PLAQUE STABILISATION IN ACUTE CORONARY SYNDROMES: CLINICAL CONSIDERATIONS

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Heart 2003;**89**:1268–1272

The large secondary prevention trials of statin treatment in coronary artery disease were characterised by separation of the survival curves in the first 6–18 months after randomisation.[w1–3] This was too soon to be fully explained by changes in disease progression, so the concept of plaque stabilisation arose, described largely in terms of cap strength and lipid pool.[w4 w5] This concept, however, has no direct parallel in acute coronary syndromes because the plaque has, by definition, already ruptured and thrombosis has occurred with variable obstruction of the arterial lumen.[1 2] The process of plaque rupture occurs against a background of inflammation and endothelial dysfunction which are generalised throughout the coronary arteries, accounting for recent intravascular ultrasound findings of multiple ruptured plaques in patients with acute coronary syndromes, often located remotely from the index artery.[3] In order to achieve plaque stabilisation, therefore, with healing of the ruptured plaque and restoration of luminal patency, the following targets must be achieved:

- Dissolution of thrombus
- Reduction of inflammatory activity
- Passivation of the coronary endothelium.

These targets are not mutually exclusive and most of the strategies used clinically for secondary prevention are effective through several different mechanisms. Timing is critical because event rates are not a linear function of time, but are front-loaded, the period of greatest risk being the early hours and days after presentation (fig 1). Nearly all these events are caused by thrombus extension or re-thrombosis, usually in relation to the index plaque or, less often, to ruptured plaques elsewhere in the coronary circulation. Clearly, therefore, plaque stabilisation must be achieved very early after presentation if lives are to be saved, and the main target must be the thrombus itself and those mechanisms which are driving the thrombotic process.

DISSOLUTION OF THROMBUS

Thrombolytic treatment

Thrombolytic treatment is well established for plaque stabilisation in the acute phase (first 12 hours) of ST elevation myocardial infarction,[w6] although it does not improve the course of less severe coronary syndromes.[w7] These drugs activate plasminogen to form plasmin which degrades fibrin. Treatment is directed at dissolution of coronary thrombus and restoration of luminal patency in order to achieve at least TIMI (thrombolysis in myocardial infarction) III flow when appreciable reductions in myocardial injury occur.[w8] The most effective thrombolytic regimen in the GUSTO (global use of strategies to open occluded coronary arteries) trial was accelerated tissue plasminogen activator (t-PA) plus intravenous heparin which achieved 54% TIMI III patency, associated with effective preservation of left ventricular function, and a 30 day mortality of only 6.3% compared with > 7% for the other thrombolytic regimens under investigation.[w9] More recently "single shot" t-PA mutants (reteplase, tenecteplase) have been shown to have similar efficacy and are now preferred because they are easier to use.[w10 w11]

Percutaneous intervention

TIMI III flow is achieved in only about half of patients treated with accelerated t-PA,[w8] but in > 80% of patients who receive percutaneous coronary intervention (PCI), presumably accounting for its superiority for reducing mortality in acute myocardial infarction.[w12 w13] PCI is legitimately regarded as plaque stabilising treatment in acute coronary syndromes, first by mechanical dispersal of thrombus, second by increasing coronary flow in the expanded lumen and discouraging rethrombosis, and third by stent induced plaque compression to seal the intimal tear and allow healing.[4]

Antiplatelet drugs

Aspirin irreversibly inhibits platelet cyclooxygenase, blocking thromboxane synthesis and inhibiting platelet aggregation and thrombus formation. Endothelial prostacyclin production is also partially blocked and ADP induced platelet activation unaffected, ensuring that antithrombotic effects

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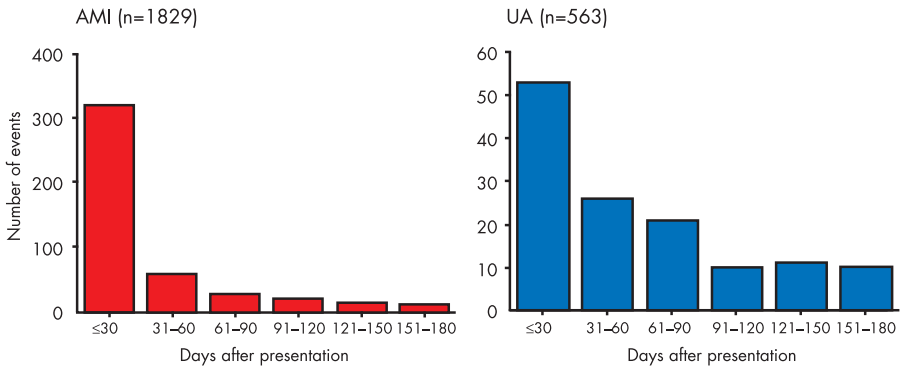

