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TOPIC HIGHLIGHT

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Coronary thrombus in patients undergoing primary PCI for STEMI: Prognostic significance and management

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Abstract

Acute ST-elevation myocardial infarction (STEMI) usually results from coronary atherosclerotic plaque disruption with superimposed thrombus formation. Detection of coronary thrombi is a poor prognostic indicator, which is mostly proportional to their size and composition. Particularly, intracoronary thrombi impair both epicardial blood flow and myocardial perfusion, by occluding major coronary arteries and causing distal embolization, respectively. Thus, although primary percutaneous coronary intervention is the preferred treatement strategy in STEMI setting, the associated use of adjunctive antithrombotic drugs and/or percutaneous thrombectomy is crucial to optimize therapy of STEMI patients, by improving either angiographical and clinical outcomes. This review article will focus on the prognostic significance of intracoronary thrombi and on current antithrombotic pharmacological and interventional strategies used in the setting of STEMI to manage thrombotic lesions.

Key words: ST-elevation myocardial infarction; Intracoronary thrombosis; Primary percutaneous coronary intervention; Antithrombotic therapies; Coronary thrombectomy

Core tip: Intracoronary thrombosis, is the basic pathophysiologic event in acute ST-elevation myocardial infarction (STEMI), and thrombi are very frequently detected in STEMI patients undergoing primary percutaneous coronary intervention (PPCI). Thrombus burden and components are important determinants of prognosis in STEMI, being well-known risk factors for long-term adverse cardiovascular events, distal embolization and stent thrombosis. As a result, percutaneous management of lesions with a consistent thrombotic burden is still challenging in the setting of PPCI for STEMI. Therefore, several pharmacological and interventional strategies, such as thrombectomy have been developed in order to improve PPCI's safety and efficacy, by reducing thrombus burden.

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INTRODUCTION

Intracoronary thrombosis, subsequent to plaque rupture and causing partial or complete occlusion of a coronary

artery, is the basic pathophysiologic event in acute ST-elevation myocardial infarction (STEMI)[1]. Actually, although angiography seems to understimate the presence of thrombi, they are very frequently detected in STEMI patients undergoing primary percutaneous coronary intervention (PPCI) and tend to be larger than in non ST-elevation acute coronary syndromes (ACS). Sianos *et al*[2] reported that up to 91.6% of STEMI patients undergoing PPCI showed intracoronary thrombosis at angiography.

Intracoronary thrombus burden and components are important determinants of prognosis in STEMI, being well-known risk factors for long-term adverse cardiovascular events, distal embolization and stent thrombosis[2-8]. As a result, percutaneous management of lesions with a consistent thrombotic burden is still challenging in the setting of PPCI for STEMI. Therefore, several pharmacological and interventional strategies, such as thrombectomy, aiming at reducing thrombus burden, have been developed in order to improve PPCI's safety and efficacy, patients' survival and their quality of life.

CORONARY THROMBOSIS IN STEMI PATIENTS

Atherosclerotic plaque rupture or erosion are usually followed by hemorrhage into the plaque, luminal thrombosis, and vasospasm, which may cause sudden, partial or total, flow obstruction, and hence the onset of ischemic symptoms in the setting of STEMI[1,9,10]. Inflammation and increased oxidative stress seem to play an important role in the pathogenesis of plaque instability[11-13]; while the clinical manifestation of an acute thrombotic event is determined by the balance between the propensity for thrombus formation, proportional to the kind and extent of exposed plaque components and to the local flow disturbances, and the efficacy of endogenous thrombolytic processes[14]. However, plaque disruption and thrombosis do not always coincide with the onset of symptoms[15,16]. Actually, post-mortem investigation and, more recently, histological studies of *in vivo*-derived thrombectomy specimens of STEMI patients, revealed that approximately 50% of the aspirated thrombi were days to even weeks old, which further suggests that thrombus formation starts at a variable time before symptoms onset[17,18].

