Review Article

Large intracoronary thrombus and its management during primary PCI

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ABSTRACT

Large intracoronary thrombus has been reported in significant number of patients with STEMI. Primary PCI is the current standard of care in patients of STEMI. Despite the availability of dual antiplatelets, GP IIb/IIIa inhibitor and effective anticoagulation regimens, large intracoronary thrombus remains one of the biggest challenge to interventional cardiologists during primary PCI. Large intracoronary thrombus may lead to distal embolization, no/slow reflow or embolization into a non-culprit vessel and is associated with adverse cardiovascular outcome. There is no ideal management strategy. We hereby discuss the current available methods/strategies to deal with large thrombus burden encountered during primary PCI, in the current manuscript.
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1. Introduction

Acute ST Elevation Myocardial Infarction (STEMI) is usually due to disruption of an atherosclerotic plaque, followed by thrombus formation leading to the complete occlusion of a major epicardial coronary artery. Angiographic evidence of thrombus can be seen in 91.6% of patients who present with STEMI.[1] Massive intracoronary thrombus has been reported in 16.4% of patients with acute coronary syndrome (ACS).[2] Primary percutaneous coronary intervention (PCI) is the current standard of care in STEMI but may be challenging in case of massive intracoronary thrombus. Despite the availability of potent antiplatelet and anticoagulant regimens, intracoronary thrombus remains a risk factor for distal embolization, no reflow, stent thrombosis and long-term adverse cardiovascular events.[1,3]

1.1. Pathophysiology of thrombus formation

It is established now that atherosclerotic plaque disruption or erosion, leading to superimposed thrombus is the immediate cause of acute coronary syndromes, particularly STEMI. In about 70% of cases, acute coronary thrombosis occur after a disrupted atherosclerotic plaque and in the remaining 30%, plaque erosion is the cause of acute thrombus formation.[4] Plaque erosion is more commonly seen in female, diabetics and patients with hypertriglyceridemia. Most plaques vulnerable to disruption or erosion are having thin fibrous cap and large lipid core that is heavily infiltrated by lipid-filled macrophages (foam cells). Shoulder region of plaque is the weakest part for plaque disruption.[5]

Erosion of an atherosclerotic plaque leads to exposure of thrombogenic sub endothelial matrix to circulating platelets leading to platelet adhesion, aggregation and formation of white thrombus. Concomitant release of tissue factor from the arterial injury site activates the extrinsic coagulation cascade leading to generation of thrombin, which in turn converts fibrinogen to fibrin. This process leads to formation of red thrombus which consist of platelets, erythrocytes, inflammatory cells and fibrin which is denser, more fibrin-rich and becomes progressively more difficult to disrupt.[6]

Furthermore, activated platelets release powerful vasoconstrictive compounds and aggregation agents such as serotonin, adenosine diphosphate, thromboxane A2, oxygen-derived free radicals, endothelin and platelet activating factor which leads to further progression of thrombus.[7]

Abbreviations: MI, myocardial infarction; STEMI, ST elevation myocardial infarction; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; SVG, saphenous venous graft; IRA, infarct related artery; DAPT, dual antiplatelet therapy; GPI, Gp IIb/IIIa inhibitor; UFH, unfractionated heparin; IV, intravenous; IC, Intracoronary; MBG, myocardial blush grade; MACE, major adverse cardiac events; EPD, Embolic protection devices; BMS, bare metal stent; TLR, target lesion revascularisation; TG, thrombus grade; LTB, large thrombus burden.

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1.2. Quantification of coronary thrombi

Angiography is commonly used for quantification of the thrombus burden. Angiographically, intracoronary thrombus is defined as the presence of a filling defect with reduced contrast density or haziness. Most widely used TIMI scale (Table 1) relies on the relative estimated size of the thrombus and of the affected vessel, using a score ranging from grade 0 (no thrombus), to grade 5 (very large thrombus with complete occlusion).[8]

Sianos G et al[1,10] suggested that when grade 5 thrombus is encountered, either a guide wire or a 1.25–1.5 mm balloon is used to recanalize the artery. As soon as antegrade flow is restored, underlying residual thrombus can be further categorized as: grade 0 (no residual thrombus), grade 1–3 (small residual thrombus) and grade 4–5 (large residual thrombus). Niccoli et al[9] proposed a simple classification in which only 2 thrombus grades are used: a low grade is assigned to the TIMI grades 1–3 and a high grade corresponds to TIMI grades 4–5.

1.3. Angiographic indicators of large thrombus burden

Yip and colleagues,[11] suggested six angiographic morphologic features indicated "high-burden thrombus formation":

1. A cut-off pattern of occlusion
2. Accumulated thrombus proximal to the occlusion
3. A reference lumen diameter of the IRA of >4.0 mm
4. An incomplete obstruction with an angiographic thrombus with the greatest linear dimension more than 3 times the reference lumen diameter
5. The presence of floating thrombus proximal to the lesion
6. A persistent dye stasis distal to the occlusion

1.4. Factors favoring formation of a large intracoronary thrombus[10]

The thrombus burden during acute coronary syndrome depends on various factors related to patient, lesion related, disease related or PCI related as shown in Table 2.

