Thrombus aspiration during primary percutaneous coronary intervention for acute myocardial infarction: A review of clinical evidence and guidelines

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Abstract
Acute ST segment elevation myocardial infarction (STEMI) is characterized by complete thrombotic occlusion of a major coronary artery. Early recanalization of the infarct-related artery is most efficiently delivered by primary percutaneous coronary intervention (PPCI), however this does not always restore normal myocardial perfusion, mainly due to distal embolization of the thrombus and microvascular obstruction. Early evidence for manual thrombus aspiration during PPCI was promising and this was once considered an important aspect of the procedure, especially in patients with a high thrombus burden. However, a large body of evidence from recent major randomized controlled trials (notably TASTE and TOTAL) does not support the routine use of manual thrombus aspiration in patients with STEMI undergoing PPCI.

Key words: Primary percutaneous coronary intervention; Clinical evidence; Stroke; Acute myocardial infarction; Thrombus aspiration

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Core tip: The role of manual thrombus aspiration during primary percutaneous coronary intervention (PPCI) for acute ST segment elevation myocardial infarction (STEMI) has been a matter of significant research and intense debate recently. The rationale for manual thrombus aspiration during PPCI is the removal of intracoronary thrombus, thus avoiding the complication of downstream embolization leading to impaired myocardial perfusion. In this review article, we present the data from early clinical trials and meta-analyses of thrombus aspiration during PPCI, and the more recent evidence from larger multi-center randomized controlled trials that have had a major influence on clinical practice. We highlight the relevant major society guidelines for thrombus aspiration during PPCI and provide the reader with an overview of this technology and its role in contemporary management of STEMI.
INTRODUCTION

The common pathophysiological mechanism of acute coronary syndrome is sudden disruption of a coronary arterial plaque due to rupture, fissuring or superficial erosion leading to obstructive intracoronary thrombosis. Other less frequent mechanisms include acute plaque expansion, embolism, spontaneous dissection or coronary inflammation[1]. Acute ST segment elevation myocardial infarction (STEMI) is characterized by complete thrombotic occlusion of a coronary artery, with a great potential to cause a large myocardial infarction if not treated promptly. The primary therapeutic goal in STEMI, therefore, is early restoration of normal coronary blood flow, most efficiently delivered by primary percutaneous coronary intervention (PCI) in combination with adjunctive pharmacological treatment. PCI aims to achieve myocardial salvage, electrical stability and preserve left ventricular function, improving both early and late outcomes after STEMI.

However, restoration of epicardial coronary artery patency does not always equate with normal myocardial reperfusion. The hallmarks of reperfusion failure despite achieving arterial patency are microvascular obstruction and the no-reflow phenomenon. A high burden of intracoronary thrombus and subsequent distal embolization during PCI are possible major contributors to these events. Myocardial reperfusion failure clinically manifests as persistent ST segment elevation, poor myocardial blush grade (MBG) and low thrombolysis in myocardial infarction (TIMI) flow grade[2].

Earlier investigations revealed that angiographically distal embolization occurred in around 15% of patients undergoing PCI[3]. Distal embolization was associated with impaired myocardial reperfusion, larger infarct size and an unfavorable prognosis. Further evidence of distal embolization and its impact on myocardial reperfusion is provided by intravascular ultrasound analysis (IVUS). In a study of 35 patients undergoing PCI for myocardial infarction, Kotani et al[4] applied volumetric IVUS analysis before and after PCI to assess the plaque reduction as evidence of distal embolization. Plaque reduction following PCI was associated with impaired myocardial reperfusion. “The enhanced myocardial efficacy and recovery by aspiration of liberated debris (EMERALD)” trial investigators, while investigating a distal balloon occlusion and aspiration system, demonstrated that visible debris was retrieved in 73% of the patients undergoing PCI[5]. Avoidance of distal embolization is hence a considerable therapeutic challenge during STEMI.

PHARMACOLOGICAL AND MECHANICAL MEANS OF REDUCING THROMBUS

Pharmacological agents (especially glycoprotein IIb/IIIa inhibitors), mechanical thrombectomy devices, embolic protection devices and manual aspiration thrombectomy catheters have been investigated over the past couple of decades as adjunctive therapies during PCI with the aim of reducing thrombus burden and subsequent distal embolization. Glycoprotein IIb/IIIa inhibitors inhibit the final common pathway of platelet activation and are a useful adjunct to PCI, albeit with an increased risk of bleeding. While theoretically attractive, the clinical value of mechanical thrombectomy and embolic protection devices during PCI is unproven, after several negative trials. Manual thrombus aspiration (thrombectomy) during PCI is the focus of this review article.

