artery disease; CK = creatine kinase; IABP = intra-aortic balloon pump; IMA = internal mammary artery; LTB = large thrombus burden; MI = myocardial infarction; PCI = percutaneous coronary intervention; STB = small thrombus burden.

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Kappa statistics were calculated for estimating the intraobserver (kappa = 0.95) and interobserver (kappa = 0.91) variability of the proposed thrombus classification after selecting randomly and reanalyzing half of the films.

Results

Complete follow-up information was obtained in 798 (98.3%) patients treated with DES (mean duration 18.2 ± 7.8 months), and both clinical follow-up and thrombus burden classification was available in 792 (97.5%) patients. Minimum follow-up for patients who survived the index hospitalization was 12 months. Baseline demographic and procedural characteristics of the total population and according to thrombus burden are presented in Table 1.

Angiographic classification of thrombus burden. Thrombus burden grading is presented in Table 2. More than half of the patients (57%) presented with an occluded IRA (G5). Reclassification into a thrombus category (G0 to G4) was achieved in 449 (98.7%) patients; in 305 (67.9%) after some flow achievement with guidewire crossing, and in 144 (32.1%) after a deflated 1.5-mm balloon passage or dilation (mean dilation pressure was 6.8 atm and mean duration of dilation was 16.6 s). An example of thrombus reclassification after wire crossing is presented in Figure 1. In 2 patients, thrombus G5 was sustained (no flow achievement), and in 4 patients reclassification was not possible because of inadequate angiographic documentation. Finally, thrombus burden was estimated in 792 (99.2%) patients.

In the reclassified G5 group, there were more G4 patients compared with the group with open IRA (33.0% vs. 22.4%, p = 0.001).

Clinical outcome. The 2-year cumulative clinical outcomes of the total population are presented in Figure 2, and 2-year cumulative mortality and MACE rate according to thrombus score after G5 reclassification are depicted in Figures 3A and 3B. Patient groups G1, G2, and G3 had similar 2-year cumulative mortality (7.8% vs. 9.6% vs. 7.9%, respectively, p = 0.95) and MACE rates (15% vs. 13.8% vs. 12.8%, respectively, p = 0.78), whereas groups G0 and G4 had higher rates (mortality 14.6% and 13%, respectively, p = 0.22; MACE rate 24.4% and 24.9%, respectively, p = 0.001) compared with the former groups. The G0 group compared with G1 to G3 had more multivessel PCI (20.6% vs. 11.1%, p = 0.029) and more left main stem and less right coronary artery involvement (4.8% vs. 1.4% and 19% vs. 37.1%, respectively, p < 0.001).

Based on the aforementioned results, we stratified thrombus burden in 2 groups of patients with STB, combining

Table 2 Classification of Thrombus Burden

Thrombus Score	Thrombus Burden* Reference (n = 798)	Reference Non-G5† (n = 343)	G5 Reclassified† (n = 455)	Reclassified Final (n = 798)
G5	455 (57.0)	0 (0)	2 (0.4)	2 (0.3)
G4	77 (9.6)	77 (22.4)	148 (32.5)	225 (28.2)
G3	61 (7.6)	61 (17.8)	80 (17.6)	141 (17.7)
G2	95 (11.9)	95 (27.7)	113 (24.8)	208 (26.1)
G1	68 (8.5)	68 (19.8)	87 (19.1)	155 (19.4)
G0	42 (5.3)	42 (12.2)	21 (4.6)	63 (7.9)
Not available‡	0 (0)	0 (0)	4 (0.9)	4 (0.5)

Data are presented as n (%). *Reference is the classification that includes patients with occluded vessels at presentation (G5), and reclassified is the one after thrombus evaluation in this group following minimal intervention. †p < 0.001 for the comparison of G0, G1, G2, G3, G4 between "Reference Non-G5" and "G5 Reclassified" groups. ‡In 4 patients, reclassification was not possible because of inadequate angiographic documentation.

