Anti-platelet therapy for Acute Coronary Syndrome
(Aspirin, Clopidogrel, Prasugrel, Ticagrelor and what next?)

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INTRODUCTION

The term ‘Acute Coronary Syndrome’ (ACS) refers to a range of acute myocardial ischaemic states which include unstable angina, non ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI). Despite significant advances in the diagnosis and management, ACS remains a significant global problem with very high mortality and morbidity. The pathogenetic process central to the initiation of an ACS is disruption/fissuring of an atheromatous plaque and consequent exposure of core constituents such as lipid, smooth muscle, and foam cells, leading to the local generation of thrombin and deposition of fibrin. This in turn promotes platelet aggregation and adhesion and the formation of intracoronary thrombus.

Significant advances in the management of ACS are happening on an on-going basis. After the advent of coronary angioplasty (in 1977) and subsequent development of stenting techniques, the focus of attention moved significantly towards the restoration of epicardial coronary arterial patency as the mainstay of the management strategy during 1990s. Lately however, it has been recognized that although this is still necessary but by no means is the only goal in ACS management.

Increasing recognition of the crucial role played by platelets in the pathogenesis of ACS and the limitations in the clinical efficacy of Aspirin as the sole anti-platelet agent, attracted much wider attention for the research. As a result anti-platelet therapy gradually evolved as a cornerstone of ACS management and several new anti-platelet agents were introduced in the market over the last few years. Moreover using a combination of 2 or more anti-platelet agents (dual or triple anti-platelet therapy) is increasingly being utilized in the management of ACS.

Given the expanding number of anti-platelet agents available clinicians have to make difficult decisions about the choices, dosage, combination and timing of these agents. Selecting the right drug(s), at the right time, for the right patient with a careful assessment of the risk of bleeding and adverse events is crucial.

PLATELETS AND PRIMARY HAEMOSTASIS

Blood platelets are formed from megakaryocytes in bone marrow. They are the smallest corpuscular component in the circulating blood with a diameter of 2-3 µm in the resting stage. They do not have a cell nucleus and as anucleate cells they lack genomic DNA but contain megakaryocyte-derived messenger RNA (mRNA) and the translational machinery needed for protein synthesis. In the resting phase platelets have a discoid shape with an average surface area of 8µm². Activation of platelets leads to a significant change in their size and shape with formation of pseudopods due to protrusions of the plasma membrane and thus increasing surface area to as much as 13µm².

Platelet count in the peripheral blood is normally between 150,000 and 450,000 per µL (microlitre) of blood (150-450 x 10⁹/L). Their average physiological life span in the peripheral blood stream is about 7 (5 to 9) days with a daily renewal rate of about 20% of the total platelet count. Degradation of platelets occurs in the reticulo-endothelial...
system and old platelets are destroyed by phagocytosis in the spleen and by Kupffer cells in the liver. Around one third of the platelets are stored in the spleen and released in the circulation when necessary.

**Activation of platelets**
Platelet activation is a series of cascading responses which allow blood platelets to react to an injury in the vessel wall in order to achieve adequate haemostasis. Platelets are essential for primary haemostasis and repair of the endothelium, but they also play a key role in the development of thrombus and acute coronary syndromes.

The initial event in thrombus formation is the adherence of platelets to the disrupted surface of the plaque via the glycoprotein (GP) Ib receptor and von Willebrand factor (vWF). Adherent platelets become activated and degranulate, resulting in the release of substrates like serotonin, ADP, thromboxane A₂, platelet factor-4, P-selectin, vWF, plasminogen activator inhibitor-1, and fibrinogen. These mediators amplify and sustain the initial platelet response, and they recruit circulating platelets from the flowing blood to form a growing haemostatic plug. This results in further reduction of blood flow through local vasoconstriction in addition to the developing thrombus.

