Original Studies

Rationale and Design of the MGuard for Acute ST Elevation Reperfusion MASTER Trial

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Background: Primary percutaneous coronary intervention (PCI) improves survival compared with thrombolytic therapy in ST-segment elevation myocardial infarction (STEMI), with much of the benefit attributable to greater rates of normal epicardial and myocardial perfusion resulting in enhanced myocardial salvage. However, reduced tissue reperfusion after primary PCI may occur from distal thromboemboli with capillary plugging. The MGuard stent consists of a balloon-expandable metallic scaffold with mesh sleeve fibers of polyethylene terephthalate attached to its outer surface to trap friable debris/thrombi and reduce distal embolization. The *M*Guard for *A*cute *ST* *El*evation *R*eperfusion (MASTER) trial has been designed to evaluate the MGuard stent in patients with STEMI.
Study Design: The MASTER trial is a prospective, multicenter, randomized study designed to compare the incidence of complete (=70%) ST-segment resolution with PCI using bare metal or drug-eluting stents (the control arm) versus PCI with the MGuard stent, measured 60 to 90 min after the last angiogram (primary endpoint). Secondary endpoints include the rates of TIMI flow and myocardial blush, and clinical outcomes through 1-year follow-up. The study has enrolled 432 patients with STEMI undergoing primary or rescue angioplasty within 12 hr of symptom onset and includes substudies with cardiac magnetic resonance imaging and quantitative coronary angiography to evaluate infarct size, microvascular obstruction, and angiographic restenosis. **Conclusions:** Distal embolization is common during primary PCI and results in reduced myocardial perfusion and lack of reduction of infarct size. The MASTER trial is a prospective, randomized trial designed to assess the potential of the novel MGuard stent with protective mesh net to reduce embolization and enhance myocardial reperfusion compared with routine PCI in the setting of STEMI. © 2013 Wiley Periodicals, Inc.

Key words: ST elevation MI; ST resolution; myocardial reperfusion; PCI; stent

INTRODUCTION

Primary percutaneous coronary intervention (PCI) is the preferred therapy to treat ST-segment elevation myocardial infarction (STEMI). This approach has been shown to be superior to thrombolytic therapy in terms of reducing cardiac and all-cause mortality [1]. The survival benefit of primary PCI is principally due to the achievement of higher rates of normal myocardial perfusion than with fibrinolytic therapy, which is a powerful determinant of mortality and myocardial recovery after reperfusion therapy [2,3]. However, even after apparently successful PCI as evidenced by restoration of normal epicardial TIMI-3 flow, many patients suffer inadequate myocardial tissue perfusion [4]. The disparity between epicardial blood flow and myocardial perfusion and metabolism was demonstrated by Claeys

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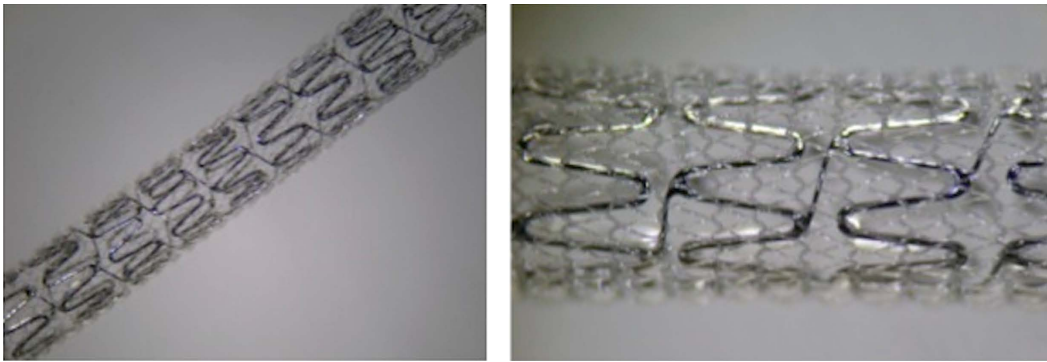
Fig. 1.   The MGuard Prime stent, expanded, showing the cobalt chromium scaffold backbone and the PET mesh. The MGuard stent appears similar, but the scaffold consists of 316-L stainless steel. [Color figure can be viewed in the online issue, which is available at wiley-onlinelibrary.com.]