Pathological analyses revealed that coronary thrombi consist of platelets, erythrocytes and fibrin, and often contain atherosclerotic inflammatory cells[19,20]. Initially, at the site of plaque disruption, platelets aggregate forming a platelet-rich thrombus which begins to protrude into the lumen. Then, the thrombus grows in association with the formation of a fibrin network entrapping a lot of erythrocytes and inflammatory cells, and forming an erythrocyte-rich thrombus[19-21], which can partially or totally occlude the vessel.

ANGIOGRAPHIC CORONARY THROMBI: DEFINITION AND CLASSIFICATION

Angiography seems to understimate the presence of thrombi. Nevertheless, intracoronary thrombi are angiographically defined as the presence of a filling defect with either a total occlusion with convex, irregular, or hazy distal margins and post injection contrast retention or staining, or a partial occlusion circumferentially outlined by contrast medium[22].

When angiographycally detected, the thrombus burden can be classified according to the thrombolysis in myocardial infarction (TIMI) thrombus grade (TG)[23]. TIMI TG 0 corresponds to no angiographic evidence of thrombus; in TIMI TG 1, angiographic characteristics suggestive of thrombus are detected (*i.e.,* reduced contrast density, haziness, irregular lesion contour or a smooth convex meniscus at the site of total occlusion suggestive but not diagnostic of thrombus); in TG 2, there is definite thrombus, with greatest dimensions $\leqslant 1/2$ the vessel diameter; in TG 3, there is definite thrombus but with greatest linear dimension $> 1/2$ but < 2 times the vessel diameter; in TG 4, there is definite thrombus, with the largest dimension $\geqslant 2$ vessel diameter; and in TIMI TG 5, there is total occlusion and the size of thrombus cannot be assessed.

In STEMI setting, there is a high incidence of total coronary occlusion, thus, as was shown by Sianos *et al*[2], the prevalence of TG 5 and unknown thrombus size is almost 60% of the patients. Therefore, a modified TG classification was recently suggested by Sianos *et al*[2], where, grade 5 lesions are reclassified into one of the other TIMI grade categories, after flow achievement with either guidewire crossing or a small (diameter 1.5 mm) deflated balloon passage or dilation. According to this new classification, most lesions (99%) can be classified. Particularly, TIMI TG 0-3 are defined as small thrombus burden (STB), while TIMI TG 4 is defined as large thrombus burden (LTB).

PROGNOSTIC SIGNIFICANCE OF ANGIOGRAPHICALLY DETECTED CORONARY THROMBI

Angiographically detection of coronary thrombi in the setting of PPCI for STEMI is a well known negative prognostic factor, associated with a higher incidence of in-hospital and long-term adverse cardiac events[2,6,24,25]. Actually, intracoronary thrombi can impair both epicardial and myocardial perfusion, by spontaneous or PPCI-induced occlusion of an epicardial vessel or its branches, or distal embolization of plaque and thrombotic components. Data derived from PPCI for STEMI studies, showed that PPCI resulted in about 6% to 18% distal embolization rate[3,4,25-28]. Moreover, patients with distal embolization, compared to those without, showed lower procedural success rates with higher slow/no-reflow rates, lower left ventricular ejection fraction (LVEF), larger enzymatic infarctions, with increased in-hospital and late mortality rates[25,29].

Size and thrombus composition are the major predictors of distal embolization, as well as slow TIMI flow

grade before PCI, long target lesion and large vessel diameter[3,4,30]. A LTB and a high plaque burden were shown to be independent predictors of distal embolization[2,5,7,29], and correlated with worse final TIMI flow/myocardial blush grades, as well as 2-year mortality and major adverse cardiac event (MACE) rates[2]. In STEMI setting, thrombus burden is higher than in the other types of ACS. Particularly, a significant association between TG and vessel size has been reported (*i.e.*, large right coronary arteries, aneurismatic coronary arteries and aged degenerated saphenous vein grafts). Moreover, some clinical scenarios, such as STEMI occuring for stent thrombosis (ST), are associated with the presence of a LTB. Actually, Chechi *et al*[31] reported a significantly higher incidence of LTB (TG $\geqslant$ 3) in patients with STEMI due to ST, compared to those with STEMI due to *de novo* coronary thrombosis.