Figure 1 Recurrent events in the first six months after acute coronary syndromes. Date from Newham General Hospital coronary care unit database.

are sufficiently modest to promote plaque stabilisation in acute coronary syndromes without substantial bleeding risk. Thus pre-treatment with aspirin reduces the thrombotic response to plaque rupture and increases the odds of presenting with non-ST elevation rather than ST elevation myocardial infarction.[5 6] Treatment in the acute phase reduces biochemical markers of injury[6] and improves survival across the whole range of acute coronary syndromes. Long term treatment reduces the risk of recurrent events.[w14]

Clopidogrel

The benefits of aspirin have prompted development of further drugs to increase antiplatelet activity and achieve more effective plaque stabilisation through reductions in thrombosis. In every case, however, clinical benefit has been bought at the cost of an increased bleeding risk. Inhibition of ADP induced platelet activation in the CURE (clopidogrel in unstable angina to prevent recurrent events) trial, for example, confirmed that in patients with non-ST elevation coronary syndromes treated with aspirin, the addition of clopidogrel reduced by 20% the risk of the primary end point (death, non-fatal myocardial infarction, stroke), regardless of TIMI risk scores.[7 w15] The risk reduction, however, was driven almost exclusively by reductions in non-fatal myocardial infarction, there being no clear mortality benefit, and was associated with a 37% increase (1% absolute) in the risk of major bleeding. This raised concerns about the clinical value of treatment with clopidogrel[w16]; however, confidence in the drug is now increasing with the recent publication of follow up data for the CURE cohort which has confirmed clear prognostic benefit out to 12 months for combination treatment with aspirin and clopidogrel.[8]

Glycoprotein IIb/IIIa inhibitors

Yet more profound inhibition of platelet aggregation occurs in response to glycoprotein IIb/IIIa inhibition. The benefits of these drugs for patients undergoing coronary stenting are now well established,[w17] but indications for their use in acute coronary syndromes have been slower to develop, bleeding risk again weighing against clinical benefit in many cases.

Aspirin in acute coronary syndromes

- Increases odds of presenting with non-ST elevation
- Reduces biochemical markers of injury
- Reduces risk of recurrent events
- Improves survival

Indeed, oral glycoprotein IIb/IIIa inhibitors have been either unhelpful or harmful in acute coronary syndromes, but in high risk patients with non-ST elevation coronary syndromes, particularly troponin positive or diabetic patients or those with ST segment changes, the benefits of intravenous treatment with tirofiban or eptifibatide for reducing death or myocardial infarction are generally accepted.[w18] Certainly, for any patients requiring urgent percutaneous intervention, infusion of glycoprotein IIb/IIIa inhibitors (evidence is best for abciximab) should be regarded as mandatory.[w19]

Thrombin inhibitors

Indirect thrombin inhibition with unfractionated heparin has a time honoured and evidence based role in the management non-ST elevation acute coronary syndromes,[w20] but has been largely superseded by low molecular weight heparin. Thus randomised trials have confirmed the superior efficacy of enoxaparin (not dalteparin or nadroparin) compared with unfractionated heparin for preventing recurrent ischaemic events.[w21 w22] Randomised trials have also confirmed superior efficacy for direct thrombin inhibitors compared with heparin,[w23] although bleeding risk is increased significantly and a clear clinical role has yet to be identified for this class of drugs.[w24]

REDUCTION IN INFLAMMATORY ACTIVITY

In acute coronary syndromes, inflammatory processes interact importantly with thrombus development, such that the antithrombotic interventions described above are all variably anti-inflammatory.[9] Thus endothelial cells and smooth muscle cells express tissue factor in response to various inflammatory mediators found in coronary plaques, and on exposure to blood following plaque rupture thrombosis ensues. Products of thrombosis, including thrombin and platelet derived growth factor, cause vascular smooth muscle cells to augment interleukin (IL)-6 production inducing an acute phase response with increased hepatic synthesis of fibrinogen, plasminogen activator inhibitor (PAI)-1, and C reactive protein (CRP). In this way the products of coronary thrombosis serve to amplify inflammatory responses and promote a systemic procoagulant effect, representing a truly vicious cycle of thrombosis and inflammation (fig 2). Breaking this cycle with antithrombotic treatment, therefore, passively reduces inflammation which contributes to risk reduction. Interestingly, aspirin may also have direct anti-inflammatory effects, even at the low doses used clinically. Thus, in acute coronary syndromes CRP concentrations are lower in patients pretreated with aspirin,[10] while in stable angina aspirin lowers

