Impact of Thrombus Burden on Outcomes After Standard Versus Mesh-Covered Stents in Acute Myocardial Infarction (from the MGuard for Acute ST Elevation Reperfusion Trial)

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Large thrombus burden negatively affects the results of percutaneous coronary intervention (PCI) for acute ST-segment elevation myocardial infarction (STEMI). We investigated the impact of thrombus burden in patients with STEMI undergoing primary PCI with the mesh-covered MGuard stent (InspireMD Ltd., Tel Aviv, Israel) versus a control bare-metal or drug-eluting stent. In 433 patients with STEMI randomized to the MGuard stent versus a control stent, angiographically visible thrombus was identified in 383 patients (88.5%), with median thrombus area 30.15 mm^2 (22.70, 41.93). Lesions with large thrombus (area > median) were treated with more frequent use of manual aspiration (80.8% vs 65.8%, p = 0.0009) and longer (22.1 ± 5.9 vs 19.4 ± 5.4 mm, p <0.0001) and larger (3.46 ± 0.40 vs 3.29 ± 0.36 mm, p <0.0001) stents. PCI of lesions with large thrombus burden had more thrombotic complications (30.6% vs 15.9%, p = 0.0007) and reduced angiographic success (80.3% vs 91.1%, p = 0.003). In large thrombus lesions, the MGuard stent was more effective than control stents in achieving Thrombolysis In Myocardial Infarction-3 flow (87.9% vs 74.5%, p = 0.02) and tended to result in less slow flow or no reflow (8.8% vs 17.6%, p = 0.07). ST-segment resolution was improved with the MGuard, and clinical outcomes were favorable in both stent groups, regardless of thrombus burden. In conclusion, reperfusion success is reduced after primary PCI in lesions with large thrombus burden, an outcome that may be modified by the MGuard stent. **(Am J Cardiol 2015;115:161−166)**

Mechanical reperfusion is the standard of care for patients with ST-segment elevation myocardial infarction (STEMI).[1,2] The amount or "burden" of thrombus in patients with STEMI undergoing primary percutaneous coronary intervention (PCI) has been identified as a major determinant of outcomes, having been associated with reduced procedural success and worse early and late event-free survival.[3−6] The MGuard embolic protection stent (InspireMD Ltd., Tel Aviv, Israel) is a mesh-covered metallic stent designed to trap and exclude friable thrombotic and atheromatous material, which has shown promise in reducing distal embolization and thrombotic complications during PCI.[7−12] Whether the MGuard stent is particularly effective in patients with large thrombus burden is unknown. We therefore investigated the impact of thrombus burden on angiographic and clinical outcomes in patients with STEMI undergoing primary PCI with the MGuard stent versus conventional stents in the MGuard for Acute ST Elevation Reperfusion (MASTER) trial.[11]

Methods

The design and principal outcomes of the MASTER trial have been previously reported.[11,13] In brief, 433 patients with STEMI of ≤12 hours duration and a single de novo lesion ≤33 mm in length in a native coronary vessel 3.0 to 4.0 mm in diameter were randomized 1:1 to PCI with the MGuard stent versus any commercially available bare-metal or drug-eluting stent. All patients were treated with aspirin (75 to 162 mg/day) indefinitely and a $P2Y_{12}$ inhibitor for 1 year. For the purpose of the current analysis, only patients with an angiographically evident thrombus (as assessed by independent angiographic core laboratory analysis) were included. The performance of manual thrombus aspiration and/or predilatation was left to operator discretion.

Baseline and final quantitative coronary angiography analyses were performed by technicians blinded to randomization with standard method using validated software for quantitative analysis (QAngio XA version 7.3, Medis, Leiden, the Netherlands). Anterograde coronary blood flow was determined according to the Thrombolysis In Myocardial Infarction (TIMI) classification. Corrected TIMI frame count was assessed as previously described.[14] Myocardial blush grade (MBG) was graded according to previously

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See page 165 for disclosure information.

