The Prevention of Atherothrombotic Events in Adults with Acute Coronary Syndromes

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Abstract: The term acute coronary syndrome is used to describe a range of conditions that share a common underlying pathology of interrupted blood flow and subsequent damage to the myocardium. Acute coronary events are unpredictable and can rapidly become life-threatening, largely as a result of clot formation, and one of the primary treatment aims is to limit thrombosis. Such events are a major cause of hospitalization and death worldwide and thus the impact of advances in thrombocardiology is enormous. Acute coronary syndromes can be difficult to diagnose, and a successful clinical outcome depends on accurate assessment of individual risk which is then used to determine the treatment strategy. Recent advances fall in to two main areas: firstly the improvement in understanding of the clinical markers that allow more accurate risk stratification and, secondly, the development of new anti-thrombotic drugs. This review considers current approaches for the management of acute coronary syndromes, highlighting recent advances.

Keywords: acute coronary syndromes, STEMI, NSTEMI, antithrombotics
Background

The term ‘acute coronary syndrome (ACS)’ describes a spectrum of events that involve an interruption of normal blood supply to the myocardium. The factors that underlie the development and clinical manifestations are unpredictable and may rapidly progress into a life-threatening situation: implicit in this description is the instability of the condition, which ranges from unstable angina (UA) through to transmural myocardial infarction (MI). The common underlying cause is atherosclerosis of the coronary arteries, complicated by thrombus formation. Although our understanding of the molecular nature of atherosclerosis and the risk factors contributing to its development have increased rapidly over the past two decades, it remains the case that ACS are associated with poor clinical outcomes.

Clinical management of ACS is complicated by the fact that no simple definition exists: diagnosis is based on a combination of patient history, presenting symptoms, ECG findings and the presence/absence of biomarkers considered specific for myocardial damage. As yet, there are no international standards applied, although attempts have been made to address this through the establishment of the Global Registry of Acute Coronary Events (GRACE) which has permitted observation of the variation in hospital management and outcomes of ACS around the world.

However, despite such variation, many aspects of clinical management remain the same, including the concept of risk stratification. Patients with ACS are at risk of death and recurrent ischemic events, and both the immediate and long-term management is based upon the predicted risk. Secondly, regardless of risk, treatment for all patients will involve some form of anti-thrombotic therapy which, while helping to prevent further events will also increase the risk of bleeding which can prove fatal. Recent advances in the treatment of ACS fall into two main areas: Firstly, the identification of new markers that improve risk assessment, ensuring the correct treatment strategy, and secondly the development of new anti-thrombotic drugs with better safety profiles.

Atherosclerosis and the Concept of the ‘Vulnerable Plaque’: Not All Plaques are Equal

Atherosclerosis is a response to injury, occurring against a backdrop of chronic inflammation and increased oxidative stress. This environment leads to endothelial damage and dysfunction, and as part of the ensuing immune response, circulating monocytes migrate to the site and become activated, entering into the vessel intima. Here, monocytes complete their differentiation into macrophages, expressing scavenger receptors that allow the cells to accumulate large amounts of oxidized-LDL (ox-LDL). As a result of increased NF-κB signalling, these macrophage-derived foam cells produce cytokines, chemokines and inflammatory proteins which all contribute to the development of the plaque.

Risk Stratification

Patients who have experienced ischemic chest pain lasting for at least 20 minutes should be suspected of having an ACS, and a 12-lead ECG should be taken and interpreted as a matter of urgency. The critical point with respect to the ECG is the presence or absence of ST-segment abnormalities. The presence of an ST-elevation (or new onset bundle branch block) is indicative of an ST-elevation myocardial infarct (STEMI), although this will be confirmed by biomedicale tests. Patients presenting with STEMI are at highest risk, and treatment will involve consideration of reperfusion protocols and the initiation of adjunctive pharmacotherapeutic interventions as discussed below. Other ECG findings initially attract a general diagnosis of ‘non-ST elevation ACS (NSTE-ACS)’ and the final diagnosis of NSTEMI or UA depends on further test results. The clinical approach for NSTE-ACS is determined by risk scoring: there are a number of such tools in use, but all consider a combination of the medical history and the clinical presentation. High risk patients are likely to be treated as for STEMI, in that revascularisation should be considered, with the aim being to establish a complete and sustained reperfusion. Options for reperfusion include percutaneous coronary intervention (PCI, angioplasty), coronary artery bypass grafting (CABG) or fibrinolysis, with the exact course of action depending not only on the presenting features but also the facilities available. Patients in all groups will receive pharmacological interventions, and a major part of this treatment includes drugs used to either break down existing thrombus or prevent further formation.
These include MCP-1, promoting further monocyte recruitment, and PDGF which stimulates the proliferation and migration of smooth muscle cells from the underlying media. These cells also accumulate lipid, becoming smooth muscle cell-derived foam cells, but they also secrete extracellular matrix proteins (notably collagen I and III), forming the cap which stabilizes the plaque structure. Eventually, cell death and subsequent release of cellular contents leads to the formation of a lipid-rich necrotic core. Activity of a number of inflammatory mediators, including TNF-α, induces osteogenic genes leading to mineral deposition—advanced plaques are often associated with significant calcification.

Initially, as the lesion grows, so does the artery itself, meaning that as the wall thickens, the lumen size remains constant. However, the processes that promote smooth muscle cell proliferation also drive a continued process of remodelling, and the resulting stenosis begins to significantly disturb blood flow. This flow disturbance is sufficient to cause clinical symptoms such as stable angina, but life-threatening acute events occur when the plaque cap ruptures, exposing collagen and triggering thrombus formation. Less frequently, thrombus formation will be precipitated by other physical disturbances such as endothelial erosion, intraplaque hemorrhage or erosion of a calcium nodule. In addition to the effects in the immediate vicinity, the release of plaque fragments into the circulation may promote distal embolization. Physical disturbance of the plaque and thrombotic events are therefore critical events in the development—and potential targets in the treatment—of ACS. ACS patients are likely to have a high plaque burden yet an event may well be caused by the destabilization of a single plaque. This has led to the notion of the ‘vulnerable plaque’ and the search for its key morphologic and biochemical characteristics that may allow high-risk lesions to be identified.

It is clear that there are certain physical characteristics associated with so-called ‘culprit lesions’. Perhaps surprisingly, the majority of MIs are associated with arteries that are only slightly stenosed. As the artery undergoes remodelling, it seems that as the stenosis increases, so does the plaque stability, largely as a result of an increase in cap thickness, which acts to defray cap stress. The plaque appears to be physically most vulnerable at the point at which stenosis begins to occur, although other mechanical factors are likely to influence plaque vulnerability. Within a given plaque, rupture is likely to occur at the point of maximum stress, and these stresses are not evenly distributed. Forces are maximal at the shoulder—the edge of the plaque, near to the border with apparently normal intima. Interestingly, vulnerable plaques have thin (<65 μm) caps, especially in the shoulder region. Shear stresses (as well as pulsatile deformation) contribute to rupture, explaining at least in part why high blood pressure (especially increased pulse pressure) is a risk factor for ACS.

