Efficacy of an Embolic Protection Stent as a Function of Delay to Reperfusion in ST-Segment Elevation Myocardial Infarction (from the MASTER Trial)

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The ability of stent implantation to improve indexes of reperfusion may depend on the time to reperfusion in acute ST-segment elevation myocardial infarction (STEMI) and may also vary with stent type. The purpose of this prespecified analysis from the randomized MGUARD for Acute ST Elevation Reperfusion trial was to evaluate the impact of delay to reperfusion on outcomes in patients with STEMI undergoing primary percutaneous coronary intervention with the MGuard embolic protection stent or standard metallic stents. A total of 431 patients were divided according to symptom-onset-to-balloon time (SBT) into 2 groups: SBT ≤3 hours (167 patients; 39%) and SBT >3 hours (264 patients; 61%). Complete ST-segment resolution (STR) after percutaneous coronary intervention was more often achieved in patients with shorter SBT (58.6% vs 47%, p = 0.02). At 1 year, the all-cause mortality rate was lower in patients with shorter SBT (0% vs 3.5%, p = 0.02). STR was achieved in 58% of MGuard patients and in 45% of the control stent patients (p = 0.008). STR was 57% in the MGuard group versus 38% in the control group (p = 0.002 for SBT >3 hours) and 60% versus 57% (p = 0.72), respectively, for SBT ≤3 hours (p for interaction = 0.11). In conclusion, longer delay to mechanical reperfusion remains an important factor negatively influencing outcomes in patients with STEMI. Use of the MGuard embolic protection stent compared with conventional metallic stents resulted in superior rates of complete STR, even in patients with longer delays to reperfusion. **(Am J Cardiol 2014;114:1485−1489)**

Primary percutaneous coronary intervention (PCI) is the recommended method of reperfusion in patients with ST-segment elevation myocardial infarction (STEMI).[1] However, extended delay from symptom onset to mechanical reperfusion has a negative impact on clinical outcomes. This may be explained by larger infarct size with more frequent transmural infarction, larger areas of microvascular dysfunction and myocardial edema, and lower procedural success.[2−5] The longer time to reperfusion may promote larger and more organized thrombus formation and render both pharmacologic and mechanical (aspiration thrombectomy) strategies less effective. It is unknown if this limitation may be overcome with a novel embolic protection stent design geared to reduce distal embolization. The purpose of this analysis from the MGuard for Acute ST Elevation Reperfusion (MASTER) trial was to evaluate the impact of delay to reperfusion on outcomes in patients with STEMI undergoing primary PCI according to the type of stent placed.

Methods

MASTER was an open-label, prospective, randomized, multicenter trial comparing the MGuard embolic protection stent (InspireMD, Tel Aviv, Israel) versus conventional metallic stents in patients undergoing primary PCI for STEMI. Study design and results were previously published.[6] In brief, patients presenting with STEMI ≤12 hours, with ≥2 mm of ST-segment elevation in ≥2 contiguous leads, and intended for primary PCI were eligible for enrollment. Angiographic eligibility required planned PCI of a single de novo lesion ≤33 mm in length and reference vessel diameter ≥3.0 to ≤4.0 mm by visual estimation, amenable to coverage by a single study stent. Patients were not eligible if a ≥50% left main stenosis was present or if the target lesion was ostial in location or involved a bifurcation with a ≥2.0-mm side branch. In the case of an occluded infarct vessel, angiographic eligibility was assessed only after restoration of Thrombolysis In Myocardial Infarction (TIMI) flow grade ≥2 by a guidewire, manual aspiration, or

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The trial is registered at *http://www.clinicaltrials.gov* (NCT01368471).

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See page 1489 for disclosure information.