et al., who reported that one-third of patients undergoing successful, uncomplicated primary PCI have persistent ST-segment elevation, a finding that strongly correlates with increased death, reinfarction, and late repeat hospitalization [4]. Other studies with contrast echocardiography, Doppler, PET, and technetium-99m macro-aggregated microspheres have confirmed that normal tissue perfusion may be achieved in <50% of patients after primary PCI (and less frequently after PCI for failed thrombolysis), even if TIMI-3 flow is restored [5,6].

Reduced tissue perfusion after recanalization of the infarct artery may be due to myocardial edema, microvascular spasm, or loss of microvascular integrity, as well as to distal thromboemboli with capillary plugging [7]. Capillary plugging with platelet and red blood cell thromboemboli, as well as embolic lipoid material and atheroma (including components of the necrotic core of the ruptured atherosclerotic plaque), have been found in pathologic specimens after angioplasty and surgery in patients with acute or recent MI [8]. This phenomenon may be responsible for the 5–10% of patients in whom TIMI-3 flow is not restored after primary PCI, as well as many of those with suboptimal myocardial perfusion.

The recently developed MGuard[TM] stent (InspireMD, Tel Aviv, Israel) consists of a balloon-expandable, metallic bare metal stent (BMS) platform with mesh sleeve fibers of polyethylene terephthalate (PET; fiber width of 20 μm) attached to its outer surface. These fibers act like a net (aperture size 150 × 180 μm) preventing distal embolization of friable plaque and thrombus by trapping it between the vessel wall and the stent. The metallic frame in the first generation MGuard device was made of 316-L stainless steel (strut width = 100 μm), whereas the current MGuard Prime platform is composed of cobalt chromium (strut width = 80 μm) (Fig. 1). The mesh is the same in

both stents. In case reports using optical coherence tomography imaging, this device has been shown to trap thrombus behind the mesh net when used in STEMI [9]. This study has been designed to demonstrate the superiority of the MGuard[TM] stent over commercially approved BMS or drug-eluting stents (DES) in achieving superior myocardial reperfusion in patients undergoing PCI for treatment of STEMI.

STUDY DESIGN AND STUDY POPULATION

The MASTER trial is a prospective, multicenter, randomized study in which up to 432 subjects with STEMI at 66 sites in 10 countries will be randomized 1:1 to the MGuard[TM] stent versus any commercially approved BMS or DES for treatment of STEMI. To be considered eligible for enrollment, patients must present with symptoms consistent with acute myocardial infarction with =2 mm of ST segment elevation in =2 contiguous leads, consented within 12 hr of symptom onset. Patients enrolled must be intended for primary percutaneous intervention or rescue intervention after failed thrombolytic therapy. In addition, these patients must have angiographic anatomy suitable for PCI and anticipated stent placement. Table I lists the clinical and angiographic inclusion and exclusion criteria.

Patients will be consented prior to diagnostic angiography but are formally enrolled and randomized only after achievement of TIMI 2 or 3 flow and visualization of vessel anatomy distal to the culprit lesion, to allow confirmation that all angiographic entry criteria are present. TIMI 2 or 3 flow may be achieved by wire passage, undersized balloon angioplasty (=1.5 mm), or aspiration catheter use at the operator's discretion. Figure 2 shows the study flowchart. If baseline TIMI 2 or 3 flow is present allowing visualization of the target lesion and distal vessel, pre-dilation or aspiration will not be performed prior to randomization.