Non-mechanical factors also contribute, with the thickness of the necrotic core being one of the most significant. Stability of the plaque depends upon the integrity of the collagen cap, and this can be broken down by the activity of metalloproteinase enzymes (MMP-1 and MMP-9). Ruptured plaques have both an increase in MMP expression and a concomitant decrease in the metalloproteinase inhibitor (TIMP) and there is evidence to suggest that this shift is mediated by macrophage activity. High risk lesions are associated with particularly large numbers of macrophages infiltrating the thinning shoulder regions, and these cells have been shown to secrete myeloperoxidase (MPO). MPO generates hypochlorous acid, a powerful reactive oxygen species which not only enhances MMP activity (while decreasing TIMP expression) but also provides a mechanism for LDL-oxidation and endothelial damage, notably causing the erosion associated with acute events. Furthermore, this ox-LDL upregulates monocyte expression of the urokinase receptor, signalling through which directly enhances MMP-9 expression. Vulnerable plaques also show significant infiltration by T-lymphocytes which express receptor activated by NF-κB ligand (RANKL), which activates its receptor (RANK) on monocytes within the plaque, thus further enhancing NF-κB signalling. Immunostaining for both RANK and RANKL has been shown to be highest in regions of plaque rupture. Interestingly, the role of the T-cell gives support for the notion that ACS may have an infective component: specific T-cell sub-populations (CD4+CD28null) have been shown to be expanded in patients with UA compared to those with stable angina, and it appears that this clonal expansion is triggered by an exogenous antigen common to patients with UA. The persistence of these clones may...
be due to defective removal, but it may also be that the trigger remains, and indeed bacteria such as *Chlamydia pneumoniae* and *Porphyromonas gingivalis* have been isolated from human plaques. Finally, neutrophils have also been identified at sites of plaque rupture, where they have been shown to secrete both elastase and MPO. Neutrophils also express neutral endopeptidase, a membrane protein which modulates inflammatory responses. In a study by Naroko et al, all culprit lesions studied after fatal MI were shown to contain neutrophils within the plaque. In contrast, they were very rarely seen in coronary artery lesions obtained from patients who had died from non-cardiovascular causes. Neutrophils are similarly rare in plaque causing stable angina, but common in plaque associated with UA, further supporting the notion that neutrophils are associated with acute syndromes.

**Thrombus Formation**

Thrombus formation is triggered by the ‘solid phase’ events described above, but also requires the presence of what has been described as a ‘highly thrombogenic blood milieu.’ The lipid core itself is highly thrombogenic: rich in tissue factor (TF), it can trigger the extrinsic clotting cascade (Fig. 1), as well as platelet adhesion and activation. Tissue factor activity depends on the presence of phosphatidyl serine (PS), an anionic phospholipid which during apoptosis is deposited in large amounts in the cell membrane. Ruptured plaques shed PS-rich membrane fragments into the circulation, and these enhance TF activity and the formation of downstream emboli. TXA2 and ADP released by platelets induce platelet activation and TF promotes thrombin formation, which converts fibrinogen to fibrin, stabilizing the clot. The role of the platelet in this process is detailed in Figure 2, and it is worthy of note that platelet aggregation is a complex phenomenon, involving multiple pathways with a high degree of redundancy which makes pharmacological intervention difficult. ACS are associated with a state of platelet hyperactivity which persists for months after the original event and contributes to the risk of recurrence.

The existence of thrombotic emboli is a dynamic process: all the factors described above promote the formation, but some degree of lysis will occur in response to plasmin activity, which in turn is controlled by the action of endogenous tissue plasminogen activator (TPA). Plasminogen activator inhibitor-1 (PAI-1) inhibits these fibrinolytic mechanisms and thus promotes thrombus formation, and the balance between these two proteins will have a significant impact on the thrombogenicity of the blood. Interestingly, both diabetes and obesity are associated with elevated levels of PAI-1.

Also of importance is the balance in expression of TXA2 and PGI2. TXA2, produced by platelet COX-1 and acting through the TP receptor, promotes vasoconstriction and platelet degranulation, while PGI2, produced primarily by endothelial cells in response to COX-1 and COX-2 activity, prevents platelet activation. The significance of this relationship is demonstrated by the problems associated with the use of selective COX-2 inhibitors.

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**Figure 1.** Simplified flow diagram of the clotting pathway focusing on pharmacological targets. Thromboplastin is a combination of tissue factor and phosphatidyl serine.
inhibit PGI₂ production while leaving platelet-derived TXA₂ unaffected, shifting the balance in favour of platelet activation and degranulation. This is likely to be the mechanism responsible for the increased incidence of adverse cardiovascular events associated with this drug class, although the exact in vivo role of PGI₂ is not clear, as it may be that physiological levels are not high enough to reproduce the effects observed in vitro.15

Recovery from an acute coronary event depends on a number of issues.21 Critically, perfusion must be restored to the affected areas, while necrotic areas must heal, a process that must include restoration of the microcirculation, requiring angiogenesis. In order to maintain perfusion and prevent recurrent events, it is essential to render the blood environment less thrombogenic. Finally, it is important that further plaque growth is inhibited and that existing plaques are stabilized as much as possible. Stabilization and inhibition of further thrombotic events is particularly critical in the phase immediately following plaque rupture: a number of studies suggest that an incident of ACS is followed by a rapid worsening in atherosclerosis, particularly in the coronary arteries.38–40 Unless the culprit lesion has been treated by angioplasty, it continues to develop, and there is a similar accelerated development of lesions which initially may have been considered insignificant. This global destabilization is referred to by Rioufol and colleagues as ‘pancoranaritis,’ and it is likely to account for the very high risk of recurrent events observed in the early period after presentation with ACS.40 Assessment of patients with ACS using intravascular ultrasound revealed that that the vast majority had at least one or more lesion showing ‘rupture criteria’ in an artery distinct from the one containing the culprit lesion.41,42

Myocardial Damage
Thrombus at the site of ruptured or eroded plaque combined with distal embolization (caused largely by platelet activity) is responsible for the eventual myocardial necrosis associated with ACS.543 However, platelets are not the only cells involved: it has been shown that myocardial injury also involves the recruitment and activation of neutrophils. As well as their role in plaque destabilization these cells also undergo degranulation within the coronary circulation during ACS.27 Activated neutrophils release MPO which, in addition to the effects described above, also catalytically consumes endothelial-derived NO, reducing its bioavailability and inhibiting its vasodilatory and anti-inflammatory actions, therefore enhancing myocardial damage. The loss of cardiac myocyte membrane integrity results in the release of a number of cellular components into the systemic circulation, including cardiac troponins, which are considered the ‘gold standard’ marker of myocardial injury.1,4,44–46 It is also worth noting that myocardial damage is
likely to involve electrical conduction pathways, and this is why many patients with ACS present with additional complications such as atrial fibrillation that may further complicate treatment plans. 47–49

Markers of myocardial damage and acute events
Troponins are probably the most established diagnostic and prognostic markers. They have been shown to reliably predict risk of recurrent events, especially within the period immediately following presentation, but also allow the identification of patients who are most likely to benefit from anti-platelet therapy, including GPIIb/IIIa receptor antagonists. 44–46 It is recommended that troponin levels are measured as part of the initial assessment, and if the initial result is negative, then reassess after 6–12 hours, with further measurements being made after every episode of chest pain. It is worthy of note that assay sensitivity has continually improved in recent years, with the result that very small changes can be detected. This has led to differences in the way that ACS are defined around the world. 1

However, it is important to recognise that troponins are evidence of myocardial injury, so the search continues for earlier markers of risk, and another recent advance is the recognition of potential markers that may become useful in risk stratification.

Degranulated platelets have been shown to rapidly form aggregates with circulating monocytes, and these appear to be a sensitive marker of platelet activation. Elevated levels can be detected very shortly after both MI and NSTE-ACS and are predictive of future events. 21–50 Other markers released on platelet activation include sCD40L, a protein which has been shown to predict adverse outcomes. 4,51,52 ACS are also associated with measurable differences in a number of inflammatory mediators. TNF-α production by monocytes normally triggers the release of IL-10, an anti-inflammatory cytokine that attenuates the inflammatory response. It has been suggested that this negative feedback response is blunted in patients with ACS, who have lower levels of IL-10 than controls, 53 although more recent studies indicate that high levels of IL-10 are associated with adverse outcomes. 54,55

Both tissue factor and the PS-rich membrane microparticles described above can also be detected in the plasma. Microparticle elevation can be detected 8 days after the initial event and may well be a useful prognostic marker of future events. 26,56,57 Circulating levels of activated neutrophils also show a positive correlation with risk of MI, as do MPO levels, which have been shown to be an independent marker of clinical prognosis in patients with ACS. These and other studies suggest that neutrophil activation may well be a pathological event associated with ACS and that it is distinct from platelet activating events. 14 Interestingly, these markers may have particular use in identifying a high-risk subgroup of patients whose TnT levels are low.

