Antiplatelet therapy in acute coronary syndromes

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Pathophysiology

Acute coronary syndrome (ACS) is an epiphenomenon of atherothrombosis encompassing a heterogeneous group of clinical presentations.[1] When atherosclerotic plaques rupture, core contents come into contact with flowing blood and platelets undergo shape change, degranulation, activation and aggregation with fibrin cross-linking. The resulting size of thrombus determines the degree of ischaemia and myocardial damage. Platelets thus play a pivotal role in the genesis of, and outcome from, ACS.[2]

Clinical presentation

The continuum of ACS comprises three clinical entities:

1 *Unstable angina*, characterised by chest discomfort often, but not always, with ST-segment and T-wave changes on ECG but undetectable cardiac biomarkers.
2 *Non-ST-segment elevation myocardial infarction* (NSTEMI), as above but characterised by raised cardiac biomarkers.
3 *ST-segment elevation myocardial infarction* (STEMI): ST-segment elevation on ECG accompanied by raised cardiac biomarkers – a result of complete thrombotic coronary occlusion with extensive myocardial necrosis.

Antiplatelet agents

Three antiplatelet agents are most commonly used.

Aspirin

Aspirin inactivates platelet isoenzyme cyclooxygenase-1 (COX-1) (Fig 1) leading to suppression of thromboxane production, a potent platelet activator.[3] Platelets are anucleate and thus unable to resynthesise COX-1, so this action is irreversible. Platelet life span is approximately 10 days with fresh platelets continuously released into the bloodstream; daily dosing of aspirin is essential to optimise efficacy.[4]

Laboratory studies confirm aspirin to be effective in reducing thrombus burden and embolisation after deep arterial injury.[5] Benefits are replicated in clinical studies with low-dose aspirin (75–150 mg daily), the cornerstone of secondary prevention in ACS.[6] Aspirin use following STEMI results in a 9% reduction in cardiovascular mortality and is additive to the effect of thrombolytic therapy.[7]

A meta-analysis of antiplatelet trials by the Antithrombotic Trialists' Collaboration found doses of 75–150 mg to be optimal. Higher doses (500–1,500 mg daily) caused increased adverse effects with no added benefit.[8] Importantly, benefit is sustained with aspirin continuation, therefore therapy should be lifelong.

In summary, early use of low-dose aspirin is mandatory in patients presenting with suspected ACS, irrespective of the clinical presentation and levels of cardiac enzymes. Once ACS is confirmed, aspirin therapy should be (wherever possible) lifelong.

Thienopyridines

Clopidogrel and ticlopidine induce irreversible alterations of the platelet receptor $P2Y_{12}$ – a receptor for adenine nucleotides (Fig 1). This mediates inhibition of stimulated adenylcyclase activity by adenosine diphosphate leading to inhibition of platelet aggregation. Thienopyridines target different platelet receptors to aspirin so can be expected to have additive effects. Ticlopidine is associated with neutropenia and thrombocytopenia and has been superseded by clopidogrel.

Dual therapy with aspirin and thienopyridines

In the Clopidogrel in Unstable angina to prevent Recurrent ischaemic Events (CURE) study, combined therapy with clopidogrel and aspirin in ACS significantly reduced cardiovascular end-points (11.4% to 9.3%, relative risk (RR) 0.80, 95% confidence interval (CI) 0.72–0.90, $p<0.001$).[9] Dual therapy was associated with fewer cardiovascular events in patients undergoing percutaneous coronary intervention (PCI).[10]

The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) evaluated combined aspirin and clopido-

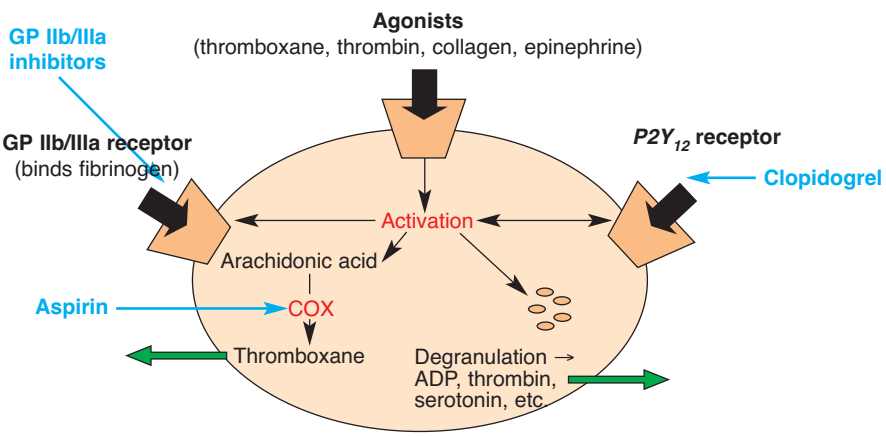

Fig 1. Schematic diagram of platelet activation pathways with sites of action of antiplatelet agents. COX = cyclooxygenase; GP = glycoprotein.

grel treatment versus aspirin following STEMI. Addition of clopidogrel produced a 9% proportional reduction in death, reinfarction or stroke (9.2% *v* 10.1%, p=0.002), corresponding to nine fewer events per 1,000 patients treated.[11] The mechanism for this benefit may be improved patency rates of infarct-related arteries resulting in reduced ischaemic complications.[12]

In summary, dual antiplatelet therapy (clopidogrel and aspirin) is recommended in unstable angina and NSTEMI. Contemporary evidence suggests significant benefit following STEMI.