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0002-9149/14/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2014.10.016

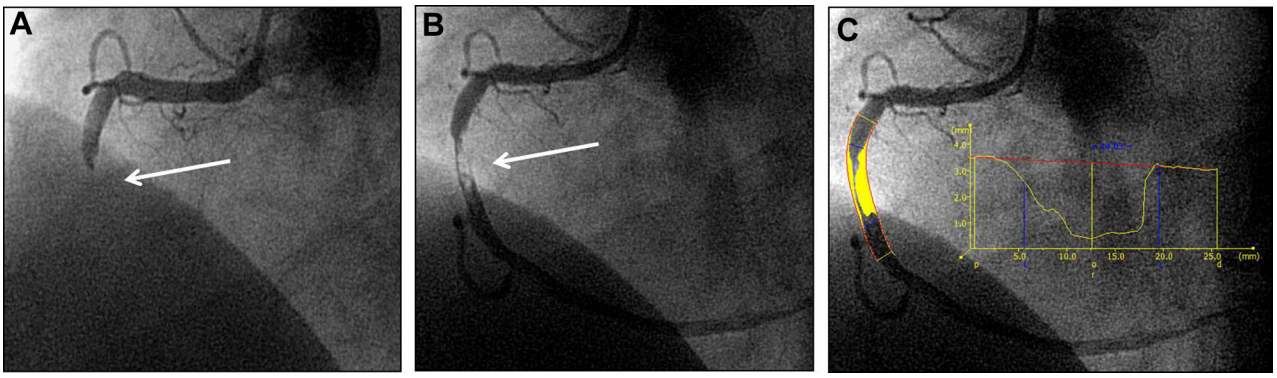

Figure 1. Quantitative determination of thrombus area. *(A)* Right coronary artery with total occlusion in its midportion at baseline (*white arrow*). *(B)* Flow restored after guidewire passage, allowing estimation of thrombus burden (*white arrow*). *(C)* Quantitative coronary angiography analysis. Thrombus area was calculated as follows: 14.03 mm (thrombus length) × 3.28 mm (reference diameter) × 1.0 (diameter stenosis at baseline) = 46.02 mm^2.

Table 1
Baseline clinical characteristics and presentation to primary percutaneous coronary intervention

Variable	All Patients			Small Thrombus			Large Thrombus		
	Small Thrombus (n = 190)	Large Thrombus (n = 193)	p Value	MGuard (n = 97)	Control (n = 93)	p Value	MGuard (n = 91)	Control (n = 102)	p Value
Age (years)	58.8 ± 11.6	59.6 ± 10.7	0.69	58.2 ± 10.6	59.4 ± 12.5	0.48	60.2 ± 10.5	59.1 ± 10.8	0.47
Women	50 (26%)	38 (20%)	0.12	25 (26%)	25 (27%)	0.86	18 (20%)	20 (20%)	0.99
Diabetes mellitus	26 (14%)	32 (17%)	0.43	10 (10%)	16 (17%)	0.17	13 (14%)	19 (19%)	0.42
Hypertension, medically-treated	82 (44%)	87 (46%)	0.67	39 (40%)	43 (48%)	0.30	38 (43%)	49 (49%)	0.39
Dyslipidemia, medically-treated	50 (27%)	52 (28%)	0.77	26 (27%)	24 (26%)	0.91	23 (26%)	29 (30%)	0.63
Smoker (current)	98 (52%)	100 (53%)	0.92	53 (56%)	45 (48%)	0.31	51 (57%)	49 (49%)	0.29
Prior angina pectoris	26 (14%)	20 (10%)	0.32	10 (10%)	16 (17%)	0.17	8 (9%)	12 (12%)	0.50
Prior myocardial infarction	7 (4%)	18 (9%)	0.03	1 (1%)	6 (7%)	0.06	5 (6%)	13 (13%)	0.08
Prior percutaneous coronary intervention	5 (3%)	13 (7%)	0.058	1 (1%)	4 (4%)	0.20	5 (6%)	8 (8%)	0.52
Symptom to device time (minutes)	257.5 ± 147.3	266.3 ± 164.8	0.58	251.4 ± 133.7	263.9 ± 160.9	0.56	244.7 ± 145.5	285.6 ± 178.8	0.08