Other candidate markers include B-type natriuretic peptide and its N-terminal fragment. 58–66 Higher levels of BNP are associated with higher Killip class and lower left ventricular function as well as higher levels of many of the other markers including peak troponin. Patients with high N-BNP levels are also more likely to have ECG changes associated with a poorer clinical outlook. In contrast, median N-BNP levels are seen to be significantly lower in long-term survivors of ACS.

Gender differences in markers of ACS
It has been known for some time that women are more likely to present with atypical symptoms of ACS, and this is likely to contribute to the poorer prognosis observed for this group. 61 ECG data is also less likely to be reliable: ST-elevations are less frequently observed when compared with men, and more ST-depressions, T-wave inversions and non-specific alterations are seen. Similarly, gender differences can be observed with respect to the biochemical markers. Elevated troponins, considered the marker of choice for evaluating acute risk in patients with ACS without persistent ST-elevation, are less commonly seen in females and it has been suggested that multiple markers are likely to be of better prognostic value across all groups. 61,62

Treatment of ACS
Treatment of the acute phase aims to reduce ischemic damage by addressing the thrombotic process, both in terms of preventing new thrombus formation, but also clearing existing thrombi and plaque debris. This must give way to longer term treatment and managing the balance between complications of thrombosis and pathological bleeding is difficult, meaning that treatment regimens are often complex. There are a number of agents that are useful in this aim and these are described below. Figure 3 describes the typical
Antithrombotics for the management of acute coronary syndromes

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Figure 3. Risk stratification in acute coronary syndromes. Risk stratification includes measurement of troponins. High risk NSTE-ACS should be treated as STEMI.

Reperfusion strategies
Percutaneous coronary intervention (PCI; balloon angioplasty) involves the introduction of a very fine catheter bearing a balloon on the tip into the lumen of the occluded coronary artery. Inflation of the balloon generates pressures in the order of several atmospheres, and repeated inflation cycles ablate the plaque and its associated thrombus, restoring patency. Comprehensive review of the data generated from many randomized clinical trials has shown that PCI is superior to fibrinolysis for the treatment of STEMI. Consistency of benefit was seen across all patient subgroups, although the greatest benefit was observed in patients treated within 12 hours of first onset of symptoms. Consequently, PCI is considered to be the optimal treatment for STEMI, and indeed for high risk NSTE-ACS: many of the more recent trials indicate that an early invasive strategy yields better results than a more conservative one, and therefore PCI should be considered.

Thrombolysis: It is recognized that cardiac catheterization may not always be possible: facilities and/or expertise may not exist, or the patient may have to travel some distance before being treated. In such cases, thrombolysis may be an appropriate alternative for patients with STEMI and high risk NSTE-ACS and it is worthy of note that despite the superiority of PCI, thrombolysis is the most frequently used means of reperfusion worldwide. Such an approach is generally recommended when PCI is not available within 90 minutes of onset of symptoms, although it is associated with a lower degree of myocardial salvage, and is of little use if treatment is delayed much beyond 6 hours. Streptokinase is the oldest of the thrombolytic agents, and is still routinely used in clinical practice. The Fibrinolytic Therapy Trialists’ Collaborative Group performed a meta-analysis of the data from trials involving the use of streptokinase in the treatment of acute MI. The results indicate an overall benefit in patients with STEMI, an
effect that was seen to be consistent across all patient subgroups, although—as would be expected—early treatment is associated with better outcomes.\textsuperscript{75,76}

More recent developments include the recombinant tissue plasminogen activators, such as alteplase and early trials revealed that alteplase was superior to streptokinase with regard to arterial patency.\textsuperscript{76} An accelerated dosing regimen was developed that appeared even more effective in establishing early reperfusion, and was shown to translate into a reduction in mortality (equivalent to saving an additional 10 lives per thousand) in the Global Use of Strategies To Open Occluded Coronary Arteries (GUSTO-I) study.\textsuperscript{77} This increased benefit persists even when the risk of bleeding is taken into account, and is seen across all patient subgroups, although the absolute benefit was seen to be highest in high-risk patients, such as those with anterior MI, findings that were confirmed by the TIMI-4 trial.\textsuperscript{78} Although a number of tPA derivatives have been developed, these have not been shown to be superior to alteplase in most clinical settings\textsuperscript{79,80} and alteplase remains the ‘gold standard’ for fibrinolysis. Thrombolytic therapy only completely restores coronary blood flow in approximately 50% of cases, with the outcome being particularly poor in elderly patients and those with cardiogenic shock. A systematic review of randomized clinical trials indicates that in patients who do not respond fully to thrombolysis, the preferred option is to perform ‘rescue PCI’ rather than adopt a conservative management strategy.\textsuperscript{81} This was backed up by a recent observational analysis of a Canadian population-based cohort of patients enrolled in the follow-up phase of the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study\textsuperscript{82} who had all been hospitalized with STEMI, where rescue PCI was seen to be associated with a significant reduction in risk of death and future ACS.

Coronary artery bypass grafting (CABG): This is an alternative revascularization procedure and number of trials have shown that that this procedure significantly reduces the likelihood that patients will require repeat revascularization procedures. Indeed, in the FRISC II trial, PCI was associated with 14.3% incidence of repeat revascularization, compared with only 1.6% for CABG (reviewed in\textsuperscript{41}). However, some trials have also shown that this procedure is associated with a higher mortality, although this may reflect the fact that CABG tends to be favored over PCI in patients with 3-vessel disease or left main stenosis, or with impaired left ventricular function. It is, of course, possible to use PCI to temporarily improve vascularization while waiting for optimum timing for CABG procedures.

**Pharmacological intervention**

Regardless of the initial approach taken in the management of ACS, pharmacological intervention will be essential, either in the form of adjunct therapy or as the main treatment strategy. All the drugs are antithrombotics of some sort, and the first aim of treatment is to select both the optimal drug and the optimal dosage regimen for the specific clinical situation. Similarly, the clinical presentation may suggest that particular drug combinations are warranted: aspirin plus clopidogrel is one of the most commonly used combinations across the spectrum of ACS, and dual antiplatelet therapy is the gold standard following stent insertion. The use of triple therapy (dual antiplatelet plus an anticoagulant) is becoming increasingly common, especially in patients whose clinical situation is complicated by atrial fibrillation (AF) and acute pharmacological intervention is different from that used for longer term management. Tables 1 and 2 describe indications and evidence for the use of particular drug combinations in the acute and long-term phases respectively (reviewed in\textsuperscript{81}).

**Antiplatelet agents**

Antiplatelet therapy has been shown to be effective in the prevention of serious cardiovascular events and this is true both the long and the short term. The value of antiplatelet therapy was demonstrated by the Antithrombotic Trialists Collaborative Study, a meta-analysis of data from 145 randomized clinical trials involving 100,000 patients, 70,000 of which had been identified as being at high risk for cardiovascular disease. The results indicated that antiplatelet therapy gave a relative risk reduction of 25% for a combination endpoint of MI, stroke and vascular death.\textsuperscript{82}

**Aspirin**

Aspirin is the oldest and most widely studied of the antiplatelet agents. It is an irreversible, non-selective COX inhibitor and in healthy individuals, a 100 mg dose is sufficient to completely block TXA\textsubscript{2} production without any significant effect on PGI\textsubscript{2} production.\textsuperscript{4,30}
### Table 1. Evidence supporting the use of drug combinations in the acute management of ACS. In summary, the addition of a parenteral anticoagulant improves clinical outcomes in patients receiving aspirin, aspirin + a fibrinolytic agent or aspirin + a thienopyridine.