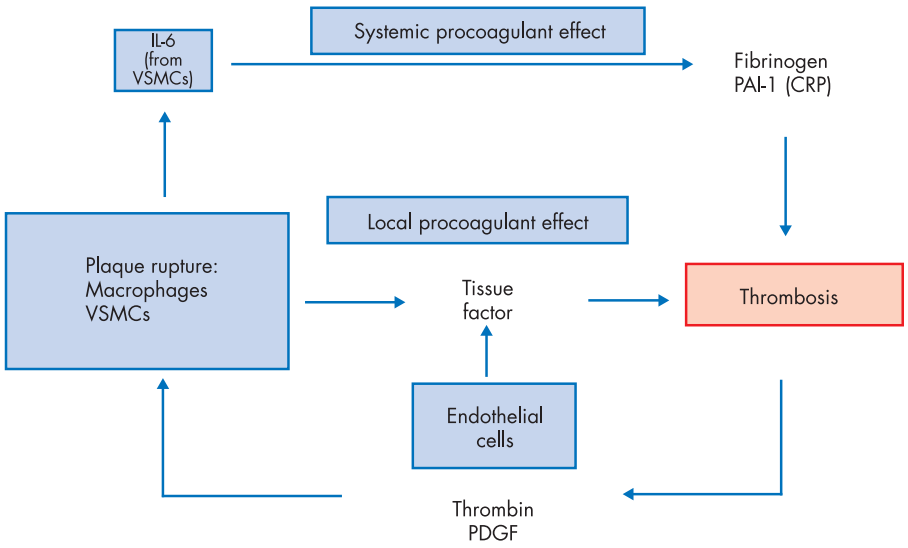

Figure 2 Inflammation and thrombosis in acute coronary syndrome: the cloth thickens. CRP, C reactive protein; IL, interleukin; PAI, plasminogen activator inhibitor; PDGF, platelet derived growth factor; VSMCs, vascular smooth muscle cells. Adapted from Libby *et al*.[9]

CRP and proinflammatory cytokines.[11] The more recent findings that low dose aspirin inhibits cell proliferation[12] and also suppresses vascular inflammation with increases in plaque stability in murine atherosclerosis[13] suggests that these clinical observations might indeed reflect direct anti-inflammatory effects.

The close interaction between thrombosis and inflammation in acute coronary syndromes is itself inseparable from the influence of the coronary endothelium, which is the source of multiple mediators that modify platelet function, fibrinolytic balance, and vascular tone, as well as the inflammatory status of the vessel wall. The coronary endothelium is, therefore, a primary therapeutic target in acute coronary syndromes and many of the anti-inflammatory and anti-thrombotic properties of angiotensin converting enzyme (ACE) inhibitors and statins are mediated directly or indirectly by its passivation.

Angiotensin converting enzyme inhibition

The demonstration that ventricular remodelling is modified in response to ACE inhibition following experimental coronary occlusion led to clinical trials in acute myocardial infarction.[w25 w26] These confirmed that ACE inhibition reduced mortality, but this was largely independent of the severity of ventricular injury and started too early to be wholly explained by effects on the remodelling process.[w27] Indeed in ISIS-4 (fourth international study of infarct survival), survival curves for captopril versus placebo were separating within the first few days, a time frame favouring plaque stabilisation as the likely mechanism of early benefit, mediated presumably by the anti-inflammatory and antithrombotic effects of treatment.[14] Thus, ACE inhibition has important vasculoprotective effects and in experimental models modifies inflammatory mediators in the vascular endothelium and reduces prothrombotic activity.[w28] Similar benefits have been confirmed clinically in acute coronary syndromes—for example, ramipril improved fibrinolytic balance by reducing the activity of plasminogen activator inhibitor in the first 24 hours after myocardial infarction.[w29] In another clinical study,[w30] administration of enalapril in the first two weeks after infarction reduced tissue factor expression and ameliorated the prothrombotic state (fig 3). The anti-inflammatory, antithrombotic effects of ACE inhibition in acute coronary syndromes are complemented by—indeed largely caused by—passivation of the coronary endothelium. This was confirmed in the TREND (trial on reversing endothelial dysfunction) study in which patients with coronary artery disease randomised to treatment with quinapril showed variable recovery of vasodilator responses when challenged with intracoronary acetylcholine.[15]

Clearly, therefore, the plaque stabilising effects of ACE inhibitors are achieved not only by anti-inflammatory activity but also by other important mechanisms that combine to reduce mortality in acute myocardial infarction. Current recommendations are for ACE inhibition in all patients with

