Thrombus Aspiration: Review Article

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Abstract
One of the most important therapeutic challenges in the management of ST-segment elevation myocardial infarction (STEMI) is the establishment of normal coronary blood flow after percutaneous coronary intervention (PCI). Reduced flow is closely associated with reperfusion injury, which can lead to arrhythmias, contractile dysfunction, microvascular impairment, and irreversible myocardial damage. Thrombus aspiration during PCI for the treatment of STEMI has been widely used. Reduced myocardial perfusion is also associated with heart failure and death. One single centre trial showed thrombus aspiration before stenting of the infarcted artery seems to improve the 1-year clinical outcome after PCI for STEMI compared with conventional PCI. Routine intracoronary thrombus aspiration before PCI in patients with STEMI has not been proved to reduce both short and long-term mortality. Recent trials have questioned its value and safety. The aim of this review was to discuss the efficacy of thrombus aspiration in primary PCI.

Key words: Thrombus Aspiration, STEMI, Primary PCI, Clinical evidence.

Introduction
Acute myocardial infarction (MI) with ST-segment elevation is caused by rupture or erosion of an atherosclerotic plaque, initiating intraluminal thrombosis resulting in occlusion of a coronary artery. Primary percutaneous coronary intervention (PCI) has emerged as the preferred treatment of acute MI if logistically feasible and has been proven to be a very effective method to obtain patency of the infarct-related artery. However, microvascular dysfunction with diminished myocardial perfusion is seen in a significant proportion of patients with a patent epicardial vessel after primary PCI and has been associated with larger infarct size, less recovery of left ventricular ejection fraction, and increased mortality.

Two major impediments to normalization of microvascular function are considered to be reperfusion injury and microvascular obstruction. Reperfusion injury refers to the inability to reperfuse myocardium that is already necrotic through ischemic cell death. Microvascular obstruction is believed to be caused by the embolization of soft plaque gruel (atheroembolization) and/or thrombotic material (thromboembolization) in the downstream bed of the infarct-related artery. The embolization may occur spontaneously after plaque rupture, but recent studies emphasize mechanical crushing and fragmentation of the culprit lesion during PCI as the major cause. Distal embolization induced by PCI therefore potentially results in further myonecrosis.

Myocardial reperfusion failure clinically manifests as persistent ST segment elevation, poor myocardial blush grade (MBG) and low thrombolysis in myocardial infarction (TIMI) flow grade. The EMERALD (The enhanced myocardial efficacy and recovery by aspiration of liberated debris) trial investigators, while investigating a distal balloon occlusion and aspiration system, demonstrated that visible debris was retrieved in 73% of the patients undergoing PPCI. Avoidance of distal embolization is hence a considerable therapeutic challenge during STEMI. Thrombus aspiration (TA) is a well-established technique for removal of thrombus and restoration of blood flow in the setting of 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 PPCI 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 PPCI albeit with an increased risk of bleeding. While theoretically attractive, the clinical value of mechanical thrombectomy and embolic protection devices during PPCI is unproven, after several negative trials. Manual
Thrombus aspiration (thrombectomy) during PPCI plays an important role. 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 lacking17.

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 PPCI. In the initial REMEDIA (Randomized evaluation of the effect of mechanical reduction of distal embolization by thrombus-aspiration in primary and rescue angioplasty) trial, 100 patients with STEMI were randomized to PPCI with or without manual thrombus aspiration with 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%)19. In EXPIRA (Thrombectomy with Export Catheter in Infarct-Related Artery during Primary Percutaneous Coronary Intervention) trial, 175 patients with STEMI were randomized to PCI with or without manual thrombus aspiration. The primary end points of MBG 2 or more (88% vs 60%) and STR of 70% or more (64% vs 39%) occurred more often in PCI with thrombus aspiration group compared with standard PCI. Patients in the aspiration group had less microvascular obstruction and smaller infarcts20. 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 PCI21.

In the INFUSE-AMI (Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction) trial, which involved 452 high-risk patients with proximal or mid occlusion of the left anterior descending coronary artery, thrombus aspiration was not associated with a reduction in ischemic events at 30 days but was associated with a significant reduction in rehospitalization for heart failure and a nonsignificant reduction in reinfarction at 1 year22,23. Recently, observational data from 1498 patients with STEMI that was identified in a randomized trial of treatment with drug-eluting stents showed that clinical outcomes with thrombus aspiration were similar to those with stenting alone24.

Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) trial

The first large randomized controlled trial (RCT) evaluating use of manual thrombus aspiration (Export® catheter) during PPCI was TAPAS trial. 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 postprocedural 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 groups25. A 1-year follow-up study showed reduced rates of cardiac death 3.6% (19 of 535 patients) vs 6.7% (36 of 536 patients) and cardiac death or non-fatal reinfarction 5.6% (30 of 535 patients) vs 9.9% (53 of 536 patients) in the thrombus aspiration group26. 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 (0.2% vs 0.6% and 0.7% vs 1.5%). In TAPAS, the mortality benefit and the reduced reinfarction rates in the thrombus aspiration group were probably associated with less thrombotic complications associated with the treatment26. Thrombus aspiration reduced the source of distal embolization by removing the clots as well as atherosclerotic plaque material exposed to the luminal surface after plaque rupture. Histopathological analysis of aspirated clots in TAPAS showed both so-called white clots, composed mainly of platelets, and red clots composed of fibrin and red blood cells25. The findings of TAPAS form the basis for major society guidelines recommending manual thrombus aspiration as an adjunct for PPCI. The trial,
however, was criticized for being underpowered for clinical events and susceptibility to selection bias (single center study)\textsuperscript{17}.

**Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) and the Trial of Routine Aspiration Thrombectomy with PCI vs PCI Alone in patients with STEMI (TOTAL) trials**

**TASTE trial:** The above inconsistent results were followed by the two major randomized controlled trials in the field, the TASTE and the 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\textsuperscript{27}. The primary end point of all cause mortality at 30 d was not different between the two groups: 2.8% (103 of 3621) for thrombus aspiration with PCI vs 3% (110 of 3623) 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) 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 PPCI, use of glycoprotein IIb/IIIa drugs and importantly thrombus burden. Routine thrombus aspiration before PCI in patients with STEMI did not reduce the rate of death from any cause or the composite of death from any cause, rehospitalization for myocardial infarction, or stent thrombosis at 1 year\textsuperscript{28}. 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. A substudy (Thrombus aspiration in patients with large anterior myocardial infarction: A Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia trial substudy) of TASTE trial included 1826 patients with large anterior STEMI: mid or proximal left anterior descending coronary artery infarct lesion, thrombolysis in myocardial infarction 0 to 2 flow, and symptom onset to PCI time ≤ 5 hours. In patients with STEMI and large area of myocardium at risk, thrombus aspiration did not affect outcome within 1 year\textsuperscript{29}.

**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\textsuperscript{30}. 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% (347 of 5033) in the thrombectomy group vs 7% (351 of 5030 patients) 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. The rate of incomplete ST-segment resolution (less than 70%) was 27.0% in the thrombectomy group versus 30.2% in PCI-alone group (P<0.001). Rates of TIMI 3 flow after PCI were the same (93.1%) in the two groups (P = 0.12), and were similar for no-reflow rates on angiography (2.4% vs. 2.8%, P = 0.28). The rate of distal embolization was reduced with thrombectomy (1.6% vs. 3.0%, P<0.001). 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\textsuperscript{31}. 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. 1- year follow-up of the prospective randomized TOTAL trial showed that the primary outcome at 1 year occurred in 395 (8%) of 5035 patients in the thrombectomy group compared with 394 (8%) of 5029 in the PCI alone group (p=0.99). Cardiovascular death within 1 year occurred in 179 (4%) of the thrombectomy group and in 192 (4%) of 5029 in the PCI alone group (p=0.48).
The key safety outcome, stroke within 1 year, occurred in 60 patients (1.2%) in the thrombectomy group compared with 36 (0.7%) in the PCI alone group (p=0.015). Routine thrombus aspiration during PCI for STEMI did not reduce longer-term clinical outcomes and might be associated with an increase in stroke. As a result, thrombus aspiration can no longer be recommended as a routine strategy in STEMI23. In the TOTALCT sub-study of patients undergoing primary PCI for STEMI, manual thrombectomy did not reduce pre-stent thrombus burden at the culprit lesion compared with PCI-alone. Both strategies were associated with low thrombus burden at the culprit lesion after the initial intervention to restore flow33. A strategy of routine manual thrombectomy was associated with an increased risk of stroke compared with a strategy of PCI alone with thrombectomy reserved for only bailout. Future thrombectomy trials need to carefully collect stroke outcomes to determine their safety in addition to efficacy44. A strategy of routine thrombectomy compared to PCI alone was associated with an increased risk of stroke within 30 days that was apparent within 48 h. There was an increase primarily in ischaemic strokes but also in haemorrhagic strokes and in strokes of all degrees of disability. In addition to traditional risk factors for stroke, randomization to thrombectomy was an independent predictor of stroke. A possible explanation of the increase in ischaemic stroke in the thrombectomy group would include embolization of thrombus from the coronary vasculature to the systemic vasculature. In addition, operators may have used more aggressive guide catheter manipulation to successfully cross lesions with the thrombectomy catheter and this could lead to dislodgement of atheroma from the aorta. As well, procedural times were longer in the routine thrombectomy arm34.

