ANTIPLATELET THERAPY IN PERCUTANEOUS CORONARY INTERVENTION: A REVIEW

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ABSTRACT

The goal of antiplatelet therapy for patients with acute coronary syndromes undergoing percutaneous coronary intervention (PCI) is to reduce the risk of ischaemic events without increasing the risk of bleeding. Aspirin, P2Y12 inhibitor including Clopidogrel and GP IIb/IIIa inhibitors are discussed. Aspirin, the most widely used antiplatelet agent, is effective, safe, and inexpensive and is recommended for all patients undergoing PCI. Clopidogrel, the Thienopyridines agent, has been shown to reduce the rates of adverse cardiac events and mortality when given in a loading dose before PCI and in a maintenance dose thereafter. It has been extensively studied in patients with non–ST-elevation myocardial infarction (NSTEMI), but less so in patients with ST-elevation myocardial infarction (STEMI). Used with PCI, glycoprotein (GP) IIb/IIIa inhibitors reduce the rates of death, myocardial infarction, and urgent target-vessel revascularization in patients with STEMI and NSTEMI. Although GP IIb/IIIa inhibitors are most often used at the time of PCI, early administration in the emergency department or ambulance may improve clinical outcomes. All antiplatelet agents carry a risk of bleeding, which may significantly affect clinical outcomes

Keywords: Antiplatelet agents, percutaneous coronary intervention, acute coronary syndromes, Aspirin, Thienopyridines, Glycoprotein IIb/IIIa inhibitors.

INTRODUCTION

Percutaneous coronary intervention (PCI) in patients with coronary artery disease is on the increase worldwide. During this procedure, trauma commonly occurs to the arterial endothelium that causes the activation and aggregation of platelets. Because platelet aggregation may lead to coronary thrombosis in a patient, antiplatelet agents are essential adjunctive therapies in patients with ACS undergoing PCI. The goal of antiplatelet therapy is to provide maximal protection against thrombosis without increasing the risk of bleeding. Aspirin, Thienopyridines, and glycoprotein (GP) IIb/IIIa inhibitors are the mainstays of antiplatelet therapy in patients undergoing PCI.

Aspirin:

Aspirin irreversibly inhibits cyclo-oxygenase-1, preventing the conversion of arachidonate to thromboxane (TX) A_2; a potent platelet agonist **(1).** This agent reduces the frequency of ischemic complications after PCI by 64 to 77 percent **(2, 3).** Although the minimum effective aspirin dose is not known, doses ranging between 80 and 325 mg are generally given 2 or more hours before PCI. Aspirin- intolerant patients may be treated with Thienopyridines blockers of platelet adenosine diphosphate (ADP) receptors, such as ticlodipine (250 mg twice daily) **(3)** or Clopidogrel (300 mg loading dose followed by 75 mg daily), but these agents should be given earlier than 24 hours prior to elective PCI TO achieve maximum platelet inhibition **(4).** Because the role of aspirin in ACS is well defined and undisputed. The balance of this article will focus primarily on the clinical use of Thienopyridines and GP IIb/IIIa inhibitors, about which questions remain.

Thienopyridines:

Ticlopidine is an oral thienopyridine molecule that requires metabolism in the liver into a biologically active form that irreversibly binds to, and inhibits, the P2Y12 subunit of the platelet ADP receptor. Due to this need for first pass metabolism, when given to healthy volunteers at a standard dose (250mg twice daily), ticlopidine required 3 to 4 days to achieve maximal platelet inhibition **(5).**

In patients undergoing stent implantation, ticlopidine, as an adjunct to aspirin, reduces the frequency of 30 day clinical events, including the occurrence of subacute thrombosis **(6,7).** In a clinical trial of 517 patients at" high risk'' for stent thrombosis after Palmaz-schatz stenting, those treated with aspirin plus ticlopidine experienced a 75 reduction in early complications in comparision to those who received aspirin plus intravenous heparin plus phenprocoumon **(6).** Patients receiving antiplatelet therapy also had an 82 percent lower risk of myocardial infarction and a 78 percent lower need for repeat balloon PTCA than did patients receiving anticoagulation therapy.242 Bleeding complications were also lower in patients treated with antiplatelet therapy **(6).** Clinical events, including subacute thrombosis, were reduced by 85 percent patients treated with aspirin plus ticlopidine **(7).**

However, despite favorable effects on platelets, ticlopidine use is limited by its side effects, which include diarrhea, rash, and agranulocytosis **(8).**

Clopidogrel:

This newer thienopyridine inhibitor of ADP- mediated platelet aggregation has also been used in patients undergoing stent placement **(9, 10).** Clopidogrel is also a prodrug that is converted to its active form by the CYP2C19 enzyme in the liver, with less than 15% of the prodrug being converted to active metabolite **(11).**

