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Thrombus management in the catheterization laboratory in the setting of primary percutaneous coronary intervention: what is the current evidence?

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Abstract
Primary percutaneous coronary intervention (PCI) has become the preferred option in the treatment of acute ST-elevation myocardial infarction (STEMI) due to its rapid and effective re-establishment of epicardial coronary flow. Distal embolization of coronary thrombus may occur in 15% of the primary PCI population, and is a common cause of periprocedural complications. It may result in occlusion of the microvascular bed, resulting in suboptimal reperfusion and impaired prognosis due to increased infarct size, reduced ventricular function, and a fivefold increase in 5-year mortality. Several strategies used for the prevention of distal embolization are the evolving role of intravenous glycoprotein IIb/IIIa inhibitors (GPIs), use of adjunctive mechanical devices (manual or mechanical thrombus aspiration catheters and proximal/distal protection devices), and specifically designed stents for thrombus entrapment. Based on recent evidence, the administration of GPIs is associated with improvement in clinical outcomes and manual thrombus aspiration is an attractive concept, easy to use, and may improve the 1-year clinical outcome for STEMI patients undergoing primary PCI.
INTRODUCTION

Recently, primary percutaneous coronary intervention (PCI) has become the preferred option in the treatment of acute ST-elevation myocardial infarction (STEMI) due to its rapid and effective re-establishment of epicardial coronary flow [1-3]. Randomized controlled trials have shown the superiority of primary PCI with an overall 40% reduction of major adverse cardiovascular events (MACE) compared to fibrinolytic treatment [4].

One of the technical issues that arises in primary PCI is how to prevent embolization of atherothrombotic material, that occurs in 15% of the primary PCI population [5], and is a common cause of periprocedural complications. Once embolization occurs, distal emboli can: (1) mechanically ‘plug’ the microvasculature, leading to continued ischemic necrosis of the myocardium; (2) promote local in situ platelet adhesion and thrombosis, causing impairment of tissue reperfusion and a higher chance of the so called “no-reflow phenomenon”; and (3) may also provoke microvascular spasm and local inflammatory reactions that may further complicate recovery due to more extensive myocardial necrosis (Figure 1) [6,7].

Indeed, distal embolization of thrombus may result in occlusion of the microvascular bed, resulting in suboptimal reperfusion [7] and impaired prognosis due to increased infarct size, reduced ventricular function and a fivefold increase in 5-year mortality [8-11].

Furthermore, STEMI patients with a large thrombus burden suffer from a higher incidence of infarct related artery stent thrombosis compared to patients with a small thrombus burden (8.2% vs. 1.3%, p<0.001) [12]. Therefore, an appropriate and aggressive management of the thrombus is needed for the prevention of distal embolization and to achieve a better acute reperfusion result as well as better long-term result.

Figure 1. The hypothesis of distal embolization (an illustration). Distal embolization of atherothrombotic material (red and blue circles) can ‘plug’ the microvasculature (a), promote local platelet adhesion (b), and cause spasm (c) that can lead to serious impairment of tissue reperfusion and the no reflow phenomenon. Arrows indicate the distal embolization of thrombotic material into the microvasculature.
ACUTE REPERFUSION PARAMETERS

Acute reperfusion parameters during primary PCI are important tools for immediate evaluation of the success of reperfusion treatment. The most commonly used parameters are the thrombolysis in myocardial infarction (TIMI) flow, myocardial blush grade (MBG) and ST segment resolution on ECG after the procedure [13].

The TIMI flow grading assesses flow in the large epicardial coronary vessels, but myocardial perfusion takes place at the microvascular level, while MBG assesses contrast filling in distal microvessels as a measure of myocardial perfusion (Figure 1) [13,14]. Myocardial perfusion after primary PCI is the strongest predictor of mortality independent of infarct related artery re-opening as shown by Stone and colleagues [15]. Patients with MBG 0 or 1 have a higher mortality compared to patients with MBG 2 and 3 (18.3% vs. 13.2% vs. 6.8%, p=0.004). A successful primary PCI is indicated by achieving TIMI 3 flow [16] (better epicardial artery flow), MBG 3 [17], and complete ST segment resolution [18] (better microvascular perfusion) after the index procedure and is associated with lower mortality.