A major technical advantage of a manual thrombus aspiration device is its simplicity, consisting of a monorail catheter containing a central lumen that connects one or more large holes at the distal end to an aspiration syringe at the proximal end. The commonly used aspiration devices in clinical practice are Export™ (Medtronic, MN, United States), Eliminate™ (Terumo), Pronto™ (Vascular solutions, MN, United States) Diver™ CE (Invatec, Italy), QuickCat (Spectranetics Inc, United States) and Hunter™ (IHT Cordynamic, Barcelona, Spain). All these devices are formed on the same principle and convincing clinical advantage of one particular device over the other is lacking.

CLINICAL EVIDENCE

Randomized controlled trials

A number of studies, including randomized clinical trials and subsequent meta-analyses have evaluated the clinical efficacy of routine manual thrombus aspiration during PCI. In the initial “randomized evaluation of the effect of mechanical reduction of distal embolization by thrombus-aspiration in primary and rescue angioplasty (REMEDIA)” trial, 100 patients with STEMI were randomized to PCI with or without manual thrombus aspiration (Diver™ CE). More patients in the manual thrombus aspiration group achieved MBG 2 or more and ST segment resolution (STR) of 70% or more (46% vs 25%)[6]. In “Thrombectomy with Export Catheter in Infarct-Related Artery During Primary Percutaneous Coronary Intervention” (EXPIRA) trial, 175 patients with STEMI were randomized to PCI with or without manual thrombus aspiration. The primary end points of MBG 2 or more and ST segment resolution (STR) of 70% or more (46% vs 25%) occurred more often in PCI with thrombus aspiration group compared with standard PCI. Patients in the aspiration group had less microvascular obstruction and smaller infarcts[7]. After 24 mo, major adverse cardiac events were 4.5% vs 13.7% and cardiac death was 0% vs 6.8%, respectively, in patients with PCI with manual thrombus aspiration compared with standard PCI.
Thrombus aspiration during primary percutaneous coronary intervention trial

The first large randomized controlled trial (RCT) evaluating use of manual thrombus aspiration (Export® catheter) during PCI was “thrombus aspiration during primary percutaneous coronary intervention (TAPAS”). In this single-center all-comers RCT, 1071 patients with STEMI were randomized, to either thrombus aspiration during PCI or standard PCI alone, prior to coronary angiography. The primary end-point was the post-procedural frequency of a MBG of 0 or 1. All patients received standard pharmacological therapy including the glycoprotein IIb/IIIa inhibitor abciximab, unless contraindicated. Ninety-two percent patients underwent stent implantation in both groups. A MBG of 0 or 1 occurred less frequently in the thrombus aspiration group compared with the conventional PCI group (17% vs 26%, P < 0.001). Complete ST-segment resolution was more frequent in the manual thrombus aspiration group (56% vs 44%, P < 0.001). Atherothrombotic material was retrieved in 73% of the patients in thrombus aspiration group. Clinical outcomes at 30 d, including the rate of death and major adverse cardiac events, were significantly related to the MBG and ST-segment resolution. Rates of target vessel revascularization were similar between the two groups[10]. A 1-year follow-up study showed reduced rates of cardiac death (3.6% vs 6.7%) and cardiac death or non-fatal reinfarction (5.6% vs 9.9%) in the thrombus aspiration group[11]. The benefit of manual thrombus aspiration was irrespective of vessel size, infarct-related coronary artery or visible thrombus on the angiogram. A total ischemic time of less than 180 min was associated with a trend towards increased benefit (P = 0.09). Angiographically proven acute stent thrombosis (< 24 h) occurred with a similar frequency between both groups (0.2%) but subacute (1-30 d) and late stent thrombosis (> 30-365 d) was observed less frequently in the thrombus aspiration cohort (RR = 0.5, 95%CI: 0.19-1.32). The findings of TAPAS form the basis for major society guidelines recommending manual thrombus aspiration as an adjunct for PCI. The trial, however, was criticized for being underpowered for clinical events and susceptibility to selection bias (single center study).