described method.[15,16] Thrombus was defined as the presence of an intraluminal radiolucent or "negative" contrast density, with or without defined borders, usually separated from the adjacent vessel wall, with or without contrast staining.[17] Thrombus was also classified into 4 types as follows: globular, filling defect, haziness, or total occlusion. During PCI, intraprocedural thrombotic events were defined as the development of new or increasing thrombus, abrupt vessel closure, no reflow, slow reflow, distal embolization, side branch closure, or intraprocedural stent thrombosis occurring at any time during the procedure, as reported by the core laboratory after frame-by-frame review.[11] Thrombus area was measured as shown in Figure 1 using the following formula: reference diameter (mm) × lesion ("thrombus") length (mm) × diameter stenosis (0 to 1.0). In case of a total occlusion, thrombus length was determined after flow restoration within the target vessel.

Prespecified efficacy endpoints included (1) complete ST-segment resolution (≥70% reduction in the extent of ST-segment elevation in the summed 12-lead electrocardiogram from baseline to postprocedure); (2) final TIMI flow and corrected TIMI frame count in the infarct-related coronary artery; and (3) postprocedure MBG. All electrocardiographic analyses were determined by a blinded, independent electrocardiographic core laboratory as previously described.[11,13] Major adverse cardiovascular events were defined as the composite of cardiac death, reinfarction, or ischemia-driven target lesion revascularization.[11] Stent thrombosis was defined according to the Academic Research Consortium's criteria.[18] Adverse clinical events were adjudicated by an independent clinical events committee blinded to treatment assignment.

Categorical variables are presented as counts and frequencies and were compared with the chi-square or Fisher's exact test. Continuous variables are presented as mean ± SD and were compared with the Student *t* test. Analyses were performed in subgroups according to whether the infarct lesion had small thrombus burden (≤median measured thrombus area) or large thrombus burden (>median measured thrombus area) as determined by the angiographic core laboratory. Interaction testing was performed by logistic regression. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). A p value <0.05 was considered statistically significant.

Table 2
Baseline quantitative core laboratory angiographic findings

Variable	All Patients			Small Thrombus			Large Thrombus		
	Small Thrombus (n = 190)	Large Thrombus (n = 193)	p Value	MGuard (n = 97)	Control (n = 93)	p Value	MGuard (n = 91)	Control (n = 102)	p Value
Target coronary artery									
Left anterior descending	72 (38%)	71 (37%)	0.82	35 (36%)	37 (40%)	0.60	34 (37%)	37 (36%)	0.88
Left circumflex	19 (10%)	15 (8%)	0.44	11 (11%)	8 (9%)	0.53	7 (8%)	8 (8%)	0.97
Right	99 (52%)	107 (55%)	0.51	51 (53%)	48 (52%)	0.89	50 (55%)	57 (56%)	0.90
Thrombus type									
Globular	34 (18%)	44 (23%)	0.23	20 (21%)	14 (15%)	0.32	20 (22%)	24 (24%)	0.80
Filling defect	22 (12%)	21 (11%)	0.83	14 (14%)	8 (9%)	0.21	9 (10%)	12 (12%)	0.68
Haziness	22 (12%)	12 (6%)	0.07	12 (12%)	10 (11%)	0.73	8 (9%)	4 (4%)	0.16
Total occlusion	112 (59%)	116 (60%)	0.82	51 (53%)	61 (66%)	0.07	54 (59%)	62 (61%)	0.84
Thrombus area (mm^2)	21.92 ± 5.69	47.05 ± 17.76	<0.0001	21.50 ± 5.95	22.36 ± 5.39	0.30	48.28 ± 20.07	45.94 ± 15.44	0.37
Aneurysm	0 (0%)	6 (3%)	0.03	0 (0%)	0 (0%)	-	3 (3%)	3 (3%)	>0.99
Lesion class C*	27 (14%)	44 (23%)	0.03	15 (16%)	12 (13%)	0.61	25 (28%)	19 (19%)	0.14
TIMI flow grade									
0/1	143 (75%)	154 (80%)	0.29	65 (67%)	78 (84%)	0.007	74 (81%)	80 (78%)	0.62
2	26 (14%)	22 (11%)	0.50	19 (20%)	7 (8%)	0.02	10 (11%)	12 (12%)	0.87
3	21 (11%)	17 (9%)	0.46	13 (13%)	8 (9%)	0.29	7 (8%)	10 (10%)	0.61
Myocardial blush grade									
0/1	163 (87%)	171 (89%)	0.67	81 (84%)	82 (90%)	0.24	81 (89%)	90 (88%)	0.87
2/3	24 (13%)	22 (11%)	0.67	15 (16%)	9 (10%)	0.24	10 (11%)	12 (12%)	0.87
Quantitative measures									
Lesion length (mm)	13.3 ± 5.6	16.8 ± 8.0	<0.0001	13.9 ± 6.2	12.7 ± 4.8	0.12	17.3 ± 9.7	16.3 ± 6.1	0.43
Reference vessel diameter (mm)	3.05 ± 0.38	3.28 ± 0.40	<0.0001	3.05 ± 0.36	3.05 ± 0.39	0.97	3.29 ± 0.42	3.27 ± 0.40	0.72