1.5. Management of large intracoronary thrombus

Current guidelines[12] recommend primary PCI as the preferred treatment option, in STEMI patients. Compared to thrombolysis, primary PCI is more effectively obtain patency of the infarct-related artery (IRA), resulting in smaller infarcts, less number of acute and long-term adverse events, including recurrent MI and death. Management of lesions with a large thrombus burden during primary PCI is still challenging. Several pharmacological and mechanical approaches have been suggested in reducing thrombus burden.

1.6. Pharmacologic agents

Early administration of DAPT (Dual antiplatelet therapy) can decrease thrombus burden and improve clinical outcome. Aspirin can be given orally by chewing, or intravenous in a loading dose of 150–300 mg to inhibit thromboxane A2 mediated platelet inhibition. Onset of action of aspirin starts within 30–60 min and lasted upto life span of platelets. A potent P2Y12 inhibitor (prasugrel 60 mg or ticagrelor 180 mg or or clopidogrel 600 mg if these are not available or are contraindicated) must be used for more aggressive platelet aggregation(Class 1) Prasugrel and Ticagrelor have a more rapid onset of action, greater potency, and are superior to clopidogrel in clinical outcomes. Ticagrelor may cause

transient dyspnoea at the onset of therapy, which rarely leads to permanent discontinuation. An intravenous P2Y12 agent (eg. cangrelor) may also be considered in patients not pre-treated with oral P2Y12 receptor inhibitors at the time of PCI or in those who are intubated or unable to have oral agents.[12](Class IIb; LOE: A). Table 3 describes the pharmacological properties of P2Y12 inhibitors.[13]

1.7. GP IIb/IIIa Inhibitors(GPI)

GPIs (abciximab, tirofiban and eptifibatide) inhibit the final pathway of platelet aggregation by competing with vWF and fibrinogen for GPIIb/IIIa receptor binding. These agents inhibit the platelet response to all agonists leading to rapid and nearly complete inhibition of platelet aggregation and are therefore more potent antiplatelet agents than P2Y12 inhibitors.[14] Table 4 describes the pharmacological properties of currently available intravenous Gp IIb/IIIa inhibitors.[15]

GPIs have been found to be effective in dissolving angiographically proven thrombus and in restoring TIMI flow.[16] Most clinical experience with GPIs in the setting of patients with STEMI undergoing primary PCI is with abciximab. Despite the proven efficacy of GPIs in the setting of primary PCI, high bleeding rates remain a concern.[17] In a meta-analysis of 10,123 patients undergoing primary PCI, nonfatal MI at 30 days was reduced from 8.3 to 5.1% ($p < 0.001$) with use of GPIIb/IIIa inhibitors at the expense of a significant increase in the risk of minor bleeding (3 vs. 1.7%; $p < 0.001$) and thrombocytopenia (0.8 vs. 0.04%; $p = 0.004$).[18]

The pre-hospital upstream use of glycoprotein (GP) IIb/IIIa inhibitors before primary PCI was evaluated in two trial. Abciximab in Patients With Acute ST-Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention After Clopidogrel Loading.

(BRAVE 3) trial did not demonstrated a significant benefit.[19] In contrast, The Effect of Pre Hospital Glycoprotein IIb–IIIa Inhibitors on Angiographic Outcome in STEMI Patients who are Candidates for Primary PCI study demonstrated reduced initial thrombus burden ($P = 0.035$) as well as a trend toward a reduction in large thrombus burden (LTB) (69.4% vs. 74.5%, $P = 0.055$). Initiation of tirofiban was shown to be more effective when given very early after the onset of symptoms and with high thrombus burden.[20]

Based on available data, recent Guideline[12] states that routine use of upstream GPIs in STEMI patients undergoing PPCI is not recommended and should be considered only for bailout therapy (Class IIa, C) if there is evidence of large thrombus burden, slow or no-reflow or a thrombotic complication, or could be administered upstream only in high-risk patients undergoing transfer for Primary PCI (Class IIb, B).

Table 1
TIMI (Thrombolysis in Myocardial Infarction)thrombus scale.[8]

Grade	Description
0	No angiographic evidence of thrombus
1.	Possible thrombus: decreased contrast density or haziness, irregular lesion contour, a smooth convex meniscus at the site of a total occlusion suggestive, but not firmly diagnostic of thrombus
2.	Definite thrombus presents in multiple angiographic Defined by marked irregular lesion contour with a filling defect Greatest dimension of thrombus is < 1/2 vessel diameter
3.	Definite thrombus appears in multiple angiographic views with greatest dimension from >1/2 to <2 vessel diameters
4.	Definite large size thrombus present with greatest dimension >2 vessel diameters
5.	Complete thrombotic occlusion of a vessel

Table 2
Factors favoring large thrombus burden (**Modified from** Topaz O et al)0.10.