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Table 1
Baseline characteristics

Variable	Symptom Onset to Balloon Time (hours)		p-Value
	≤3 (n = 167)	>3 (n = 264)	
Age (years)	57 [50, 65]	60 [51, 67]	0.02
Male	81%	73%	0.055
Body mass index (kg/m^2)	27.2 [24.7, 30.3]	26.9 [24.4, 30.3]	0.10
Medically treated hypertension	46%	45%	0.88
Medically treated hyperlipidemia	27%	28%	0.84
Diabetes mellitus	15%	15%	0.96
Insulin-treated	4.5%	4.4%	0.86
Previous angina	9%	13%	0.18
Previous myocardial infarction	7%	5.7%	0.53
Previous percutaneous coronary intervention	5.4%	4.2%	0.56
Previous coronary artery bypass grafting	0%	0%	–
Smoker	71%	61%	0.03
Current	59%	47%	0.02
Former	12%	13%	0.67
Symptom onset to balloon time (minutes)	135 [114, 159]	305.5 [241.5, 427.5]	<0.0001

Values are presented as percentages or medians [interquartile range].

Table 2
Concomitant medications, angiographic and interventional details

Variable	Symptom Onset to Balloon Time (hours)		p-Value
	≤3 (n = 167)	>3 (n = 264)	
Aspirin	99%	99%	1.00
Adenosine diphosphate antagonist	97%	96%	0.53
Clopidogrel	70%	72%	0.80
Ticlopidine	0%	0.4%	1.00
Prasugrel	23%	21%	0.65
Ticagrelor	6.2%	7.5%	0.60
Glycoprotein IIb/IIIa receptor inhibitors	87%	81%	0.12
Bivalirudin	8.4%	14%	0.08
Target coronary artery			
Left anterior descending	37%	42%	0.31
Left circumflex	8.4%	8.7%	0.91
Right	55%	49%	0.29
TIMI grade flow pre- percutaneous coronary intervention			
0/1	72%	70%	0.62
2	14%	17%	0.36
3	15%	13%	0.75
Procedure(s) before stenting			
None	9.0%	13%	0.26
Only aspiration	50%	36%	0.004
Only predilatation	20%	23%	0.41
Any aspiration performed	71%	64%	0.12
Stents implanted			
Any stent	100%	99.6%	1.00
>1 stent	12%	12%	0.94
Stent Type			
MGuard	50%	48%	0.66
Bare metal stent	28%	32%	0.29
Drug-eluting stent	23%	20%	0.52
Stent implantation without balloon predilatation	59%	49%	0.04

TIMI = Thrombolysis In Myocardial Infarction.

balloon angioplasty. Patients were then randomized 1:1 to either the MGuard stent or any commercially available bare-metal stent or drug-eluting stent (the control stent group). The primary efficacy end point was the rate of complete ST-segment resolution (STR), defined as ≥70% reduction in the summed 12-lead ST-segment elevation from the baseline to the 60- to 90-minute postprocedural electrocardiogram. Electrocardiographic analysis was performed by a blinded independent electrocardiography core laboratory.

For the purpose of this prespecified analysis, the MASTER trial patient cohort was divided according to the symptom-onset-to-balloon time (SBT) into 2 groups: SBT ≤3 hours and SBT >3 hours. Clinical outcomes at 30 days and 1 year were analyzed for the occurrence of major adverse cardiovascular and cerebral events (the composite of all-cause death, reinfarction, stroke, or ischemia-driven target lesion revascularization), major adverse cardiovascular events (the composite of cardiac death, reinfarction, or ischemia-driven target lesion revascularization), ischemia-driven target vessel revascularization, stroke, stent thrombosis (Academic Research Consortium definition),[7] and bleeding (TIMI classification).[8] All events were adjudicated by an independent clinical events committee. The influence of stent type (MGuard vs control) on STR and clinical outcomes was assessed in the 2 SBT groups.

Data are presented as percentage or median with interquartile range, as applicable. Differences in categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using Wilcoxon rank sum test. All tests were 2 tailed, and a p value <0.05 was considered statistically significant. All statistical analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

A total of 431 patients were included in this analysis. SBT was ≤3 hours in 167 patients (39%) and >3 hours in 264 patients (61%). Patients with SBT ≤3 hours were younger and had higher rates of previous smoking (Table 1). Pharmacologic treatment, target vessel location, and preprocedural TIMI flow grade were similar in both groups. Patients with shorter SBT were more likely to be treated with stent implantation without balloon predilation after thrombus aspiration. There was no difference in the type of implanted stent (MGuard vs control) between groups (Table 2).