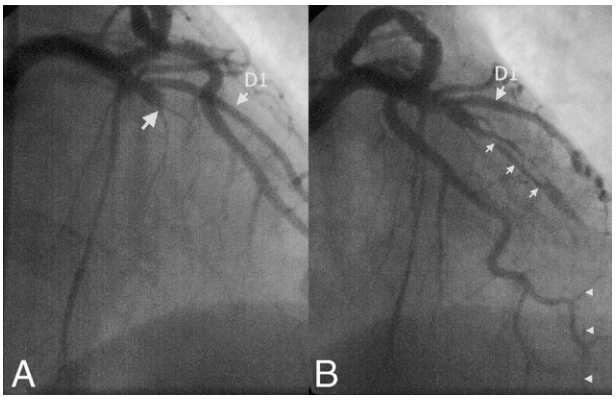

Figure 1 Thrombus Burden Evaluation in a Patient Presenting With an Occluded Infarct-Related Artery

(A) An occluded left anterior descending coronary artery **(arrow)** after the take-off of the first diagonal branch (D1) in a patient who presented with anterior myocardial infarction. **(B)** After crossing the occlusion with an angioplasty guidewire **(arrowheads)** and without further intervention, Thrombolysis In Myocardial Infarction flow grade 1 was restored, allowing the visualization of a large thrombus **(arrows)**.

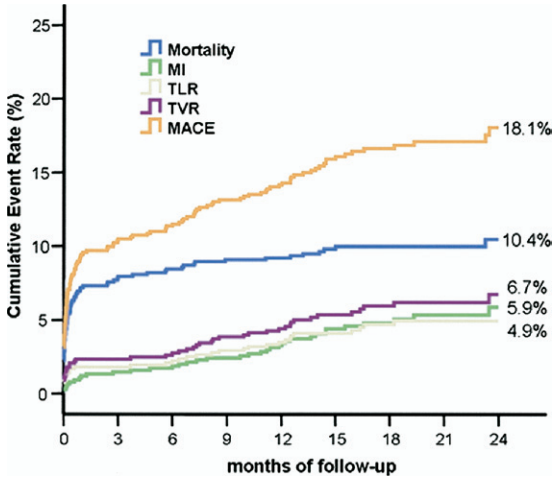

Figure 2 Overall Clinical Outcomes

Two-year cumulative mortality, repeat nonfatal myocardial infarction (MI), infarct-related artery lesion repeat revascularization (TLR), infarct-related artery repeat revascularization (TVR), and major adverse cardiac event (MACE) (death, MI, TVR) rates of patients treated with drug-eluting stents.

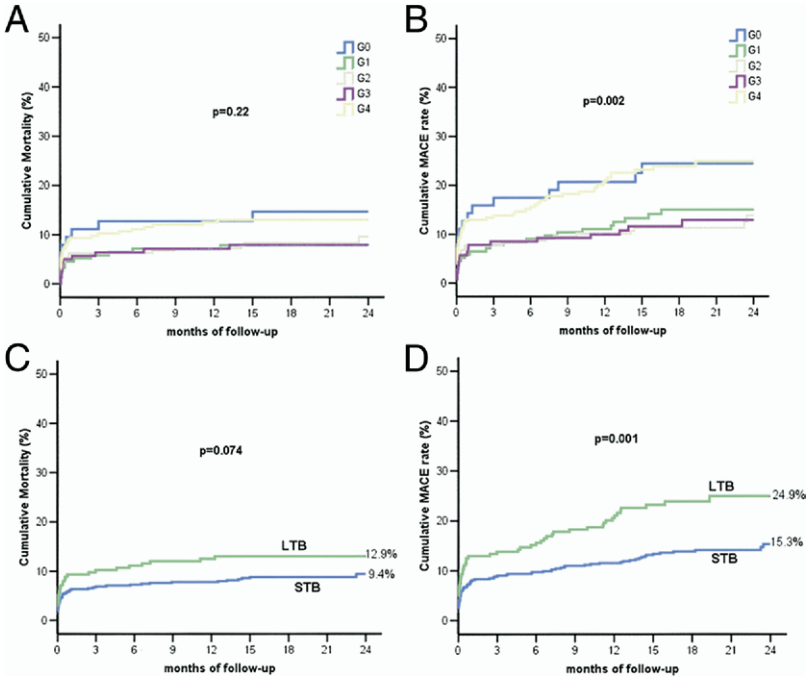

Figure 3 **Mortality and MACE According to Thrombus Burden**

Two-year cumulative mortality and MACE (death, repeat nonfatal myocardial infarction, or infarct-related artery repeat revascularization) rates according to the reclassified thrombus grades before **(A, B)** and after stratification in large thrombus burden (LTB) and small thrombus burden (STB) **(C, D)**. Other abbreviations as in Figure 2.

groups G0 to G3, and LTB, same as G4. The LTB group had higher in-hospital mortality (7.6% vs. 5.1%, p = 0.18). Two-year mortality and MACE rate were increased in LTB patients compared with the STB patients (Figs. 3C and 3D). The difference in mortality became evident early, at 30 days (Fig. 4A), and there was no difference beyond 30 days between the 2 groups (Fig. 4B). An LTB was an independent predictor of 30-day mortality (hazard ratio 1.96, 95% confidence interval 1.12 to 3.43, p = 0.019), as well as 2-year mortality and MACE (Table 3).