Category	Factor
Patient related factors	Hypercoagulability-hypercholesterolemia, hyperhomocystenemia
	Hyperglycemia
	Leukocytosis
	Smoking
	Substance abuse-Cocaine and methamphetamine
	Vasculitis
	Male sex
Lesion-related Factors	Acute plaque rupture and complex morphology
Vessel-related Factors	Slow coronary flow
	Morphology: large artery >4 mm, ectasia, aneurysm, old SVG
	Right coronary artery
	(tends to have a larger
	burden of thrombus probably because of proximal
	propagation of thrombus related to fewer branch points)
Disease-related (MI related) Factors	Late presentation (>12 h)
	Established Q-wave MI with ongoing ischemia
	Cardiogenic shock
	Failed thrombolysis
PCI related Factors	Triggering of the thrombus formation with guide
	wire, balloon, or stent-the "angry clot" phenomenon
	Inadequate anticoagulation
	Inadequate Dual anti platelet
	Heparin induced thrombocytopenia

1.8. Intracoronary GP IIb/IIIa

Intracoronary administration of Abciximab in the infarct-related artery has theoretical advantage over IV route that it can provide higher local concentration, resulting in a higher receptor occupancy leading to higher rate of thrombus resolution.[21] Some small studies have shown benefits of intracoronary bolus admnistration of abciximab[22] but these results have not been confirmed in large-scale clinical trial. Abciximab intracoronary versus intravenous drug application in ST-elevation myocardial infarction trial (AIDA-STEMI) trial (N = 2065) comparing intracoronary bolus (via guide catheter) versus intravenous (IV) abciximab in patients with STEMI showed no difference in the composite primary endpoints of all cause mortality, recurrent infarction or new congestive heart failure at 90 days.[23] In contrast, a meta-analysis by Shimada et al, demonstrated a favourable effect of intracoronary bolus of GPI during PCI on TIMI flow as well as on target vessel revascularization and short-term mortality with no increase in bleeding risk.[24] However in the absence of conclusive evidence, the role of intracoronary bolus of GPIs still need to be established by large randomized trials.

2. Anticoagulants

Effective anticoagulation must be maintained during primay PCI to inhibit the coagulation cascade and progression of thrombus. Anticoagulant options for primary PCI include UFH (unfractionated heparin), enoxaparin, and bivalirudin. Table 5 describes the pharmacological properties of anticoagulants used during primary PCI.[25] Although there has been no placebo-controlled randomized

Table 3
Pharmacological properties of P2Y12 inhibitors (Modified from reference number 13).

	Clopidogrel Theinopyridine	Prasugrel Theinopyridine	Ticagrelor Triazolopyrimidine	Cangrelor Adenosine analogue
Prodrug	Yes	Yes	No	No
Receptor blockade	Irreversible	Irreversible	Reversible	Reversible
Dose	600 mg LD;	60 mg LD;	180 mg LD;	30 μg/kg bolus;
	75 mg OD, PO	10 mg OD, PO	90 mg BD, PO	4 μg/kg/min infusion during PCI
Onset of action	2–8 h	30min–4h	30min–4h	3–5min
Interaction with CYT-P	Yes	No	No	No
Contra-indication	Hypersensitivity active bleeding	Prior CVA, high bleeding risk age<60, wt < 60	Prior ICH high bleeding risk liver dysfunction	Hypersensitivity, renal failure Cr Cl < 30 ml/min

Table 4
Pharmacological properties of Gp IIb/IIIa inhibitors (Modified from reference number 15).

	Abciximab	Eptifibatide	Tirofiban
Type	Chimeric mono-clonal Antibody	Cyclic Heptapeptide	Non-peptide derivative of 2Tyrosine
MW (Da)	47,600	832	495
Receptor Binding	Noncompetitive	Competitive	Competitive
GP IIb-IIIa specificity	Nonspecific Inhibitor	specific	specific
Antigenicity	Present	Absent	Absent
Plasma half-life	10–30 min	2.5 h	2 h
Recovery of platelet function	Slow (24–48 h)	Fast (\4 h)	Fast (4–8 h)
Thrombocyto-penia risk	High (5%)	Low (1%)	Low (1%)
PCI dosing	Bolus: 250 μg/kg	Bolus: 180 μg/kg* plus	Bolus: 25 μg/kg
	Infusion: 0.125 μg/kg/min (12 h)	180 μg/kg (after 10min) Infusion:2 μg/kg/min (12–24 h)	Infusion: 0.15 μg/kg/min (up to18 h)
Renal adjustment	No	Dose reduced to half in Cr Cl < 50 ml/min	Dose reduced to half in Cr Cl < 30 ml

trial evaluating UFH in primary PCI, but there is a large body of experience with this agent. That's why routine use of UFH during primary PCI is class I A recommendation.[12]

In the ATOLL trial, IV bolus of enoxaparin 0.5 mg/kg, compared with UFH, did not significantly reduce the primary composite endpoint of 30 day death, MI, procedural failure, or major bleeding but it did reduce the secondary endpoints of death, recurrent MI or ACS, or urgent revascularization events without a significant difference in bleeding endpoints.[26] In contrast,a meta-analysis involving 23 PCI trials (30,966 patients, 33% primary PCI), demonstrated superiority of enoxaparin over UFH in reducing mortality and bleeding outcomes, particularly in patients undergoing primary PCI.[27] Based on these data, routine use of IV enoxaparin during primary PCI has given class IIa recommendation in recent ESC guidelines.[12]