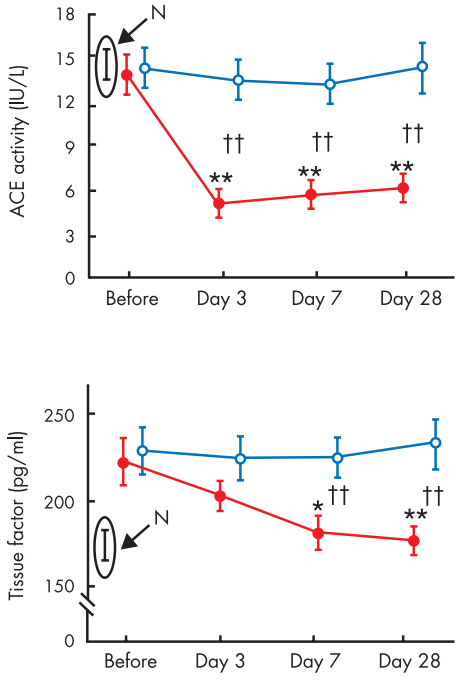

Figure 3 Enalapril versus placebo in acute myocardial infarction: effects on ACE activity and tissue factor (n = 32). N indicates normal range. Adapted from Soejima *et al*.[w30]

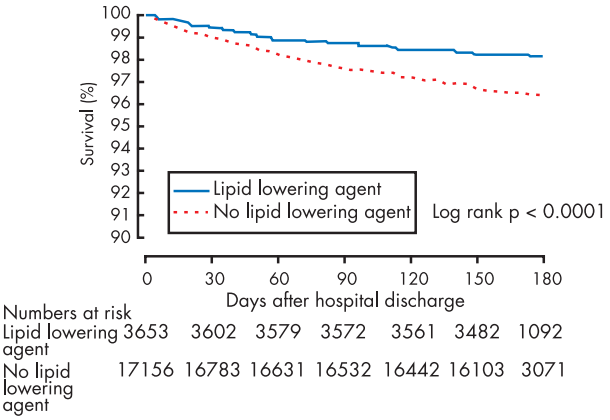

Figure 4 Lipid lowering treatment and early mortality after acute coronary syndromes: GUSTO IIb and PURSUIT. Adapted from Aronow *et al*.[w33]

ST elevation acute myocardial infarction, treatment starting within the first 24 hours if blood pressure permits. Evidence for ACE inhibition in the acute phase of less severe coronary syndromes is unavailable, although the HOPE (heart outcomes prevention evaluation) study showed that treatment protects these high risk individuals in the longer term and should be considered as part of the secondary prevention regimen.[16]

Statins

The value of lipid lowering treatment for secondary prevention of coronary artery disease is well established. Data from GUSTO IIb (global use of strategies to open occluded coronary arteries)[w31] and PURSUIT (platet glycoprotein IIb/IIIa in unstable angina: receptor suppression using Integrilin therapy)[w32] for patients with acute coronary syndromes discharged on lipid lowering treatment showed clearly that outcome in the first six months was significantly better for treated patients, with very early separation of the survival curves within days of discharge (fig 4).[w33] In order to get closer to the acute event when event rates are at their height, the MIRACL (myocardial ischemia reduction with aggressive cholesterol lowering) investigators randomised patients with non-ST elevation acute coronary syndromes to atorvastatin or placebo within 96 hours of presentation.[w34] Atorvastatin treatment was associated with a 16% risk reduction for the combined end point of death, non-fatal myocardial infarction, cardiac arrest or worsening angina, driven largely by reductions in worsening angina. Mechanisms of this early benefit cannot easily be attributed to altered lipid profiles, but more likely reflect passivation of the coronary endothelium and effects on platelet aggregation. Thus in the placebo controlled RECIFE (reduction of cholesterol in ischemia and function of the endothelium) trial in patients with acute coronary syndromes, pravastatin treatment for six weeks produced significant increases in flow mediated dilatation of the brachial artery whereas placebo produced no change.[w35] This effect of pravastatin reflected a significant early improvement in endothelial function, arterial responses to glyceryl trinitrate remaining unaffected.