MANAGEMENT STRATEGIES PREVENTING DISTAL EMBOLIZATION OF CORONARY THROMBUS

Currently, there are several strategies available for ‘fighting’ distal embolization of coronary thrombus including:

a. Pharmacologic approaches to dissolve the thrombus (with a special role for glycoprotein IIb/IIIa inhibitors (GPIs))

b. Use of adjunctive mechanical devices (thrombus aspiration and embolic protection devices)

c. Dedicated stent for thrombus entrapment (e.g., MGuard stent)

ROLE OF GLYCOPROTEIN IIB/IIIA INHIBITORS

GPIs are effective and potent intravenous platelet aggregation inhibitors that have been studied in the wide spectrum of acute coronary syndrome especially in the setting of PCI with highly thrombotic lesions; abciximab (large molecule), eptifibatide and tirofiban (small molecule) are the available GPI agents [19-23]. An important issue is which GPI agents should be used and when in our daily clinical practice.

Small molecule versus large molecule GPI

A meta-analysis that was performed by De Luca et al. [24] showed that patients receiving abciximab in the setting of primary PCI had lower 30 day mortality compared to the control group of patients not receiving abciximab (2.4% vs. 3.4%, p=0.047), and this beneficial effect was even seen at 6 and 12 months follow-up (4.4% vs. 6.2%, p=0.01).

Benefits from small molecule administration (tirofiban and eptifibatide) as compared with abciximab among patients who underwent primary PCI were studied in a meta-analysis involving 2197 patients, and showed no significant difference in clinical outcomes between the two groups in terms of death, final TIMI flow grade, and ST segment resolution [25]. A larger report analysing the role of eptifibatide and abciximab was derived from the SCAAR
registry involving 11,479 patients who underwent primary PCI and found non-inferiority of the two treatments when compared to each other [26]. Another meta-analysis comparing tirofiban and eptifibatide (n=4653) to abciximab (n=2696) was performed by Ottani et al; this analysis also documented non-inferiority of small molecules compared to abciximab in STEMI patients treated with primary PCI [27].

The statement from the 2011 American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) PCI guideline executive summary mentions that “In patients undergoing primary PCI treated with UFH (unfractionated heparin), it is reasonable to administer a GPIIb/IIIa Inhibitor (abciximab, double bolus eptifibatide or high bolus dose tirofiban), whether or not patients were pretreated with clopidogrel” as class IIa indication [28]. This statement has clearly put the same position for all three GPs.

Timing of GPI administration

The proper time of administering GPs has been studied recently (early vs. delayed administration) and showed conflicting results [29,30]. Theoretically, the faster the GPI being given, the more rapid platelet aggregation inhibition would be expected.

A meta analysis by De Luca et al. [31], which involved seven randomized trials on early GPI administration in primary PCI, showed that early abciximab group patients (n=357) had significantly lower mortality (p=0.02), more patients had post-procedural TIMI 3 flow (p=0.04), MBG 3 (p=0.03), and complete ST segment resolution (p<0.0001) with less embolization (p=0.02), compared to the late abciximab group (n=365).

Results from the Leiden MISSION study (n=179) was in favour of early in-ambulance abciximab administration and this was associated with a smaller infarct size, improved left ventricular function and a lower risk of heart failure during clinical follow-up compared to in-hospital abciximab administration [32]. The ON-TIME 2 study (n=984) by van’t Hof et al. has further emphasized the routine (early) pre-hospital initiation of high-bolus dose tirofiban to improved ST segment resolution and clinical outcome after primary PCI, without increasing the bleeding risk [33].

However, another study, the recently published MISTRAL trial (n=256), failed to demonstrate a clinical benefit of early in-ambulance administration of abciximab in STEMI patients [34]. It is postulated that especially very early (<2 hours of onset of complaints) GPI administration may be of benefit for primary PCI patients, which would make sense since no firm clot has been formed yet.

