Review Article

Adjunctive Pharmacologic Agents and Mechanical Devices in Primary Percutaneous Coronary Intervention

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Abstract

Primary percutaneous coronary intervention (PPCI) has been shown to be superior to thrombolysis in patients presenting with ST-segment elevation acute myocardial infarction (STEMI) in reducing death, stroke and re-infarction. However, bleeding and thrombotic complications can occur despite successful PPCI and slow flow/no-reflow or poor microvascular reperfusion can occur in a significant minority despite a technically successful procedure. Bleeding or need for peri-procedural transfusion has been shown to increase short- and long-term mortality. Newer anticoagulants appear to reduce the bleeding risk and improve overall clinical outcomes. A novel combination of antiplatelet agents also appears to further improve the outcomes after PPCI. Although PPCI can achieve high rates of epicardial artery patency, some patients experience suboptimal microvascular perfusion, which affects long-term prognosis. Several pharmacologic agents have been shown to improve microvascular perfusion and left ventricular function, although none impacts on clinical outcomes. Of the mechanical devices available to reduce distal embolisation, the simple aspiration catheter holds the most promise in reducing clinical adverse events. Additional research and well designed studies are needed to further enhance the outcomes after PPCI.

Ann Acad Med Singapore 2010;39:230-6

Key words: Anticoagulant, Antiplatelet agents, Distal protection devices, Myocardial infarction, Pharmacotherapy, Primary angioplasty, Thrombectomy

Introduction

Primary percutaneous coronary intervention (PPCI) has been shown to be superior to thrombolysis in patients presenting with ST-segment elevation acute myocardial infarction (STEMI), with regard to reduction of death, stroke and re-infarction.[1] However, bleeding and thrombotic complications can occur despite successful PPCI and slow flow/no-reflow or poor microvascular reperfusion can occur in up to 20% to 40% of patients despite a technically successful procedure.[2,3] Bleeding or the need for peri-procedural transfusion has been shown to increase short- and long-term mortality, even after accounting for baseline characteristics,[4] and incomplete microvascular reperfusion portends a worse clinical outcome and decreased survival.[2,3,5]

Several pharmacotherapeutic agents are currently under investigation for use during PPCI with the hope of decreasing thrombotic events and bleeding risk and increasing microcirculatory reperfusion. Mechanical devices have been studied to reduce the risk of distal clot embolisation and preserve microvascular perfusion. These agents and devices will be the subject of this review.

Pharmacotherapeutic Agents

In addition to dual antiplatelet therapy, with aspirin and clopidogrel, the commonly used agents are the glycoprotein IIb-IIIa inhibitors (Gp 2b/3a-inh), abciximab, eptifibatide and tirofiban. Aspirin and clopidogrel are reviewed elsewhere and will not be further discussed. Amongst the Gp 2b/3a-inh, the majority of studies have used abxicimab (a monoclonal antibody), and it has been shown that this agent reduces reinfarction, target vessel revascularisation and mortality when used during PPCI.[6,7] Less data are available for the small molecules – eptifibatide and tirofiban – although a recent meta-analysis suggests that they provide similar clinical benefits and have the same bleeding risks as abciximab.[8] However, the more interesting question is whether Gp 2b/3a-inh should be used during current day

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PPCI practice where high-dose clopidogrel is routinely administered as the BRAVE-3 and ASSIST randomised studies showed no additional benefit from these agents.[9,10] A pooled analysis of randomised PPCI trials, where clopidogrel was routinely administered, also showed no additional benefit of Gp 2b/3a-inh, except for the highest risk patients.[11] Therefore with current practice, perhaps only the highest risk PPCI patients should be considered for additional Gp 2b/3a-inh.