TABLE I. MASTER Trial Inclusion and Exclusion Criteria

Clinical inclusion criteria
1. The patient must be ≥18 years of age
2. ST-segment elevation (≥2 mm in ≥2 contiguous leads)
3. Symptom onset ≤ 12 hr
4. The patient is willing to comply with specified follow-up evaluations
5. The patient or legally authorized representative has been informed of the nature of the study, agrees to its provisions, and has provided written informed consent, approved by the appropriate Medical Ethics Committee (MEC), Institutional Review Board (IRB), or Human Research Ethics Committee (HREC)

Angiographic inclusion criteria
1. Single de novo lesion in the target (culprit) vessel
2. Target lesion maximum length is 33 mm (by visual estimation), able to be covered by a single stent maximum
3. Reference vessel diameter must be ≥3.0 to ≤4.0 mm by visual estimation

Clinical exclusion criteria
1. Pregnant or nursing patients and those who plan pregnancy in the period up to 1 year following index procedure
2. Left bundle branch block, paced rhythm, or other ECG abnormality interfering with assessment of ST-segment resolution
3. Patient has a history of or known impaired renal function (serum creatinine > 2.0 mg/dL or 177 μmol/L) or on dialysis
4. Prior coronary artery bypass graft surgery
5. Patient has a history of bleeding diathesis or coagulopathy or patients in whom anti-platelet and/or anticoagulant therapy is contraindicated
6. Patient has a known hypersensitivity or contraindication to aspirin, both heparin and bivalirudin, clopidogrel, ticlopidine, prasugrel or ticagrelor, stent or mesh material, and/or contrast sensitivity/allergy that cannot be adequately pre-medicated
7. Patients undergoing cardiopulmonary resuscitation
8. Cardiogenic shock (defined as systolic blood pressure <80 mm Hg for >30 min, or requiring IV pressors or emergency intra-aortic balloon pump for hypotension)
9. Indication for chronic warfarin anticoagulation
10. Left ventricular ejection fraction ≤20%
11. Patient has other medical illness not related to the acute myocardial infarction (e.g., cancer, known malignancy, or congestive heart failure) or known history of substance abuse (alcohol, cocaine, heroin, etc.) that may cause non-compliance with the protocol, confound the data interpretation or is associated with a limited life expectancy (i.e., less than 1 year)
12. Currently participating in another investigational drug or device study that has not reached its primary endpoint

Angiographic exclusion criteria
1. Left main coronary artery disease with >50% stenosis
2. Ostial target lesion—left anterior descending or left circumflex artery within 3 mm of the left main artery, or right coronary artery within 5 mm of the aorta
3. Failure to visualize vessel anatomy distal to the culprit lesion
4. Moderate to heavily calcified target lesion or vessel
5. Target lesion or vessel has excessive tortuosity possibly making stent delivery or deployment difficult
6. Target lesion involves bifurcation with a side branch ≥2.0 mm in diameter that would require jailing the side branch with the study stent
7. A significant (>50%) stenosis proximal or distal to the target lesion is present that cannot be covered by same single stent
8. Diffuse disease distal to target lesion with impaired runoff
9. Any prior stent proximal to the target lesion, or within 10 mm distal of the target lesion
10. Percutaneous coronary intervention of another lesion performed within 6 months before the index procedure
11. Target lesion located in a saphenous vein graft

To ensure an equal distribution of the LAD as the culprit vessel, and use of aspiration in either treatment group, randomization will be stratified by these two factors in randomly alternating block sizes of 6. Once randomized, subjects are considered enrolled in the study and will be analyzed as the intent-to-treat (ITT) population. The randomization assignment is not blinded. Clinical follow-up (telephone contact or visit) will occur at 30 ± 7 days, 6 months ± 15 days, and 1 year ± 15 days.

Medications

All patients will receive a loading dose of aspirin (300–325 mg chewed or an IV dose of 250–500 mg per standard hospital practice) prior to the procedure, regardless of the use of aspirin at home. A loading dose of 600 mg of clopidogrel, or 60 mg prasugrel or 180 mg of ticagrelor will also be administered prior to PCI. After the procedure, patients will be treated with aspirin (75–162 mg/day) indefinitely, and clopidogrel for 12 months (75 mg/day; up to 150 mg/day in the first week may be used if local standard of care), regardless of the type of stent deployed. If prasugrel (5 or 10 mg/day) or ticagrelor (90 mg bid) are used instead of clopidogrel, they should also be prescribed for 12 months.