* According to the American College of Cardiology/American Heart Association classification—the following variables were considered for type C lesion: diffuse lesion (>20 mm in length); excessive tortuosity of proximal segment (target lesion distal to three bends ≥ 75 degrees); extremely angulated, >90 degrees; and inability to protect major side branch.

Results

Of the 433 patients enrolled in the MASTER trial, 383 patients (88.5%) had infarct lesions with angiographically evident thrombus, with median area of 30.15 mm^2 (22.70, 41.93). These patients were divided into 2 groups according to thrombus size, large thrombus (mean thrombus area 47 ± 18 mm^2) and small thrombus (mean thrombus area 22 ± 6 mm^2).

Baseline clinical characteristics are listed in Table 1. Apart from previous myocardial infarction, there were no significant clinical differences between the groups with large and small thrombus burden. However, those with large thrombus had more complex lesion morphology, longer lesion lengths, and larger reference vessel diameters (Table 2). Manual thrombus aspiration was more frequently performed in the large thrombus group, and this group was treated with longer and larger diameter stents (Table 3). Intraprocedural thrombotic events occurred more frequently in patients with large versus small thrombus (30.6% vs 15.9%, p = 0.0007), and stenting lesions with large thrombus was associated with lower rates of final TIMI flow grade 3 and MBG 2/3 (Figure 2), and greater TIMI frame counts (Table 3). There were no significant differences in 30-day event rates in patients with large versus small thrombus burden, including major adverse cardiovascular events (3.1% [n = 6] vs 1.1% [n = 2], p = 0.16), cardiac death (1.6% [3] vs 0.5% [1], p = 0.33), and definite or probable stent thrombosis (1.6% [3] vs 0.5% [1], p = 0.32).

Overall, baseline clinical and angiographic characteristics were similar between the MGuard and control stent groups (Tables 1 and 2). In the large thrombus group, patients treated with the MGuard stent compared with a control stent tended to develop less slow flow or no reflow (8.8% vs 17.6%, p = 0.07), were more likely to have TIMI-3 flow restored, had lower (better) post-PCI corrected TIMI frame counts, and higher rates of angiographic success (Table 3). In the small thrombus group, less distal embolization was noted after the MGuard stent despite greater use of multiple stents during procedure compared with conventional stents (Table 3). There were no significant differences in TIMI-3 flow or MBG 2/3 between stent types in the small thrombus group. Postprocedure rates of TIMI-3 flow, MBG 2/3, and complete ST-segment resolution in the small and large thrombus groups according to stent type are shown in Figure 2. Interaction testing demonstrated nonsignificantly different effects of the MGuard stent on these 3 parameters in patients with large and small thrombus burden (interaction p values = 0.49, 0.65, and 0.57, respectively). Major adverse cardiovascular event rates at 30 days were not significantly different in patients treated with the MGuard versus control stents for large thrombus (3.3% [n = 3] vs 2.9% [n = 3], p = 0.89, respectively) or small thrombus (1.0% [n = 1] vs 1.1% [n = 1], p = 0.97, respectively).