Recently, the development of thrombectomy and distal protection devices has enabled the evaluation of antemortem coronary thrombi, thus facilitating analysis of thrombi components, given that previous autopsy studies were unable to differentiate coronary thrombi responsible for STEMI from post-mortem clots. However, even for in vivo-derived thrombectomy thrombi, a sampling bias must be considered, related to the unability to determine whether retrieval of the thrombus was complete and which part of the thrombus has been extracted, and to the potential distortion of the samples that might have occurred during aspiration through a catheter lumen. Nevertheless, recent studies have demonstrated that erythrocyte-rich component in aspirated coronary thrombi is closely associated with thrombus size that increases the incidence of distal embolization during PPCI in STEMI patients[4,32]. Actually, data on aspirated thrombi from 164 STEMI patients within 12 h from symptoms onset, revealed that thrombi from patients with distal embolization had a greater erythrocyte-positive area and more myeloperoxidase (MPO)-positive cells than those from patients without distal embolization, and that thrombus size was positively correlated with the erythrocyte component and the numbers of MPO-positive cells[32]. These results reflect the above mentioned mechanism of thrombosis whereby the thrombus, initially platelet-rich, becomes erythrocyte-rich with inflammatory cells entrapped during thrombus growth[21,33,34]. Moreover, MPO-positive cells, constituted by neutrophils and only occasionally by macrophages[35], and erithrocyte-rich thrombi were shown to be associated with impaired coronary microcirculation, as assessed by ST-segment resolution and myocardial blush grade after PPCI in STEMI patients[36,37]. Finally, independently from the histopathology of aspirated thrombi, patients with fresh thrombus tended to have better ST-segment resolution than patients with older thrombus[38].

Prediction of thrombus burden and composition, as well as plaque volume and composition, before the procedure in patients with STEMI undergoing PPCI, may contribute to optimize percutaneous treatment of these highly thrombotic lesions, guiding utilization of pharmacological agents or interventional strategies, in order to reduce thrombus burden and improve both epicardial and myocardial perfusion. Grade Ⅲ ischemia on electrocardiogram, defined as distortion of the terminal portion of the QRS complex, and red cell distribution width (RDW), a marker of variation in the size of circulating red cells routinely reported as a part of blood count analysis, were shown to be independent predictors of coronary thrombus burden in STEMI patients undergoing PPCI, and to be associated with angiographic no-reflow and impaired epicardial and myocardial perfusion[39-41]. Probably, also the evaluation of thrombus burden using, not only coronary angiography, but also intravascular imaging modalities, such as ultrasound, optical coherence tomography or virtual histology, may provide important informations about the amount and composition of coronary thrombi, thus facilitating the choice of treatment strategies.

PHARMACOLOGIC AND PERCUTANEOUS INTERVENTIONAL MANAGEMENT OF CORONARY THROMBI

PPCI is the preferred treatment option, compared to thrombolytic therapy, in STEMI patients, being effective in obtaining patency of the infarct-related artery (IRA)[42], and resulting in smaller infartcs, less acute and long-term clinical events, including recurrent myocardial infarction and death[43,44]. However, a substantial number of STEMI patients, up to 40%, treated with PPCI shows poor procedural outcomes[25], above all because of the presence of intracoronary thrombi that can lead to micro and macro distal embolization, thus reducing the benefits of PCI[25]. Actually, although PPCI effectively restores flow in the IRA, myocardial perfusion often remains suboptimal, with persistent ST-segment elevation, abnormal myocardial blush grade and abnormal TIMI frame count, due to microvascular obstruction, mostly attributed to distal embolization[45]. As a result, management of lesions with a consistent thrombotic burden is still challenging during PPCI for STEMI. This has led to the employment and development of drugs and adjunctive percutaneous devices, aiming at reducing distal embolization and therefore improve myocardial perfusion. Particular subgroups of STEMI patients may benefit more from these adjunctive pharmacological and interventional strategies; these include patients with large anterior myocardial infarction, LTB, residual thrombus, side-branch involvement, and those with slow or no-reflow. Finally, attention must be paid on stenting strategies in order to further reduce PCI complications.

