Periprocedural Myocardial Injury during percutaneous coronary intervention: How can it be prevented?

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ABSTRACT

Percutaneous coronary intervention (PCI) has become the predominant procedure for coronary revascularization in patients with both stable and unstable coronary artery disease (CAD). Over the past two decades, technical advances in PCI have resulted in a better and safer therapeutic procedure with minimal procedural complications. However, about 30% of patients undergoing elective PCI sustain myocardial injury arising from the procedure itself, the extent of which is significant enough to carry prognostic importance. The peri-procedural injury which accompanies PCI might therefore reduce some of the beneficial effects of coronary revascularization. The availability of more sensitive serum biomarkers of myocardial injury such as creatine phosphokinase MB isoenzyme (CK-MB) and Troponin I has enabled the quantification of previously undetectable myocardial injury. The identification of CAD patients at greatest risk of sustaining periprocedural myocardial injury (PMI) during PCI would allow targeted treatment with novel therapies capable of limiting the extent of PMI or reducing the number of patients experiencing PMI.

Keywords: Percutaneous coronary intervention, Ischaemia, Reperfusion, Myocardial infarction.

INTRODUCTION

Percutaneous coronary intervention (PCI) has become a standard revascularization procedure for patients with coronary artery disease (CAD). Periprocedural myocardial injury (PMI) occurs in 5-30% of patients after PCI. Guidelines for the universal diagnosis of myocardial infarction (MI) recommend elevation of cardiac biomarkers above the 99th centile upper reference limit (URL) for the confirmation of PMI if a normal baseline troponin value can be assumed. Elevation of more than five times the 99th centile URL is defined as a PCI-related MI (MI type 4a). Indeed outcomes after PCI with very high procedural CK-MB levels (>5×or>8×the upper limit of normal) have prognostic implications similar to those of spontaneous acute MI. Any troponin elevation was associated with a significantly increased

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mortality risk. The most recent meta-analysis applied the universal definition of periprocedural MI (type 4a) using a troponin elevation of $5 \times$ the URL as the cut-off point. It included 7578 patients undergoing non-emergency PCI with normal baseline troponin levels. Troponin elevation occurred in 28.7% of the procedures and the incidence of type 4a MI was 14.5%. Type 4a MI increased the risk of major adverse cardiac events compared with those patients without troponin elevation at an average follow-up of about 17.7 months. Patients with elevation of troponin less than 5 x the URL did not have a worse prognosis during follow-up. The identification of CAD patients at greatest risk of sustaining periprocedural myocardial injury (PMI) during PCI would allow targeted treatment with novel therapies capable of limiting the extent of PMI or reducing the number of patients with PMI.

### Mechanisms of myocardial injury during PCI:

PMI can result from procedural complications such as distal embolisation, side-branch occlusion (SBO), coronary dissection, disruption of collateral flow and silently after uneventful PCI procedures. PMI is classified into two types: Type 1 (proximal type), which is in proximity to the target lesion of PCI and may be due to SBO, and Type 2 (distal type), which is in the perfusion territory of the treated coronary artery and mainly due to structural and functional microvascular obstruction (MVO). Fifty to 75% of all the PMI is Type 2 (distal type).

### Therapeutic strategies to prevent periprocedural myocardial injury:

![Strategies to prevent PMI](image)

**Oral Antiplatelet Agents:**

**Aspirin**

Pretreatment with aspirin before PCI was associated with a decreased incidence and significance of acute coronary thrombosis. Since then a relatively large, prospective study has shown that pretreatment with aspirin compared with placebo significantly reduces the incidence of transmural infarction during or soon after balloon angioplasty (9% vs. 1.6%). The CURRENT OASIS-7 trial performed in patients with acute coronary syndrome (ACS) scheduled for PCI showed no significant difference in ischaemic events or major bleeding when 'standard' dose daily aspirin (300-325 mg) was compared with low-dose aspirin (75-100 mg). If patients are not taking maintenance aspirin or when there is doubt about drug compliance, a loading dose of 500-600 mg orally should be given more than 3 h before PCI.