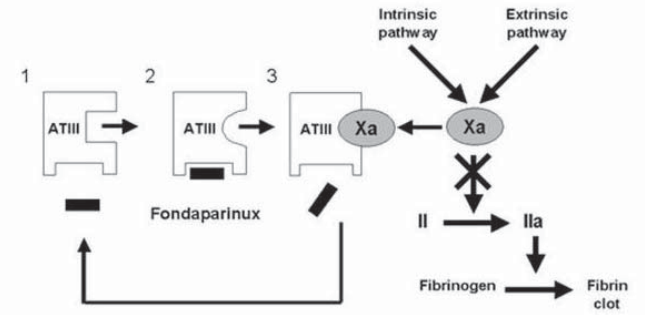
Facilitated PPCI is where a full dose lytic is administered before PPCI or when a combination of half dose lytic and Gp IIb-IIIa inhibitor is administered before PPCI with the intention of improving infarct vessel recanalisation/patency before PPCI. These regimens have been shown to produce worse outcomes compared to PPCI alone in the ASSENT-4 and Finesse trials.[12,13] Two meta-analyses of randomised trials again confirmed that there was no benefit of facilitated PPCI over PPCI alone, and may even be harmful (increased major bleeding).[14,15] Therefore these regimens have no role in routine PPCI, although very recent studies suggest that a well selected subgroup of patients may derive benefit.[16-18]

Newer Anticoagulant Agents

Results of 2 newer anticoagulants recently used as an alternative or addition to unfractionated heparin (UFH) in PPCI have been recently reported[19,20] – fondaparinux (Fig. 1), a synthetic pentassacharide that selectively binds antithrombin and rapidly inhibits Factor Xa, and bivalirudin (Fig. 2), a synthetic congener of hirudin (derived from the leech) that is a direct reversible thrombin inhibitor with a half life of approximately 20 minutes.

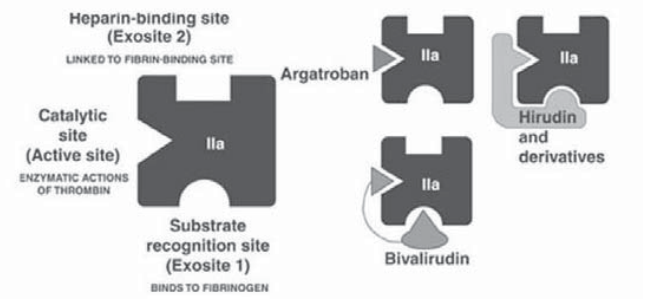
Fondaparinux has shown promise as an alternative anticoagulant agent in patients with acute coronary syndromes without ST-segment elevation (OASIS-5 trial).[21]

In the OASIS-6 trial, 12,092 patients with STEMI were randomised to receive fondaparinux vs placebo or UFH.[19] A total of 3789 (28.9%) patients underwent PPCI. The primary composite endpoint of death or reinfarction at 30 days was significantly reduced with fondaparinux [absolute risk reduction 1.5%; hazard ratio (HR), 0.86; 95% confidence interval (CI), 0.77-0.96; $P = 0.008$], without an increase in bleeding or strokes. Although mortality was reduced throughout study, there was no benefit in those undergoing PPCI, with respect to the composite endpoint of death or reinfarction, and death or reinfarction alone. Of greater concern was the higher rate of catheter thrombosis with fondaparinux (22 vs 0; $P < 0.01$) and increased coronary complications (abrupt vessel closure, new angiographic thrombus, catheter thrombus, no reflow, dissection or perforation) (270 vs 225; $P = 0.04$). The overall death or reinfarction rate in the PPCI group however was not different between fondaparinux vs control; thus, the increase in procedural complications did not negate the overall



Fondaparinux binding to antithrombin III (AT III) potentiates AT III-mediated factor Xa inhibition exclusively. Unlike direct factor Xa inhibitors, it mediates its effects indirectly through AT III, but unlike heparin, it is selective for factor Xa.

Fig. 1. The mechanism of action of fondaparinux.



Bivalirudin (unlike UFH) inhibits thrombin in both its plasma fluid and fibrin-bound phase, providing for a more complete inhibition of thrombin, as well as inhibition of thrombin-mediated platelet activation. It binds directly to thrombin without the need for the antithrombin cofactor required by UFH.

Fig. 2. The mechanism of action of bivalirudin.

benefits. These complications were also not significantly different between the groups among the 496 patients who also received UFH heparin prior to PPCI. This may suggest that the use of UFH with fondaparinux is safe and avoids complications. However, given the limited time for antithrombotic therapy prior to PPCI, and the need for UFH during the procedure, it appears that there is little advantage of using fondaparinux in those intended for PPCI. Perhaps one situation where it would be extremely useful would be in a patient presenting with a STEMI and with a history of heparin-induced thrombocytopenia.