A recent meta-analysis of 5 trials showed no mortality advantage of bivalirudin over UFH, but a reduction in the risk of major bleeding, at the cost of an increased risk of acute stent thrombosis was shown.[28] Based on these data, bivalirudin should be considered in STEMI, especially in patients at high bleeding risk (Class IIa recommendation). In patients with heparin-induced thrombocytopenia, bivalirudin is recommended as class I anticoagulant agent during primary PCI.[12] Use of fondaparinux in the context of primary PCI was associated with potential harm in the Organization for the Assessment of Strategies for Ischemic Syndromes 6 (OASIS 6) trial and therefore is not recommended.[29]

2.1. Vasodilators

Several vasodilators have been used intracoronary during primary PCI in large thrombus burden to decrease risk of distal embolization and no-reflow. They can be delivered directly through the guiding catheter, or via an infusion catheters or infusion balloon.

These agents can be classified as:

1 Vasodilators that predominantly dilate the epicardial coronary arteries with little or no effect on the microcirculation (e.g., nitroglycerin).
2 Vasodilators with mixed activity that dilate both the large epicardial and small resistance arterioles (e.g., nitroprusside).
3 Vasodilators that primarily dilate the coronary microcirculation (e.g., adenosine, calcium channel blockers).

2.2. Nitroglycerin

Nitroglycerin is an endothelium dependent coronary vasodilator. It produces major biological effect by releasing nitric oxide, which subsequently activates cyclic GMP leading to reduction in intracellular calcium resulting in smooth muscle relaxation. Werner et al used intracoronary nitroglycerin injections prior to the verapamil injections in 82% of the patients and found no significant difference in TIMI frame counts, before and after nitroglycerin.[30] Nitroglycerine may be useful when there is associated spasm of epicardial coronary artery. It has been shown to cause coronary artery dilation with doses as little as 5 μg. The use in moderate doses (50–200 μg) produces maximal or nearly maximal dilation, while larger doses (>450 μg) result in no further dilation.

2.3. Nitroprusside

It produces more balanced arterial and venous dilation compared to nitroglycerin. It is effective at dilating both the epicardial coronary arteries and the small resistance arterioles. Nitroprusside is an endothelial-independent direct donor of nitric oxide. Intracoronary nitroprusside has been shown to be a safe and effective therapy for no-reflow during primary PCI in the setting of intracoronary thrombi. Doses of 50-to 100-μg bolus can be used intracoronary and repeated as needed.[31]

2.4. Adenosine

Adenosine is an endogenous purine nucleoside with a very short half-life (5–10 s). It is primarily a vasodilator of small coronary resistance arterioles (<100 μm in size) with no effect on the large epicardial arteries. Its action is endothelium-independent. It has been shown to decrease slow flow/no-reflow, during primary PCI in presence of intracoronary thrombi.[32] Intracoronary bolus doses of 30–60 ug have a lower incidence of flushing, headache and dyspnea compared to IV dose. Contraindications are high-grade AV block or sick sinus syndrome or active or severe bronchospastic lung disease.

2.5. Calcium channel blockers

Intracoronary calcium channel blockers predominantly dilate the small resistance arterioles but may also inhibit platelet aggregation in the microvasculature. In RECOVER trial,[33] a total of 102 patients with no-reflow in primary PCI were randomized to receive

Table 5
Pharmacological properties of Anticoagulants used during primary PCI (Modified from reference number 25).

	UFH	Enoxaparin	Bivalirudin
Source	Sulphated polysaccharide derived from pig intestine	Enzymatic modification of UFH	Synthetic analogue of Hirudine
Factor Xa:IIa Activity	1:1	3-4 : 1	only IIa
Mechanism of Action	Iindirect through AT III	Indirect through AT III	Direct thrombin inhibition
Inhibits fibrin Bound thrombin	No	No	Yes
Half life	30–60 min	4 h	25 min
Renal clearance	No	Yes	Partial
HIT	< 0.5%	< 0.1%	No
Reversal with protamine	Yes	Partial	No
Dose during Primary PCI	70–100U/kg without GPI 50–70U/kg bolus with GPI	0.5 mg/kg IV bolus	0.75 mg/kg IV bolus; 1.75 mg/kg/h infusion

intracoronary infusion of diltiazem, verapamil, or nitroglycerin ($n = 34$ in each group) through selective microcatheter. Compared with nitroglycerin group, there was a significant improvement in corrected TIMI frame count (CTFC) after drug infusion in the diltiazem and verapamil groups. The improvement in CTFC was similar between the diltiazem and verapamil groups.