**Clopidogrel**

Pretreatment with clopidogrel has been shown to provide clinical benefit in patients undergoing PCI for ACS and lack of clopidogrel pretreatment is independently associated with an increased rate of PMI. The ARMYDA-2 trial proved that clopidogrel preloading with 600 mg significantly reduces the rate of periprocedural MI compared with 300 mg (administered 4-8 h before PCI). In the recent CURRENT OASIS-7 trial enrolling patients with ACS undergoing PCI, a loading dose of clopidogrel 600 mg vs. 300 mg followed by 150 mg vs. 75 mg daily for 1 month reduced cardiovascular death, MI and stroke by 15%. This risk reduction comprised a 22% reduction in MI and a 42% reduction in the risk of definite stent thrombosis. Currently the ESC guidelines for PCI recommend early pretreatment with clopidogrel in patients who are scheduled for PCI (300 mg at least 6 h before, or 600 mg at least 2 h before). It is clear that pretreatment with 600 mg is better than 300 mg if PCI is intended in a short timeframe, but in stable elective patients presenting for ad hoc PCI, pretreatment remains debatable as some patients will not proceed to PCI. PRAGUE-8 suggests avoiding pretreatment before coronary angiography as this may save costs and reduce bleeding risk.
Prasugrel and Ticagrelor

The novel thienopyridine, prasugrel, and ticagrelor, a novel non-thienopyridine ADP receptor blocker, have shown promising results compared with clopidogrel in patients with ACS\textsuperscript{12,13} and prasugrel reduced periprocedural MI in patients with ACS (4.9 vs. 6.4%).\textsuperscript{14} As yet there is no evidence that these newer drugs are better in reducing PMI in elective PCI, but as patients with aspirin and/or clopidogrel resistance have worse clinical outcomes\textsuperscript{15,16} these newer antiplatelet agents with their enhanced and more predictable impact on platelet function could be beneficial.

Intravenous Antithrombotic Agents:

Heparins

Unfractionated heparin (UFH) has been used for decades to prevent thrombosis during PCI but there are no placebo-controlled trials specifically examining its effectiveness. An intravenous bolus either under activated clotting time guidance or in a weight-adjusted manner is used.\textsuperscript{7} Disadvantages of UFH include marked variability in bioavailability and as a consequence intravenous low-molecular weight heparin (LMWH) have been tested in the setting of elective or urgent PCI. A meta-analysis of 13 trials including 7318 patients showed that the use of intravenous LMWH during PCI reduces major bleeding but does not affect hard ischaemic end points in comparison with intravenous UFH.\textsuperscript{17}

Bivalirudin

Direct thrombin inhibitors have been established in clinical practice in recent years and offer several advantages over UFH and LMWH (eg, establishing a more predictable anticoagulant response). The ISAR-REACT 3 trial performed in patients with stable and unstable angina who underwent PCI after pretreatment with clopidogrel showed that bivalirudin did not provide a net clinical benefit in comparison with UFH, but it did significantly reduce the incidence of major bleeding.\textsuperscript{18}

Glycoprotein IIb/IIIa antagonists

The final step in the formation of thrombus is the binding of fibrinogen to the platelet glycoprotein IIb/IIIa receptor.\textsuperscript{19} The ISAR-REACT trial enrolled patients undergoing elective PCI, who were loaded with 600 mg of clopidogrel, and found no benefit of additional abciximab.\textsuperscript{20} The ISAR-SWEET study performed in diabetic patients loaded with 600 mg of clopidogrel undergoing elective PCI showed no benefit from additional abciximab.\textsuperscript{21} Before GPls can be discarded in elective PCI several points need to be considered. First, in ISAR-REACT, pretreatment with 600 mg of clopidogrel was done at a median of 7.4 h before PCI and GPls might still have a role if ad hoc PCI is performed in patients without timely and adequate clopidogrel pretreatment.\textsuperscript{22} Second, it is important to note that despite pretreatment with aspirin and clopidogrel significantly lower troponin T release was demonstrated in patients who additionally received GPls.\textsuperscript{23} Similar results were shown for eptifibatide in the CLEAR PLATELETS study.\textsuperscript{24} In summary, discarding GPls in all patients with stable CAD appears to be premature. GPls continue to have a role in patients with ACS and elevated baseline troponin levels and in the case of threatening/actual vessel closure, visible thrombus or no/slow-reflow phenomenon.\textsuperscript{7} Additionally, GPls might have a role in elective patients receiving multiple stents for complex anatomy and those who are not pretreated with clopidogrel at the time of PCI or have clopidogrel resistance. Prasugrel, ticagrelor or other newer more potent oral antiplatelet agents may further reduce the role of GPls in stable patients.