Pharmacologic agents

Several pharmacologic agents, delivered intravenously or *via* the intracoronary route, can be used in the catheterization laboratory, to manage lesions with consistent thrombus burden during PPCI for STEMI. When possible, STEMI patients undergoing PPCI should receive dual

antiplatelet therapy (aspirin plus one of the ADP receptor blockers) and one parenteral anticoagulant. Moreover glycoprotein Ⅱb/Ⅲa inhibitors (GPI) and vasodilators drugs may be useful to manage lesions with consistent thrombus burden and to improve epicardial and myocardial perfusion. Particularly, these pharmacological measures are useful in the presence of slow or no-reflow, which is related to a combination of distal embolization of plaque debris and thrombus, vasocontriction and reperfusion injury[25].

Anticoagulants

Anticoagulant options for PPCI include unfractionated heparin (UFH), enoxaparin and bivalirudin. UFH titrated to an appropriate activated clotting time is a familiar and well-tested strategy for anticoagulant therapy in the setting of PPCI[46,47], compared to enoxaparin which has been studied less extensively in this setting. Moreover, the ATOLL trial comparing intravenous enoxaprin with UFH for PPCI failed to meet its primary composite endpoint (30-d death, complication of myocardial infarction, procedural failure and major bleeding)[48]. Thus, European guidelines recommend UFH in Class Ⅰ, level of evidence C, while enoxaparin has an indication of Class Ⅱb, level of evidence B[42]. However, European guidelines stated that enoxaparin should be preferred over UFH[42], based on the considerable clinical experience with enoxaparin in other PCI settings[42] and on considerations derived from the ATOLL trial[48]. Particularly, although the primary endpoint was not reached, there were reductions in the composite main secondary endpoint of death, recurrent myocardial infarction or ACS or urgent revascularization, and in other secondary composite endpoints, such as death, or resuscitated cardiac arrest and death, or complication of myocardial infarction, and there was no indication of increased bleeding from use of enoxaparin over UFH[48]. Moreover, a recent meta-analysis of 23 trials, including 30966 patients undergoing PCI (33.1% PPCI for STEMI, 28.2% rescue PCI, and 38.7% with non ST-elevation ACS or stable patients), showed that enoxaparin was associated with a significant relative and absolute risk reduction of mortality, along with a significant reduction of major bleeding, especially in patients treated with PPCI for STEMI[49]. Bivalirudin is a direct thrombin inhibitor. In the HORIZONS-AMI trial[50], reporting on 3602 STEMI patients randomized to UFH plus a GPI or to bivalirudin alone, the later showed lower major bleeding rates at 30-d, 1 and 3 years[50-52], with significantly lower rates of death from cardiac causes and all causes[50]. Conversely, the use of bivalirudin was associated with an initial increase in ST, which disappeared after 30 d[50]. Based on these data, European guidelines recommend the use of bivalirudin, over UFH, in STEMI patients, with a Class I indication, level of evidence B, with use of GPI restricted only to bailout[42].