Intracoronary Nicardipine (200 μg) appears to offer more potent and prolonged microvascular dilation with minimal negative chronotropic and inotropic effects as compared to IC verapamil (200 μg) and diltiazem (1 mg). It has been shown to be safe and effective for the reversal of no-reflow during interventions of native and SVG lesions.[34]

2.6. Intracoronary thrombolysis

Intracoronary delivery of thrombolytic agent can result in higher concentration of thrombolytics at the site of thrombus and may result in more effective thrombolysis. Small studies of local delivery of fibrinolytics as an adjunct to primary PCI demonstrated promising results in STEMI patients with a large thrombus burden and failed manual aspiration and showed reduced thrombus burden and improved myocardial reperfusion without any major bleeding.[35] The first randomised trial of intracoronary thrombolysis was DISSOLUTION (delivery of thrombolytics before thrombectomy in patients with STEMI undergoing primary PCI) trial,[36] in which a total of 102 patients with STEMI and angiographic evidence of massive thrombus in the culprit artery were randomly assigned to receive intracoronary bolus of 200,000 U of urokinase ($n = 51$) or saline solution ($n = 51$) through an infusion microcatheter, followed by manual aspiration thrombectomy. The use of intracoronary urokinase was associated with a significantly higher incidence of TIMI flow grade 3, more myocardial blush grade, more ST segment resolution and lower TIMI frame count. In contrast, recent trial by McCartney et al,[37] including 440 patients with acute STEMI presenting within 6 h of symptoms, adjunctive low-dose intracoronary alteplase 10 mg or 20 mg)given during the primary PCI did not reduce microvascular obstruction and major adverse cardiac events (cardiac death, nonfatal MI, unplanned hospitalization for heart failure) were also not different between the placebo group and 10-mg or 20 mg alteplase group. At present there is no sufficient data for intracoronary use of fibrinolytics. There are currently two ongoing Phase III trials to evaluate intracoronary low-dose alteplase, the Adjunctive Low-dose tPA in Primary PCI for STEMI (STRIVE) trial and tenecteplase, the Restoring Microcirculatory Perfusion in STEMI (RESTORE-MI) trial which may further address the issue.

2.7. Percutaneous devices

Currently two types of devices are available: thrombectomy devices and embolic protection devices. Thrombectomy devices aim at reducing thrombus burden, while embolic protection devices aim at capturing the debris liberated during PCI.

2.8. Thrombectomy devices

Thrombectomy devices are broadly divided into two groups: manual and mechanical.

2.9. Manual thrombus aspiration

First aspiration catheter system was developed by Auth and colleagues in 1995. Newer devices are user-friendly because of their low crossing profile, hydrophilic coating, flexibility, and tapered distal tip. Catheter system is advanced over the guide wire and distal end of catheter system is placed proximal to the thrombus and proximal end is attached to a suction device. With the continued suction, the catheter is advanced distally through the thrombus to allow complete retrieval of the thrombus. Most commonly used manual TA devices in clinical practice are Export AP (Medtronic).

The first randomized trial using manual thrombectomy in primary PCI was the Randomized Evaluation of the Effect of Mechanical Reduction of Distal Embolization by Thrombus Aspiration in Primary and Rescue Angioplasty (REMEDIA) trial.[38] It showed that manual aspiration was associated with significantly higher ST resolution and MBG and decreased no reflow and distal embolization, although it did not translated into clinical benefit. Similarly, TAPAS (Thrombus aspiration during percutaneous coronary intervention in acute myocardial infarction study) trial involving 1071 patients with STEMI, showed decrease in MACE (death, reinfarction and target-vessel revascularization) with thrombus aspiration as compared to primary PCI alone.[39] In contrast, two large studies, TASTE (Thrombus aspiration during ST-segment elevation myocardial infarction)[40] and TOTAL (ThrOmbecTomy with PCI versus PCI Alone)[41] have not shown benefit of routine thrombus aspiration. Based on available data, current European Society of Cardiology (ESC) 2017 guideline stated that routine use of thrombus aspiration before primary PCI is not recommended (class III recommendation, Level of Evidence A), however, a selective and bailout aspiration thrombectomy in patients with large residual thrombus burden after opening the vessel with a guide wire or a balloon may be considered (Class IIb, LOE C-LD).[12]

2.10. Mechanical thrombectomy devices

The most commonly used mechanical thrombectomy device is the **Angiojet rheolytic thrombectomy** (RT) catheter. Angiojet uses high velocity saline jets, which leads to dissolution of thrombus and creates a strong suction of approximately 600 mm Hg at the catheter tip, which produces Venturi effect leading to suction of the thrombus. The JETSTENT (Comparison of AngioJet Rheolytic Thrombectomy Before Direct Infarct Artery Stenting With Direct Stenting Alone in Patients with Acute Myocardial Infarction) trial enrolled 501 STEMI patients with visible thrombus (grades 1–5). The study did not find significant differences between mechanical thrombectomy and direct stenting in terms of ST segment resolution, TIMI 3 flow, TIMI blush grade 3 or infarct size. However, the mechanical thrombectomy group had reduced MACE at 1 and 6 months and improved 1-year event-free survival rates.[42] Based on available literature, it may be concluded that the Angiojet is beneficial in patients with large thrombus burden but not in minimal thrombus. Also, there is concern for hemolytic anemia with prolonged use of the rheolytic thrombectomy system; therefore total device time use should be limited to 10 min. Hemolysis induces the release of adenosine, which can precipitate bradyarrhythmias. Placement of a temporary pacing wire is recommended, especially when performing thrombectomy in the right coronary artery.