Procedural outcome. There were 7 (0.9%) procedural deaths (procedural mortality: LTB group 1.8% vs. STB group 0.5%, p = 0.1). Patients with LTB had a worse final TIMI flow grade, myocardial blush, and complete thrombus removal, as well as more cases of no reflow and distal embolization compared with STB patients (Table 4).

Incidence and predictors of stent thrombosis. Two-year cumulative stent thrombosis, IRA-ST (Fig. 5), and non–IRA-ST rates were 3.8 ± 0.7% (26 events), 3.2 ± 0.7% (22 events), and 0.6 ± 0.3% (4 events), respectively.

IRA-ST. The 2-year cumulative IRA-ST rate was significantly higher in LTB (16 events) compared with STB (6 events) patients (Fig. 5). An LTB was the most hazardous independent predictor of IRA-ST (Table 5). The LTB patients treated with RT had a lower 2-year cumulative IRA-ST (0% vs. 11.3%, p < 0.001) compared with LTB patients without RT.

In relation to antiplatelet medication, 9 (40.9%) IRA-STs occurred under dual antiplatelet therapy, 4 (18.2%) shortly (≤30 days) and 9 (40.9%) long (>30 days) after clopidogrel discontinuation. Chronologically, 4 (18.2%) patients had acute, 5 (22.7%) subacute, 2 (9.1%) late, and 11 (50%) very late IRA-ST. There were 3 additional events beyond the 2 years at 884, 1,067, and 1,074 days; 2 of them with LTB at baseline procedure.

There was no difference in the 2-year cumulative IRA-ST rate between PES and SES both for the total population (PES 3.7 ± 0.9% [18 events] vs. SES 2.1 ± 1.06% [4 events], p = 0.314) and the LTB group (PES 7.5 ± 2.1% [12 events] vs. SES 10.5 ± 4.9% [4 events], p = 0.598).

In patients presenting with stent thrombosis at the index procedure, the 2-year cumulative IRA-ST rate was 20.5 ± 9.2% (4 events), all with LTB. Stent thrombosis at presentation was an independent predictor of IRA-ST (Table 5).

Impact of IRA-ST on clinical outcome. Of the 22 IRA-ST patients, 4 (18.2%) presented with unstable angina, 16 (72.7%) suffered a nonfatal repeat MI, and there were 2 (9.1%) deaths; all underwent TLR. Two-year cumulative mortality attributable to IRA-ST was only 0.3%.

The LTB patients had increased 2-year cumulative repeat MI (Fig. 6A) and TLR (Fig. 6C) rates compared with STB patients. The 2-year cumulative repeat MI rate attributable to IRA-ST (2.4%, 16 events) accounted for 40.7% of the

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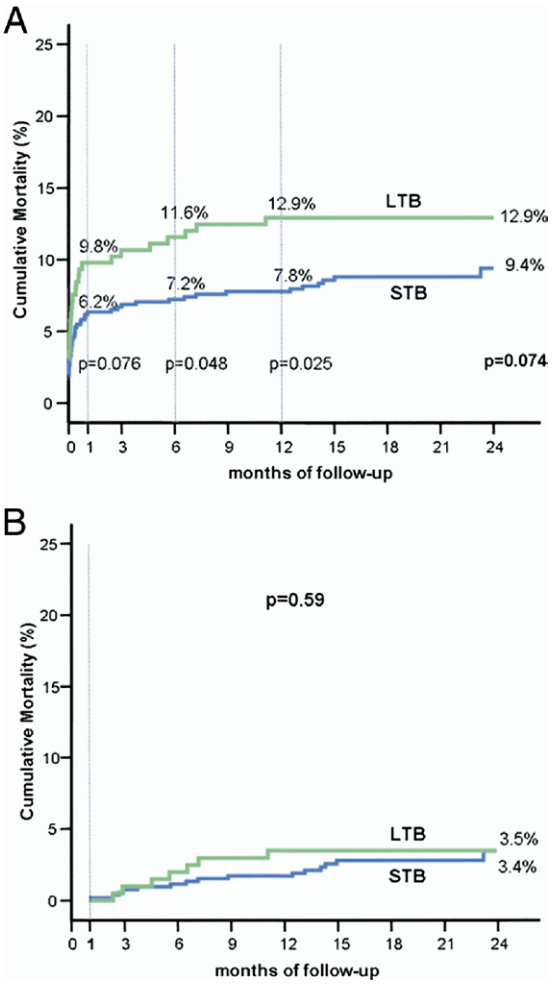