<table>
<thead>
<tr>
<th>Combination</th>
<th>Evidence for benefit in STEMI</th>
<th>Evidence for benefit in NSTE-ACS</th>
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<tr>
<td>(Aspirin + Fibrinolytic) + UFH</td>
<td>Meta-analysis of 6 studies (total: 68000 patients admitted with suspected MI). All patients received aspirin alongside fibrinolytic therapy and either UFH or placebo (or no UFH). Risk of 10-day mortality reduced by 6%, incidence of re-infarction reduced by 10%. (NB risk of major bleeding significantly increased).</td>
<td>Meta-analysis of 6 trials (total: 1353 patients with confirmed NSTE-ACS). All patients were receiving aspirin alongside fibrinolytic therapy and either UFH or placebo (or no UFH). The addition of UFH to the treatment regimen reduced the rate of composite endpoint (death or MI) by one third. (No significant increase in major bleeding)</td>
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<td>[Aspirin (or Aspirin + Clopidogrel)] + LMWH</td>
<td>Meta-analysis of 3 studies (16842 patients diagnosed with STEMI). Addition of LMWH to aspirin or aspirin and clopidogrel treatment reduced the rate of re-infarction in the first 7 days: 1.6% compared with 2.2% (OR: 0.72). Mortality rates were also reduced (7.8% compared with 8.7%; OR: 0.9).</td>
<td>The Fondaparinux in ST-elevation MI Safety and Efficacy Trial (OASIS-6) involved 12092 patients with STEMI. All were receiving aspirin treatment, approximately 50% also received clopidogrel. During the first 8 days, patients received either fondaparinux (2.5 SC, bid) or UFH or placebo. In the subset of patients with no indication for UFH, fondaparinux reduced 9-day risk of composite end-point (death and re-infarction): 8.5% vs. 11.1; RR 0.76.</td>
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<td>[Aspirin (or aspirin + clopidogrel) ] + fondaparinux</td>
<td>The Fondaparinux in ST-elevation MI Safety and Efficacy Trial (OASIS-6) involved 12092 patients with STEMI. All were receiving aspirin treatment, approximately 50% also received clopidogrel. During the first 8 days, patients received either fondaparinux (2.5 SC, bid) or UFH or placebo. In the subset of patients with no indication for UFH, fondaparinux reduced 9-day risk of composite end-point (death and re-infarction): 8.5% vs. 11.1; RR 0.76.</td>
<td>No information.</td>
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Higher doses will affect PGI₂ production and are associated with a significantly increased risk of gastrointestinal bleeding. The overall effect is to reduce platelet aggregation by about 50%. However, this translates into a relatively weak clinical effect, as it is estimated that only 20% of platelet response is necessary for thrombus formation. This, combined with the observation that approximately 10% of patients are unresponsive to aspirin treatment, means that aspirin is usually administered alongside another antiplatelet drug, most commonly clopidogrel. Aspirin has benefits other than its effect on platelets—it reduces inflammation generally, and it has also been shown to reduce oxidative stress in animal models. Data from the Antithrombotic Trialists Study\(^82\) (including updates from this study)\(^30\) suggest that aspirin is no less effective than other antiplatelet agents in preventing adverse cardiovascular outcomes, although it is more effective in reducing the incidence of MI than any other clinical event. Typically, aspirin is administered as a loading dose of 150–325 mg, although maintenance doses vary enormously. Aspirin therapy is standard for secondary prevention of cardiovascular events, and on the basis of the US Physicians Health Study was recommended for primary prevention. This study consisted of 22,701 healthy physicians taking a single 325 mg dose on alternate days. The results indicated a 44% reduction in the incidence of first MI, although (as might be expected) the benefits were highest in those over the age of 50 years\(^83\). These results were supported by the outcomes of the UK Thrombosis Prevention Trial,\(^84\) in which subjects were given 75 mg aspirin daily, and saw a 20% risk reduction in respect of the combined endpoint of coronary death and non-fatal MI, although by far the larger part of the risk reduction came from the
reduction in non-fatal events. Aspirin treatment is therefore recommended for all acute coronary syndromes, and in practice, usage appears to be universal. Other studies that have also shown a primary preventative benefit for aspirin include the Hypertension Optimal Treatment Trial, although more recent evidence has questioned the benefit with regard to primary prevention in all groups.

Thienopyridines

Thienopyridines prevent ADP from signalling through its platelet receptors and thus block the downstream events which include morphological changes, adhesion to the endothelium, aggregation and degranulation. The contents of the α-granules include fibrinogen and thrombospondin, which potentiase aggregation via interaction with the GPIIb/IIIa platelet receptor, while the β-granules release a number of platelet activators, including ADP (see Fig. 3). Members of this class include ticlopidine, clopidogrel and prasugrel, although ticlopidine is rarely used now because approximately 2.4% of patients experience neutropenia, which in approximately one-third of cases is severe. Platelet aggregation is mediated by the binding of ADP to the seven-transmembrane proteins P2Y_1, P2Y_12 and the ion channel P2X_1, which facilitates calcium influx. Activation of both the 7-TM receptors is required for ADP to activate platelet fibrinogen receptor (GPIIb/IIIa).

Like the other thienopyridines, clopidogrel is a prodrug and bioavailability depends on intestinal absorption and hepatic CYP450 transformation to generate the active metabolite. Absorption appears to involve an ABCB1-mediated process, and polymorphisms in this gene may affect response to the drug. Hepatic CYP2C19, 1A2 and 2B6 are all involved in the conversion of clopidogrel to 2-oxo-clopidogrel. This intermediate is a substrate for CYP3A, 2B6, 2C9 and 2C19 which yield the active metabolite. Interestingly, both the parent compound and

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Table 2. Evidence supporting the use of drug combinations in the long-term management of ACS. In summary, warfarin reduces the frequency of recurrent events but has no effect on mortality. The new factor Xa antagonists show some promise, but large scale phase III trials are required to establish groups most likely to benefit.

<table>
<thead>
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<th>Combination</th>
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<td>Aspirin + warfarin</td>
<td>Two meta-analyses have considered this. The first involved data from 10 studies of patients recovering from MI treated with aspirin. Patients also received either warfarin or placebo (or no warfarin). All these studies involved a titrated warfarin dose aimed to achieve a target INR of 2–3. Warfarin treatment was associated with a reduced annual risk of MI (2.2% v 4.1; RR 0.56), stroke (0.4% v 0.8; RR 0.46) and revascularization (11.5% v 13.5; RR 0.8). NB The risk of major bleeding was more than doubled. A second analysis included all studies regardless of INR. No difference was seen with warfarin. However, analysis of a subset of the data (including studies with INRs of 2–3) saw a reduction in the rate of composite endpoint (death, MI, stroke): 9.4% v 12.4; RR 0.73</td>
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<td>[Aspirin (or aspirin + clopidogrel)] + apixaban</td>
<td>APPRAISE-1 study: A dose-escalation study over 6 months in 1715 patients with either STEMI or NSTEMI. Patients received standard antiplatelet therapy (all on aspirin, 75% also received clopidogrel) as directed by clinician, and either apixaban or placebo. Doses of 2.5 or 10 mg b.i.d. apixaban were associated with a non-significant reduction in the rate of composite endpoint, but there was an increased risk of major bleeding.</td>
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<td>[Aspirin (or aspirin + clopidogrel)] + rivaroxaban</td>
<td>ATLAS-TIMI-46 trial: a phase II dose-escalation study of 6 months duration in 3491 patients recovering from STEMI or NSTEMI. Patients were receiving standard antiplatelet therapy and either rivaroxaban or placebo. Patients treated with rivaroxaban saw a non-significant reduction in the rate of composite endpoint.</td>
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</table>
2-oxo-clopidogrel are inhibitors of CYP1A2, 2B6 and 2C19, which explains why polymorphic variation in the CYP2C19 gene is associated with altered efficacy with regard to the antiplatelet effects. Due to the necessity for biotransformation, it may take up to 5 days for clopidogrel to deliver peak efficacy. Like aspirin, clopidogrel’s effect on the platelet is irreversible, so its effects last for the lifetime of the platelet—approximately 7–10 days.

The Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial involved a randomized head-to-head comparison of a 75 mg daily dose of clopidogrel with 325 mg aspirin. 19,185 patients were enrolled on the study, all of whom had existing cardiovascular disease, and the type of disease was used to assign each to one of three study groups: those with recent MI, those with recent stroke and those exhibiting symptoms secondary to peripheral arterial disease. The average follow up time was 1.9 years, and the results indicated a relative risk reduction of 8.7% for a combined endpoint of MI, ischemic stroke and vascular death.90–92 Severe bleeding events were also slightly lower in the clopidogrel group, with a significantly lower incidence of GI bleeding. In practical terms, however, this translates into a clinical effect that could only be described as modest, and clopidogrel treatment is considerably more expensive than aspirin.93 However, it would appear that the benefits are more marked in high-risk subgroups, including those undergoing PCI.

Typically, a loading dose of 3–400 mg is given, followed by a maintenance dose of 75 mg, which results in an inhibition of platelet aggregation in the order of 50%–60%. The drug is eliminated both renally (50%) and in the feces (50%). Interestingly, a significant number of patients will show resistance to clopidogrel, and studies have estimated the frequency of this to be between 4%–30%, depending on the population studied. The mechanism of this effect is not understood, but it may well arise as a result of differences within background level of inflammation, or possibly may reflect polymorphic variation in the CYP450s involved in its biotransformation/metabolism: specifically, the CYP2C19*2 allele is associated with non-response.89 Clopidogrel is commonly used as the antiplatelet of choice following PCI, and it is also suggested for use as adjunctive therapy for thrombolysis if the patient is unable to take aspirin.

Prasugrel is even more potent than clopidogrel, requiring a loading dose of only 40 or 60 mg and a once daily maintenance dose of 10–15 mg.87 Like clopidogrel, prasugrel requires biotransformation to yield the active drug: intestinal esterases convert the parent compound to a thiolactone derivative, which is a substrate for hepatic and GI CYP3A, 2B6, 2C9 and 2C19. 2C19 polymorphisms have not been shown to significantly affect the antiplatelet actions of this drug. In terms of its pharmacokinetic profile, prasugrel has a rapid onset of action and gives a sustained and consistent inhibition of platelet aggregation. The efficacy of prasugrel was compared with standard clopidogrel therapy in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI-38).94–96 This involved 13,600 patients with high to moderate risk ACS and a planned treatment strategy of PCI. Prasugrel reduced the incidence of major cardiovascular events by 12.1%, compared with 9.9% for clopidogrel. However, this was accompanied by an increase in major (including fatal) bleeding events. The conclusions of the trial and its subsequent post hoc analyses were that prasugrel offered superior clinical benefit to clopidogrel in certain circumstances, namely, STEMI, ACS with underlying diabetes and patients undergoing stent insertion. There were also 3 distinct subclasses for whom prasugrel treatment was potentially detrimental: patients with a history of stroke or TIA, those weighing less than 60 kg and those over the age of 75. Prasugrel is, as yet, untested in combination with anticoagulants, and is not therefore recommended for triple therapy. Ongoing trials are investigating whether or not reducing the maintenance dose of prasugrel from 10 to 5 mg will increase the risk: benefit ratio.

Aspirin and Clopidogrel Combinations
A number of trials have indicated the additional benefits gained from using aspirin and clopidogrel dual therapy. The CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial was a randomized, multicenter, double-blind study that recruited 12,562 patients with NSTE-ACS from 428 centers in 28 countries.97–100 6259 participants received clopidogrel (300 mg loading dose, 75 mg daily for maintenance) and aspirin (75–325 mg daily at the local physician’s discretion). 6303 patients received aspirin plus placebo, and the
mean duration of the study was 9 months. The use of the combination therapy was associated with a 20% risk reduction for the primary composite endpoint of non-fatal MI, non-fatal stroke and CV death. There was also a 14% risk reduction for a second primary composite endpoint of CV death, stroke, non-fatal MI and refractory ischemia, although this reduction was primarily attributable to the decrease in incidence of MI. Importantly, these benefits were observed across all patients, regardless of what other medication they were taking. With regards to side-effects, the combination was seen to be associated with a higher risk of serious bleeding events, particularly in patients undergoing CABG. However, a risk: benefit analysis of CURE participants undergoing such intervention procedures suggested that the benefits outweigh the risks even in patients proceeding to CABG.

Data from the CURE trial also indicate that most of the benefit from clopidogrel/aspirin combinations arises from the risk reduction in the period immediately after the primary event, and most guidelines thus recommend that the treatment period is limited to 12 months. Clopidogrel and aspirin combinations are also particularly valuable in preventing thrombotic complications associated with stenting and are recommended for 30 days after bare metal stent implantation and for 1 year with drug eluting stents although there is some more recent data suggesting that triple therapy (with the addition of an oral anticoagulant) may be of even greater benefit. The reduced efficacy of clopidogrel when administered with a PPI may well be due to effects on the CYP2C19 mediated metabolism.

Interestingly, the benefits of clopidogrel/aspirin combinations appear to be independent of the aspirin dose. The Antithrombotic Trialists Collaboration Study identified 10 trials that have compared different aspirin doses in combination with clopidogrel. Treatments were considered as being low dose (75–325 mg aspirin daily) or high dose (500–1500 mg daily). Across these trials, there was no significant difference in cardiovascular event rates, but increasing aspirin doses were associated with increased risk of bleeding and therefore lower doses are recommended to minimize this risk. The impact of clopidogrel dose has also been investigated in the CURRENT OASIS-7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events—Optimal Antiplatelet Strategy for Intervention) trial, which involved 25,086 patients presenting with either STEMI or NSTE-ACS with an initial treatment plan of angiography and potential PCI. Patients were randomized to receive aspirin and either normal dose clopidogrel (300 mg loading dose, 75 mg daily maintenance) or double-dose (600 and 150 mg respectively). The primary endpoint was a composite of 30-day MI, CV death or stroke. Overall, there were no significant differences between the groups, with the exception of the rate of stent thrombosis, which was significantly lower in the double-dose group. However, analysis of the subgroup who proceeded to PCI revealed a significant reduction in the rate of the primary endpoint, although this was accompanied with a higher risk of bleeding. The timing of the clopidogrel dose is also important. Both the Clopidogrel for the Reduction of Events During Observation (CREDO) and the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) trials indicate that best results are obtained when clopidogrel is administered as soon as possible after presentation.

Problems Associated with the Use of Clopidogrel/Aspirin Combinations

Upper GI bleeding is a particular risk of aspirin treatment, although some groups are at increased risk, and this is potentiated by thienopyridine use. Patients at increased risk of GI bleeding include those with prior GI bleeding, advancing age and infection with H pylori. In such patients, proton pump inhibitors (PPIs) or H2-receptor antagonists have been commonly prescribed alongside dual antiplatelet therapy. However, there is evidence to suggest that PPIs may inhibit the antiplatelet effect of clopidogrel, and the worst effect seems to be caused by omeprazole. This effect may be particularly apparent in patients who are poor metabolizers of clopidogrel, but the results of several observational studies and one randomized clinical trial are inconsistent. The thienopyridines themselves do not cause GI bleeding or erosions, but their antiplatelet effect is likely to potentiate bleeding from existing lesions (or those caused by other drugs including aspirin) and there is evidence to suggest that PPIs are much more effective than H2RA in protecting patients on clopidogrel combinations.

The reduced efficacy of clopidogrel when administered with a PPI may well be due to effects on CYP2C19 mediated metabolism. All PPIs are weak bases that are converted to the active form in the acid.
environment of the stomach and they are all primarily metabolized by CYP2C19 (and to a lesser extent, 3A4). It is thus possible that PPIs may competitively inhibit the generation of clopidogrel metabolites. This is likely to be a particular problem for those individuals who have certain CYP2C19 polymorphic variants: the *2, *3 and *4 alleles are all associated with decreased production of the active metabolite. A number of ex-vivo studies have shown that omeprazole significantly reduces the antiplatelet effects of both clopidogrel and prasugrel (reviewed in\textsuperscript{105}). There are studies involving other PPIs which suggest that the effects are specific to omeprazole, but these involve different study populations. The ongoing SPICE (evaluation of the influence of Statins and Proton-pump Inhibitors on Clopidogrel antiplatelet Effects) trial will directly compare a number of PPIs, as well as an H\textsubscript{2}RA (ranitidine). This is an ex-vivo study and will take into account CYP2C19 genotype.