Guidelines for dual therapy

The European Society of Cardiology recommends dual therapy for:[1]

- all patients with unstable angina and NSTEMI, with treatment to continue for at least 9–12 months
- all patients scheduled for angiography, unless there is a likelihood that the patient will proceed to urgent surgery (within five days)
- all patients receiving intracoronary stents
- patients intolerant of aspirin.

The National Institute for Health and Clinical Excellence (NICE) recommends dual therapy for all patients after NSTEMI for up to 12 months, but discontinuation thereafter.[13]

The guidelines predate publication of the COMMIT trial and do not address clopidogrel therapy in STEMI. We believe that current evidence supports the use of dual antiplatelet therapy acutely and for up to four weeks after STEMI.

Glycoprotein IIb/IIIa receptor inhibitors

Activated platelets expose multiple glycoprotein (GP) IIb/IIIa receptors on their surface.[14] These receptors bind fibrinogen and form bridges between activated platelets.[14] This is the final common pathway of platelet aggregation so GP inhibitors (GPIs) block platelet-dependent thrombus irrespective of the pathway responsible for its initiation. Several GPI agents are available and four intravenous (iv) preparations have been studied in ACS:[15]

1 *Abciximab*: a monoclonal antibody, a non-specific blocker with tight receptor binding causing slow reversibility of platelet inhibition.
2 *Eptifibatide*: a cyclic peptide with a short half-life which selectively inhibits GP IIb/IIIa receptors.
3 *Tirofiban*: a small non-peptide antagonist which causes rapid (5 min) selective blockade of receptors; its effect is reversible (4–6 hours).
4 *Lamifiban*: a synthetic, non-peptide selective receptor blocker with a half-life of four hours.

Unstable angina and NSTEMI

There is an absolute treatment benefit of early GPI therapy in unstable angina and NSTEMI, additional to the effects of aspirin and heparin use. A meta-analysis of six trials found a 9% reduction in death or myocardial infarction at 30 days (10.8% *v* 11.8%, odds ratio (OR) 0.91, 95% CI 0.84-0.98, p=0·015) (Fig 2).[15] Most benefit was observed in patients with raised troponin concentrations and/or undergoing PCI. The benefit of upstream use is restricted to small molecule GPIs (tirofiban, eptifibatide, lamifiban) whereas the benefit following abciximab is restricted to patients undergoing PCI.[16]

STEMI

There is no mortality benefit with GPI as adjunct to thrombolytic therapy in STEMI. Trials demonstrated a lower rate of inhospital reinfarction after STEMI but this was offset by increased non-cerebral bleeding.[17] As an adjunct to primary PCI, the use of abciximab is limited to high-risk cases.

Percutaneous coronary intervention

The benefit of GPI has been established during primary PCI, as shown in a cumulative analysis of GPI trials. Overall 30-day mortality was significantly reduced (OR 0.73, 95% CI 0.55–0.96, p=0.024), with evidence of benefit preservation to six months.[18] Oral GPIs have shown no benefit in ACS, possibly due to their marked variability in platelet inhibition.[19]

Guidelines for glycoprotein receptor inhibitor therapy

The European Society of Cardiology recommends GPI therapy for:[1]

- patients with NSTEMI undergoing PCI
- patients with unstable angina who are at 'high-risk' (Table 1) and scheduled for early angiography and/or revascularisation.

Routine use in STEMI is not recommended.

NICE recommends GPI administration for all unstable angina or NSTEMI patients, even if PCI is not planned[16] (these agents must be initiated as soon as 'high-risk' status is determined, even before knowledge of troponin levels). GPI use is not licensed in the UK as adjunct to thrombolytic therapy.