Bivalirudin has been shown in large scale, randomised trials to reduce major and minor bleeding and thrombocytopenia with similar rates of ischaemic outcomes after PCI in patients with stable angina, unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI),[22-24] resulting in net clinical benefit. This has become even more important as recent data suggest that bleeding or need for peri-procedural transfusion increases short- and long-term mortality, even after accounting for baseline characteristics.[4]

In the Horizons-AMI trial,[20] bivalirudin was studied in patients undergoing PPCI. Patients (n = 3602) presenting

within 12 hours of symptom onset with planned PPCI were randomised to bivalirudin alone or heparin plus a Gp 2b/3a-inh. The 2 primary endpoints of this study were major bleeding and combined adverse clinical events (i.e., net adverse clinical events), which was defined as the combination of major bleeding or major adverse cardiovascular events (MACE), including death, target vessel revascularisation for ischaemia, and stroke within 30 days. Bivalirudin was found to result in reduced net adverse clinical events (9.2% vs 12.1%; RR, 0.76; 95% CI, 0.63-0.92; $P = 0.005$) due to a lower rate of bleeding. There was also a significantly lower rate of cardiac death (1.8% vs 2.9%; RR, 0.62; 95% CI, 0.40-0.95; $P = 0.03$) and all-cause death (2.1% vs 3.1%; RR, 0.66; 95% CI, 0.44-1.00; $P = 0.047$). There was, however, an increased risk of stent thrombosis within 24 hours in the bivalirudin group although this was not different at 30 days. At 1-year, the net clinical benefit still favoured bivalirudin with significantly lower major bleeding (5.8% vs 9.2%; RR, 0.61; $P < 0.0001$), similar MACE (11.9% vs 11.9%; $P = 0.98$), and significantly lower cardiac mortality (2.1% vs 3.8%; RR, 0.57; $P = 0.005$) and all-cause mortality (3.5% vs 4.8%; HR, 0.71; $P = 0.037$).[25] These data suggest that using bivalirudin can produce better short- and mid-term outcomes as compared to UFH and Gp 2b/3a-inh, and may become the standard of care in the future. The main factor limiting more widespread adoption of bivalirudin is undoubtedly cost as it is at present still an expensive pharmacologic agent.

Triple Antiplatelet Therapy

In a large (n = 4203) non-randomised registry of patients undergoing PPCI within 12 hours of symptom onset using drug-eluting stents, addition of cilostazol (an inhibitor of phosphodiesterase in both platelets and vascular smooth muscle cells) as a third antiplatelet agent was studied compared to the usual dual antiplatelet therapy with aspirin and clopidogrel.[26] This combination (aspirin and clopidogrel ≥6 months and cilostazol ≥1 month) produced superior clinical outcomes with regard to cardiac death [HR, 0.52; $P = 0.007$]; all-cause death [HR, 0.60; $P = 0.01$]; and MACE [HR, 0.74; $P = 0.019$], without any increase in major bleeding events (0.4% dual antiplatelet therapy vs 0.2% triple antiplatelet therapy; $P = 0.24$). Though promising, it has to be considered that this study was not randomised and drug-eluting stents (DES) were used in all patients. Even though baseline patient characteristics were similar, confounders may have affected the outcomes and these results may also not apply to patients who have bare metal stents implanted during PPCI.

Agents to Improve Microvascular Perfusion

Adjunctive low-dose intracoronary (IC) streptokinase (SK) was tested in a small randomised study to improve microvascular perfusion. It has been hypothesised that in-situ thrombosis might contribute to impaired microvascular perfusion during PPCI, and IC SK could theoretically attenuate this phenomenon. IC SK (250 kU) was administered after PPCI via the guide catheter in one group whereas no additional therapy was performed in the other group. Invasively measured coronary flow indices (markers of coronary microvascular perfusion) 2 days after PPCI was significantly better with IC SK.[27] However, the main limitation of this study was the small patient numbers (n = 41).