Benefits of ACE inhibition in acute myocardial infarction

- Protects against ventricular remodelling
- Reduces inflammation
- Reduces prothrombotic activity
- Passivates coronary endothelium

Markers of platelet activation and coagulation factors were unaffected in the RECIFE trial, but in an experimental model utilising porcine aortic media, pravastatin reduced to normal platelet deposition from the blood of hypercholesterolaemic subjects at low and high sheer rates, indicating that antithrombotic effects may indeed contribute to the early benefits of statins in acute coronary syndromes.[w36]

Whatever the precise contributions of anti-inflammatory and antithrombotic responses to statin treatment in stabilising plaques early during the course of acute coronary

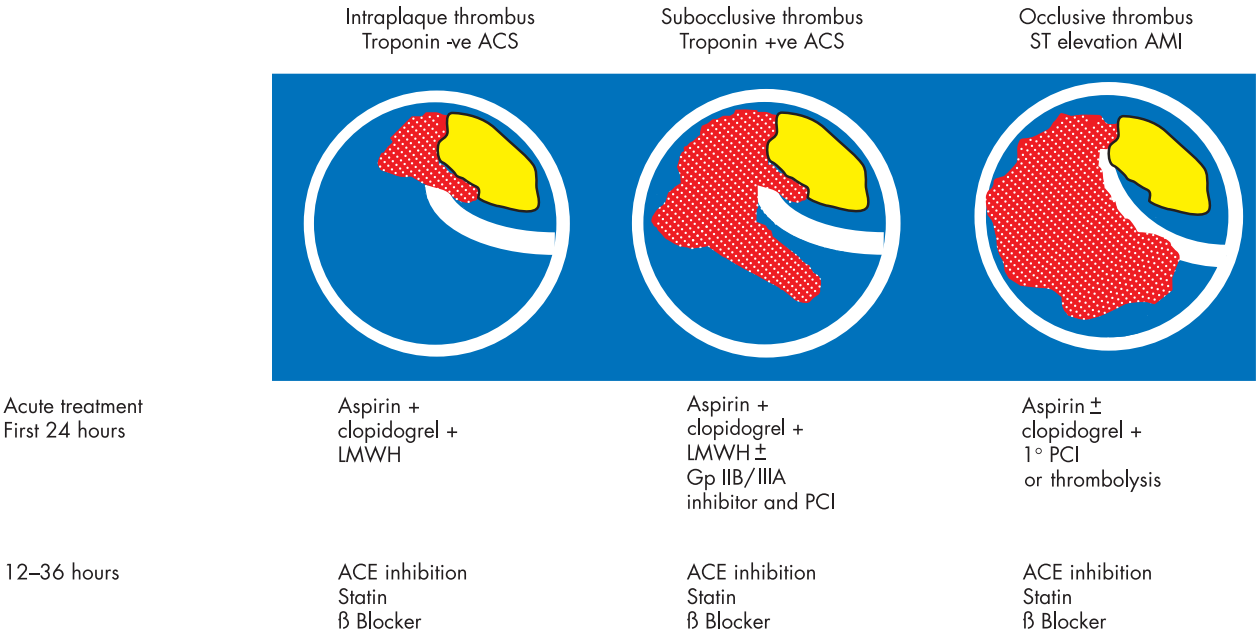

Figure 5 Plaque stabilisation in acute coronary syndromes. ACE angiotensin converting enzyme; ACS, acute coronary syndrome; AMI, acute mycocardial infarction; GP, glycoprotein; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention.

syndromes, the evidence is overwhelming that longer term benefits are directly attributable to low density lipoprotein reduction which doubtless produces further plaque stabilisation through reductions in the lipid pool as well as slowing the progression of disease. Certainly, the risk profile of patients with acute coronary syndromes demands that all should receive statin treatment, and the data from MIRACL confirm that treatment can safely be started early after hospital admission.

β Blockers

β Blocker treatment in the acute phase of myocardial infarction[w37] and early afterwards reduces mortality,[w38 w39] although the mechanism is unclear. There is no evidence for a direct effect of the sympathetic nervous system on endothelial function, although indirect effects on the endothelial production of vasoactive substances, mediated by variations in blood flow and sheer stress, are well documented.[w40 w41] Direct effects of β blockade on platelet function have also been postulated, but although β receptors have been identified on platelets, antithrombotic effects have been hard to confirm.[w42–44] Certainly, β blockers reduce sympatho-adrenal activation[w45] and it is likely that the predictable haemodynamic and antiarrhythmic consequences, rather than any direct plaque stabilising attributes, largely account for the benefits of treatment in acute myocardial infarction.

CONCLUSION

Plaque stabilisation in acute coronary syndromes demands early and effective antithrombotic treatment which should always include aspirin with the addition of thrombolytic treatment, and other antiplatelet agents (clopidogrel, glycoprotein IIb/IIIa receptor inhibitors), depending on the mode of presentation and the need for invasive management (fig 5). Additional treatment with ACE inhibitors and statins passivates the coronary endothelium, reducing inflammation and providing further antithrombotic support.

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Additional references appear on the *Heart* website—www.heartjnl.com/supplemental.

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Adam D Timmis

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