Discussion

The principal observations of this analysis from the MASTER trial are as follows: (1) by core laboratory analysis,

Table 3
Procedural details and outcomes

Variable	All Patients			Small Thrombus			Large Thrombus		
	Small Thrombus (n = 190)	Large Thrombus (n = 193)	p Value	MGuard (n = 97)	Control (n = 93)	p Value	MGuard (n = 91)	Control (n = 102)	p Value
Glycoprotein IIb/IIIa inhibitor use	157 (83%)	168 (87%)	0.23	84 (87%)	73 (79%)	0.14	75 (82%)	93 (91%)	0.07
Unfractioned heparin	182 (96%)	189 (98%)	0.23	94 (97%)	88 (95%)	0.49	88 (97%)	101 (99%)	0.34
Bivalirudin	25 (13%)	18 (9%)	0.24	8 (8%)	17 (18%)	0.04	11 (12%)	7 (7%)	0.21
Aspiration performed	125 (66%)	156 (81%)	0.0009	62 (64%)	63 (68%)	0.58	78 (86%)	78 (77%)	0.10
Balloon predilatation	91 (48%)	88 (46%)	0.65	49 (51%)	42 (45%)	0.46	42 (46%)	46 (45%)	0.88
Type of stent implanted									
MGuard	94 (50%)	87 (45%)	0.36	93 (97%)	1 (1%)	<0.0001	87 (96%)	0 (0%)	<0.0001
Bare metal stent	56 (30%)	64 (33%)	0.46	2 (2%)	54 (58%)	<0.0001	1 (1%)	63 (62%)	<0.0001
Drug-eluting stent	39 (21%)	42 (22%)	0.79	1 (1%)	38 (41%)	<0.0001	3 (3%)	39 (38%)	<0.0001
>1 stent implanted	22 (12%)	27 (14%)	0.48	16 (17%)	6 (7%)	0.03	11 (12%)	16 (16%)	0.47
Nominal stent length (mm)	19.4 ± 5.4	22.1 ± 5.9	<0.0001	19.8 ± 5.5	19.0 ± 5.3	0.34	22.5 ± 5.6	21.8 ± 6.1	0.47
Nominal stent diameter (mm)	3.29 ± 0.36	3.46 ± 0.40	<0.0001	3.29 ± 0.33	3.28 ± 0.33	0.90	3.45 ± 0.37	3.46 ± 0.43	0.83
Final morphology									
Thrombus	4 (2%)	12 (6%)	0.04	2 (2%)	2 (2%)	>0.99	4 (4%)	8 (8%)	0.32
Distal embolization	7 (4%)	22 (11%)	0.004	1 (1%)	6 (7%)	0.06	10 (11%)	12 (12%)	0.87
Slow flow or no reflow	7 (4%)	26 (14%)	0.0006	4 (4%)	3 (3%)	>0.99	8 (9%)	18 (18%)	0.07
TIMI flow grade									
0/1	6 (3%)	10 (5%)	0.32	1 (1%)	5 (5%)	0.11	3 (3%)	7 (7%)	0.34
2	11 (6%)	27 (14%)	0.007	6 (6%)	5 (5%)	0.81	8 (9%)	19 (19%)	0.05
3	173 (91%)	156 (81%)	0.004	90 (93%)	83 (89%)	0.39	80 (88%)	76 (75%)	0.02
Myocardial blush grade									
0/1	24 (13%)	64 (34%)	<0.0001	13 (14%)	11 (12%)	0.77	29 (32%)	35 (35%)	0.65
2/3	161 (87%)	127 (67%)	0.45	82 (86%)	79 (88%)	0.77	62 (68%)	65 (65%)	0.65
Corrected TIMI frame count (frames)	17.9 ± 10.8	24.0 ± 18.0	<0.0001	17.9 ± 10.9	17.9 ± 10.8	0.97	21.4 ± 12.9	26.3 ± 21.3	0.058
Angiographic success	173 (91%)	155 (80%)	0.003	90 (93%)	83 (89%)	0.39	80 (88%)	75 (74%)	0.01
Procedural success	188 (99%)	190 (98%)	>0.99	96 (99%)	92 (99%)	>0.99	90 (99%)	100 (98%)	>0.99