In a subsequent extended study with larger patient numbers (n = 95),[28] the infarct size was shown to be smaller with IC SK compared to the control group (22.7% vs 32.9%; $P = 0.003$) and the left ventricular ejection fraction (LVEF) was significant higher with IC SK (57.2% vs 51.8%; $P = 0.018$). These results suggest that immediate low-dose IC SK after PPCI not only improves short-term microvascular perfusion, but also limits infarct size and preserves LVEF in the longer term. Larger trials will be required to corroborate these interesting findings, and to determine if clinical outcomes would actually be improved.

Adenosine, a vasodilator, also lowers neutrophil count in infarct zones, maintains endothelial integrity and might have cardioprotective effects similar to ischaemic preconditioning.[29] In a small trial, IC high-dose (4 mg) adenosine was randomised against placebo during PPCI within 3 hours of symptom onset.[30] Epicardial perfusion and ventricular function recovery in the infarct zone were enhanced, resulting in an improved clinical course. Recently, a larger randomised study (n = 448) comparing high-dose IC adenosine vs placebo, however, showed no improvement in markers of microvascular perfusion or 30-day clinical outcomes.[31] Side effects such as hypotension and transient first- and second-degree atrioventricular blocks were significantly more frequent with IC adenosine, although all side effects disappeared within 2 to 3 minutes and no clinical sequelae were seen.[31] Intravenous (IV) administration of adenosine also did not improve clinical outcome as demonstrated by the AMISTAD-II trial. This trial randomised 2118 patients (of whom 40% received PPCI) to IV adenosine or placebo. Although infarct size was reduced with high-dose adenosine infusion, clinical outcomes were not significantly different.[32] Therefore, the use of adenosine in PPCI is probably of no benefit and cannot be recommended.

Nicorandil, a mitochondrial potassium-channel opener, has been used in PPCI. The mitochondrial potassium channel is closely involved in ischaemic preconditioning, and nicorandil could be protective against ischaemic injury. Small studies have shown that IV nicorandil was associated with improved microcirculation, reduced infarct size and better clinical outcomes.[33,34] Ischaemia and subsequent reperfusion causes intracellular calcium overload, which

may lead to a hypercontractile state and cell death.[35] Small randomised studies of IC nisoldipine or IC verapamil (both calcium antagonists), administered during PPCI, suggest that these agents seem to attenuate myocardial stunning and enhance recovery of LV function.[36,37] Although IC niroprusside and nitrates have been shown to improve microcirculation angiographically,[38] it is uncertain if there would be meaningful clinical benefit. Several other agents have been investigated in the setting of PPCI to improve microvascular perfusion; one agent (KAI-9803) has produced some promising initial first-in-man data[39] while others have mostly produced disappointing results, and will not be further discussed.

Mechanical Devices

Various devices to prevent or reduce distal embolisation have been studied as it is believed that distal embolisation during mechanical reperfusion is an important contributor to microvascular dysfunction.[40] In fact, a recent study using Doppler flow wires to detect embolic signals demonstrated that distal embolisation was universal during PPCI.[41] Embolisation occurs mainly during initial balloon angioplasty and stent deployment. The greater the embolic burden, the worse the microvascular perfusion and left ventricular function recovery. Therefore, mechanical devices including embolic protection or thrombectomy devices are designed to reduce thrombus burden and/or distal embolisation. A meta-analysis pooling all studies comparing the use of mechanical devices vs PPCI alone concluded that these adjunctive devices were associated with a higher rate of postprocedural TIMI 3 flow (89.4% vs 87.1%; $P = 0.03$), postprocedural myocardial blush grade (MBG) 3 (48.8% vs 36.5%; $P < 0.0001$), and less distal embolisation (6.0% vs 9.3%; $P = 0.008$). However, there was no benefit in terms of 30-day mortality (2.5% vs 2.6%; $P = 0.88$).[42] Although this meta-analysis included a large number of patients (3721), it did not differentiate different types of aspiration devices (which may have produced different outcomes) and it also did not include the TAPAS trial.[43] This large recently reported randomised study of manual aspiration during PPCI demonstrated improved clinical outcomes with the device (a first for any mechanical device).