Whether or not these observations translate into a clinical effect is unclear. Some studies have shown small but significant associations between PPI use and CV events, while others do not, and it is possible that any such effect is overestimated as PPIs tend to be given to high-risk patients. Although concerns prompted an FDA safety review, the conclusions were that more research is required, but physicians should proceed with caution: if a patient is at low risk of a GI bleed, then a PPI is not recommended.\textsuperscript{105}

Reversible inhibitors of PY\textsubscript{12} receptors

This class of drugs includes ticagrelor, cangrelor and clinogrel, none of which require biotransformation and thus their antiplatelet effect is achieved rapidly. Their reversibility means that the effect also wears off, and they are considered to provide additional benefit in patients requiring greater antiplatelet effects than those provided by clopidogrel alone.\textsuperscript{106}

Ticagrelor is a cyclopentyltriazalopyrimidine, which binds to the PY\textsubscript{12} receptor at a site distinct from ADP.\textsuperscript{107,108} The precise mechanism of action is not entirely clear—it does not bind to the ADP binding site and indeed does not appear to significantly affect ADP-binding. However, probably through an allosteric mechanism, it prevents activation of downstream events. Peak inhibition of platelet activity is seen within 2 hours of administration of the loading dose and it has a plasma half-life of 8–12 hours, with platelet activity returning to normal within 5 days (compared with 10 for clopidogrel). Inhibition of platelet activation is greater and the effect more consistent than that observed with clopidogrel in patients with ACS,\textsuperscript{109} and the clinical benefit is not affected by the genetic polymorphisms which affect clopidogrel treatment.\textsuperscript{110} Initial safety and tolerability studies indicated that while higher doses were not associated with increased risk of bleeding, they were associated with adverse effects, including dyspnea.\textsuperscript{111} This led to the selection of a twice-daily 90 mg dose for the PLATlet inhibition and patient Outcomes (PLATO) study, a trial comparing the efficacy of ticagrelor with clopidogrel.\textsuperscript{112} This multicenter, double-blind trial, involved 18,624 patients hospitalized with ACS (with or without ST-elevation) and randomized to receive either clopidogrel (300–600 mg loading dose, 75 mg daily maintenance dose) or ticagrelor (180 mg loading dose, 90 mg twice-daily maintenance dose). The primary endpoint for this trial was a composite of death from vascular causes, MI or stroke, and after 12 months, event rates were significantly lower in the ticagrelor group (9.8% compared with 11.7% for clopidogrel). In addition to the outcome benefits, there was no overall increase in the rate of major bleeding events, although there was an increase in the rate of non-procedural related bleeding events for the ticagrelor group. In contrast to the TRITON-TIMI study with prasugrel, the PLATO trial also demonstrated that ticagrelor reduced cardiovascular and all-cause mortality, making ticagrelor a particularly promising agent for the treatment of ACS. A number of possible explanations have been suggested for this: prasugrel was associated with an increase in the incidence of major bleeding events which increased mortality in this group. It has also been suggested that ticagrelor upregulates expression of adenosine receptors, which has been shown to be cardioprotective.\textsuperscript{113} However, Servi and Savonitto\textsuperscript{114} suggest that it is more likely to be differences in the study populations (TRITON-TIMI only enrolled patients selected for PCI), and that further analysis of the data offers useful insights into which populations are likely to benefit most from the newer therapy. They point out that patients with STEMI benefit particularly from either prasugrel or ticagrelor (compared with clopidogrel), but that ticagrelor treatment is particularly valuable in treating patients who are
selected for conservative management, and those selected for CAGB. However, a separate consideration of the PLATO data for a subset of patients selected for PCI suggests that ticagrelor is superior to clopidogrel for this group as well. Interestingly, the PLATO trial data suggested that patients from the United States did not see these benefits, with the result that the drug has not yet been approved for use in this country. Mahaffey and colleagues, in a more detailed consideration of this aspect of the data, suggest two possible explanations for this: firstly, the possibility of chance could not be excluded but secondly, patients from the USA were typically receiving higher maintenance doses of aspirin than patients from elsewhere. There are drug-drug interactions that may be problematic in patients being treated with ticagrelor, not least that with diltiazem. Ticagrelor has recently been approved for use in ACS and represents a significant step forward in treatment.

Cangrelor is an ADP analog, administered IV and has a very short half-life due to rapid dephosphorylation, which gives it the advantage of having a rapid onset of action, but also a rapid ‘offset’ meaning that in theory it may be less likely to cause excessive bleeding. Phase II trials were promising, leading to the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) trials. However, the results of these trials were disappointing, resulting in the trials being cut short as it became apparent that cangrelor was not superior to clopidogrel in reducing the primary endpoint (a composite of death, MI and ischemia-driven revascularization at 48 h). However, it has been suggested that this may have resulted from the fact that primary endpoint was evaluated at 48 h, and that follow up did not extend beyond 30 days: it is possible that different results may have been obtained if the study had been extended. In addition to this, it is also worth pointing out that an antiplatelet drug that does not have to be administered orally would be particularly valuable in the significant number of patients who present with cardiac arrest or intractable emesis.

Elinogrel is a competitive inhibitor of the PY_a receptor, and shows promise for treatment of ACS. An initial phase II dose escalation study (the Early Rapid Reversal of Platelet Thrombosis with Intravenous Elinogrel before PCI to ERASE-MI) showed it was well-tolerated, with no significant increase in incidence of major bleeding. A further phase II study (INNOVATE-PCI) was a randomized double-blind study involving 800 patients selected for PCI and randomized to receive either clopidogrel (loading dose of 300–600 mg, followed by 75 mg daily maintenance dose) or elinogrel (80 mg IV, followed 50–100 mg oral daily dose). Elinogrel was seen to deliver a more rapid and potent antiplatelet effect when compared with clopidogrel, and this effect was sustained in the maintenance period. Elinogrel may be of particular use in clopidogrel non-responders, and a large (24,000 patient) phase III trial is planned to investigate its benefits in STEMI.

GPIIb/III_a inhibitors
The final common pathway of platelet aggregation results in fibrinogen cross-linking between activated platelets, mediated by the GPIIb/III_a receptor (Fig. 2). The prototype antagonist of this receptor is abciximab, but other members of the class include tirofiban and eptifibatide. Initially, these drugs were administered as IV infusions and were shown to be beneficial in acute settings, especially in reducing the risk of recurrent ischemic events in patients undergoing invasive procedures such as PCI. The development of oral agents potentially allowed the extension of these short-term benefits, although the results of a number of trials have revealed this not to be the case. Trials involving oral GPIIb/III_a inhibitors include EXCITE (Evaluation of Oral Xemilofiban in Controlling Thrombotic Events), OPUS-TIMI 16 (Orbofiban in Patients with Unstable Coronary Syndromes), SYMPHONY (Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Events Post Acute Coronary Syndromes), 2nd SYMPHONY and BRAVO (Blockade of the GPIIb/III_a Receptor to Avoid Vascular Occlusion). A meta-analysis of the data from these studies (involving a total of 45,523 patients) reveals no significant protection from ischemic events, but a 35% relative increase in the risk of death. Some of this risk (as with all antithrombotic agents) is due to the increased risk of bleeding, but it is also due to a paradoxical increase in the number of ischemic events. A number of theories have been advanced to account for these observations, including the possibility that the GPIIb/III_a antagonists may have partial agonist effects at the receptor, inducing pro-aggregatory effects such
as the production of TXA₂. There is also evidence to suggest that at low levels of inhibition, the antagonists increase platelet P-selectin expression, which promotes formation of platelet-leukocyte aggregates and increases plasma levels of sCD40L.\textsuperscript{125}