Guideline statement on the timing of GPI administration

Because of the conflicting results, the 2011 ACCF/AHA/SCAI PCI guideline executive summary has indicated GPI administration as class III indication for routine pre-catheterization laboratory (e.g., ambulance or emergency room) as part of an upstream strategy for patients with STEMI undergoing PCI [28], while the recent 2012 European Society of Cardiology (ESC) guideline on STEMI has indicated it as class IIb [35]. Larger randomized trials are needed to analyse further the proper timing of GPs.
Intracoronary vs intravenous GPI administration

A higher local GPI concentration by intracoronary administration might disrupt platelet cross-linking, thus augmenting thrombus disaggregation [36,37], and is associated with improved clinical outcome in acute coronary syndrome patients undergoing PCI [38]. The recently published INFUSE-AMI trial [39] showed that infarct size at 30 days was significantly reduced by bolus intracoronary abciximab delivered to the infarct lesion site compared to the no abciximab group (p=0.03).

A meta-analysis involving small to moderate scale trials has shown beneficial clinical effects of intracoronary versus intravenous GPI administration [40]; however, another medium scale randomized study (CICERO trial) [41] showed no improvement in myocardial reperfusion as assessed by ST segment resolution in the intracoronary group compared to intravenous GPI administration during primary PCI (64% vs. 62%, p=0.562), with similar incidence of 30 days MACE (5.5% vs. 6.1%, p=0.786).

These unsolved issues with regard to the route of GPI administration need to be confirmed further by larger randomized trials; meanwhile, the recent guideline on PCI has indicated class IIb indication for intracoronary abciximab administration in primary PCI [28].

ADJUNCTIVE MECHANICAL DEVICES: THROMBUS ASPIRATION CATHETER
(MECHANICAL VERSUS MANUAL THROMBUS ASPIRATION)

There are two approaches available for thrombus aspiration [42]:

a. Mechanical thrombus aspiration, for example, Angiojet, X-Sizer, Rinspirator catheters, etc.

b. Manual thrombus aspiration, for example, Thrombuster II, Export, Diver catheters, etc (Figure 2).

The use of thrombus aspiration catheters has been widely adopted in almost all primary PCI procedures due to the result from the TAPAS trial [43]. From TAPAS, we learned that manual thrombus aspiration is applicable in a large majority of STEMI patients and results in a better reperfusion parameter shown by a lower proportion of patients achieving MBG 0 or 1 compared to conventional PCI group (17.1% vs. 26.3%, p<0.001). Moreover, 1 year mortality was significantly lower in the thrombus aspiration group compared to conventional PCI without aspiration (3.6% vs. 6.7%, p=0.02) [44]. On the other hand, the use of mechanical thrombus aspiration has failed to show a clinical benefit compared to the manual aspiration catheter as shown by a pooled analysis of individual patient data from 11 STEMI trials involving 2686 patients [45]. We are eagerly awaiting the results of the TOTAL trial [46] (n=4000) and TASTE trial [47] (n=5000) as they are the largest randomized studies comparing routine aspiration thrombectomy followed by PCI versus conventional PCI in STEMI patients undergoing primary PCI that are currently ongoing.
Figure 2. Picture of a 6F manual thrombus aspiration catheter (A). Manual thrombusuction device, the syringe (arrow head) and filter (small arrow) (B). The tip of thrombus aspiration catheter. Small arrow indicates the guidewire lumen and arrow head indicates lumen for aspiration of thrombus (C).
Larger lumen vs smaller lumen of thrombus aspiration catheter

It has been postulated that larger lumen catheters will retrieve more thrombus particles compared to smaller lumen catheters. However, a sub-analysis of the TAPAS trial has shown that there was no significant difference in MBG or electrocardiographic outcome between the Diver catheter (internal lumen 0.062 inches) compared to the Export catheter (internal lumen 0.041 inches); size distribution of retrieved thrombotic particles was similar per device, indicating that a larger internal lumen diameter does not automatically result in retrieval of larger thrombotic particles [48].

Thrombectomy plus GPI

Burzotta et al. have shown the advantage of GPI administration in combination with thrombus aspiration from a pooled analysis of trials on thrombectomy in acute myocardial infarction based on individual patient data by showing that patients receiving GPI plus thrombectomy had lower mortality compared to thrombectomy alone, GPI alone, or neither GPI/thrombectomy (3.3% vs. 4.8% vs. 5.0% vs. 7.4%, p=0.02) [45].