Procedural anticoagulation may consist of unfractionated heparin plus an intravenous glycoprotein IIb/IIIa inhibitor or bivalirudin monotherapy at the investigator's discretion. Heparin alone may not be used in this protocol. If a GPIIb/IIIa inhibitor is used, it should be continued for 12 hr postprocedure. Intracoronary use of a GPIIb/IIIa inhibitor is not permitted in this protocol; nor is low-molecular-weight heparin or fondaparinux.

Optimal medical therapy is strongly recommended in all patients, including high-dose statins, β-blockers, and ACE inhibitors or angiotensin receptor blockers in the absence of contraindications.

Devices and PCI

If the patient is randomized to control, the decision to use a DES or BMS is left to the discretion of the operator, as this choice does not affect the achievement of ST-segment resolution. Stent implantation technique will be according to local laboratory standards. If the patient is randomized to the MGuard arm, either the stainless steel or cobalt chromium platform may be selected, according to device availability. The specifications of these two devices are shown in Table II. The MGuard stent is not recommended in heavily calcified lesions, arterial segments with highly tortuous anatomy, lesions that require stent overlapping, lesions distal to an existing stent or lesions that would require jailing of major side branches (=2.5 mm). Jailing of side branches <2.5 mm diameter is allowed.
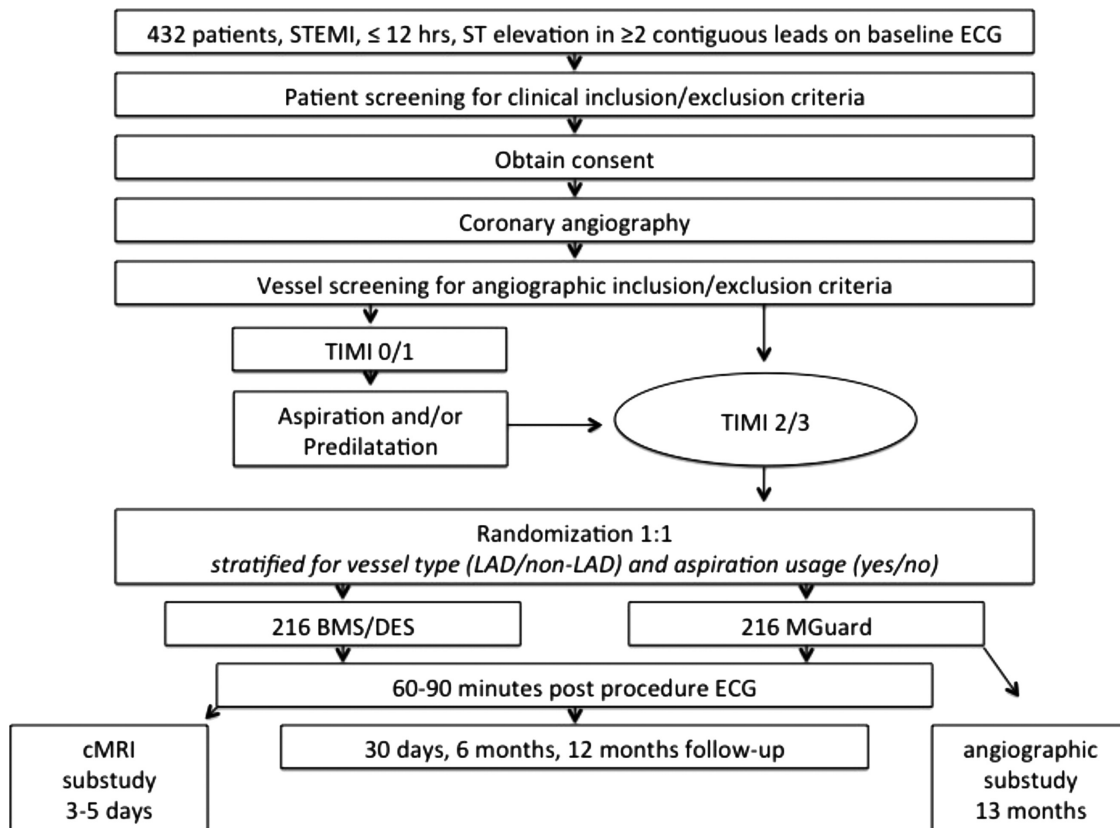
Fig. 2. Patient flow and study procedures in the MASTER trial. STEMI: ST elevated Myocardial Infarction; ECG: Electrocardiogram; TIMI: Thrombolysis in Myocardial Infarction; LAD: Left anterior descending artery; BMS: Bare metal stent; DES: Drug-eluting stent; cMRI: Cardiac magnetic resonance imaging.