**Observational studies:** In a single-center retrospective analysis of 2567 consecutive STEMI patients treated with PPCI, aspiration thrombectomy (n = 1095, using Export catheter in 93%) was associated with improved post-procedure TIMI 3 flow as well as reduced in-hospital (P = 0.027) and long-term (P = 0.028) mortality rates (4.5% vs 9.0%), over a mean follow-up of 9.9 months. 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 min35. However, critics of the study called the extent of mortality reduction excessive and implausible36.

In a retrospective observational cohort study of 10929 STEMI patients treated with PPCI 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 years37.

**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 PPCI16. 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 PPCI 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 stroke59.

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)60.

Another meta-analysis of PPCI-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 months. A trend towards a higher risk of stroke was noted with mechanical thrombectomy41.

Unlike the previous meta-analyses, two recent metaanalyses 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 PPCI (TOTAL). A recent meta-analysis of 26 PPCI 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 PPCI does not significantly reduce all-cause mortality (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 groups42.

In another recent meta-analysis of 16 randomized trials in PPCI 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 postprocedural TIMI 3 flow, MBG 2-3 and ST-segment resolution.

A recent meta-analysis included the 3 eligible randomized trials (TAPAS, TASTE and TOTAL trials) which enrolled 19,047 patients, of whom 18,306 underwent PCI and were included in the primary analysis. Cardiovascular death at 30 days occurred in 221 of 9155 patients (2.4%) randomized to thrombus aspiration and 262 of 9151 (2.9%) randomized to PCI alone (P=0.06). Stroke or transient ischemic attack occurred in 66 (0.8%) randomized to thrombus aspiration and 46 (0.5%) randomized to PCI alone (P=0.06). There were no significant differences in recurrent myocardial infarction, stent thrombosis, heart failure, or target vessel revascularization. In the subgroup with high thrombus burden (TIMI [Thrombolysis in Myocardial Infarction] thrombus grade ≥3), thrombus aspiration was associated with fewer cardiovascular deaths (170 [2.5%] versus 205 [3.1%]; P=0.03) and with more strokes or transient ischemic attacks (55 [0.9%] versus 34 [0.5%]; P=0.04). However, the interaction P values were 0.32 and 0.34, respectively. This meta-analysis concluded routine thrombus aspiration during PCI for ST-segment-elevation myocardial infarction did not improve clinical outcomes. In the high thrombus burden group, the trends toward reduced cardiovascular death and increased stroke or transient ischemic attack provide a rationale for future trials of improved thrombus aspiration technologies in this high-risk subgroup.

**Guideline**

2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction changed the prior Class IIa recommendation for aspiration thrombectomy on the basis of the results of TASTE and TOTAL trials. Routine aspiration thrombectomy before primary PCI is now not recommended (Class III: No Benefit, Level of evidence A). There are insufficient data to assess the potential benefit of a strategy of selective or bailout aspiration thrombectomy (Class IIIb). “Bailout” aspiration thrombectomy is defined as thrombectomy that was initially unplanned but was later used during the procedure because of unsatisfactory initial result or procedural complication.

**Conclusion**

Removal of thrombus before percutaneous coronary intervention (PCI) may reduce distal embolization and microvascular obstruction. However, recent meta-analysis concluded routine thrombus aspiration during PCI for STEMI did not improve clinical outcomes.

**References**


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