Embolic Protection Devices

These devices are deployed downstream from the site of the culprit lesion to "trap" embolic debris from entering the microcirculation. The distal protection systems comprise balloon-occlusive systems or distal filters. More recently, a proximal protection system has been developed (Proxis System, St. Jude Medical, Minneapolis, MN), and limited data on its use in PPCI suggest that microvascular perfusion may be improved compared to standard PPCI alone.[44]

It was thought that the balloon-occlusive system would have an advantage over distal filters since it has a lower crossing profile (and theoretically would cause less embolisation at the point of lesion crossing) and aspiration of the stagnant blood column would allow for removal of neurohumoral mediators (which may contribute to impaired microvascular perfusion).[40] The EMERALD trial, the largest randomised study using the Percusurge Guardwire balloon-occlusive system (Medtronic Inc, Minneapolis, MN) vs standard PPCI within 6 hours of symptom onset showed that even though the system effectively retrieved embolic debris, there was no difference in ST-segment resolution 30 minutes after PPCI or infarct size (as determined by radionuclide imaging) at 14 days of mortality or MACE at 6 months.[45] In the smaller ASPARAGUS trial (also using the Guardwire device), the primary endpoint of postprocedure MBG was not improved although the incidence of slow flow/no-reflow was significantly lower in the Guardwire group (5.3% vs 7.4%; $P = 0.05$).

Distal filter devices allow antegrade flow during "protection" and may induce less ischaemia. Embolic debris liberated during PPCI would be "trapped" although particles <100 μm would be able to pass through the filter pores. These devices have been investigated in several randomised trials, none of which showed any benefit in improving microvascular perfusion.[46-48]

Reasons proposed for the lack of benefit are that the embolic protection devices may promote distal embolisation during lesion crossing, incomplete removal of embolic debris, potential for embolisation into side branches, and pre-dilatation of the lesion is needed in some cases to facilitate passage of the device.[40] Thus, distal protection does not seem to offer benefit in PPCI and cannot be recommended on a routine basis.

Thrombectomy Devices

Several types of devices are available: manual aspiration catheters, rheolytic thrombectomy (AngioJet device, Possis Medical Inc, Minneapolis, MN), and the X-Sizer (ev3 Inc, Plymouth, Minn) which employs a helical distal cutter to break thrombus, that is then removed by an external vacuum source. Although the X-Sizer had initial positive results in improving microvascular perfusion,[49-51] it is no longer available for clinical use.

The AngioJet rheolytic thrombectomy (Fig. 3) removes thrombus by utilising high-velocity saline jets directed from its tip back to the more proximal catheter creating a Venturi effect that entrains thrombus towards the inflow windows. A small randomised study demonstrated that microvascular perfusion was improved and infarct size was reduced using this device in PPCI.[52] However, the larger and more recent AIMI trial did not show any benefit in microvascular perfusion with the AngioJet device, and paradoxically final

Table 1. Trials of Manual Aspirations Devices in PPCI

Study	N	Device	Gp IIb-IIIa use, %	Primary endpoint	Results	Conclusion
Positive trials						
TAPAS[43,58]	1071	Export catheter	93.4	MBG 0 Cardiac death/ MI at 1 year	17.1% vs 26.3% (P <0.001) 5.6% vs 9.9% (P = 0.009)	Improved microvascular perfusion and clinical outcomes.
DEAR-MI[57]	148	Pronto catheter	100	ST resolution MBG 3	68% vs 50% (P <0.05) 88% vs 44% (P <0.0001)	Improved microvascular perfusion only.
De Luca[56]	76	Device CE	Not reported	End diastolic volume at 6 months	138.1 vs 152.5 mL (P = 0.0001)	Improved microvascular perfusion, less LV remodelling. No difference in MACE
REMEDIA[55]	99	Diver	68	MBG ≥2 ST resolution ≥70%	68% vs 58% (P = 0.20) 44.9% vs 36.7% (P = 0.034)	Improved microvascular perfusion only.
Negative trial						
Kaltoft[54]	215	Rescue catheter	96	Myocardial salvage	13% vs 18% (P = 0.12)	No improvement in myocardial salvage. Final infarct size greater with thrombectomy

Adapted from Srinivasan et al[40]