Figure 4 **Impact of Thrombus Burden on Mortality**

Two-year **(A)** and post-30-days cumulative mortality **(B)** according to the presence of large thrombus burden (LTB) or small thrombus burden (STB) at the index procedure.

total 2-year cumulative repeat MI rate (5.9%, 36 events). The 2-year cumulative TLR rate attributable to IRA-ST (3.2%, 22 events) accounted for 67.3% of the total 2-year cumulative TLR rate (4.9%, 34 events). After excluding patients with IRA-ST, there was no significant difference between LTB and STB patients in the 2-year cumulative repeat MI and TLR rates (Figs. 6B and 6D).

The LTB patients had a worse 2-year and post-30-days cumulative MACE rate compared with STB patients (Figs. 7A and 7B). The 2-year cumulative MACE rate attributable to IRA-ST (3.2%, 22 events) accounted for 17.7% of the total 2-year cumulative MACE rate (18.1%, 132 events). The post-30-days cumulative MACE rate attributable to IRA-ST (1.2%, 13 events) accounted for 21.9% of the total post-30-days cumulative MACE rate (9.6%, 58 events). After excluding patients with IRA-ST, there was no significant difference in the post-30-days cumulative MACE rate between LTB and STB patients (Fig. 7C). The LTB patients treated with RT had a lower MACE rate compared with LTB patients without RT (10.7% vs. 30% at 2 years, $p = 0.006$) but similar to that of STB patients (10.7% vs. 15.3% at 2 years, $p = 0.5$).

Discussion

We report our experience on a large cohort of consecutive patients presenting with STEMI and treated with PCI and DES. This is the first report accounting for thrombus burden. An LTB is a fundamental factor for adverse clinical outcomes because it is related to increased 30-day mortality and very high rates of IRA-ST, which account for the majority of the post-30-days MACE.

Thrombus burden. Almost 60% of the patients with STEMI presented with an occluded IRA (G5). This is essentially a flow classification (TIMI flow grade 0), and consequently excludes these patients from any analysis focusing on thrombus burden. We propose a method that allows thrombus burden estimation in almost 99% of these patients after flow restoration with minimal intervention. Minimal antegrade flow (even TIMI flow grade 1) allowing contrast penetration beyond the occlusion is adequate to allow thrombus evaluation.

There was no difference in the clinical outcome of patients with thrombus G1 to G3, both in the univariate and the multivariate analysis. This was the rationale for stratifying these groups as a single category defined as STB. Patients with no thrombus (G0) at presentation showed worse outcomes compared with G1 to G3 patients and similar outcomes compared with G4 patients. Despite their increased risk, these patients were included in the STB group because it is obvious that therapeutic strategies to improve their clinical outcome should not target thrombus.

Incidence of stent thrombosis during STEMI. Randomized trials of elective BMS implantation using dual antiplatelet therapy reported stent thrombosis rates of 0.4% to 1.3% (28,29). Stent thrombosis rates were reported to be similar (around 0.6%) between BMS and DES in a meta-analysis of 10 randomized trials of elective angioplasty (30). Concerns were recently raised that DES might be more thrombogenic compared with BMS in the long-term, especially when implanted in more complex patient subsets (31).

Acute coronary syndromes have been associated with increased rates of stent thrombosis. In registries representing "real world" practice, which included patients with acute coronary syndromes and STEMI treated either with BMS (16,17) or DES (18,32,33), higher rates of stent thrombosis (1.2% to 1.9%) were reported. In 4,607 patients treated with BMS for acute coronary syndromes, an even higher rate of 2.9% of stent thrombosis was observed (15). In the TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Angioplasty) trial, which randomized STEMI patients to SES or BMS, the nonangiographic stent thrombosis was 3.4% and 3.6%,