GPIs

GPIs (abciximab, tirofiban and eptifibatide) inhibit final common pathway of aggregation process by preventing fibrinogen from binding to activated platelets and forming white thrombus. All GPI agents have been found to achieve their benefits by reducing the clot burden at the epicardial coronary level, by improving microvascular flow and reducing no-reflow and infarct size, and thus by improving short- and long-term outcomes[53,54]. Although, GPIs are frequently administered to ACS patients undergoing PCI, a strategy supported by several randomized clinical trials, their role in STEMI patients, treated with PPCI and dual antiplatelet therapy, has been conflicting, especially because of bleeding concerns[50,55-57]. The most profund evidence has been found for abciximab, which remains the drug of choice in PPCI, in combination with heparin[58,59]. The recent 2013 ACC/AHA guidelines[47] have given the routine use of upstream GPIs in STEMI patients undergoing PPCI, a Class Ⅱb recommendation. However, upstream administration of GPIs, may be considered among high-risk patients within the first 4 h from symptoms onset, when the larger amount of myocardium at risk and viable myocardium may justify this approach[60]. Actually, the On-TIME 2 trial showed that upstream administration of GPI was associated with a higher rate of an open artery and a lower initial thrombus burden, with these benefits restricted only to early presenters (< 76 min)[61]. Therefore, GPIs, as stated by European guidelines[42], should be considered only for bailout therapy (Class Ⅱa, C) if there is evidence of LTB, slow or no-reflow or a thrombotic complication, or could be administered upstream only in high-risk patients undergoing transfer for PPCI (Class Ⅱb, B). Generally, GPIs are administered intravenously. Recently, intracoronary bolus of abciximab has been tested, with the rationale that intracoronary drug concentration may increase drug efficacy, and that the continuous intravenous infusion may not be beneficial to further improve outcomes, but may increase the risk of bleeding, especially in the contemporary era of PPCI, in which more potent ADP receptor blockers and thrombus aspiration are available for most of the STEMI patients. However, to achieve these favorable effects, it is advisable to administer intracoronary abciximab bolus after thrombus penetration by the PCI guidewire, and when the risk of bleeding is an issue, intracoronary bolus of GPI and no infusion strategy may be useful. Some small studies showed infarct size reduction, decrease in microvascular obstruction, improvement in the LVEF, and improvement in myocardial blush, but no significant difference in the clinical outcomes with intracoronary bolus admnistration of abciximab, with and without subsequent infusion[62-65]. However, meta-analyses published recently, demontrated not only a favorable effect of intracoronary bolus on TIMI flow, but also on target vessel revascularization and short-term mortality after PCI with no increase of bleeding complications[66,67]. In summary, the role of intracoronary bolus of GPIs still need to be established by randomized trials comparing intravenous and intracoronary GPIs administration, with and without subsequent infusion, in combination with

modern PPCI strategies.

Vasodilators

Vasodilators that have been used in PPCI setting include nitroprusside, adenosine and diltiazem or verapamil. When used, they are administered intracoronary, in order to achieve a higher local concentration. Thus, they can be delivered directly through the guiding catheter, or *via* a distal over-the-wire balloon, infusion catheters or infusion balloons[68].

Adenosine is considered a cardio-protective agent, because it antagonizes many of the factors implicated in the reperfusion injury, and has been shown to reduce post-ischemic ventricular dysfunction and myocite necrosis and apoptosis. Moreover, several studies showed beneficial effects on coronary flow[69,70]. Compared to the other drugs, adenosine has the advantage to have a very short half-life, and therefore, adverse effects are rapidly resolved.

Nitroprusside is a direct donor of nitric oxide, functioning as a potent venous and arterial vasodilator. Selective intracoronary nitroprusside administration is safe, generally well-tolerated, and provides stimulus to promote vascular dilation and improve tissue perfusion, especially in patients who develop slow or no-reflow after PCI. Moreover, if administered before balloon or stenting angioplasty, intracoronary nitroprusside, as well as adenosine, may decrease rates of no-reflow, increase myocardial blush scores, and shorten procedural times. In cases of impaired flow during PCI, combination therapy of adenosine and nitroprusside has been shown to be safe and provides better improvement in coronary flow and MACE, as compared with adenosine alone[68].

Small trials suggest that there may be a role for prophylactic use of intracoronary calcium channel blockers, especially verapamil, because they seem to prevent no-reflow in some patients by reversing the calcium-mediated distal microvascular spasm[71,72].

Although the benefit of intracoronary delivery of adjunctive pharmacologic agents such as calcium channel blockers, adenosine and nitroprusside is limited to small studies showing reduction of embolization rates and not clinical outcomes, they are still useful in the catheterization laboratory.

Percutaneous devices

The rationale for thrombectomy and embolic protection devices use is the reduction of the incidence of distal embolization, and improvement of myocardial perfusion and clinical outcomes. Particularly, thrombectomy devices aim at reducing thrombus burden, while embolic protection devices aim at capturing the debris liberated during PCI.