2.11. X-sizer thrombectomy system

The power-sourced X-Sizer thrombectomy catheter (ev3, Minneapolis, MN, USA) is considered one of the most user-friendly mechanical thrombectomy devices. It consists of a helical cutter enclosed within a protective housing, attached to a dual-bore catheter shaft containing guide wire and vacuum extraction lumens. Activation of the handheld controller rotates the helical cutter at 2100 rpm, which entraps and macerates the thrombus, and extracts it into a vacuum collection bottle. X-TRACT-AMI (X-
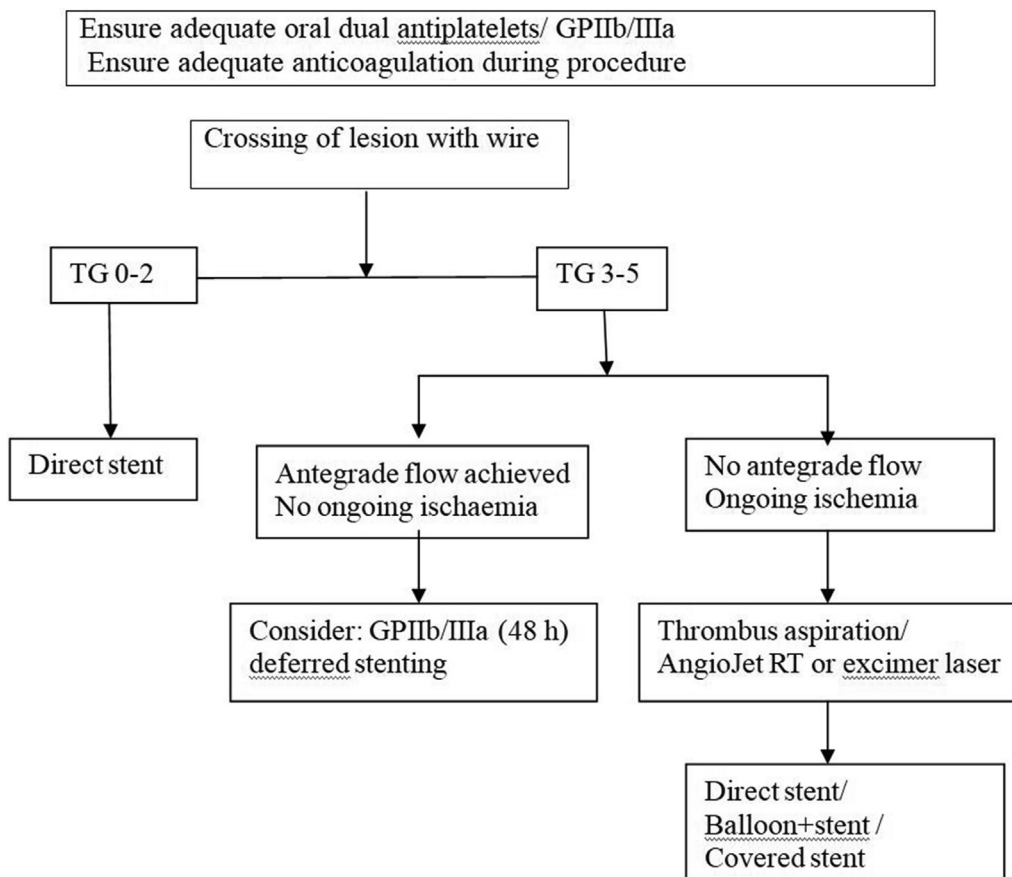
Fig. 1. Proposed algorithm for management of large thrombus burden during primary PCI (modified from reference 58).

Sizer for Treatment of Thrombus and Atherosclerosis in Coronary Interventions Trial in Acute Myocardial Infarction)[43] enrolled 216 patients (220 target lesions) including 10% old bypass SVGs. It showed improvement in TIMI III flow and MBG post procedure. Furthermore, at 30 and 360 days, 93% and 81%, of patients were free of MACE. The X-Sizer in Acute MI for Negligible Embolization and Optimal ST Resolution (X AMINE ST) trial included 201 patients with STEMI undergoing Primary PCI. Although the study demonstrated improved ST segment resolution at 60 min post-PCI and reduced distal embolization and no reflow rates, but it did not demonstrate any significant clinical benefit at 1 and 6-months.[44]

2.12. Excimer laser coronary atherectomy (ELCA)

The CVX-300 cardiovascular laser Excimer system (Spectranetics) is the only coronary laser-emitting device currently approved by the US-FDA. It uses Xenon chloride (XeCl) as the active medium. It generates pulses of short wavelength, high-energy ultraviolet (UV) light having a wavelength of 308 nm (in the UV-B spectrum). Laser-generated acoustic shock waves can separate thrombus from the vessel wall, dissolve clot and vaporize procoagulant mediators. Laser also has an inhibitory effect on platelet aggregation leading to 'stunned platelet phenomenon'. Despite the theoretical advantages, there are limited data to support its use in primary PCI. The Cohort of Acute Revascularization of Myocardial infarction with Excimer Laser (CARMEL)[45] multicentre registry, enrolled 151 Acute MI patients, 65% of who had large thrombus burden. Following ELCA, TIMI flow grade was significantly increased (1.2–2.8), with an improvement in angiographic stenosis

(83–52%). The maximal effect was observed in arteries with a large angiographic thrombus burden.