However, this data is drawn from across the spectrum of ACS. Further consideration of the trial data indicates that use of GPII\textsubscript{b}/III\textsubscript{a} inhibitors is beneficial in certain subgroups of patients, namely those undergoing invasive procedures such as PCI.\textsuperscript{125,131–133} diabetic patients\textsuperscript{134} and, particularly, diabetic patients undergoing PCI.\textsuperscript{134} More recent data suggest that GPII\textsubscript{b}/III\textsubscript{a} inhibitors may be especially useful in invasive therapies when combined with clopidogrel treatment upstream of the procedure. Synergism with clopidogrel is likely—expression of the GPII\textsubscript{b}/III\textsubscript{a} receptor is upregulated by ADP activation of the PY\textsubscript{12} receptor\textsuperscript{91,135}—but the combination therapy is also likely to provide additional coverage for clopidogrel non-responders. Data from the EARLY-ACS trial suggests that epifibatide combined with upstream clopidogrel may reduce the 30-day ischemic risk in patients with NSTE-ACS undergoing diagnostic angiography.\textsuperscript{31}

The failure of GPII\textsubscript{b}/III\textsubscript{a} inhibitors to deliver with regards to all patients has seen a reduction in usage, but there is a strong case for their use in particular circumstances and an important part of the initial diagnosis and risk stratification in patients admitted with ACS is recognising those who are likely to benefit.\textsuperscript{1}

Platelet thrombin receptor antagonists

Platelet thrombin receptor antagonists are a promising new class of antiplatelet drugs, which seem likely to enhance existing dual antiplatelet therapy. PAR inhibition targets a separate mechanism of platelet activation (see Fig. 2) and because it does not impact upon thrombin-dependent fibrin generation and coagulation, it has the potential to offer additive antiplatelet coverage theoretically without incurring significant additional bleeding risk. There are two such agents that are currently under development, SCH530348 (vorapaxar) and E-5555 (atopaxar). The future of these drugs is unclear. While they have been shown to be effective with regards to platelet inhibition, there have been concerns about adverse effects.\textsuperscript{136,137}

Initial trials with atopaxar included the Lessons from Antagonizing the Cellular Effects of Thrombin in ACS (LANCELOT-ACS) and LANCELOT-CAD. Both trials showed that the drug was effective in reducing platelet activity, but the LANCELOT-CAD trial was associated with an increased risk of major bleeding. Furthermore, the drug was also seen to prolong the QT\textsubscript{c} interval, as well as cause an asymptomatic elevation in liver transaminases, all of which are a cause for concern. Similarly, trials involving vorapaxar have raised concerns—the Trial to Assess the Effects of SCH530348 in Preventing Heart Attack and Stroke in Patients with Atherosclerosis (TRA2P-TIMI50) saw an increased risk of intracranial hemorrhage in patients with a history of stroke, and the trial has been altered to exclude these patients. The Trial to Assess the Trial to Assess the Effects of SCH530348 in Preventing Heart Attack and Stroke in Patients with Acute Coronary Syndromes (TRACER) has been terminated early because enough endpoints have occurred to meet the proposed outcome of the study and will report shortly.\textsuperscript{136}

Statins

Although the main cardiovascular benefits of statins are likely to result from the inhibition of endogenous cholesterol synthesis, leading to a reduction in plasma LDL-C levels, the risk reduction is not entirely explained by this mechanism. There is a significant body of evidence to indicate that statins have anti-inflammatory effects and these include a reduction in platelet aggregation, resulting from increased bioavailability of NO.\textsuperscript{138} Indeed, trials such as PROVE-IT TIMI 22\textsuperscript{139} and MIRACL (Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes)\textsuperscript{140} have shown that statin treatment is associated with a significant reduction in recurrent events. The mechanism of action is likely to result from changes in gene expression within both the solid and fluid phase of the plaque environment, including downregulation of a number of proteins involved in platelet activation. It is worthy of note that these benefits may, in fact, be underestimated. Most of the trials that have been concerned with the lipid-lowering effects of statins with regards to primary and secondary prevention have included recent ACS in their exclusion criteria. Stopping statin therapy is associated with a profound rebound phenomenon\textsuperscript{138,141} with respect to NO, and one study, involving a subgroup of patients on the Platelet Receptor Inhibition in Ischemic Syndrome...
Management (PRIISM) trial, showed a three-fold increase in the number of thrombotic events in patients with ACS when simvastatin therapy was stopped and replaced with lower doses of fluvastatin.\(^{138}\)

**Anticoagulants**

Anticoagulants inhibit thrombin generation and are therefore useful in combination with antiplatelets. Commonly used anticoagulants in the treatment of ACS include unfractionated heparin (UFH), low molecular weight heparin (LMWH) and vitamin K ‘antagonists’ such as warfarin. UFH is the most widely used parenteral anticoagulant, but its use is associated with thrombocytopenia and complicated by wide inter-individual variability in response. LMWH and synthetic pentasaccharides such as fondaparinux have proved to be superior in ACS, but can be problematic when rapid reversal of anticoagulation may be required. Bivalirudin and the newer generation oral direct thrombin inhibitors are proving valuable in this regard.

**Unfractionated heparin**

Heparin is a heterogenous polysaccharide mixture made up of molecules with molecular weights ranging from 2–30 KDa.\(^{142,143}\) A proportion of these molecules (typically one-third) contain the so-called pentasaccharide sequence which binds to antithrombin, increasing the rate at which antithrombin inhibits factor Xa. Heparin components have Factor IIa-inhibitory effects, but as this requires binding to and bridging of both thrombin and antithrombin, the pentasaccharide-containing molecules must contain at least 18 saccharide units. Heparin mixtures are poorly absorbed subcutaneously, so are administered IV, and the narrow therapeutic window means that close monitoring is required. Treatment must be maintained throughout the initial period because there can be a transient reactivation of coagulation which slightly increases the risk of CV events, even if the patient is also taking aspirin. The relative risk of death or MI is 0.67 with heparin treatment (although this is largely accounted for by the reduction in MI and the benefits are not sustained after the treatment period because of the ‘rebound’ described above.

**Low molecular weight heparin (LMWH)**

Derived from heparin, this mixture contains molecules ranging from 2–10 KDa.\(^{142,143}\) The mixture still includes molecules with the pentasaccharide sequence, and this is the basis of its anti-Xa activity. However, there are fewer of the longer polysaccharide chains present in the mix, with the result that the anti-IIa activity is less than that seen with heparin. LMWH is readily absorbed subcutaneously and the improved pharmacokinetics mean a closer relationship between the dose and the clinical effect, and there is also a lower risk of heparin-induced thrombocytopenia. Drugs in this class include enoxaparin, and trials have demonstrated its superiority compared with UFH both in patients being treated for NSTE-ACS by medical intervention,\(^{144}\) and STEMI patients undergoing PCI.\(^{145}\)

These are also synthetic drugs modelled on the heparin pentasaccharide sequence whose anticoagulant effect is a result of anti-Xa-selective inhibition of thrombin formation. This class of drugs includes fondaparinux which is approved for use in acute coronary syndromes. The Fifth Organisation to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial compared fondaparinux with enoxaparin in patients with NSTE-ACS and found it to be not inferior to enoxaparin, but that major bleeding events by day 9 were significantly reduced (2.4% v 5.1), indicating a superior risk: benefit ratio. The OASIS-6 trial also showed that fondaparinux was of benefit in patients with STEMI: at 30 days, there was a significant reduction in mortality in the fondaparinux arm and the rates of major bleeding were similar in the two groups (reviewed in\(^{146}\)).

**Oral vitamin K ‘antagonists’**

Oral vitamin K ‘antagonists’ have a long history of use in a variety of clinical contexts including ACS and these are reviewed elsewhere.\(^{143,147}\) However, they are associated with a number of problems that limit their use, not least the fact that they have a delayed onset and offset of action that tends to prolong the length of hospital stay. Polymorphic variations in genes involved in their metabolism accounts at least in part for the wide inter-patient variation in response and the very narrow therapeutic window means that close monitoring is essential. Despite great care in adjusting dosing regimens, INRs often fall outwith the target range, meaning that the patient either has insufficient anticoagulation cover or is at a dangerously increased risk of bleeding. These problems have driven the
search for agents with better tolerability. Warfarin is the best known of this class of drugs and the indications for its use are discussed in Table 2.