Complete STR after PCI was more often achieved in patients with shorter SBT. There was no significant difference in epicardial flow (TIMI grade) after PCI between groups; however, a significant difference was found in both corrected TIMI frame counts and myocardial reperfusion (myocardial blush grade) favoring patients with shorter SBT (Table 3).

Complete STR was observed more often in patients receiving the MGuard than control stent (58% vs 45%,

Table 3
Reperfusion parameters after percutaneous coronary intervention

Variable	Symptoms Onset to Balloon Time (hours)		p Value
	≤3 (n = 167)	>3 (n = 264)	
ST-segment resolution			
Complete (≥70%)	59%	47%	0.02
Partial (30−70%)	24%	36%	0.01
Absent (≤30%)	21%	22%	0.90
Median [IQR]	78.81 [46.44, 92.74]	66.17 [39.61, 86.75]	0.007
TIMI grade flow after PCI			
0/1	3.0%	4.2%	0.65
2	6.6%	11%	0.16
3	90%	85%	0.12
Corrected TIMI frame count after PCI	15.0 [12.0, 20.0]	18.0 [12.0, 24.0]	0.005
Final myocardial blush grade			
0	0.6%	1.9%	0.41
1	9.6%	17%	0.03
2	10%	12%	0.53
3	80%	69%	0.01
2/3	90%	81%	0.01

Values are presented as percentage or median [interquartile range].
TIMI = Thrombolysis In Myocardial Infarction.

p = 0.008). When analyzing the effect of randomized stent type on STR according to SBT, as delay to reperfusion increased, the MGuard stent achieved relatively greater rates of STR than conventional stents (Figure 1). A formal test for interaction did not reach statistical significance, however (p for interaction = 0.11). Similar relations were observed when analyzing TIMI flow grade after PCI according to stent type and SBT (p for interaction = 0.67).

The rate of clinical events was relatively low at 30 days, and no significant differences between SBT groups were found. At 1 year, mortality was lesser in patients with shorter SBT, and a trend toward fewer major adverse cardiovascular and cerebral events was also observed with shorter SBT. When results were analyzed according to stent type, a trend toward lesser mortality was found after treatment with MGuard compared with control stents at 30 days and 1 year in patients with SBT >3 hours. Conversely, no deaths through 1-year follow-up occurred with either stent in patients with SBT ≤3 hours. Higher 1-year rates of ischemia-driven target lesion revascularization and target vessel revascularization were observed in the MGuard group compared with the control stent group, regardless of SBT (Table 4).

Discussion

In the present analysis of the MASTER trial, we confirmed that longer SBT is associated with lower rates of optimal reperfusion (assessed by electrocardiographic and angiographic parameters) and worse clinical outcomes in patients with STEMI treated with primary PCI. Use of the mesh-covered embolic protection MGuard stent may, in part, alleviate the negative impact of longer delays to reperfusion.

Extended delays from symptom onset to mechanical reperfusion have a negative impact in STEMI. The effectiveness of reperfusion in myocardial infarction is time dependent, and myocardial necrosis increases with the duration of ischemic time. This relation was confirmed by higher rates of transmural necrosis and microvascular obstruction in cardiac magnetic resonance and sestamibi imaging studies.[2,3] Increased time to reperfusion also influences clinical outcome of patients with STEMI. De Luca et al[9] showed that each additional 30-minute delay to mechanical reperfusion was associated with a relative 7.5% risk increase in 1-year death. Analysis of the Global Registry of Acute Coronary Events registry database also revealed an association between longer treatment delay and greater 6-month mortality in patients with STEMI treated with primary PCI.[10] The adverse relation between time to reperfusion and prognosis may be driven in part by lower procedural success in patients with longer time from symptoms to reperfusion. In the present analysis, longer delays were associated with lower rates of optimal reperfusion assessed by STR, corrected TIMI frame count, and myocardial blush grade. This may be due to the presence of larger and more organized thrombus, which is less likely to be aspirated or modified by aggressive pharmacotherapy with delays to reperfusion. Conversely, patients with shorter delays to reperfusion were more likely to have only aspiration thrombectomy before stenting, reducing the potential for distal embolization. Our results suggest that use of the MGuard embolic protection stent in such situations may in part offset the negative impact of longer SBT. The potential mechanism for this effect is trapping of plaque debris and thrombus (whether organized or not), thereby reducing distal embolization. This is supported by the Deferred Stent Trial in STEMI trial results, which showed that a reduction in stenting-related distal embolization during primary PCI by deferred (4 to 16 hours) compared with immediate stenting resulted in reduced no or slow reflow and increased myocardial salvage.[11] Our findings are in contrast to some studies in which the benefit of preventing distal embolization with aspiration was particularly notable in patients with shorter delay to reperfusion, before marked myocardial destruction has already occurred.[12,13] In this regard, the MGuard stent may be preferred in older, more organized thrombus that is less effectively aspirated. Moreover, reperfusion is a complex and multifactorial process, and infarct size may be influenced by not only time but also the completeness of coronary occlusion and the presence of collateral circulation, preconditioning and postconditioning, age, and infarct location.[14]