Clopidogrel has been shown to be as effective as aspirin in the prevention of ischaemic events in patients at risk **(12).** Because Clopidogrel and aspirin affect distinct pathways in the coagulation cascade, they are most often used in combination, which has been shown to decrease the incidence of ischaemic events by 20% in patients with NSTEMI or UA compared with aspirin alone **(13).** In healthy subjects treated with aspirin plus a loading dose of 300mg Clopidogrel, inhibition of an *ex vivo* model of arterial thrombosis occurs within 1.5 hours, though the peak effect is delayed by 6 hours, consistent with Clopidogrel need to undergo first pass metabolism prior to taking effect **(14).** Pharmacodynamic studies conducted in patients with stable CAD undergoing PCI similarly showed that platelet reactivity remained high 4 hours following a loading dose of 300mg **(15).**

GP IIb/IIIa inhibitors:

Unlike P2Y12 receptor antagonists, which inhibit platelet activation upstream of platelet aggregation, glycoprotein IIb/IIIa receptor antagonists exert their antiplatelet effect via blockade of the glycoprotein IIb/IIIa receptor, which is involved directly in binding fibrin and allows for aggregation of adjacent platelets. First studied in the mid-1990s, these drugs, which include tirofiban, eptifibatide, and abciximab, inhibit platelet aggregation nearly completely within 15 minutes of intravenous bolus, theoretically making them ideal antiplatelet agents for use in PCI **(16).** In contrast, tirofiban and eptifibatide are reversible inhibitors of the glycoprotein IIb/IIIa receptor with short plasma half-lives, with platelet aggregation returning to normal within 4 hours of cessation of an infusion **(17).**

Antiplatelet therapy in percutaneous coronary intervention for ST-elevation myocardial infarction

Primary percutaneous coronary intervention:

Percutaneous coronary intervention, usually with stenting, performed within 90 min of first medical contact, is the treatment of choice for most patients presenting with STEMI **(18).** Antiplatelet therapy is used before, during, and after PCI to reduce the risk of peri-procedural and post-procedural ischaemic events **(19).**

Aspirin:

The benefits of antiplatelet drugs in patients with STEMI were first conclusively demonstrated in the Second International Study of Infarct Survival (ISIS-2) trial which randomized 17187 patients presenting within 24 hours of onset of suspected STEMI to intravenous streptokinase, aspirin 162.5 mg/day for 30 days, both, or neither **(20).**

At the end of 5 weeks, aspirin reduced the risk of vascular death by 23% and non-fatal myocardial infarction or stroke by 49% and 46%, respectively, with no increase in major or intracranial bleeding. Despite

the use of aspirin and thrombolytic; however, 20% of STEMI patients did not obtain reperfusion of the infarct-related artery, and an additional 4%–6% of patients developed re-occlusion of the infarct-related artery during the index hospitalization **(21).** Furthermore, as many as 10% of patients with acute coronary syndromes (ACS) who are treated with long-term aspirin experience myocardial infarction, stroke, or death during the next 2–3 years **(22).**

Thienopyridines:

Clopidogrel as a potent antiplatelet agent is administered in patients with ST elevation myocardial infarction (STEMI). In the CLARITY trial, the benefit of Clopidogrel plus aspirin for prevention of cardiovascular events after stenting was extended to patients with STEMI **(23, 24).** In CLARITY, patients with STEMI treated with Fibrinolytic received Clopidogrel (300mg loading dose, followed by 75mg daily) or placebo, prior to undergoing coronary angiography 2 to 8 days (median 3 days) after presentation **(23).**

The CLARITY study included 1863 patients with STEMI who underwent PCI after Fibrinolytic **(25).** In the Clopidogrel group, there was a 46% reduction in the 30-day rate of cardiovascular death, recurrent MI, or stroke compared with the placebo group (P = 0.008). Clopidogrel treatment improved outcomes consistently whether PCI was performed on an urgent or elective basis and regardless of the time from drug initiation until the procedure. The ideal duration of Clopidogrel treatment after PCI for STEMI is unknown, but is influenced by the type of stent placed and the patient's risk for bleeding **(26).**

GP IIb/IIIa inhibitors:

Of the three available GP IIb/IIIa inhibitors, only abciximab has been extensively studied in patients with STEMI undergoing primary PCI. In a meta-analysis comparing glycoprotein IIb/IIIa inhibitors to placebo or usual care in patients undergoing PCI, use of glycoprotein IIb/IIIa inhibitors significantly reduced 30-day mortality by 21% (0.92% vs. 1.33%, RR 0.79, 95% CI 0.64–0.97), and a combined endpoint of death or recurrent MI by 34% (5.05% vs. 7.04%, RR 0.66, 95% CI 0.60–0.72) **(27).**

The efficacy of tirofiban in ST-segment elevation myocardial infarction (STEMI) has been demonstrated when administered in patients being managed with primary percutaneous coronary intervention (PCI).

These trials primarily studied tirofiban utilizing the high-dose bolus regimen (25 μg/kg bolus followed by a maintenance infusion of 0.15 mg/kg/min for 18–24 hours). The On-TIME (Ongoing Tirofiban in Myocardial Infarction Evaluation) 2 trial assessed early administration of the high-dose bolus regimen of tirofiban either at the referral centre or in the ambulance, in patients being transferred to a primary PCI centre. Early use of tirofiban resulted in both a significant increase in the rate of complete resolution of ST-segment deviation pre- and post-PCI, and improvement in clinical outcomes at 30 days.