Direct thrombin inhibitors
The role of thrombin is central to clot formation: it is involved in the conversion of fibrin to fibrinogen, activates a number of substrates involved in the coagulation cascade, and also activates the platelet protease activated receptors. These processes occur as a result of substrate interaction with specific binding sites on the thrombin molecule, which include a direct binding site and two secondary sites (exosites 1 and 2), and direct thrombin inhibitors work by binding to these sites. Direct thrombin inhibitors include hirudin (rarely used because of its narrow therapeutic window) and bivalirudin, which is administered intravenously. Bivalirudin monotherapy has been shown to significantly reduce mortality in patients undergoing PCI in both STEMI and NSTE-ACS when compared with heparin and routine use of GPIIb/IIIa inhibitors, largely because of a comparatively lower incidence of major bleeding.

Oral direct thrombin inhibitors
Melagatran (the active metabolite of the prodrug ximelagatran) was the first such drug to be developed but, although phase III trials indicated it was as effective as warfarin and had a much wider therapeutic window, concerns about hepatotoxicity prevented it from receiving FDA approval. A highly specific treatment regimen of ximelagatan/melagatran gained European approval for the prevention of post-operative deep vein thrombosis, but the drugs were removed from the market due to cases of serious liver damage. However, the trials did indicate that the drug was effective in providing a predictable anticoagulant effect with similar efficacy to—and a wider therapeutic window than—warfarin, and this led to the development of other drugs including dabigatran. Dabigatran is a univalent thrombin inhibitor which directly interacts with the binding site, and thus is not only able to inhibit free thrombin, but also that which is fibrin-bound. It is administered as the prodrug dabigatran etexilate, and is converted to its active form as a result of hydrolytic cleavage by gut, liver and plasma esterases. Encapsulation with tartaric acid enhances absorption, although the poor bioavailability means that relatively high doses must be administered to achieve effective plasma concentrations. Peak plasma concentrations are typically reached within 2 hours after administration, and excretion is primarily through the renal route, and this is likely to account for the differences in half-life between younger and older age groups (approximately 9 and 13 hours respectively). Unlike many of the older anticoagulants, there are relatively few significant drug interactions to be aware of, although also unlike heparin and warfarin, there is no antidote for dabigatran, which makes the management of bleeding events potentially more problematic. A number of clinical trials support its use in prevention of venous thromboembolism (VTE), but there is much less in the way of clinical evidence to support its use in ACS. So far, there has been one phase II trial, the Dose Finding Study for Dabigatran Eteixilate in Patients with Acute Coronary Syndrome (RE-DEEM). This involved 1861 patients with ACS and at least one cardiovascular risk factor, who were randomized to receive either placebo or dabigatran, twice daily, at either 50, 75, 110 or 150 mg). The result revealed a significant dose-related increase in the occurrence of major bleeding events, and clinical event rate was low, although the study was not powered to assess this. At the present time, there is no information to suggest whether large phase III trials for the use of dabigatran in ACS are likely to go ahead.

Factor Xa inhibitors
Factor Xa plays a major role in the coagulation cascade, occupying a key position at the beginning of the common pathway of coagulation, and this makes it an attractive target for antithrombotic therapy. It is also possible that because it has no antithrombin activity, it may allow a small amount of thrombin formation and thus potentially have a lower incidence of adverse bleeding events. Members of this class of drugs are capable of inhibiting both free and prethrombinase bound FXa, and include rivaroxiban and apixaban, edoxaban, betrixaban, darexaban, otamixaban and TAK-442. Most of the newer drugs are tested in the context of additional benefit conferred over and above existing guideline-based therapies. Rivaroxoraban is no exception. The ATLAS-ACS 1-TIMI 46 trial was a dose-escalation study that indicated that rivaroxaban
shows promise in combination with either aspirin or aspirin and clopidogrel.\textsuperscript{157,158} Rivaroxaban is administered orally and has a high bioavailability. Its pharmacokinetics and dynamics are predictable: plasma levels of the drug correlate with its anti-coagulant effect. The results of the trial indicated a non-significant trend towards a reduced rate of the primary composite endpoint of death, MI, stroke or recurrent severe ischemia requiring revascularization. However, the secondary endpoint of death, MI or stroke was significantly lower in patients receiving rivaroxaban (see Table 2), and there was a trend towards greater efficacy in the lower doses (2.5 and 5.0 mg b.i.d.). This led to the dose selection for the ongoing ATLAS-ACS 2-TIMI-51 trial,\textsuperscript{157} a large scale randomized, multi-center, placebo-controlled, event-driven phase III trial which has recruited in excess of 15,570 patients and will investigate the effects of rivaroxaban in combination with existing guideline-based therapy on a number of clinical outcomes.

Apixaban is the only other member of this class to so far make it to phase III clinical testing, although all the phase III trials so far have investigated the ability of the drug to prevent VTE following major orthopedic surgery, and these trials are not discussed here. Like rivaroxaban, the drug has good bioavailability and does not seem to be problematic with regard to drug and food interactions.\textsuperscript{159} A phase II dose-escalation study (APPRAISE-1) showed that at all doses, apixaban was associated with an increased risk of clinically relevant bleeding (and indeed the two higher-dose trial arms were discontinued). This notwithstanding, the 5 and 10 mg total daily doses were associated with a non-significant reduction in ischemic events when compared with placebo in patients receiving standard antiplatelet therapy. The subsequent phase III trial (APPRAISE-2) has been halted early due to unacceptably high rates of major bleeding.

The other members of this class are at various stages in clinical development, although as yet these are primarily being tested for the prevention of thrombotic events not including ACS. Otamixaban has undergone phase II testing suggesting that it has a favourable safety profile when compared with UFH plus eptifibatide, and it is being investigated as a potential adjunct to PCI.\textsuperscript{159}

### List of Abbreviations

ACS, Acute coronary syndrome(s); BNP, Brain natriuretic peptide; CABG, Coronary artery bypass grafting; COX, Cyclo-oxygenase; GRACE, Global Registry of Acute Coronary Events; IL, Interleukin; INR, International Normalized Ratio; LDL, Low-density lipoprotein; MCP, Monocyte chemotactant protein; MI, Myocardial infarction; MMP, Matrix metalloproteinase; MPO, Myeloperoxidase; NF-κB, Nuclear factor-κB; NSTE-ACS, Non-ST segment elevation acute coronary syndrome(s); Ox-LDL, Oxidized low-density lipoprotein; PAI-1, Plasminogen activator inhibitor-1; PCI, Percutaneous coronary intervention; PDGF, Platelet-derived growth factor; PGI\textsubscript{2}, Prostacyclin; PPI, Proton pump inhibitor; PS, Phosphatidyl serine; RANK, Receptor activated by NF-κB; RANKL, Receptor activated by NF-κB ligand; STEMI, ST-segment elevation myocardial infarction; TIMP, Tissue metalloproteinase inhibitor; TF, Tissue factor; TNF-α, Tumor necrosis factor-α; TXA\textsubscript{2}, Thromboxane A\textsubscript{2}; UA, Unstable angina; VTE, Venothromboembolism.

### Conclusion

The past decade has seen a significant increase in the number of clinical agents available for the treatment of the thrombotic events responsible for acute coronary syndromes, and many of the newer agents appear to be particularly valuable in improving outcomes for those patients in high-risk groups. However, since the ability to interfere with the clotting response is at the heart of the mechanism of action of all these drugs, the reality is that a reduction in the risk of recurrent ischemic events is offset by a concomitant increase in the number and severity of clinically significant bleeding events. Maximizing outcome depends on accurately assessing individual risk and selecting not just the appropriate drug, but also the most effective dosing strategy. One of the major advances in thrombocardiology has been the attempt to correlate event and treatment intervention data from around the world, allowing physicians to continue to refine treatment protocols and establish optimal treatment plans for different patient groups.
Disclosure

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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