Only the acute infarct lesion may be treated during the index procedure. Patients with other non-culprit lesions in different target vessels may undergo a staged procedure, performed =72 hr after the index procedure.

Principal Endpoints

The primary endpoint is the incidence of complete ST-segment resolution (defined as =70% ST-segment resolution) [10] measured 60 to 90 min after the final angiogram. Secondary endpoints include the incidence of TIMI 3 flow and MBG 2 or 3, as well as the rate of composite major adverse cardiac events (MACE), defined as cardiac death, reinfarction (Q wave or non-Q wave), or repeat ischemia-driven target lesion revascularization (TLR) through 1-year follow-up. The complete list of endpoints appears in Table III.

Substudies

The MASTER Trial protocol includes two pre-specified substudies. In the first substudy, angiographic follow-up at 13 months post-procedure will be performed in 50 consecutive patients at participating sites in whom the MGuard stent was implanted. The purpose of this substudy is to evaluate in-stent and in-segment late lumen loss as well as binary restenosis rates with the MGuard stent, with comparison to historical control parameters. In the second substudy, 60 randomized patients (30 MGuard[TM] and 30 control) at qualified participating sites will undergo cardiac magnetic resonance imaging (MRI) at 3–5 days post-enrollment. The major endpoints to be examined from this substudy are infarct size and microvascular obstruction.

Core laboratory assessment of ST-segment resolution and cardiac MRI data will be performed at the Cardiovascular Research Foundation, NY. Core laboratory angiography and clinical event adjudication will be performed at the Cardiovascular Research Center, São Paulo, Brazil. Both core laboratories are blinded to randomization assignment.

Sample Size Determination and Statistical Analysis

Sample size calculation was based on the primary endpoint of the study, the rate of complete ST-segment

TABLE II. MGuard and MGuard Prime Specifications

System	
Stent sizes available	2.0–4.0 mm diameter, 11–39 mm length (MGuard)
	2.5–4.0 mm diameter, 13–38 mm length (MGuard Prime)
Compatible with	Guiding catheter: 6F (ID 1.68 mm /0.07")
	Usable catheter length: 1420 mm
	Guidewire: 0.014"/0.36 mm
Aperture size (expanded)	150 × 180 μm
Crossing profile	1.0–1.3 mm (MGuard)
	1.0–1.2 mm (MGuard Prime)
Visual profile	1.1–1.4 mm (MGuard)
	1.3–1.5 mm (MGuard Prime)
Sterilization	ETO
Delivery System	
Radiopaque markers	Proximal and distal
Balloon characteristic	Semi-compliant
Nominal pressure	8 atm
Rated burst pressure	16 atm
Net:	
Technology	Micron Circular-Knitting Technology
Net material	Poly ethylene terephthalate (PET)
Fiber diameter	20 μm
Stent	
Stent material	Stainless steel 316 (MGuard)
	Cobalt Chromium (CoCr) L605 (MGuard Prime)
Stent design	Low profile
Strut thickness	100 μm (MGuard)
	80 μm (MGuard Prime)

resolution measured 60 to 90 min after the final study angiogram. We estimate that 412 total patients with analyzable paired ECGs (pre and at 60–90 min post-procedure) would provide 80% power to demonstrate a relative 21% increase in the frequency of complete ST-segment from 60% to 73% with a two-sided $\alpha = 0.05$. Assuming that analyzable paired ECGs will be available from 95% of patients, 432 patients will be randomized to provide sufficient power for the primary hypothesis of the study.

