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Periprocedural myocardial injury during elective percutaneous coronary intervention: is it important and how can it be prevented?

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ABSTRACT
Periprocedural myocardial injury (PMI) is common after percutaneous coronary intervention (PCI). Periprocedural infarction (myocardial infarction type 4a) occurs after at least 10% of PCI procedures and has an impact on long-term prognosis. Measurement of biomarkers to allow assessment of PMI is an important tool for clinical and research purposes and should be routine after every PCI (troponin I or T and CK-MB). The importance of oral and intravenous antiplatelet agents and other drugs which have been proven to reduce PMI is discussed.

PERIPROCEDURAL MYOCARDIAL INJURY: MECHANISMS, ASSESSMENT, INCIDENCE AND CLINICAL RELEVANCE

Percutaneous coronary intervention (PCI) has become a standard revascularisation procedure for patients with coronary artery disease (CAD). Remarkable advances have improved its safety and PCI has a central role in the management of patients with both stable and unstable CAD.

Periprocedural myocardial injury (PMI) occurs in 5—30% of patients after PCI[1] and can result from procedural complications such as distal embolisation, side-branch occlusion, coronary dissection and disruption of collateral flow. Importantly, PMI can also occur silently after uneventful PCI procedures. Recently published 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.[2] Elevation of more than three times the 99th centile URL is defined as a PCI-related MI (MI type 4a)[2] (see table 1).

The clinical significance and long-term prognostic impact of PMI was disputed initially. Early, small studies with short follow-up found no increased risk[3] but subsequent large prospective trials have proved that higher elevation of myocardial necrosis markers after PCI are clinically relevant.[4—6] 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.[6—8] More recent studies have suggested that the degree of subsequent risk correlates with the extent of rise of troponin or CK or CK-MB,[9—11] and imaging studies have demonstrated that post-procedural levels of troponin I represent new irreversible myocardial injury on delayed-enhancement MRI.[12] Thus it is

generally agreed that the rate of early and late clinical end points is increased when post-procedural enzyme release reaches levels consistent with MI type 4a.

In patients with lower levels of enzyme elevation (<3× the upper limit of normal) it may be difficult to find evidence of procedural complications and there is persistent debate about whether these enzyme rises are clinically significant.

A large meta-analysis of 23 000 patients with stable or unstable angina undergoing PCI with follow-up for 6—34 months compared patients with normal and elevated post-procedural CK-MB. It showed a dose—response relationship of progressively higher mortality for increasing levels of CK-MB, with even a minor increase of CK-MB 1—3× conferring a relative risk of death of 1.5 (95% CI 1.2 to 1.8).[13]

After the introduction of troponin as a better myocardial biomarker, a large single-centre study of 1949 patients with normal post-PCI CK-MB levels and a median follow-up of 26 months then showed that an isolated elevation of troponin T in patients with normal CK-MB after PCI provides long-term prognostic information about mortality and MI.[14]

Subsequently, a later meta-analysis of 20 studies and 15 581 patients with stable angina undergoing elective PCI showed that overall troponin was raised in 32.9% of patients after an elective PCI. Any troponin elevation was associated with a significantly increased mortality risk (follow-up period 3—67 months; mortality 4.4% vs 3.3%, p=0.001; OR=1.35, 95% CI 1.13 to 1.60).[15]

The most recent meta-analysis applied the universal definition of periprocedural MI (type 4a) using a troponin elevation of 3× the URL as the cut-off point. It included 7578 patients from 15 cohort and registry studies of patients undergoing non-emergency PCI with normal baseline troponin levels. Seven of these studies included patients with unstable angina. Troponin elevation occurred in 28.7% of the procedures and the incidence of type 4a MI was 14.5%. In keeping with previous data, 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 (OR=2.25, 95% CI 1.26 to 4.00, p=0.006). Patients with elevation of troponin less than 3× the URL did not have a worse prognosis during follow-up (OR=1.85, 95% CI 0.80 to 4.28, p=0.15).[16]

It is increasingly clear that higher periprocedural biomarker elevations are most likely to occur in

Table 1 Clinical classification of different types of myocardial infarction (MI)[2]

Type 1	Spontaneous MI related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring or dissection
Type 2	MI secondary to ischaemia due to either increased oxygen demand or decreased supply—for example, coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension or hypotension
Type 3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST-elevation, or new left bundle branch block, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood
Type 4a	MI associated with PCI
Type 4b	MI associated with stent thrombosis as documented by angiography or at autopsy
Type 5	MI associated with coronary artery bypass grafting

patients with higher baseline risk characteristics—that is, those with more advanced disease, complex anatomy and difficult PCI procedures. Thus, part of the mortality risk conferred by periprocedural biomarker elevation is inevitably associated with the patients' higher baseline risk.[17] Nevertheless, it is reasonable to infer that all post-procedural biomarker elevations do reflect direct myocardial injury, with small leaks representing proportionately less injury and thus its prognostic impact—even though present—will be difficult to detect. This relationship between long-term risk and the level of post-procedural biomarker elevation is probably a confluence of the risk imposed by direct injury to the heart and the high-risk baseline patient characteristics.