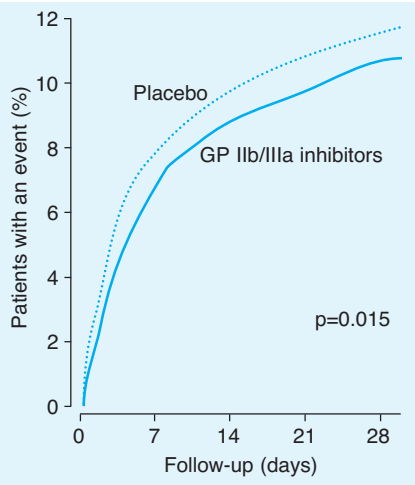

Fig 2. Kaplan-Meier estimates of cumulative occurrence of death or myocardial infarction within 30 days of randomisation to glycoprotein (GP) IIb/IIIa inhibitors or placebo (from a meta-analysis of six trials in acute coronary syndromes). Reprinted with permission from Elsevier.[15]

Antiplatelet therapy in high-risk populations

Diabetes mellitus

Meta-analysis suggests that the benefit of aspirin is limited in diabetes mellitus. Aspirin was associated with a non-significant 7% reduction in vascular events – approximately one-quarter of the observed benefit in the overall population.[8]

Patients with diabetes may derive particular benefit from GPI. A meta-analysis found that the subgroup with diabetes had significant 30-day mortality reduction (6.2–4.6%, RR 0.74, 95% CI 0.59–0.92, p=0.007).[20] Furthermore, the interaction between GPI treatment and diabetic status was significant (p=0.036).[20]

Patients on anticoagulants and elderly subjects

These patients should be treated with antiplatelet agents as above. However, bleeding risk in individual patients must be evaluated.[21]

Increased bleeding risk with antiplatelet agents

Meta-analysis of bleeding risk with low-dose aspirin (75–325 mg daily) shows increased risk of major bleeding (RR 1.71, 95% CI 1.41–2.08), including major gastrointestinal (GI) (RR 2.07, 95% CI 1.61–2.66) and intracranial bleeding (RR 1.65, 95% CI 1.06–5.99).[22] However, the absolute increase was modest in that 769 patients had to be treated with aspirin to cause one additional major bleeding episode annually. Interestingly, there was no difference between 75–162.5 mg/day and 162.5–325 mg/day aspirin, but increasing the daily dose (from 500 mg to 1,500 mg) substantially enhanced the bleeding risk.[8]

A head-to-head comparison of clopidogrel (75 mg od) versus aspirin (325 mg od) found that the RR for GI bleeding was greater with aspirin (RR 1.34, 95% CI 1.11–1.61).[23] Combined therapy with aspirin and clopidogrel had a higher bleeding risk in the long term compared with treatment with either agent alone,[13] but short-term dual therapy (up to 30 days) did not increase risk.[11]

Major bleeding complications with GPI are increased compared with placebo (2.4% (445/18,297) *v* 1.4% (180/13,105), p<0.0001),[15] while limiting the dose of adjuvant anticoagulant therapy reduces bleeding.

Key Points

- **Platelets play a central role in acute coronary syndromes**
- **Antiplatelet agents are effective and improve prognosis**
- **Aspirin remains the cornerstone of therapy; it is initiated in all patients (unless contraindicated) and continued lifelong**
- **Clopidogrel, in combination with aspirin, is of proven benefit during the acute phase and for up to one year thereafter**
- **Intravenous glycoprotein IIb/IIIa inhibitors are potent antiplatelet agents used as adjuvant therapy, but use is limited to initial acute presentation and high-risk patients undergoing percutaneous coronary revascularisation**
- **Bleeding risk is increased with prolonged combined antiplatelet therapy; caution is necessary in the elderly (>75 years)**

KEY WORDS: acute coronary syndromes, antiplatelet agents, aspirin, dual antiplatelet therapy, glycoprotein IIb/IIIa inhibitors, thienopyridines

Conclusions

Platelets are pivotal in the initiation and propagation of ACS. The evidence base for the use of oral dual antiplatelet therapy is unequivocal. Therapy should be initiated upon mere suspicion of an ACS and, once confirmed, maintained for 12 months. Intraveneous GPIs are of value in patients stratified to be at high risk (on the basis of clinical findings, ECG and biomarkers). Despite optimal

Table 1 Antiplatelet agents in acute coronary syndromes.

ACS	Aspirin	Clopidogrel	iv GP IIb/IIIa inhibitors
Unstable angina and NSTEMI	300 mg at presentation; 75–150 mg daily maintenance regimen	300 mg at presentation; 75 mg maintenance for ≤1 year depending on presence of elevated troponin levels or occurrence of PCI	Initiate at presentation in all 'high-risk' cases even if troponin results not available; continue until after PCI
ST elevation MI	300 mg at presentation; 75–150 mg daily maintenance regimen	Not recommended by existing guidelines, but evidence suggests use at presentation and continue for four weeks	Not recommended as adjuncts to thrombolytic therapy, but use if PCI performed

High-risk patients are those with: (a) recurrent chest pain or dynamic ST-segment changes, (b) raised troponin levels, (c) haemodynamic instability, (d) ventricular arrhythmia, (e) diabetes mellitus.
ACS = acute coronary syndrome; GP = glycoprotein; iv = intravenous; MI = myocardial infarction; PCI = percutaneous coronary intervention; NSTEMI = non-ST-segment elevation MI; STEMI = ST-segment elevation MI.

therapy, morbidity and mortality from ACS remain high. Newer, more powerful antiplatelet agents are on the horizon, promising incremental benefits but they await clinical trials evidence.

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