Table 3 Independent Predictors of Clinical Outcomes

Outcome	Variable	Hazard Ratio	95% Confidence Interval	p Value
2-yr mortality*	Age (per 10-yr increase)	1.76	1.4–2.22	<0.001
	Cardiogenic shock	9.47	5.87–15.28	<0.001
	Prehospital resuscitation	4.28	1.99–9.2	<0.001
	Infarct-related artery			0.024
	Right coronary artery (reference)	1.00		
	Left anterior descending coronary artery	1.66	0.97–2.82	0.064
	Circumflex coronary artery	2.07	0.94–4.55	0.069
	Left main coronary artery	4.06	1.64–10.03	0.002
	Graft	3.9	0.51–29.76	0.189
	Large thrombus burden	1.76	1.08–2.87	0.023
	Thrombus burden‡			0.168
	Grade 4 (reference)	1.00		
	Grade 3	0.51	0.25–1.05	0.066
	Grade 2	0.62	0.34–1.16	0.135
	Grade 1	0.47	0.23–0.95	0.034
	Grade 0	0.78	0.35–1.73	0.543
2-yr major adverse cardiac event†	Age (per 10-yr increase)	1.19	1.01–1.4	0.036
	Female	1.68	1.13–2.48	0.01
	Cardiogenic shock	6.31	4.28–9.28	<0.001
	Stent thrombosis presentation (at index procedure)	3.95	1.95–7.98	<0.001
	Bifurcational stenting	2.24	1.33–3.77	0.002
	Prehospital resuscitation	2.84	1.46–5.52	0.002
	Rheolytic thrombectomy	0.37	0.17–0.78	0.009
	Large thrombus burden	1.88	1.3–2.72	0.001
	Thrombus burden‡			0.005
	Grade 4 (reference)	1.00		
	Grade 3	0.5	0.29–0.88	0.016
	Grade 2	0.45	0.27–0.73	0.001
	Grade 1	0.52	0.31–0.87	0.014
	Grade 0	0.91	0.5–1.66	0.755

*Additional variables entered in the multivariate model but not found to be significant were: female gender, hypercholesterolemia, smoking, multivessel disease, multivessel percutaneous coronary intervention, intra-aortic balloon pump, glycoprotein IIb/IIIa antagonists, bifurcational stenting, direct stenting, final Thrombolysis In Myocardial Infarction flow grade, and stent type. †Additional variables entered in the multivariate model but not found to be significant were: hypercholesterolemia, previous myocardial infarction, previous percutaneous coronary intervention, infarct-related artery, multivessel disease, multivessel percutaneous coronary intervention, intra-aortic balloon pump, glycoprotein IIb/IIIa antagonists, direct stenting, final Thrombolysis In Myocardial Infarction flow grade, and stent type. ‡Similar results in the multivariate analysis (data not provided for the other predictors) were also shown when thrombus burden was inserted as a variable with 5 categories (grade 0, grade 1, grade 2, grade 3, grade 4) instead of 2 (large and small).

whereas the angiographic stent thrombosis was 2.0% and 3.4%, respectively, at 1 year (10). Similarly, in the SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent In Acute Myocardial Infarction) trial, 1-year stent thrombosis rates were 3.1% and 3.7% for SES and BMS, respectively (9).

Table 4 Procedural Outcome

Outcome	Total (n = 792)	STB (n = 567)	LTB (n = 225)	p Value*
Final Thrombolysis In Myocardial Infarction flow grade 3	726 (91.7)	538 (94.9)	188 (83.6)	<0.001
Myocardial blush grade 3†	290 (47.6)	222 (53.2)	68 (35.4)	<0.001
Complete thrombus removal	757 (95.6)	556 (98.1)	201 (89.3)	<0.001
No reflow	12 (1.5)	3 (0.5)	9 (4.0)	0.001
Distal embolization	59 (7.4)	20 (3.5)	39 (17.3)	<0.001

Data are presented as n (%). *Small thrombus burden (STB) versus large thrombus burden (LTB) group. †Myocardial blush assessment was achieved in 609 patients (417 in the STB and 192 in the LTB group).

We observed an incidence of angiographically documented stent thrombosis of 3.2% at 2 years. The angiographically documented stent thrombosis underestimates the true incidence of stent thrombosis because sudden deaths and repeat MIs also may be related to this complication. Moreover, patients continued to present with stent thrombosis beyond the 2-year time window. Similar cases of very late DES thrombosis in STEMI patients recently have been reported (34,35).

Mechanisms of early and late stent thrombosis during STEMI. Stent underexpansion, malapposition, residual dissections, and inflow/outflow disease have been well established by intravascular ultrasound as mechanical causes related to early stent thrombosis for BMS (16,36–39) and DES (40).