nearly all patients with STEMI (88.5%) had angiographically evident thrombus, as expected.[5,9] (2) Importantly, the presence of large thrombus burden was associated with a higher frequency of intraprocedural thrombotic complications and lower rates of postprocedural normal epicardial (TIMI-3 flow) and myocardial (MBG grade 2/3) reperfusions. (3) Compared with standard stent technology, use of a polyethylene terephthalate micronet mesh-covered stent improved reperfusion success, with the most profound improvements in angiographic outcomes among patients with large thrombus burden.

Large thrombus burden has been associated with PCI failure in patients with STEMI in previous retrospective, nonrandomized studies.[3–6] In the largest such study,[5] among 900 patients with STEMI treated with primary or rescue PCI, the presence of large thrombus (30% of cases) was strongly associated with higher rates of final TIMI flow grade <3, final MBG grade 0/1, and mortality at 2 years (adjusted hazard ratio = 1.66 [1.04, 2.68], p = 0.04). Rheolytic thrombectomy was used more frequently in patients with large thrombus in this study. Although rheolytic thrombectomy has fallen out of favor, manual thrombus aspiration was more frequently used in patients with large thrombus burden in MASTER. Nonetheless, TIMI-3 flow and MBG grade 2/3 were still less commonly restored in vessels containing large thrombus lesions in MASTER, outcomes which have been shown to significantly impact long-term outcomes.[15,19–21]

The optimal approach for thrombus-containing lesions is still evolving.[2,6] Recent studies have provided evidence favoring use of potent pharmacological agents during primary PCI.[22–24] Several mechanical devices designed to prevent distal embolization during PCI of thrombotic lesions have also been tested.[24–28] Although manual thrombus aspiration is frequently used in STEMI, recent studies have not shown reductions in infarct size or mortality.[24,27] Routine use of rheolytic thrombectomy may increase distal embolization, but may be effective in cases with large thrombus burden or major thrombotic complications.[26,28] In the MASTER trial, despite the use of manual thrombus aspiration before stenting in approximately 2/3 of cases (more commonly in lesions with large thrombus burden), the MGuard stent improved angiographic outcomes compared with a control bare-metal or drug-eluting stent. The results with the MGuard were most favorable in patients with large thrombus burden (the lesion subtype of greatest need for an improved therapy), although interaction testing suggests a beneficial effect in improving TIMI flow, MBG, and ST-segment resolution in both patients with large and small thrombus burden.

The method we used for thrombus burden quantification deserves comment. Before this study, thrombus burden has often been classified according to the TIMI scoring system, consisting of 5 grades depicting morphology and size, measured by the greatest thrombus dimension relative to