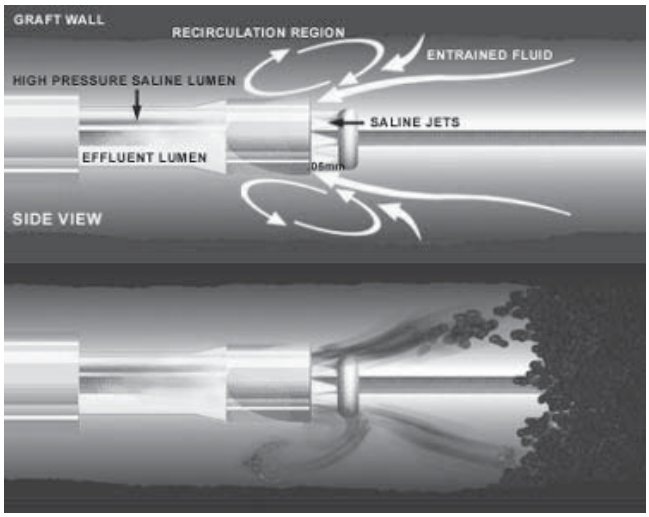


Fig. 3. The AngioJet catheter and its mechanism of action.

infarct size was larger and the 30-day MACE rate higher.[53] It is worth noting that the control arm in this study had higher rates of TIMI 3 flow (complete epicardial perfusion) in the culprit artery before PPCI (63% in the PCI alone group vs 44%; P <0.05), which is associated with smaller infarcts. Also the device was only activated after crossing the lesion which may have promoted embolisation. Despite these limitations, the AngioJet has currently no role in PPCI unless future data indicate otherwise.

Most of the evidence for improving microvascular perfusion lies with simple manual aspiration devices (Table 1). These are quick and easy to use and are comparatively inexpensive. Except for a single study which showed no improvement in myocardial salvage and a greater final infarct size,[54] all other early trials showed that microvascular perfusion was improved although there was no difference in clinical outcomes.[55-57]

Recently, in the largest trial of manual aspiration during PPCI (Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study – TAPAS), 1071 patients were randomised to aspiration group or conventional PCI group.[43] Primary endpoint (MBG of 0 or 1 – absent or minimal myocardial perfusion) occurred in 17.1% of aspiration vs 26.3% in the conventional group (P <0.001). Complete ST-segment resolution occurred in 56.5% (aspiration) and 44.2% (conventional) of patients (P <0.001). It was found that at 30 days, the rate of death was 5.2%, 2.9% and 1.0% (P = 0.003) and the rate of MACE was 14.1%, 8.8% and 4.2% (P <0.001) with MBG 0 or 1, 2 and 3 respectively. Subsequent data at 1 year showed a reduction in cardiac death (3.6% vs 6.7%; HR, 0.52; P = 0.02) and cardiac death or non-fatal reinfarction (5.6% vs 9.9%; HR, 0.55; P = 0.09).[58] Therefore, the beneficial effect on reperfusion at 30 days translated into significant clinical benefits at 1 year. It is important to note that the study was conducted in a single high-volume centre with experienced operators, and the door-to-aspiration time

was remarkably short (28 minutes; interquartile range, 14 to 42 minutes) which was similar to the door-to-balloon time (26 minutes; interquartile range, 12 to 40 minutes) in the conventional arm.[43] These results may therefore not be generalisable to less experienced centres/operators. Another confounding factor is that the majority in the aspiration group had direct stenting whereas the majority in the conventional group had balloon dilatation followed by stenting. Despite these considerations, the magnitude of benefit is impressive and this trial provides compelling evidence for the use of this simple yet inexpensive device in PPCI. Perhaps a multi-centre study will be required to determine if these results could be reproduced in centres with different volumes and operators with varying levels of experience.

Conclusion

Reperfusion therapy for STEMI has been proven to reduce mortality and PPCI has been demonstrated to be superior to thrombolysis. Newer anticoagulants and novel combination of antiplatelet agents appear to further improve the outcomes after PPCI. Although PPCI can achieve high rates of epicardial artery patency, a significant minority of patients experience suboptimal microvascular perfusion, which affects long term prognosis. Several pharmacologic agents have been shown to improve microvascular perfusion, and of the mechanical devices available to reduce distal embolisation, the simple aspiration catheter holds the most promise. Additional research and well designed studies are needed to further enhance outcomes after PPCI.

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