Other Drugs:

Statins

Different retrospective trials and meta-analyses have suggested a reduction of PMI after elective PCI in patients who are pretreated with statins.\textsuperscript{25} The ARMYDA trial clearly demonstrated that pretreatment with 40 mg of atorvastatin for 7 days markedly reduces the risk of PMI in patients who undergo elective PCI.\textsuperscript{26} A recent study clearly demonstrated that a single dose of 80 mg of atorvastatin before PCI reduces the incidence...
of MI type 4a. The ARMYDA-RECAPTURE trial showed that reloading patients who are already receiving statin treatment (application of 80 mg of atorvastatin ≥12 h before the procedure and the application of an additional pre-procedural dose of 40 mg) markedly reduces the primary end point of cardiac death, MI or unplanned revascularisation at 30 days (3.7% vs. 9.4%).

Statins are effective through different mechanisms. Treatment with a statin over 9 months can reduce fibrous-cap thickness of lipid-rich plaques and this may explain why patients receiving chronic statin treatment present differently in ACS and why these patients experience less PMI during PCI. Besides plaque stabilisation, statins can improve endothelial function and have been shown to have anti-inflammatory characteristics and reduce thrombogenic response.

**Calcium Antagonists**

Retrospective studies have suggested that pretreatment with calcium channel blockers reduces the incidence of PMI in patients undergoing elective PCI. Intracoronary nicardipine and verapamil have been successfully used in the treatment of no-reflow following PCI. Pretreatment with intragraft verapamil before PCI of saphenous vein grafts has been shown to reduce the rate of the no-reflow phenomenon but did not reduce PMI.

**β-Blockers**

Benefit from β-receptor blockers in the reduction of myocardial necrosis has been suggested experimentally. Two randomised trials have analysed the role of intracoronary propranolol during PCI. Propranolol significantly reduced CK-MB, troponin T and also clinical end points at 30 days. In a later study intracoronary propranolol administration significantly reduced PMI even in patients who received GPIs during PCI.

**Trimetazidine**

Trimetazidine is a piperazine derivative anti-anginal drug with a vasodilatory effect on coronary arteries and has been extensively studied due to its additional cardioprotective preconditioning properties. The mechanism of cardioprotection by trimetazidine appears to be modulation of mitochondrial homeostasis downstream of the preconditioning pathway. One placebo controlled, randomized, controlled trial involving 266 patients studied a loading dose of 60 mg trimetazidine 30 min before re-canalization. This study showed significant reduction in postprocedural Troponin I levels in the trimetazidine group at all time points and also a significant reduction in the total Troponin I area under the curve.

**Non-Pharmacological Interventions in Prevention of PMI:**

**Myocardial Preconditioning**

Preconditioning using intracoronary administration of adenosine has been shown to decrease myocardial damage caused by elective PCI. The use of nitroglycerin, nicorandil, bradykinin or enalaprilat has shown promising results (eg. reduction of ST segment shift, less chest pain) but reduction of PMI has not yet been demonstrated. Remote preconditioning induced by three 5 min inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5 min intervals of reperfusion, markedly improved the incidence of PMI in a recently published study and could represent an easily applicable tool to further reduce PMI during PCI.

**CONCLUSIONS**

PMI is common after PCI. Periprocedural infarction (MI type 4a) occurs after PCI in at least 10% of cases and has an important impact on long-term prognosis. Measurement of biomarkers to allow assessment of PMI is an important tool for clinical and research purposes. Aspirin, clopidogrel and statins reduce PMI and patients scheduled for PCI should be pretreated with these drugs. LMWH and bivalirudin do not clearly show better ischaemic outcomes than UFH, and the latter continues to be used in many centres during elective PCI. GPIs should be considered in patients who are not pretreated with clopidogrel at the time of PCI, those with suspected or proven clopidogrel resistance or in
patients with complex lesions who are expected to have a high prevalence of PMI. Newer oral antiplatelet agents such as prasugrel and ticagrelor have shown promising results in patients with ACS and future studies will show whether they will become a better alternative to clopidogrel in elective patients. Ischaemic preconditioning may receive more acceptance in the future as it is simple and inexpensive and could be effective.

REFERENCES