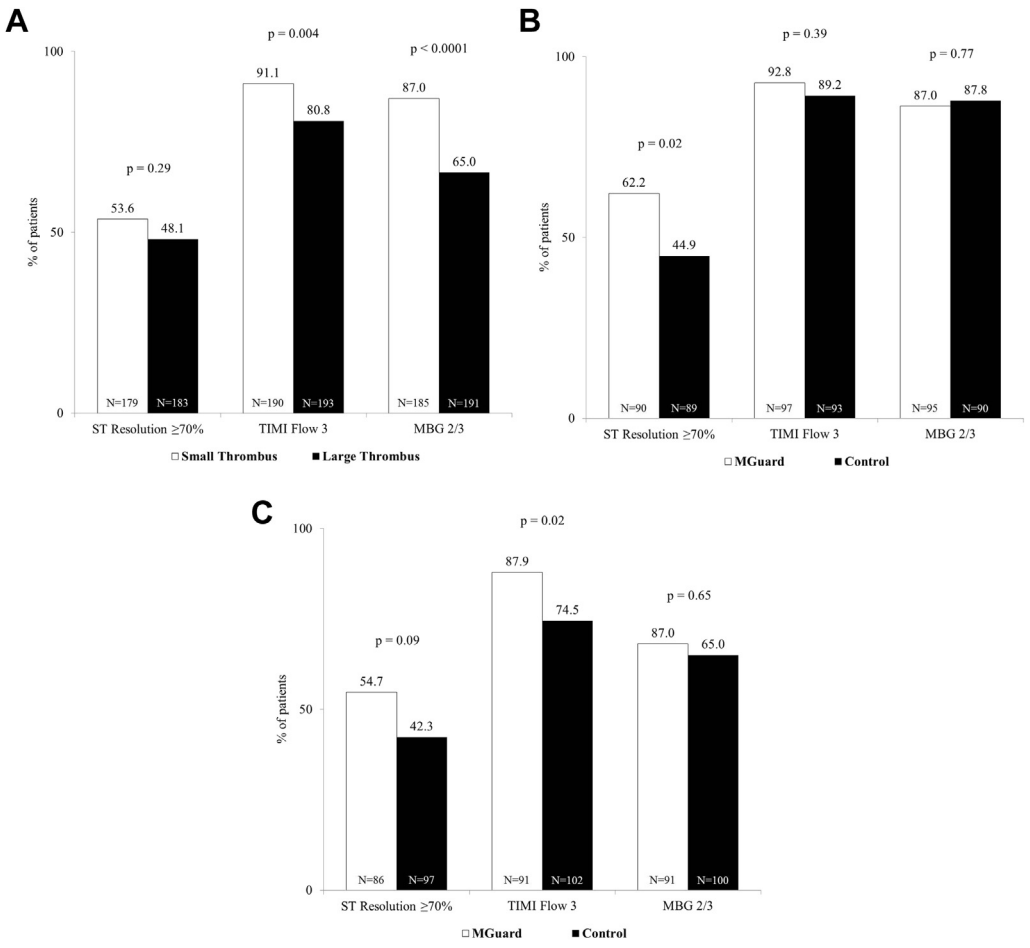

Figure 2. Myocardial reperfusion success according to thrombus burden. *(A)* Comparison between the overall large thrombus cohort versus small thrombus cohort. *(B)* Small thrombus cohort comparing MGuard versus control stent. *(C)* Large thrombus cohort comparing MGuard versus control stent.

vessel diameter.[29] Although relatively easy to use, this classification is subjective, and grade 5 thrombus, defined as "definite complete thrombotic occlusion of a vessel," does not take into account the thrombus length. Subsequent reclassification of TIMI thrombus grade 5 after vessel recanalization into 2 categories (small thrombus [grades 0 to 3] or large thrombus [grade 4]) improved prognostic utility.[5] In the present study, we used a different method for thrombus sizing, measuring the actual area occupied by thrombus within the coronary vessel by quantitative coronary angiography (at baseline or after flow restoration). Indeed, patients with larger than the median thrombus area had worse outcomes than those with smaller thrombi. Quantitative coronary angiography-based assessment of thrombus burden is more objective, and as a continuous variable, it may provide better statistical power than the categorical TIMI thrombus scale. The present study was not designed, however, to directly compare the prognostic utility of quantitative thrombus sizing to the TIMI scoring method. Both methods share the same limitation that recanalization of the occluded infarct artery, whether by a guidewire, aspiration catheter, or balloon, may result in some degree of distal embolization or local thrombus dispersion and/or removal before assessment, thereby reducing the thrombus burden at the lesion site.

Disclosures

Drs. Dudek and Silber have received research grants from and/or are consultants to InspireMD. Dr. Stone is a past consultant to Boston Scientific, InspireMD, Eli Lilly, and Daiichi Sankyo. The other authors have no conflicts of interest to disclose.

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