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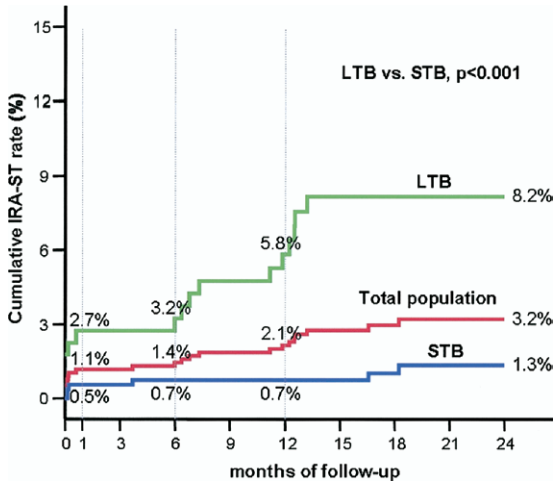

Figure 5 Infarct-Related Artery Stent Thrombosis

Two-year cumulative infarct-related artery stent thrombosis (IRA-ST) rate for the total population and according to the existence of large thrombus burden (LTB) or small thrombus burden (STB) at the index procedure.

Primary stenting during acute MI has been recognized as an independent predictor of late stent malapposition both after BMS (41) and DES (42) with an incidence 2- to 3-fold higher compared with elective stenting. Thrombus compression/displacement by the stent struts in the acute phase with abluminal thrombus resolution in the long term has been proposed as a potential mechanism. However, its incidence with DES was 31.8%, 3 times higher compared with BMS (11.5%). These intravascular ultrasound observations may well explain the negative late loss observed in STEMI trials with DES implantation and angiographic follow-up (3,6). An LTB was the strongest predictor of stent thrombosis, and LTB patients experienced an extremely high IRA-ST rate of 8.2%. It is rational that the larger the thrombotic burden, the higher will be the incidence of incomplete stent apposition that might account for the higher rates of late stent thrombosis in LTB patients in the long term. Moreover, the presence of thrombus has been clearly identified as a factor predisposing to stent thrombosis (14,36,39). Persistence of thrombus was an independent predictor of early repeat MI in the PAMI (Primary Angioplasty in Myocardial Infarction) trials (43). Patients with STB had an IRA-ST rate of 1.3%, similar to that reported during elective stenting (14,28,29).

Mechanical reasons may be inadequate to explain the stent thrombosis rates during STEMI; their incidence is common but the incidence of stent thrombosis remains relatively low. Increased platelet activity and aspirin resistance have been shown during STEMI (44). Furthermore, stent thrombosis has been associated with an impaired response to antiplatelet therapy, particularly in ACS patients (45). There is evidence that preintervention plaque composition resembling that of a STEMI setting predisposes to stent thrombosis (46).

Procedural and periprocedural factors related to stent thrombosis. Discontinuation of dual antiplatelet therapy after DES implantation has been related to an increased risk for stent thrombosis (32,33). In our study, 59% of our patients experienced IRA-ST while on aspirin monotherapy; 18% within the first 30 days after discontinuation of clopidogrel. Stent thrombosis occurred in patients while stable for very long on antiplatelet monotherapy. Dual antiplatelet therapy was not able to prevent 41% of the events. Whether it would have prevented the late cases of stent thrombosis remains unclear. The efficacy of dual antiplatelet therapy and its duration remains unclear in a STEMI setting.

Bifurcation stenting has been recognized previously as a risk factor for stent thrombosis in stable patients treated with DES (18,32). It was the second strongest independent predictor of stent thrombosis in our study, and therefore it should be avoided if not absolutely necessary.

The worse procedural outcomes observed in LTB compared with STB patients were translated into increased short-term mortality. Mortality after 30 days was comparable between the 2 groups. Similar results were recently reported in a large cohort of patients (47).

The use of thrombectomy devices during STEMI remains controversial. There were positive results reported when surrogate markers, such as ST-segment resolution, TIMI flow, or left ventricular remodeling (48–50), were used as end points, but there are no randomized studies reporting positive outcomes in hard clinical end points such as survival and MACE (23,24). The majority of these trials were underpowered for clinical outcomes, a fact that is indicative of the relative paucity of evidence, and thrombus burden was not considered. Safety issues were recently raised regarding routine application of thrombectomy in all comers with STEMI (24). Based on the current results, the potential of thrombectomy devices in STEMI should be explored selectively in patients at higher risk, such as those with LTB, in a prospective randomized fashion.