2.13. Embolic protection devices (EPD)

EPDs have been developed to decrease distal embolization during saphenous vein graft (SVG) interventions and carotid artery stenting. While there is evidence to support embolic protection devices in SVG interventions, these have not been replicated in the setting of STEMI.

EPDs can be divided into 3 distinct types based on their mechanism of operation: distal occlusion aspiration devices, distal filters, and proximal occlusion aspiration devices (see Table 6).

2.14. Distal occlusion aspiration devices

Distal occlusion aspiration devices contain an inflatable occlusion balloon mounted on a hypotube. The balloon is passed several centimeters distal to the lesion and is inflated to obstruct antegrade flow with a carbon dioxide filled syringe. The hypotube is used for the balloon angioplasty or stenting. The balloon traps plaque debris released during PCI, which subsequently removed with an aspiration catheter. Disadvantages of this procedure include the complete occlusion of flow making it difficult to see the lesion and possible formation of thrombus distal to the balloon due to the low flow state. Exploring the MEchanism of Plaque Rupture in Acute Coronary Syndrome Using Coronary CT Angiography and computationaL Fluid Dynamic (EMERALD) trial[46] and ASPiration of Liberated Debris in Acute MI with GUardWire Plus System (ASPARAGUS)

Table 6
Embolic protection devices (EPD).

EPD	Used in vessel size	Guide catheter	Crossing profile	Comments
Proximal balloon Proxis (Velocimed, Maple Grove, MN, USA))	3–5 mm	7F′	None	Advantage: Establish protection before crossing the lesion Side branch protection Complete recovery of debris and vasoactive mediators Unlimited debris removal Compatible with conventional guide wire Disadvantage: myocardial ischaemia during balloon occlusion
Distal occlusion balloon 1.PurcuSurge Guardewire (Medtronic) 2.TriActive (kensey Nash Corp.)	3–6 mm	6F′ 7,8F′	2.1F′ 2.8F′	Can capture debris <100 μm and soluble vasoactive mediators with unlimited debris capture Disadvantage: aspiration may not remove all particles Risk of embolization in side branch Choice of guide wire limited Risk of myocardial ischaemia during balloon occlusion
Distal embolic filters 1.Filterwire EZ (Boston scientific 2.Spider RX (Abbott) 3.Interceptor PLUS (Medtronic)	2.5–5.5 Mm 3–6 mm 2.5–5.5 mm	6F′ 6F′ 6F′	3.2F′ 3.2F′ 2.7F′	Maintain antegrade perfusion Can capture debris >100 um But unable to filter mediators Capacity of bag limited Risk of distal embolization during wiring and lesion crossing No side branch protection Choice of guide wire not met except Spider RX for which conventional guide wire of 0.014 inch can be used

trials[47] compared adjunctive PercoSurge to conventional primary PCI in 501 and 341 patients, respectively. These studies demonstrated safety of the devices but failed to show benefit in terms of infarct size.

2.15. Distal embolic filters

Distal embolic filters have a filter bag mounted at the distal part of a 0.014-in guide wire. The device is advanced through the guide catheter with the filter bag in a collapsed state in a delivery sheath (3.2 F) and is deployed 2.5–3.0 cm distal to the lesion. The filter bag with the accumulated plaque debris is later retrieved with a retrieval catheter (4.2F–4.9 F) after the procedure. The devices are effective at filtering particles >100–110 μm with maintaining antegrade perfusion. Disadvantages of these devices include the passage of small particles; limited capture efficiency and complications related to advancement, deployment and recovery of the filters.

The Spider Rx (eV3; MedNova, Abbott, Abbott Park, IL), the FilterWire (Boston Scientific), and the Interceptor Plus Coronary Filter System (Medtronic Vascular, Santa Rosa, CA) are examples of distal embolic filters. Filterwire system for distal protection were intuitively relevant being able to capture visible debris but randomized studies failed to show a benefit in terms of improved perfusion, limit infarct size, or reduced MACCE.[48]

2.16. Proximal occlusion aspiration devices

Proximal occlusion devices have a guiding catheter with an inflatable balloon tip that is inflated proximal to the lesion, thereby occluding antegrade flow during the procedure. These devices create a column of stagnant blood containing debris, which is later aspirated via the guiding catheter. It theoretically confers protection from distal embolization and protection of distal branches by interrupting antegrade flow while thrombus is aspirated.

Proxis system (St. Jude Medical, Minneapolis, MN) is the only FDA-approved proximal occlusion device. It can retrieve embolic material of any size and composition but usage of this system may be unfeasible in the small target vessel <2.5 mm and in the ostial and proximal target lesion because of the need of 'landing zone'.