Thrombus aspiration in STEMI in Scandinavia and the Trial of Routine Aspiration Thrombectomy with PCI vs PCI alone in patients with STEMI trials

TASTE trial: The above inconsistent results were followed by the two major randomized controlled trials in the field, thrombus aspiration in STEMI in Scandinavia (TASTE) and the Trial of Routine Aspiration Thrombectomy with PCI vs PCI alone in patients with STEMI (TOTAL). TASTE was a multi-center (29 PCI centers in Sweden, 1 each in Iceland and Denmark), randomized study that utilized the platform of population-based “Swedish coronary angiography and angioplasty registry”. A total of 7244 STEMI patients were randomized to PCI with manual thrombus aspiration or standard PCI alone[12]. The primary end point of all-cause mortality at 30 d was not different between the two groups (2.8% for thrombus aspiration with PCI vs 3% for PCI alone, P = 0.63). The majority of patients in TASTE had a low thrombus burden (thrombus grade 0-3). Bailout thrombus aspiration was performed in 4.9% patients assigned to PCI alone. The 30-d rates of secondary end-points (hospitalization for recurrent myocardial infarction, target-vessel revascularization, target-lesion revascularization, stent thrombosis and the composite of all-cause mortality or recurrent myocardial infarction) were not statistically different. The rate of stroke or neurological complication was identical (0.5%) in each group. The incidence of stent thrombosis, although statistically not significant, was lower (0.2% vs 0.5%, P = 0.06, HR = 0.47, 95%CI: 0.20-1.02) in the thrombus aspiration group. Similarly, hospital length of stay, incidence of heart failure or left ventricular dysfunction were all unaffected by manual thrombus aspiration. The failure to influence the primary end-point was consistent across all subgroups, including patients with diabetes, previous myocardial infarction, smokers and various measures of ischemic time. Outcomes in TASTE were similar irrespective of the infarct-related coronary artery, intra-arterial culprit segment (proximal vs non-proximal), TIMI flow grade before PCI, use of glycoprotein IIb/IIIa drugs and importantly thrombus burden. All-cause mortality at 1 year was a pre-specified secondary end-point of the study, which later reported no benefit of thrombus aspiration across all the major subgroups[13]. There were concerns that TASTE was underpowered to detect a difference in its primary end-point and also for its registry-based design (it was the first major trial ever to use this concept) with no separate, dedicated data monitoring and adjudicating set-up.

TOTAL trial: The most recent and so far the largest trial evaluating the benefit of manual thrombus aspiration in PPCI is TOTAL. This multi-center, prospective, randomized controlled trial assigned 10732 patients with acute STEMI to routine upfront manual aspiration thrombectomy vs PCI alone[14]. Almost 80% patients
had a high thrombus burden as assessed by TIMI thrombus grade 4 or 5. The primary outcome (composite of death from cardiovascular causes, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association class IV heart failure within 180 d) was similar between the two groups (6.9% in the thrombus aspiration group vs 7% in the PCI alone group). The key safety outcome of stroke within 30 d occurred more frequently in the thrombectomy group compared to PCI alone group (0.7% vs 0.3%, \( P = 0.02 \)). Within 180 d, stroke had occurred in 1% of patients with thrombectomy vs 0.5% in those without. The incidence of definite stent thrombosis within 180 d was similar between both groups (1.3% for thrombectomy vs 1.4%, \( P = 0.72 \)). Bailout manual thrombus aspiration was performed in 7.1% patients originally assigned to PCI alone. As noted in TASTE, the negative primary trial outcome was consistent across all pre-specified subgroups, including those with high thrombus burden, initial TIMI flow, time of symptom onset and anterior vs non-anterior myocardial infarction. The strength of the trial was the study design and the large study population. Concerns were raised towards potential selection bias of a lower-risk population (in view of lower than expected event rates for the primary outcome) and bailout thrombus aspiration in PCI alone group. The finding of increased incidence of stroke in the thrombectomy group is potentially significant, however, the absolute number of stroke events was small. The trial was also underpowered to detect a difference in stroke. It is possible that the higher risk of stroke in the thrombus aspiration group was not directly related to the thrombectomy procedure, supported by the observation that the increased stroke risk was not confined to the periprocedural period.

**Observational studies:** In a single-center retrospective analysis of 2567 consecutive STEMI patients treated with PCI, aspiration thrombectomy (\( n = 1095 \), using Export catheter in 93%) was associated with improved post-procedure TIMI 3 flow as well as reduced in-hospital (adjusted OR = 0.51, 95%CI: 0.29-0.93, \( P = 0.027 \)) and long-term (adjusted HR = 0.69, 95%CI: 0.48-0.96, \( P = 0.028 \)) mortality rates (4.5% vs 9.0%), over a mean follow-up of 9.9 mo. The study identified that the mortality benefit of thrombus aspiration was driven by results in patients with a total ischemic time of less than 180 min. However, critics of the study called the extent of mortality reduction excessive and implausible.

In a retrospective observational cohort study of 10929 STEMI patients treated with PCI at 8 centers across London, United Kingdom, manual aspiration thrombectomy (32.7%, \( n = 3572 \)) was associated with a higher procedural success rate (90.9% vs 89.2%; \( P = 0.005 \)) and lower in-hospital major adverse cardiac event rates (4.4% vs 5.5%; \( P = 0.012 \)). However, no significant differences in the primary outcome of all-cause mortality were evident between patients with or without manual thrombus aspiration (14.8% vs 15.3% respectively; \( P = 0.737 \)) during the median follow-up of 3 years.