Efficacy of DES and thrombus burden. The rate of TVR with BMS implantation for STEMI has been reported to be 8% to 10% (51–53). Experience with DES for STEMI

Table 5 Independent Predictors of Infarct-Related Artery Stent Thrombosis

Variable*	Hazard Ratio	95% Confidence Interval	p Value
Age (per 10-yr increase)	0.55	0.37–0.82	0.003
Stent thrombosis at presentation	6.24	2.06–18.92	0.001
Bifurcational stenting	4.06	1.64–10.02	0.002
Rheolytic thrombectomy	0.11	0.01–0.81	0.03
Large thrombus burden	8.73	3.39–22.47	<0.001

*Additional variables entered in the multivariate model but not found to be significant were diabetes mellitus, previous myocardial infarction, previous percutaneous coronary intervention, and direct stenting.

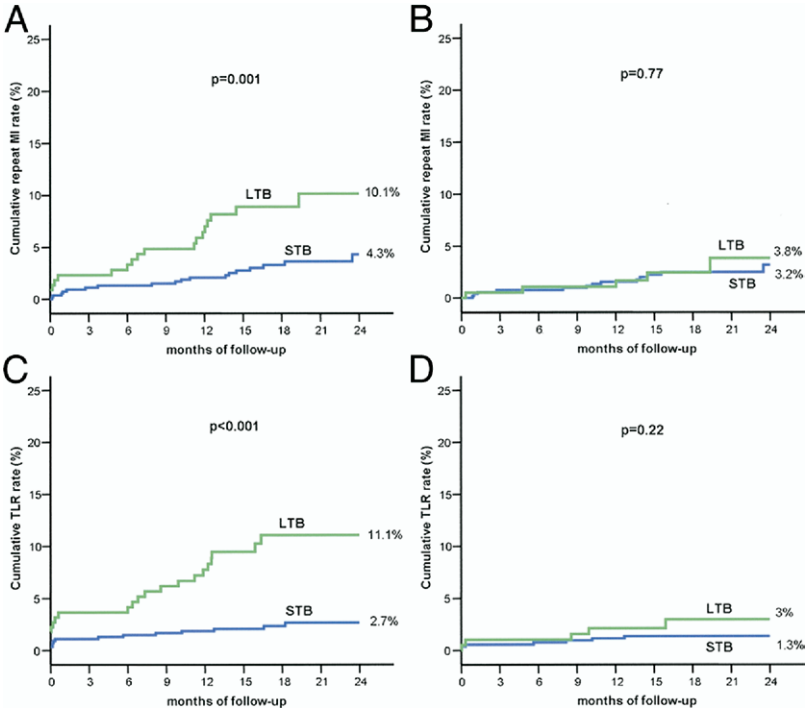

Figure 6 **Impact of Thrombus Burden and IRA-ST on Repeat MI and TLR**

Two-year cumulative **(A)** repeat myocardial infarction (MI) and **(C)** infarct-related artery lesion repeat revascularization (TLR) rates in relation to large thrombus burden (LTB) or small thrombus burden (STB) at the index procedure. The corresponding rates after excluding patients with infarct-related artery stent thrombosis (IRA-ST) are presented in **(B)** and **(D)**, respectively. After excluding IRA-ST, the total 2-year cumulative repeat MI and TLR rates are 3.3% and 1.7%, respectively.

showed lower TLR rates, around 2% to 4% (3,4,7,8,11,12). In our patients the 2-year TLR rate was 4.9%, and it was significantly higher in LTB compared with STB patients. It has been reported that thrombus can modulate stent-based drug elution and significantly alter vessel wall drug levels and potentially efficacy (54). Such concerns do not seem to be confirmed because excluding reintervention caused by IRA-ST, which is not related to restenosis, the overall TLR rate was very low (1.7%) and was comparable in LTB and STB patients.

Study limitations. This is a retrospective analysis with all of the limitations arising from such an approach. Potential thrombus burden modification related to preprocedural pharmacotherapy cannot be excluded. Angiography has inherent limitations for assessing thrombus burden, and there is no gold standard method to be compared with. However, it is the imaging modality used for decision making during PCI for STEMI, and in that respect this classification is clinically relevant. The poor outcome of G0 patients is poorly understood and should be further explored. Established parameters related to clinical outcomes such as infarct duration and myocardial blush were not available for all patients and were not included in the multivariate analysis model. No quantitative angiographic analysis was performed, and parameters such as lesion characteristics and stent length also were not accounted for.