The FASTER (The Feasibility And Safety Trial for its embolic protection device during transluminal intervention in coronary vessels: a European Registry) trial has shown the safety of Proxis system during intervention of SVG and native coronary arterial lesions.[49] Proximal Embolic Protection in Acute MI and Resolution of ST Elevation (PREPARE)[50] trial showed no benefit in STEMI. Because of paucity of data, these devices have not been recommended in current practice guidelines.

3. Stenting strategy

3.1. Direct stenting

A direct stenting strategy reduces the incidence of distal embolisation by minimal manipulation and trapping the thrombus behind the stent. There are some disadvantages of direct stenting including, underestimation of the true vessel size, failure to cross in tortuous or calcified lesions, inadequate stent expansion and late stent malapposition, that may increase the risk of restenosis or stent thrombosis. A meta analysis of five small single center trials with 754 patients, direct stenting appeared to improve reperfusion as evidenced by a significant improvement of ST-resolution and reduction of in hospital cardiac death.[51] None of these trials used contemporary drug-eluting stents and adjunctive medical

treatment. Direct stenting with or without thrombus aspiration, might be applied safely in selected patients with AMI with low thrombus grade.

3.2. Covered stent

Covered stents are made up of bare metal stent (BMS) platform covered with a fine mesh that can trap the thrombus and prevent distal embolization. Two types of coronary stents have been evaluated in randomized trials: MGuard (InspireMD) and STENTYS (STENTYS SA).

The MGuard stent consists of a balloon-expandable close cell design bare metal stent with a polyethylene terephthalate microfiber sleeve attached to its outer surface. It is compatible with 0.014 in guide wires and 6 F' guiding catheters but crossing profile is slightly higher than newer-generation bare metal stents. Limitation of MGuard stent is the increased risk of side branch (SB) occlusion due to its bulky double-layer design and high rate of stent dislodgement. Although MASTER I trial[52] demonstrated benefit of MGuard in terms of complete ST-segment resolution and lower 1-year mortality but MASTER II trial, that aimed to recruit 1114 patients, was terminated early due to a high rate of stent dislodgement (3.87%).[53]

The STENTYS is a self-apposing and self-expanding nitinol stent coated with a drug (Rapamycin) containing durable polymer and covered with fine mesh, which allows retention of the thrombus against the vessel wall. APPOSITION IV trial randomized 152 STEMI patients into the STENTYS or the Medtronic Resolute zotarolimus-eluting BE stent.[54] A significant lower percentage of malapposed struts and more covered struts were observed in the STENTYS group at 4 months. However, at 9 months, the percentage of malapposed struts and coverage were similar in both groups. APPOSITION V trial was stopped prematurely because the non-inferiority standard was not met.[55] At present, there is no sufficient data for routine use of covered stent.

3.3. Deferred stenting

Deferred strategy may potentially limit the risk of distal coronary embolization in the presence of high thrombus burden. This can allow 24—48 h of intense antithrombotic therapy, including prolonged intravenous GPIIb/IIIa inhibition and heparin anticoagulation. Subsequent angiography frequently shows reduced thrombus burden and PCI may be performed with a significantly lower risk of distal embolization.

Deferred Stenting Versus Immediate Stenting to Prevent No or Slow reflow in Acute ST-Segment Elevation Myocardial Infarction (DEFER-STEMI) trial[56] randomized 411 STEMI patients to deferred stenting versus immediate stenting and showed significantly lower rates of no-reflow/slow reflow and higher TIMI flow grade at the end of procedure in a high-risk population. In contrast, Deferred Versus Conventional Stent Implantation in Patients with ST-segment Elevation Myocardial Infarction (DANAMI 3-DEFER) study[57] involving 1215 patients demonstrated that deferred stenting for 48 h did not reduce the primary endpoint of composite of all-cause mortality, heart failure, myocardial infarction, or repeat revascularization compared with conventional PCI over a median follow up of 42 months. On the basis of the available data, routine use of deferred stenting is not recommended in the current guidelines (Class III/A).[12]

4. Summary

Large thrombus burden in STEMI can further complicate primary PCI due to distal embolization, no/slow reflow or embolization into a non-culprit vessel. There is no ideal management strategy. Each patient requires individualized approach depending upon operator experience and expertise.

In general, potent dual antiplatelet agents must be used and effective anticoagulation should be maintained. High thrombus burden may yield benefit from IV or IC administration of GP IIb/IIIa inhibitor. Direct stenting may be sufficient, if the extent of thrombus is small (TG 0-2) and absence of tortuous and calcified lesion. However, if there is large thrombus burden (TG ≥ 3), manual aspiration thrombectomy may be considered and in the presence of a very LTB (TG 5) with no antegrade flow, AngioJet RT or excimer laser may be useful. If antegrade flow is restored and large thrombus burden remains without ongoing ischaemia, one option is to use GPI with heparin and defer stenting for 24—48 h. Newer generations of DES has shown improved clinical outcomes following Primary PCI. There are some small studies documented benefit of covered stent but larger clinical outcome trials are needed to determine if this strategy of trapping thrombus with a mesh covered stent improves clinical outcomes. Fig. 1 demonstrates the proposed algorithm for management of large thrombus burden during primary PCI.[58]

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