Consistent with previously published studies, we observed that longer SBT was associated with worse clinical outcomes including greater mortality at 1 year. When stent type was factored into the analysis, a trend toward lesser mortality was found for the MGuard compared with control stents in patients with SBT >3 hours. This observation complements the electrocardiographic and angiographic results. However, the MASTER study was not powered for mortality, so these results should be interpreted with caution. In contrast, MGuard stent implantation was associated with higher rates of repeat revascularization (regardless of SBT), an expected result from a stent built on a bare-metal platform. We found a higher rate of smokers in patients with SBT ≤3 hours. However, this is unlikely to influence the results because the "smoker's paradox" described in nonreperfusion and thrombolytic studies has not been reported in the primary PCI era.[15,16]

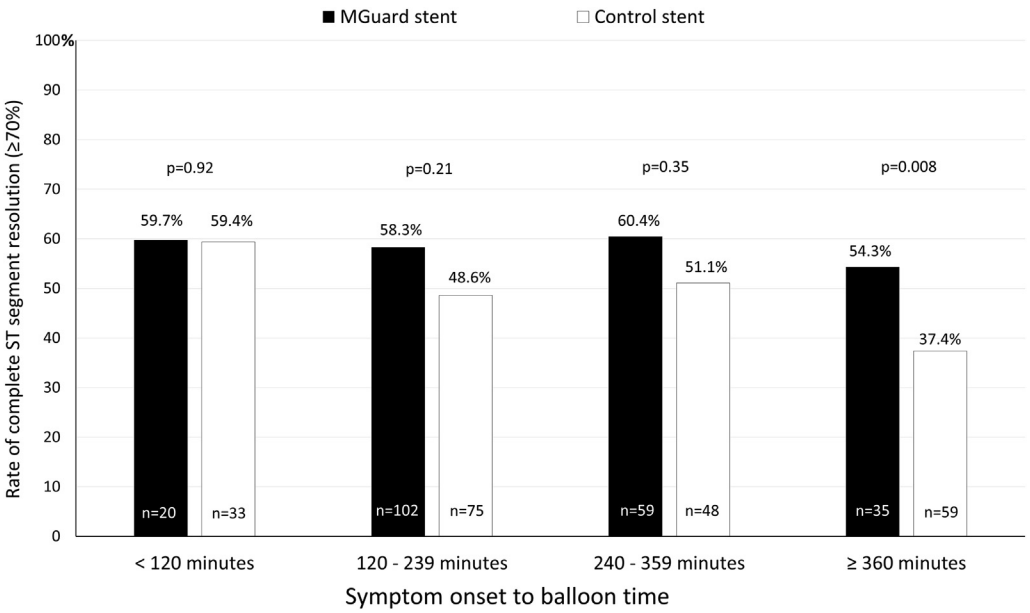

Figure 1. The rate of complete electrocardiographic ST-segment resolution 60 to 90 minutes after percutaneous coronary intervention for the MGuard stent group (*black bars*) and the control stent group (*white bars*) in predefined symptom-onset-to-balloon intervals.