Embolic protection devices

Other percutaneous strategies that have been developed in attempts to reduce embolization are the use of distal or proximal protection devices with thrombus aspiration. The use of distal protection devices in the EMERALD [49] and PROMISE [50] trials showed no benefit in terms of fast ST segment resolution, final infarct size or the incidence of MACE in 6 months. Furthermore, a meta-analysis of randomized trials showed that distal protection devices did not reduce the risk of no-reflow compared to standard PCI in STEMI patients [51]. The use of a proximal protection device (Proxis) in the PREPARE [52] study improved microvascular flow as reflected by improved immediate complete ST segment resolution; however, the study was underpowered to detect clinical benefit.

Dedicated stent for thrombus entrapment (MGuard stent)

Another alternative strategy to reduce embolization of atherothrombotic material is thrombus entrapment, blocking embolic material at its source. The MGuard stent has the capability to trap embolic material at source. It is a proprietary metal stent covered with an ultra thin, micron level flexible mesh sleeve fabricated by circular knitting. During deployment of the stent, the flexible mesh freely expands over the stent struts, and the pores open in parallel with the stent, sandwiching embolic and pro-thrombotic material between the flexible mesh and the intima. The MAGICAL trial [52] showed a promising result with 90% of patients reaching TIMI 3 flow with 0% and 1.7% major adverse cerebro-cardiovascular events at 30 days and 6 months, respectively. Although this short term result looks promising, it needs a longer follow up to observe the restenosis and stent thrombosis rate, and randomized studies are needed to address definitively the benefit of this specially designed stent.
**Guideline statement on adjunctive therapeutic devices**

Based on recent evidence, the 2011 ACCF/AHA/SCAI PCI guideline executive summary has mentioned that “adjunctive therapeutic devices with aspiration thrombectomy is reasonable for patients undergoing primary PCI”, as class IIa indication [28]. The similar statement was also mentioned in the 2012 ESC guideline on STEMI [35].

**WHAT TO DO WHEN ASPIRATION FAILS**

A report from a small case series has reported that in patients with massive residual intracoronary thrombus after repeated aspiration, local fibrinolysis with small doses of tenecteplase may improve angiographic and clinical outcomes in this difficult setting of patients with acute myocardial infarction, without systemic effects [53]. Larger randomized studies are needed to confirm the role of intracoronary fibrinolytic therapy when thrombus aspiration fails to improve reperfusion in STEMI patients undergoing primary PCI.

**HOW TO DO IMPROVED THROMBUS ASPIRATION DURING PRIMARY PCI**

Some technical considerations during manual thrombus aspiration based on our clinical experience are: (1) aspirate with a simple catheter to minimize micro/macro embolization (using, for example, Thrombuster II, Export catheter or equivalent); (2) start aspiration before crossing the lesion; (3) perform gentle & progressive crossing; (4) apply permanent negative pressure during aspiration; (5) perform a sufficient number of passes; (6) aspirate the whole catheter system after aspiration before making an angiogram evaluation (to minimize embolization of thrombotic material that was left in the inner lumen of the guiding catheter while retrieving the aspiration catheter) and; (7) if aspiration stops suddenly, the device should be removed (while maintaining negative pressure) to check whether there is a large thrombus obstructing the lumen.

Thrombus aspiration can be done several times depending on immediate reperfusion parameter evaluation. Direct stenting of the culprit lesion is advised when feasible and the true vessel diameter can be adequately estimated. Balloon predilation could be considered in selected cases. A suggested model for a clinical algorithm during primary PCI is shown in Figure 3.

Other important considerations are the onset of the infarction and age of the thrombus, vessel anatomy (tortuosity, calcification, tight lesion distal to the thrombus, small size vessel), the site of the occlusion (proximal or distal), and guiding catheter support.
CONCLUSION

Distal embolization is a relatively common phenomenon in primary PCI patients presenting with STEMI, and is associated with poor myocardial perfusion and adverse clinical outcomes. Pharmacological strategies with the use of GPIs as an adjunct to primary PCI have been demonstrated to be associated with improvements in outcomes, particularly in high-risk patients. While embolic protection devices and MGuard stents are theoretically attractive, randomized data assessing their clinical efficacy are limited. Selective manual thrombus aspiration is an attractive concept that is easy, fast, and may improve 1 year clinical outcome.

REFERENCES


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