Discontinuation of antiplatelet medication is a well-established risk factor for stent thrombosis. In our analysis, the antiplatelet medication status of the patients who developed stent thrombosis was well established, but no reliable information was possible to be obtained for patients who did not experience stent thrombosis, and therefore this parameter also was not included in the multivariate analysis. Of note, 6 months of double antiplatelet medication, the maximum prescribed in our patients, is regarded as inadequate today. All patients who developed stent thrombosis beyond 6 months were on aspirin monotherapy. We currently prescribe 12 months of double antiplatelet medication in all STEMI patients treated with DES.

Conclusions

In patients presenting with STEMI, minimal intervention with either guidewire crossing or a small (diameter 1.5 mm) deflated balloon passage or predilation restores flow enough to allow intracoronary thrombus estimation in angiographically occluded vessels. Thrombus stratification in LTB (≥2 vessel diameters) and STB has prognostic value.

Patients with STEMI treated with PCI and DES experience a high 2-year rate (3.2%) of IRA-ST, which continues to occur even beyond that time window. An LTB is a predictor of MACE. This is because of increased 30-day

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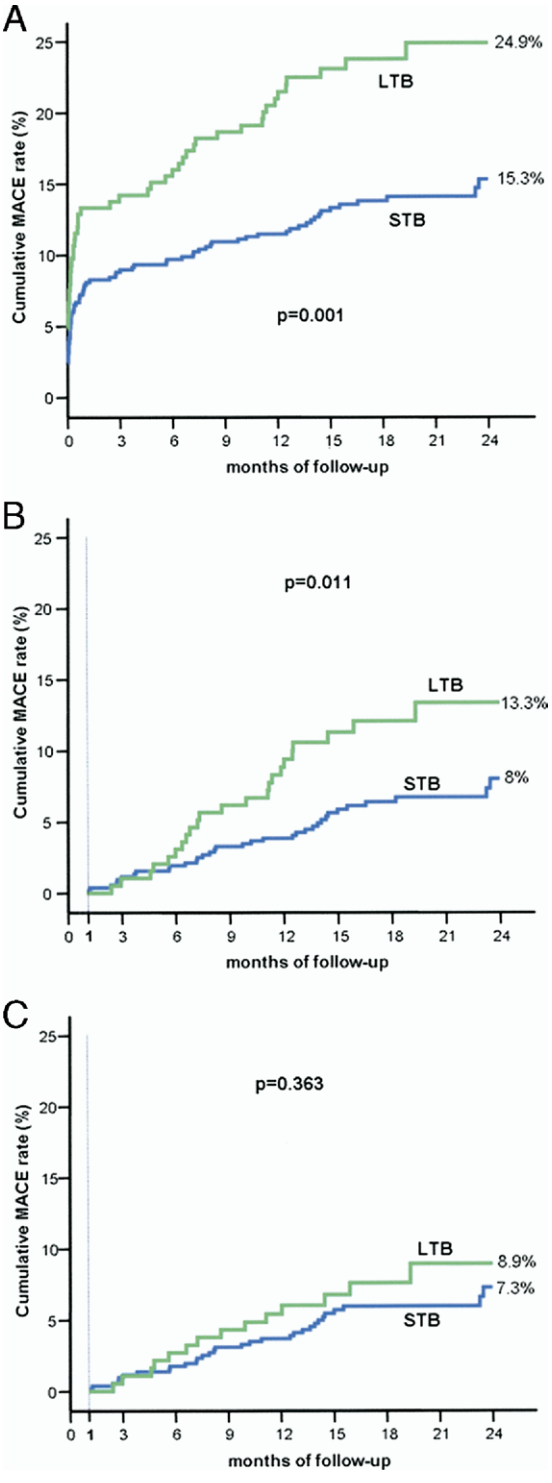

Figure 7 **Impact of Thrombus Burden and IRA-ST on MACE**

Two-year cumulative major adverse cardiac event (MACE) rate **(A)**, post-30-days cumulative MACE rate **(B)**, and post-30-days cumulative MACE rate after excluding patients with infarct-related artery stent thrombosis **(C)** in relation to large thrombus burden (LTB) and small thrombus burden (STB) at the index procedure.

mortality related to worse procedural outcome and very high rates of early and late IRA-ST in LTB patients. An LTB does not influence the clinical antirestenotic efficacy of DES.

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