The final common pathway for all agonists is the activation of the platelet integrin glycoprotein IIb/IIIa (α₂β₃), the main receptor for adhesion and aggregation. The process of activation involves changes to the shape of the platelet, as well as conformational changes to the GP IIb/IIIa receptors on its surface that are responsible for platelet aggregation. The change to the GP IIb/IIIa receptors results in the exposure of binding sites on the receptors for the circulating protein fibrinogen. By binding to active GP IIb/IIIa receptors, fibrinogen cross-links GP IIb/IIIa receptors on adjacent activated platelets, resulting in platelet aggregation, which is referred to as white thrombus. Through activation of the coagulation cascade that triggers the activity of thrombin, fibrinogen is converted to fibrin threads, which further stabilize the thrombus and is called red thrombus.

**Endothelial cells** convert arachidonic acid into prostacyclin with the help of cyclooxygenase-1 or cyclooxygenase-2 (COX-1 or COX-2) and prostacyclin synthase. Prostacyclin is a vasodilator that inhibits platelet activation in response to a variety of agonists. Prostacyclin modulates platelet-vascular interactions and, specifically, limits the response to thromboxane A₂.

**Risk Stratification and Choice of anti-platelet therapy in the management of patients with ACS**

**Risk Stratification (TIMI or GRACE risk Scoring):** The choice of anti-platelet therapy and optimal management of patients diagnosed with NSTE-ACS is crucially dependent upon an ongoing risk evaluation of these patients. Distinct patient characteristics including age, diabetes and renal insufficiency, cardiac biomarkers, and specific ECG findings have been linked with an increased rate of ischaemic events. This risk stratification can be done more objectively using a formalized risk assessment tool such as:

1. the Thrombolysis In Myocardial Infarction (TIMI) Risk Score⁷ or
2. the Global Registry of Acute Coronary Events (GRACE) Risk Score ⁸

**Guidelines for the management of ACS:** The management of patients with ACS is extremely complex given the choices available not just about pharmacotherapy but also about coronary interventional procedures. Formal risk stratification of these patients and use of any internationally recognised guidelines such as ACC/AHA, ESC, and NICE is highly recommended in order to simplify decision making, achieve optimal outcomes and avoid serious bleeding complications.

**Choice of anti-platelet therapy:** i.e. which particular agent/s to chose, number of agents used (dual/triple therapy), mode of therapy (oral/Intravenous), and the duration of treatment with individual agents will crucially depend upon:

1. Patient characteristics (Age, body weight)
2. Risk Factors profile (presence of diabetes, renal insufficiency, previous stroke/TIA)
3. TIMI / GRACE Risk Stratification of ACS
4. Choice of Early invasive vs. Conservative management
5. Choice of Coronary interventional procedures (Coronary Angioplasty vs. CABG)
6. Choice of intracoronary stents (Drug Eluting vs. Bare Metal Stents)
7. Choice of Thrombolysis vs. Primary PCI in patient with ST Elevation MI
Mechanisms of actions for Anti-platelet agents and Choosing optimal Anti-platelet therapy in ACS

Table I. Anti-platelet Medications

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<tr>
<th>Mechanism of Action</th>
<th>Anti-platelet Agents</th>
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<tr>
<td>A. TXA2 Inhibitor</td>
<td>Aspirin</td>
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<tr>
<td>B. ADP / P2Y12 Blockers</td>
<td>Ticlopidine, Clopidogrel, Prasugrel, Ticagrelor</td>
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<tr>
<td>C. GP IIb / IIIa Inhibitors</td>
<td>Abciximab, Eptifibatide, Tirofiban</td>
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<tr>
<td>D. PAR - 1 Antagonists</td>
<td>Under development</td>
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(A) Cox-1 / Thromboxane A2 Inhibitor - Aspirin:
Aspirin acts promptly to irreversibly inactivate cyclooxygenase (COX-1) activity and inhibit the conversion of arachidonic acid to prostaglandin H₂ (PGH₂) and formation of thromboxane (TXA₂), which is a potent inducer of platelet aggregation and vasoconstriction.

Aspirin has been demonstrated to be effective across the entire range of ACS. A meta-analysis of a subgroup of patients with NSTE-ACS in the Antithrombotic Trialists Collaboration, a 46% reduction in vascular events was observed with Aspirin. Similarly in STEMI, the ISIS-2 study showed significant reduction in mortality by Aspirin.