HOW CAN PERIPROCEDURAL MYOCARDIAL INJURY BE PREVENTED?
Oral antiplatelet agents
Aspirin
Pretreatment with aspirin became clinically established more than two decades ago when a retrospective study showed that antiplatelet therapy administered before PCI was associated with a decreased incidence and significance of acute coronary thrombosis.[18] Since then a relatively large, prospective study has shown that pretreatment with aspirin and dipyridamole compared with placebo significantly reduces the incidence of transmural infarction during or soon after balloon angioplasty (9% vs 1.6%, p=0.0113).[19] Lembo et al then showed that the effect relied fully on aspirin and the addition of dipyridamole did not offer additional benefit.[20]

There are no good data on optimal aspirin dosage but 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, or at least 300 mg intravenously, directly before PCI.[21]

Clopidogrel
Randomised studies have shown a reduction of event rates if combined dual antiplatelet therapy with aspirin and a thienopyridine is established after placement of coronary stents.[22 23]

Pretreatment with clopidogrel has been shown to provide clinical benefit in patients undergoing PCI for ACS,[24 25] and lack of clopidogrel pretreatment is independently associated with an increased rate of PMI[26] and increased hard clinical end points following elective PCI.[27] The CREDO trial failed to show benefit of clopidogrel at 28 days when a loading dose of 300 mg was given at least 3 h before the procedure.[28] The difference in outcomes between placebo and clopidogrel pretreated patients was not significant until >15 h pretreatment, with a 58.8% reduction (p=0.028) in the primary end point in patients pretreated with clopidogrel >15 h compared with placebo.[29]

Driven mainly by the results of the ARMYDA-2 trial,[30] which proved that clopidogrel preloading with 600 mg significantly reduces the rate of periprocedural MI compared with 300 mg (administered 4–8 h before PCI), treatment with 600 mg before the procedure has become clinical routine in many centres. Surprisingly, the PRAGUE-8 trial, which examined the question of whether pretreatment with 600 mg clopidogrel >6 h before scheduled coronary angiography (with optional ad hoc PCI) is better than administration of 600 clopidogrel just before the procedure, failed to show a difference in the rate of periprocedural MI, and patients with clopidogrel pretreatment had an increased risk of minor bleeding complications.[31] Notably, PRAGUE-8 only included patients with stable CAD, whereas in the ARMYDA-2 trial 25% of the patients had a non-ST-elevation ACS. Additionally, 13% of the patients used glycoprotein IIb/IIIa inhibitors (GPIs) in ARMYDA-2 while GPIs were used in only 0.2% and 0.4% respectively of the two groups in PRAGUE-8, confirming the higher risk of the patients in the ARMYDA-2 cohort. In the recent CURRENT OASIS-7 trial (http://www.theheart.org/article/995967.do) 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 European Society of Cardiology 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[32 33] and prasugrel reduced periprocedural MI in patients with ACS (4.9 vs 6.4%, p=0.0002).[34]

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[35 36] these newer antiplatelet agents with their enhanced and more predictable impact on platelet function could be beneficial.

INTRAVENOUS ANTIPLATELET 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.[21] 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.[37] Small, retrospective studies have shown that intravenous enoxaparin reduces PMI compared with heparin,[38] but the effect seems to be minimal.

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 (ie, it did not reduce the incidence of the composite end point of death, MI, urgent target-vessel revascularisation or major bleeding) in comparison with UFH, but it did significantly reduce the incidence of major bleeding.[39] Bivalirudin does not seem to reduce the rate of PMI in comparison with UFH in patients undergoing elective or urgent PCI.[40]

Glycoprotein IIb/IIIa antagonists

The final step in the formation of thrombus is the binding of fibrinogen to the platelet glycoprotein IIb/IIIa receptor. Numerous large randomised controlled trials have shown that the use of GPIs leads to reduced ischaemic events and mortality in patients of different risk categories.[41] [42] However, these studies were performed without clopidogrel pretreatment and were performed in mixed populations with stable and unstable angina and included patients who underwent balloon angioplasty without stenting.