All endpoints will be evaluated in the ITT and per protocol (PP) analysis sets. The PP cohort is defined as those patients in whom one or more study stents (MGuard in the treatment group and BMS or DES in the control group) were implanted.

Numerous subgroups will be examined for consistency of treatment effect for the primary endpoint, including but not limited to age, gender, diabetes, infarct artery, baseline TIMI flow, and time from symptom onset to PCI. The results from these analyses will be considered exploratory and hypothesis generating.

Study Management and Publication

The trial is funded by InspireMD. The study chairman and principal investigators in concert with the study

TABLE III. MASTER Trial Endpoints

Primary endpoint

1. The incidence of complete ST segment resolution (defined as ≥70% ST resolution) measured 60–90 min after the last angiogram

Secondary endpoints

1. The incidence of TIMI 3 flow at the end of the procedure
2. Corrected TIMI Frame Count (CTFC) at the end of the procedure
3. The incidence of Myocardial Blush Grade (MBG) 2 or 3 at the end of the procedure
4. Major Adverse Cardiac Events (MACE): defined as cardiac death, reinfarction (Q wave and non-Q wave), or repeat ischemia-driven target lesion revascularization (TLR) by percutaneous or surgical methods at hospital discharge, 30 days, 6 months, and 1 year post-procedure
5. Composite endpoint of all-cause death, reinfarction, stroke, and ischemia-driven repeat target lesion revascularization (MACCE) at hospital discharge, 30 days post-procedure, 6 months, and 1 year after baseline intervention
6. Rates for all-cause death, cardiac death, death, non-cardiac death, reinfarction, Q-wave reinfarction, non-Q-wave reinfarction, death or reinfarction, cardiac death or reinfarction, TLR, TVR and stroke at hospital discharge, 30 days, 6 months, and 1 year post-procedure
7. Acute success rates
   i. Angiographic success: attainment of <50% final residual stenosis of the target lesion and final TIMI 3 flow
   ii. Device success: attainment of <50% final residual stenosis of the target lesion using only the randomized STENT
   iii. Lesion success: attainment of <50% final residual stenosis of the target lesion using any percutaneous method
   iv. Procedure success: attainment of <50% final residual stenosis of the target lesion and no in-hospital MACCE
8. Bleeding or vascular complications at discharge
9. Stent thrombosis (definite, probable and composite definite or probable, by ARC definition) through 1-year follow-up, each sub-classified as acute (<24 hr), sub-acute (24 hr–30 days), early (<30 days) and late (30 days to 1 year)
10. Infarct size and microvascular obstruction assessed by cardiac MRI (from a sub-study of up to randomized 60 patients) at 3–5 days post-procedure
11. In-stent and in-segment late lumen loss and binary restenosis as determined by independent quantitative coronary angiographic analysis at 13 months post-procedure (from the angiographic follow-up sub-study of 50 MGuard patients)

sponsor designed the trial and are responsible for its conduct and analysis. Independent core laboratories will perform all key analyses blinded to treatment assignment. An independent clinical events committee, composed of interventional and non-interventional cardiologists who are not participants in the trial, will adjudicate all clinical endpoint events blinded to treatment assignment. An independent data safety monitoring board will oversee safety data, including serious and other significant adverse events, on an ongoing basis. The Cardiovascular Research Foundation will prepare all statistical analyses and reports. The drafting, editing, and final content of all manuscripts will be performed solely by the investigators, although the sponsor will be allowed nonbinding reviews of all manuscripts before submission. No agreements exist regarding data confidentiality.