Thrombectomy devices

In the last years thrombectomy has emerged as a useful tool to reduce thrombus burden and thus distal embolization, further enhancing benefits of PPCI. Various thrombectomy devices have been developed allowing manual or mechanical removal of intracoronary thrombi. All thrombectomy devices have shown benefits compared with conventional PPCI, when surrogate endpoints, such as angiographic flow assessment, LVEF assessment, infarct size reduction by perfusion imaging, enzymatic analysis and ST-segment resolution were used[26,29,73-79]. To date evidences about hard endpoints from randomized controlled trials, comparing manual and mechanical thrombectomy, are limited and even conflicting.

The REMEDIA trial, comparing thrombus aspiration with the Diver CE (Invatec, Brescia, Italy) before PCI *vs* conventional PPCI[73], showed no difference in clinical outcomes or peak creatine kinase, muscle and brain (CK-MB) elevation, but a significant improvement in perfusion grades and in ST-segment resolution. The EXPIRA trial, evaluating the Export catheter (Medtronic, Inc, Minneapolis, MN) in PPCI, demonstrated improvement in surrogate markers, including myocardial blush grade and ST-segment resolution[78]. The TAPAS trial is the largest randomized trial to date evaluating thrombus aspiration in PPCI for STEMI[26]. It randomized 1071 patients and demonstrated effective manual thrombus aspiration in 73% in the treatment group. There was a trend toward less MACE at 30 d.

Recently, a direct and adjusted indirect meta-analysis of studies on manual and mechanical thrombectomy in PPCI for STEMI has been published[80]. The direct meta-analysis showed comparable rates of survival, re-infarction and procedural outcomes between the two groups, even though these results are limited in sample size. On the contrary, the indirect meta-analysis showed a superior reduction in mortality with manual compared to mechanical thrombectomy. When trials, such as TAPAS and AIMI, with low percentage of patients with intracoronary thrombus (< 50%) at baseline, were excluded from the analysis, the two strategies were comparable in survival, but mechanical thrombectomy was associated with a significant reduction in re-infarction and stroke[80]. This report lends support to mechanical thrombectomy, which until now was looked upon with suspicion. Actually, despite more bulky and complex to use, mechanical thrombectomy devices may provide more consistent advantages in removal thrombus, because of their intrinsic properties. To date, the negative results associated with the use of mechanical thrombectomy devices, are mostly driven by the results of the AIMI trial[81], reporting on 480 patients randomized to AngioJet rheolytic thrombectomy (RT) and standard PPCI. In this study, the AngioJet RT group reported a higher final infarct size, a lower final TIMI flow grade 3 and a higher 30-d MACE rate. It has been speculated that the higher mortality observed in these patients may be related to a very low (and unexpected) mortality of patients treated only by PPCI (0.8% *vs* 4.6%; $P = 0.02$)[81]. Moreover, both operator experience and the tecnique used, might have influenced mortality in patients treated with AngioJet RT. Actually, in the AIMI trial enrolling centers were low-volume centers without

extensive AngioJet experience, as resulted from the high rate of coronary perforation. Furthermore, a retrograde thrombectomy tecnique was used without activation of the device prior to crossing the lesion, which might have promoted distal embolization. Finally, angiographic evidence of thrombus was absent in a large percentage of both groups[81]. Conversely, the recently published JETSTENT trial, evaluating 501 patients with LTB (thrombus grade ⩾ 3) in large vessels (⩾ 2.5 mm), randomized to AngioJet RT prior to direct stent *vs* direct stent alone, reported that patients treated with AngioJet showed a better myocardial reperfusion, with a higher rate of early ST-segment resolution (P = 0.043), without any significant differences in secondary surrogate endpoints, such as infart size at 1-mo scintigraphy, post-procedural TIMI flow and corrected TIMI frame count. On the contrary, the rate of MACE (*i.e.*, death, myocardial infarction, repeated revascularization and stroke) was significantly lower in patients treated with AngioJet either at 1-mo (P = 0.043), or 6-mo (P = 0.011) or 12-mo (P = 0.036) follow-up, primarily driven by a lower incidence of death and time to target vessel revascularization. This was attributed to better myocardial perfusion and to better stent length and diameter assessment following RT[82].