The ISAR-REACT trial enrolled patients at low and intermediate risk undergoing elective PCI, who were loaded with 600 mg of clopidogrel, and found no benefit of additional abciximab.[43] Also, the ISAR-SWEET study performed in diabetic patients loaded with 600 mg of clopidogrel undergoing elective PCI showed no benefit from additional abciximab.[44]

The ISAR-REACT results are particularly notable as 65% of the treated lesions were deemed complex (type B2 or C according to the American Heart Association classification) and there were no crossovers from the non-abciximab to the abciximab group.[43]

Before GPIs 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 GPIs might still have a role if ad hoc PCI is performed in patients without timely and adequate clopidogrel pretreatment.[45]

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 GPIs (troponin T after 24 h was detected in 69% of the patients receiving aspirin and clopidogrel versus 58% of patients receiving additional tirofiban, p<0.05).[46] Similar results were shown for eptifibatide in the CLEAR PLATELETS study.[47] These studies were small and demonstrate possible reduction of PMI but were not powered to demonstrate reduction of hard clinical end points. It is clear that there is variability in the clinical response of patients to clopidogrel and that those patients that do not respond have a higher incidence of cardiovascular events and

death.[48] Interestingly GPI have been shown to improve outcome after coronary stenting in clopidogrel non-responders[49] and in patients who received eptifibatide for PCI,[50] aspirin and clopidogrel treatment did not affect the prevalence of PMI.

In summary, discarding GPIs in all patients with stable CAD appears to be premature. GPIs 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.[21] Additionally, GPIs 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 GPIs in stable patients.

OTHER DRUGS
Statins

Chronic statin treatment has been shown to alter the initial presentation of ACS, leading to less ST elevation MIs.[51] Different retrospective trials and meta-analyses have suggested a reduction of PMI after elective PCI in patients who are pretreated with statins.[52] The ARMYDA trial clearly demonstrated that pretreatment with 40 mg of atorvastatin for 7 days in statin-naïve patients markedly reduces the risk of PMI in patients who undergo elective PCI (peak troponin I levels 0.09±0.2 vs 0.47±1.3 ng/ml, p<0.0008).[53]

Interestingly, a recent study in patients undergoing elective PCI did not confirm a reduction of PMI in patients who received a 2-day pretreatment with 80 mg of atorvastatin.[54] However, another recent study clearly demonstrated that a single dose of 80 mg of atorvastatin before PCI reduces the incidence of MI type 4a,[55] and 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%, p=0.037).[56]

Statins are effective through different mechanisms other than lipid lowering.[57] Treatment with a statin over 9 months can reduce fibrous-cap thickness of lipid-rich plaques[58] 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. These so called pleiotropic effects are not dependent on low-density lipoprotein reduction and probably explain the immediate efficacy of statins in reducing PMI.

β Blockers

Benefit from β-receptor blockers in the reduction of myocardial necrosis has been suggested experimentally[59] and two randomised trials have analysed the role of intracoronary propranolol during PCI.[60] [61] Propranolol significantly reduced CK-MB, troponin T and also clinical end points at 30 days.[60] In a later study intracoronary propranolol administration significantly reduced PMI even in patients who received GPIs during PCI.[61]

Calcium antagonists

Retrospective studies have suggested that pretreatment with calcium channel blockers reduces the incidence of PMI in

patients undergoing elective PCI.[62] Intracoronary nicardipine and verapamil have been successfully used in the treatment of no-reflow following PCI. Administration of intracoronary nicardipine failed to reduce the incidence of PMI in a prospective randomised trial.[63] Also 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.[64]

Myocardial preconditioning

Preconditioning using intracoronary administration of adenosine has been shown to decrease myocardial damage caused by elective PCI.[65] 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 (if confirmed in other trials) could represent an easily applicable tool to further reduce PMI during PCI.[66]

CONCLUSIONS

PMI is common after PCI. Periprocedural infarction (MI type 4a) occurs after at least 10% of PCI procedures 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 and should be routine after every PCI (troponin I or T and CK-MB). Aspirin, clopidogrel and statins reduce PMI and patients scheduled for PCI should be pretreated with these drugs. Absolute timing and dosing regimens remain a matter of discussion but based on current evidence patients scheduled for PCI should at least be pretreated with aspirin, clopidogrel and a statin.

LMWH and bivalirudin do not clearly show better ischaemic outcomes than UFH, and UFH will continue to be used in many centres during elective PCI. Bivalirudin usage will be determined by the operator's perception of the impact of periprocedural bleeding risk. GPIs will continue to be used for bail-out purposes and they 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 simple and inexpensive and could be effective.

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