**Meta-analyses:** A pooled analysis of 2686 patients enrolled in 11 thrombectomy trials (7 trials using manual aspiration devices such as TAPAS and EXPIRA and 4 non-manual devices trials) similarly concluded that thrombectomy (especially manual aspiration thrombectomy) significantly improves clinical outcomes, including lower all-cause mortality, in STEMI patients undergoing PCI. However, the suggestion of improved clinical outcome with thrombectomy was questioned by a meta-analysis of 21 trials (including 16 with manual thrombus aspiration devices) involving 4299 PCI treated STEMI patients which concluded that adjunctive thrombectomy, despite improving the early markers of myocardial reperfusion, does not significantly affect 30-d mortality, reinfarction or stroke. A meta-analysis of 21 trials involving 4514 patients (50% randomized to thrombectomy, either manual or mechanical) concluded that while both types of thrombectomy did improve myocardial perfusion, a trend towards short-term mortality benefit was evident only with manual aspiration. The meta-analysis also observed a trend towards higher risk of stroke with thrombectomy (\( P = 0.06 \)). Another meta-analysis of PCI-treated STEMI patients included data from 25 trials, including 18 trials with manual aspiration thrombectomy; this study suggested that use of manual thrombus aspiration, but not mechanical thrombectomy, was associated with reduced major adverse cardiovascular events, including mortality, at 6 to 12 mo. A trend towards a higher risk of stroke was noted with mechanical thrombectomy.

Unlike the previous meta-analyses, two recent meta-analyses have included data from the large TASTE trial however both were performed before the publication of the largest and most reliable trial investigating the use of manual thrombus aspiration in PCI (TOTAL). A recent meta-analysis of 26 PCI randomized trials in 11943 patients (thrombus aspiration \( n = 5969 \), PCI alone \( n = 5974 \)) and a weighted maximum follow-up duration of 10.4 mo concluded that the routine unselected use of adjunctive thrombus aspiration during PCI does not significantly reduce all-cause mortality (poll RR = 0.88; 95%CI: 0.74-1.04; \( P = 0.124 \)), reinfarction, target-vessel revascularization or definite stent thrombosis. Although thrombus aspiration was noted to be associated with reductions in failure to achieve TIMI 3 flow, MBG 3, incomplete ST-segment resolution and distal embolization, these effects were less obvious among the larger, higher quality recent trials. The risk of stroke was noted to be similar between both groups.

In another recent meta-analysis of 16 randomized trials in PCI including 10518 patients (thrombus aspiration \( n = 5256 \), PCI alone \( n = 5262 \)), routine use of manual thrombus aspiration compared to PCI alone did not reduce the rate of all-cause mortality (6.6% vs 7.4% respectively, \( P = 0.149 \)), reinfarction, target vessel...
revascularization/target lesion revascularization and stent thrombosis. The rate of stroke was similar between the two groups (0.5% vs 0.5%, \( P = 0.819 \)). Thrombus aspiration was associated with improved rates of post-procedural TIMI 3 flow, MBG 2–3 and ST-segment resolution\(^{[24]}\).

GUIDELINES

The 2014 ESC/EACTS guidelines on myocardial revascularization suggest that while routine use of manual thrombus aspiration is not essential in patients undergoing PPCI for STEMI, selected use may be useful to improve TIMI 3 flow or prevent stent thrombosis. Thrombus aspiration in selected patients during PPCI has a class IIb indication (level of evidence A). These guidelines take into account the evidence including the TASTE trial but predates the publication of TOTAL trial, so far the largest trial addressing this question\(^{[26]}\).

The 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction consider manual thrombus aspiration reasonable in patients undergoing PPCI. Thrombus aspiration in a PPCI setting is a class IIa indication in these guidelines (level of evidence B). These guidelines predate the publication of TASTE and TOTAL trials\(^{[26]}\).

CONCLUSION

The success of PPCI for STEMI is marred by suboptimal myocardial reperfusion, despite achieving epicardial coronary patency, mainly secondary to distal embolization of the thrombus and microvascular obstruction. Early evidence for manual thrombus aspiration during STEMI was promising and this was once considered an important aspect of PPCI, especially in patients with a high thrombus burden. However, recent clinical evidence from major randomized controlled trials (notably TASTE and TOTAL) does not support the routine use of manual thrombus aspiration in patients with STEMI undergoing PPCI.

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