Therefore, current evidences support the routine use of manual thrombectomy devices in PPCI, and consequently, manual thrombectomy received a Class Ⅱa indication in PPCI in the recent ESC guidelines[42]. However, when LTB is present, especially in large vessels and when experienced operators are available, mechanical thrombectomy with AngioJet system should be considered. Particularly, AngioJet may be very useful in patients with STEMI due to stent thrombosis, in which the thrombotic burden seems to be huge. A study published by Chechi *et al*[31] showed that thrombus grade ⩾ 3 was observed in all patients with STEMI due to stent thrombosis, compared to 93.9% of patients with STEMI and de-novo coronary thrombosis (P = 0.01). The OPTIMIST study, in which 110 patients with stent thrombosis treated by PCI have been evaluated, showed that a sub-optimal coronary reperfusion was related to a worse outcome, even though GPIs, intra-aortic balloon pump and mechanical thrombectomy devices were used. In this study, mechanical thrombectomy devices were under-used: only 30% of patients have been treated with these devices, and among them few have been treated with AngioJet[83]. Patients treated with mechanical thrombectomy showed a better coronary reperfusion, compared to patients in which mechanical thrombectomy devices were not used[83].

Embolic protection devices

Embolic protection devices (EPD) can be divided into proximal and distal devices. Distal EPDs consist in filterwire or occlusive distal balloon systems, while the principal proximal EPD is represented by an occlusive proximal balloon system (*i.e.*, Proxis system). Few data are available on proximal EPDs, while most of the data regard distal EPDs. Distal EPDs were first used to protect from embolization associated with PCI in diseased saphenous vein grafts, then after they were applied in PPCI setting for STEMI to protect myocardium during intervention on highly thrombotic lesions in native vessels.

The EMERALD trial demonstrated no significant improvements in the primary end points of myocardial reperfusion or infarct size with the use of the distal balloon occlusion and aspiration system, GuardWire, despite the removal of visible debris in a high proportion of patients (73%)[84]. The DEDICATION trial, evaluating patients randomized to distal protection using a filter wire (FilterWire-EZ), or a SpiderFX protection device, *vs* standard PPCI without distal protection, showed no significant difference in the primary endpoint of ST-segment resolution or in cardiac biomarker elevation or left ventricular wall motion index, and found a higher MACCE rate with distal protection[85]. Thus, although, distal EPDs showed favorable clinical benefits during PCI in saphenous vein grafts, the results in PPCI setting for native vessel were not so good. Resuming, no differences were reported on ST-segment resolution, infarct size and MACE rates with distal EPDs compared to standard PPCI[84-86]. These data were confirmed by the meta-analysis by Kunadian *et al*[87], where the use of distal EPDs resulted in no decrease of early mortality or recurrent myocardial infarction rate. Probably, the absence of benefits with the use of distal EPDs could be explained by the fact that such devices can themselves induce distal embolization when crossing highly thrombotic lesions and may not be completely effective in preventing all debris from embolizing. Theoretically, compared to distal EPDs, proximal ones offer the benefit of embolic protection without crossing the thrombus, therefore avoiding added distal embolization, while allowing effective thrombus removal. Conversely, proximal EPDs, such as the Proxis device, have several technical limitations contraindicating their use during PPCI (*i.e.*, the presence of a stenosis within 15 mm of the ostium or IRA proximal segment diameter < 2.5 or > 4.5 mm, contraindicate the use of Proxis system), and therefore making results on their use unconclusive. In the setting of STEMI, use of the Proxis device demonstrated an initial benefit in ST-resolution; however, this benefit was not maintained over time with a late catch-up in the control group.

Based on the above data, European guidelines did not recommend routine use of distal EPDs[42].

Stenting strategies

PCI strategies, including selection of vascular access, timing of stenting, sizing and type of stent, are crucial to further improve angiographic and clinical outcomes during PPCI for STEMI, along with the use of adjunctive pharmacologic drugs and thrombectomy devices.