DISCUSSION

Enrollment in the MASTER trial commenced in July 2011 and was completed in May 2012.

The MGuard^{TM} stent with its external protective net was conceived to prevent distal embolization of plaque debris/thrombus during primary PCI, a central cause of impaired myocardial perfusion after mechanical reperfusion therapy in STEMI. The MASTER Trial is a prospective, multicenter randomized study designed to evaluate whether the MGuard^{TM} stent is superior to conventional BMS and DES in achieving superior myocardial reperfusion in patients with STEMI.

Compared with balloon angioplasty alone, stent implantation has demonstrated benefit in patients with STEMI by reducing restenosis and infarct artery reocclusion [11]. The randomized Stent PAMI trial suggested that compared to balloon angioplasty, stent implantation during primary PCI may reduce TIMI-3 flow and increase mortality, presumably due to extrusion and embolization of thrombus and friable atheromatous debris through the stent struts with resultant capillary block [12]. Although subsequent larger trials, such as CADILLAC [12], did not replicate this phenomenon, distal embolization during primary PCI is believed to be ubiquitous and results in impaired myocardial perfusion and therefore myocardial recovery.

Protection of the distal microcirculation during STEMI intervention should result in improved epicardial (TIMI) blood flow and myocardial perfusion (myocardial blush), and decreased angiographic complications (transient or sustained slow or no reflow, distal thromboemboli, etc.), resulting in a more rapid, complete, and stable ST-segment resolution and improved recovery of left ventricular function, ultimately translating into improved survival. To date, however, while simple aspiration catheters have improved ST-segment resolution and reduced MACE in one single-center study [13], in others they have not, and they have not been shown to reduce infarct size [14,15]. There is no sufficient evidence that distal protection devices [16] or adjunctive pharmacotherapy such as abciximab reduce infarct size or improve long-term outcomes [17] to recommend their routine use.

The MGuard stent was initially studied in 29 patients with lesions in either native coronary arteries or saphenous vein grafts [18]. The device, procedure, and clinical success rates reported in this study were 100%, 96.4%, and 96.4%, respectively, with a single case of peri-procedural MI and no further MACE up to 30 days. Asa-Vaknin et al. reported a 100% procedure success with no in-hospital and 30-day adverse events after stenting with the MGuard in seven saphenous vein grafts [19]. Maia et al. published a single-center experience with the MGuard stent in 30 thrombotic saphenous vein graft and native coronary artery lesions [20]. The MGuard stent was successfully deployed in all cases with no angiographic complications or MACE through 30-day follow-up. At 1 year, there were no reported cases of cardiac death, two MIs (one Q-wave and one non-Q-wave), and six cases of ischemia-driven TLR. Of note, there were no cases of definite or probable stent thrombosis.

In 2010, Dudek et al. published a four-center experience with the MGuard^{TM} stent in 60 patients with STEMI presenting within 12 hr of symptom onset [21]. Aspiration devices were used in only 18.3% of cases. Final TIMI grade 3 flow was restored in 90.0% of patients, myocardial blush grade 3 was achieved in 73.3%, and complete (>70%) ST-segment resolution at 60 min was present in 61.4% of patients. The cumulative MACE rate at 6-month follow-up was only 1.7%, consisting of one case of non-Q-wave MI. Subsequent case reports using optical coherence tomography in patients with STEMI have demonstrated that the MGuard stent does indeed trap friable debris and thrombus behind the mesh net, hereby preventing its embolization [9].

CONCLUSION

The MASTER trial is the first randomized study of the MGuard stent and is designed to demonstrate enhanced myocardial perfusion and superior ST-segment resolution with this novel device compared to standard stents in patients undergoing PCI for STEMI. Given the strong relationship between ST-segment resolution and subsequent early and late mortality in STEMI [22], should the MASTER trial be positive, the MGuard stent may provide an important innovative approach in these high-risk patients.

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