(B) ADP and P2Y12 blockers (Clopidogrel, Prasugrel, Ticagrelor)
The interaction of ADP with its platelet P2Y12 receptor is essential for platelet activation. ADP is stored in and secreted from dense granules in platelets and amplifies the response to other agonists, thereby contributing to the growth and stability of a thrombus. These ADP receptor antagonists inhibit the adenosine diphosphate (ADP) pathway by specifically blocking the platelet ADP receptor P2Y12. In contrast to aspirin, which inhibits the production of thromboxane A2 by platelets virtually completely, ticlopidine and clopidogrel inhibit ADP-induced platelet aggregation only incompletely and variably.⁶

(i) Ticlopidine: was the first of the thienopyridine class, but it is no longer used in contemporary clinical practice.

(ii) Clopidogrel: Clopidogrel is an oral pro-drug requiring metabolism by the hepatic cytochrome P450 enzyme system to generate active metabolite. Following the publication of trials like CURE¹² and its sub-study PCI-CURE¹³ in 2001 and subsequent recommendations by ACC/AHA⁹ as well as ESC¹⁰, the use of Clopidogrel in addition to Aspirin (dual anti-platelet therapy) became standard form of treatment in the management of NSTE-ACS and STEMI, specifically those undergoing PCI.

Over the last few years, Clopidogrel resistance is emerging as a clinical entity with potentially serious consequences like stent thrombosis. The mechanism of resistance remains incompletely defined, but there may be clinical, cellular, metabolic and genetic factors that influence therapeutic failure with Clopidogrel.¹⁴

(iii) Prasugrel: is a newer ADP receptor blocker and has been shown to be more effective than Clopidogrel in a recent TRITON TIMI 38 Trial comparing Prasugrel with Clopidogrel in ACS ¹⁵. An excess of major bleeding was seen in patients over 75 years, those <60 kg in weight, and those with previous TIA/stroke and hence Prasugrel is not indicated in those subgroups of patients.

Prasugrel is also a pro-drug requiring hepatic cytochrome-dependent metabolism for activity; but unlike clopidogrel, it requires a single rather than a multiple-step process for activation, giving it a more predictable efficacy in platelet inhibition. NICE Guidelines in the UK recommend use of Prasugrel (in place of Clopidogrel) in patients undergoing Primary PCI for STEMI, as well as NSTE-ACS patients presenting with stent thrombosis during Clopidogrel treatment or with diabetes mellitus ¹¹.

(iv) Ticagrelor: is the latest ADP - P2Y12 receptor antagonists and the first member of a new class of cyclopentyltriazolopyrimidines (not a thienopyridine). It does not require conversion to the active metabolite to express its anti-platelet action and therefore has a faster, greater and more consistent P2Y12 inhibition than clopidogrel. Moreover, the ADP-P2Y12 receptor blockade induced is reversible, which may be valuable in case of bleeding complications. It however requires twice daily dosing.

In the recently published PLATO trial, ticagrelor has been shown to be more effective than clopidogrel in patients with ACS without increase in the rate of overall major bleeding (16). Ticagrelor is currently undergoing approval process in the US and UK and still not available for commercial use.
**C. Glycoprotein IIb/IIIa receptor inhibitors**

GP IIb/IIIa receptor inhibitors are the most potent inhibitors of platelet activity as they selectively and comprehensively block the receptors necessary for the final common pathway of platelet aggregation. Because GP IIb/IIIa inhibitors do not block Thromboxane A2 production from the activated platelets, concomitant use of Aspirin may still enhance their anti-thrombotic activity and is clinically recommended.

There are three agents currently available in this class, namely: abciximab, eptifibatide, and tirofiban. They have different molecular structures and slight difference in reversibility and duration of actions as shown in Table - II.

These are very powerful anti-platelet agents and are used intra-venously (in addition to oral Aspirin and Clopidogrel or Prasugrel, thus making it a triple anti-platelet therapy) during acute management of high risk patients with NSTE-ACS or STEMI planned for an early invasive strategy. ACC/AHA 9 as well as ESC 10 guidelines, recommend use of GP IIb/IIIa inhibitors within the first 24 hours of presentation, who have elevated troponins, ST-segment depression, or diabetes mainly as an adjunct to PCI procedures.