Compared to elective procedure, PPCI is associated with a higher rate of bleeding, because of the need for potent antithrombotic and antiplatelet agents, mostly related to the arterial puncture site. Radial approach has been shown to reduce the incidence of acute bleeding

events, both in ACS and STEMI patients, especially when operators are skilled with this arterial approach[42].

The presence of a LTB in STEMI setting, may affect stent apposition, correct stent sizing and final TIMI flow, all of which are predictors of acute ST. Thus, the best approach to stenting in PPCI seems to be thrombus guided, as reported in the SINCERE database[88]. Based on this strategy, if the extent of thrombus is small (TG 0-1), direct stenting may be sufficient. Conversely, if more significant thrombus burden is present (TG 2-3), initial aspiration with a manual device is usually prudent, by decreasing distal embolization and no-reflow, and facilitating subsequent stenting. If thrombus burden is unchanged after 2 passes, it is advisable to switch to a more aggressive thrombectomy device, such as the AngioJet system. If a very LTB is present (TG 4-5), manual thrombectomy may be insufficient and AngioJet RT may be warranted[88]. Actually, a LTB has been related to a very high rate of ST (2); moreover, if not removed, thrombus compression or displacement by the stent struts may cause distal embolization and no-reflow in the acute phase during PPCI, and in the long-term, with abluminal thrombus resolution, may cause late stent malapposition, thus increasing the risk of late ST. Therefore, a strategy of delayed stent implantation (DSI) after thrombus removal, compared to immediate stent implantation (ISI), appears attractive. To date, only few and small studies have been published comparing these two strategies[89-91], but they all showed that DSI is associated with better microvascular perfusion, less frequent distal embolization and no-reflow, compared with ISI. Certainly, in STEMI setting with LTB, DSI has to be weighed against the potential risk of recurrent ischemia and bleeding episodes during the waiting period before PCI. On the other hand, DSI could allow to perform PCI after full antithrombotic preparation, enhancing clot lysis and thrombus dissolution, and after enough time to "cool off" the culprit lesion, thus becoming more stable with a reduced incidence of adverse angiographic events.

When a stenting strategy is applied, selection of the appropriate stent diameter may be of particular importance during PPCI, since stent undersizing is one of the most powerful predictor of ST among non-elective PCI[92]. Actually, the reference vessel diameter of the IRA may be difficult to accurately assess during PPCI, because of thrombus burden, cathecholamine stimulation and inflammatory substances, that can contribute to general and localized vasocostriction[93]. Therefore, intracoronary administration of nitrates is recommended before starting the coronary angiographic sequence used for stent size selection[42].

Drug-eluting stents (DES) can be implanted during PPCI for STEMI, with a reduced risk of repeated target vessel revascularization, compared with bare-metal stents (BMS)[94]. There have been concerns about increased risks of very late ST and reinfarction with DES, compared with BMS[94]. However, use of DES has not been associated with an increased risk of death, myocardial infarction or ST on long-term follow-up[52]. Moreover, newer generations of DES seem to provide improved clinical outcomes following PPCI, with a reduced incidence of ST. The often spastic reaction of the IRA and the presence of LTB, may be the rationale for implanting stents with progressive self-apposing after their implantation. Interim results of the APPOSITION Ⅲ trial, using self-expanding BMS, are promising with a lower 30-d MACE rate. Moreover, when a LTB is present, the use of special mesh-covered stents can be useful in managing thrombi and preventing distal embolization. There are some small studies reporting on the use of the MGuard stent in STEMI setting, documented promising surrogate results, such as a better ST-resolution and a higher post-procedural TIMI 3 flow rate, when compared to standard types of stents[95-98].

CONCLUSION

Since detection of intracoronary thrombi is associated with distal embolization, myocardial damage and poor clinical outcomes, several pharmacologic agents and interventional adjunctive techniques need to be take in consideration during PPCI for STEMI, as well as a correct stenting strategy. The treatment during PPCI needs to be modified with respect to the risk profile, thrombotic burden, availability of medical resources and operators' experience.

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