Table 4
Event rates at 30 days and at 1 year according to symptom onset to balloon time and stent type

Variable	SBT ≤3 hours (n = 167)	SBT >3 hours (n = 264)	p Value	SBT ≤3 hours			SBT >3 hours		
				MGuard Stent (n = 86)	Control Stent (n = 81)	p Value	MGuard Stent (n = 130)	Control Stent (n = 134)	p Value
30 days									
MACCE	1.8%	2.7%	0.56	3.5%	0	0.09	1.5%	3.8%	0.26
Major adverse cardiac events	1.8%	2.3%	0.73	3.5%	0	0.09	0.8%	3.8%	0.1
All-cause mortality	0	1.5%	0.11	0	0	—	0	3.0%	0.05
Cardiac mortality	0	1.5%	0.11	0	0	—	0	3.0%	0.05
Reinfarction	1.2%	1.1%	0.96	2.3%	0	0.17	0.8%	1.5%	0.57
TLR, ischemia-driven	1.8%	0.8%	0.33	3.5%	0	0.09	0.8%	0.8%	1
TVR, ischemia-driven	1.8%	1.1%	0.58	4.7%	0	0.05	1.5%	0.8%	0.55
Stent thrombosis, definite/ probable	1.2%	1.1%	0.96	2.3%	0	0.17	0.8%	1.5%	0.57
Stent thrombosis, definite	1.2%	0.8%	0.65	2.3%	0	0.17	0.8%	0.8%	1
Stroke	0	0.4%	0.42	0	0	–	0.8%	0	0.32
TIMI bleeding, major or minor	1.2%	2.7%	0.3	2.3%	0	0.17	2.3%	3.0%	0.73
1 year									
MACCE	4.4%	9.2%	0.052	8.5%	0	0.009	11%	7.5%	0.37
Major adverse cardiac events	4.4%	7.3%	0.19	8.5%	0	0.009	9.5%	5.3%	0.23
All-cause mortality	0	3.5%	0.02	0	0	—	1.6%	5.3%	0.1
Cardiac mortality	0	2.3%	0.05	0	0	—	0.8%	3.8%	0.11
Reinfarction	1.2%	1.1%	0.96	2.3%	0	0.17	0.8%	1.5%	0.57
TLR, ischemia-driven	4.4%	5.1%	0.68	8.5%	0	0.009	8.7%	1.5%	0.01
TVR, ischemia-driven	5.6%	5.9%	0.83	10.5%	0	0.003	10.3%	1.5%	0.003
Stent thrombosis, definite/ probable	1.2%	1.9%	0.57	2.3%	0	0.17	2.4%	1.5%	0.65
Stent thrombosis, definite	1.2%	1.6%	0.77	2.3%	0	0.17	2.4%	0.8%	0.31
Stroke	0	1.2%	0.16	0	0	—	0.8%	1.6%	0.57
TIMI bleeding, major or minor	2.4%	4.4%	0.32	2.3%	2.5%	0.98	4.7%	4.1%	0.74

MACCE = major adverse cardiovascular or cerebral events; SBT = symptom onset to balloon time; TIMI = Thrombolysis In Myocardial Infarction; TLR = target lesion revascularization; TVR = target vessel revascularization.

The technique of MGuard stent implantation is the same as for a conventional balloon-inflated coronary stent, and no special training is required. Crossing profile and deployment pressures are not affected by the net. However, small balloon and low-pressure predilatation before stent implantation may facilitate deliverability of the stent. Use of the MGuard stent is not recommended in vessels with heavy calcification or extreme tortuosity, lesions located distally to previously

implanted coronary stents (theoretical risk of mesh entanglement), or bifurcation lesions with a large side branch.

Although the present analysis was prespecified, randomization was not stratified according to time from symptom onset. The MASTER trial was powered for STR, and differences in clinical results (and all subgroups) should be considered as hypothesis generating only. We combined the results of drug-eluting stent and bare-metal stent in the control group, although differences exist between the two, particularly with respect to repeat revascularization.

In conclusion, longer delays to mechanical reperfusion remain an important factor negatively influencing outcomes in patients with STEMI. In the MASTER trial, use of the MGuard embolic protection stent, compared with conventional metallic stents, resulted in superior rates of complete STR, particularly in patients with longer delays to reperfusion (SBT >3 hours).

Disclosures

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