**D. Thrombin and PAR1 antagonists**

Thrombin is rapidly generated at sites of vascular injury and, in addition to cleaving fibrinogen, it is a very effective platelet activator. Moreover, thrombin induces procoagulant activity on the platelet surface, which supports additional thrombin generation. Platelet responses to thrombin are largely mediated through G-protein-coupled protease-activated receptors (PARs) that convert an extracellular proteolytic cleavage event into a transmembrane signal. Platelets in humans express PAR1 and PAR4 receptors 17. PAR1 antagonists are currently being developed for the prevention and treatment of atherothrombosis 18.

However we have already got extremely powerful anti-platelet agents available for our clinical practice and their use in combination may effectively produce Inhibition of Platelet Activity (IPA) to a very high level. It is always a risk that further enhancement of anti-platelet activity may be associated with increased risks of bleeding complications and may become counterproductive. Consequently, the major challenge for clinicians and the pharmaceutical industry is to find the right balance of optimal efficacy and safety for future anti-platelet drugs and their combinations.

Other very important area of future development will be to address Inter-individual variability in therapeutic response to anti-platelet agents i.e., the problem of drug resistance. Recent advances in the pharmaco-genetics of thienopyridines open the realistic prospect of a personalized choice of the most appropriate anti-platelet agent and tailored dose adjustment for an individual patient.

**FUTURE DIRECTIONS / WHAT NEXT**

There are several anti-platelet agents in the pipeline undergoing development and testing and some will surely appear in the clinical horizon in near future. Race is on to utilise different mechanisms of platelet activation and aggregation to produce newer anti-platelet medications like thrombin-receptor antagonists, monoclonal antibodies against platelet glycoprotein Ib and glycoprotein VI, antagonists of vWF, orally active GP IIb/IIIa inhibitors as well as Intravenous ADP receptor antagonists like Cangrelor, only to mention a few. The regulation of platelet responses mediated by signalling to megakaryocytes and the alteration of the functions of these progenitor cells in vascular disease also appear to be biologically plausible and under investigations 19. Moreover previously unrecognized signal-dependent pre-mRNA splicing, translation of constitutively expressed mRNA and post-transcriptional pathways are also potential targets for molecular intervention in atherothrombosis 20.

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**CONCLUSION**

An effective anti-platelet therapy is of utmost importance for the acute therapy and for secondary prevention in patients with acute coronary syndrome. Dual anti-platelet

| Table II. Glycoprotein IIb / IIIa Receptor Inhibitors |
|---------------------------------------------|-----------------|-----------------|
| Molecular Structure                        | Abciximab       | Eptifibatide    |
| Reversibility                             | Monoclonal Antibody | Synthetic Peptide |
| Duration of anti-platelet effect           | For life of platelet | 4 hours after discontinuation |
| Half-life                                 | 10-30 minutes | 2.5 hours | 2 hours |

| Reversibility                             | No              | Yes             | Yes              |

| Duration of anti-platelet effect           | For life of platelet | 4 hours after discontinuation |

| Half-life                                 | 10-30 minutes | 2.5 hours | 2 hours |

[Table II. Glycoprotein IIb / IIIa Receptor Inhibitors]
therapy (like Aspirin and Clopidogrel) is now routinely used for a year after initial presentation with ACS. Triple anti-platelet therapy (like Aspirin, Clopidogrel/Prasugrel and an intravenous GP IIb/IIIa inhibitors), is also increasingly being used in patients with higher risk NSTE-ACS or STEMI, who are planned for early invasive strategy. Such use however should be strictly limited to carefully chosen patients according to international guidelines and administered under proper clinical supervision to avoid serious bleeding complications. Future advances may be highly desirable in developing relevant tests and protocols to find a personalised most appropriate anti-platelet medication/s for a particular patient, to address the current problem of drug resistance seen with a particular medication in some patients and excessive bleeding in others.

REFERENCES

15. TRITON-TIMI 38 Investigator: Prasugrel versus Clopidogrel in patients with Acute Coronary Syndromes; NEJM 2007;357:2001-15