In a study of 4010 patients with ACS undergoing revascularization, eptifibatide treatment failed to demonstrate a significant improvement over placebo in the composite endpoint of death, MI, or urgent revascularization at 30 days **(28).** Overall, treatment of 1000 patients with glycoprotein IIb/IIIa inhibitors would prevent 20 non-fatal MIs and 4 deaths at a cause of 8 excess bleeding events) **(27).**

Guideline recommendations for antiplatelet therapy for percutaneous coronary intervention in ST-elevation myocardial infarction:

Current clinical guidelines call for administration of aspirin to all patients with STEMI as soon as possible after diagnosis is made **(29).** Patients already on daily aspirin therapy should be 75-325 mf of aspirin before PCI; those not taking aspirin should be given 500 mg at least 3 hours before procedure or 300 mg intravenous immediately before the procedure (29). After PCI aspirin should be continued at 75-150 mg daily indefinitely **(30)**.

Clopidogrel should be administered in a loading dose of 300 mg at least 6 hours before PCI of if not possible in a loading dose of 600 mg at least 2 hours before **(29).**

Currently, the European Society of Cardiology recommends aspirin (a 300 mg loading dose and a 75–100 mg maintenance dose) in non-ST-segment elevation acute coronary syndrome (NSTEACS) patients receiving both conservative and interventional treatment (**34, 35).**

Collaborative meta-analysis showed reduced risk of cardiovascular death, myocardial infarction, and stroke by 46% in NSTEACS patients (from 13.3 to 8.0%) **(36).** The Clopidogrel in Unstable angina to prevent Recurrent ischaemic Events (CURE) study involving 12 562 patients evaluated the efficacy of Clopidogrel combined with aspirin in NSTEACS patients. The loading dose of Clopidogrel 300 mg, followed by maintenance doses for a mean of 9 months, reduced significantly the combined endpoint (cardiovascular death, non-fatal myocardial infarction, and stroke) from 11.4 to 9.3%, RR = 0.8, $P < 0.001$ as compared with placebo. There was also a significant reduction of recurrent ischemia during hospitalization among patients receiving Clopidogrel with the benefit showing within the first hours of enrolment **(37).** Moreover, patients undergoing PCI (PCI-CURE) also benefited from Clopidogrel **(38).** However, the use of Clopidogrel was associated with increased major (3.7 vs. 2.7%, $P = 0.02$) and minor (5.1 vs. 2.4%, $P < 0.001$) bleeding rates as compared with placebo.

Recent studies have shown that Clopidogrel in the standard loading dose (300 mg) may be insufficient to achieve early and more profound antiplatelet effect. In the Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty (ARMYDA-2) study, the use of a 600 mg loading dose of Clopidogrel 4–8 h prior to planned PCI was associated with a reduction of the composite endpoint (death/myocardial infarction/target vessel revascularization) within 30 days as compared with the standard loading dose (high vs. standard loading dose; 4 vs. 12%, $P = 0.041$). This favorable effect was associated mainly with reduction in risk of periprocedure myocardial infarction **(39).**The current European Society of Cardiology guidelines recommend GPIIb/IIIa inhibitors, especially in NSTEACS patients at high risk of thrombotic complications **(40).**The therapeutic outcome was most pronounced in high-risk patients including those with positive Troponin levels and patients undergoing PCI. Roffi *et al* **(41).** In a similar group of patients showed a significant reduction of 30-day mortality after the use of GPIIb/IIIa inhibitors in patients with NSTEACS and diabetes mellitus (30-day mortality: GPIIb/IIIa inhibitor vs. placebo, 6.2 vs. 4.6%, OR 0.74, $P = 0.007$; including patients undergoing PCI 4.0 vs. 1.2%, OR 0.3, $P = 0.002$). The National Registry of Myocardial Infarction confirms these findings **(42).**

Guideline recommendations for antiplatelet therapy for percutaneous coronary intervention in non–ST-elevation myocardial infarction:

Guidelines recommended aspirin for all patients with NSTE-ACS without contraindication in a loading dose of 160-325 mg (non enteric) and in a long term maintenances dose of 75-100 mg/day. Clopidogrel should be given of loading dose 600 mg followed by 75 mg/day for 12 months.

CONCLUSION

The Antiplatelet therapies inhibiting the platelets activities and prevent the thrombotic events following stent implantation. However significant question still exists regarding the optimal antiplatelet strategy. Increased potency of antiplatelet effects is associated with an increased bleeding risk, particularly in vulnerable population like the elderly and those in prior stroke or transient ischemic attack. It remains unclear whether pretreatment is beneficial in patients undergoing PCI. Genotype or platelet reactivity testing has not been proved to be beneficial. As PCI continue to evolve, these issues will be important to resolve in order to improve the outcome.

Conflicts of Interest:

There authors have no Conflicts of interest to declare.

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