Should acute MI patients receive dual antiplatelet therapy: a review of new data

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Abstract

Thrombolytic therapy in the management of acute myocardial infarction (MI) shows true evidence of benefit. Administration of a thrombolytic saves about 30 lives per 1,000 in those presenting within six hours of symptom onset but only 20 lives per 1,000 when patients receive treatment between six and 12 hours after symptom onset. After 12 hours there appears to be only a small and statistically uncertain benefit.

The aim in thrombolysis should be to increase the number of patients who achieve TIMI grade 3 flow as soon as possible after the occlusive event. Additional benefit in improving thrombolysis, particularly in reducing 30-day mortality, has been shown by adding the antiplatelet agent, aspirin, to thrombolytic therapy. The addition of a second antiplatelet agent, such as clopidogrel, has been shown to be of benefit in other, less immediately severe atherothrombotic manifestations (unstable angina and non-ST-elevation MI) and looks to be a promising development in the management of acute ST-elevation MI. The potential advantages of dual antiplatelet therapy in this setting, investigated in the recently published CLARITY study, are discussed.

Key words: acute coronary syndromes, aspirin, clopidogrel, ST-elevation myocardial infarction.

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Introduction

More than a quarter of a million people each year in the UK suffer a myocardial infarction (MI). Many die within the first two hours and at least half have succumbed within a month.[1] Even for those who survive the first month, there is an above-average risk of dying within the next five to 10 years, from recurrent MI or other problems related to the underlying cause.

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Acute MI is essentially a thrombotic event with the development of occlusive clot following the disruption of the atheromatous plaque. The key to optimal initial management of acute MI is to ensure that the blood flow is reinstated to the affected, infarcting myocardium, using treatments that dissolve clot. The introduction of thrombolytic therapy in the 1980s was a major step forward in the management of these patients, reducing mortality to between 10 and 20%.[2] However, a substantial number of patients receiving fibrinolytic therapy do not achieve adequate reperfusion and, even in those whose arteries are unblocked, reocclusion can occur. In these patients, the long-term mortality risk is doubled.[3]

The 'open artery' theory

The 'open artery' theory suggests that the short-, medium- and long-term outcome after an acute MI is determined by the degree of patency achieved in the infarct-related artery. Patency is commonly assessed by the extent to which flow has been restored in the affected artery (usually measured in trials by angiography 90 minutes after thrombolysis), using the TIMI (Thrombolysis in Myocardial Infarction) classification:

- TIMI 0 refers to the absence of any flow beyond a coronary occlusion
- TIMI 1 flow is faint coronary flow beyond the occlusion, although filling of the distal coronary bed is incomplete

- TIMI 2 flow is delayed or sluggish flow, although with complete filling of the distal territory
- TIMI 3 flow is normal flow that fills the distal coronary bed completely.

The relationship between TIMI flow and longer-term outcomes after an MI has been addressed in a number of studies. For example, data from the angiography arm of the GUSTO (Global Utilisation of Streptokinase and t-PA for Occluded coronary arteries) trial[4] show that the 30-day mortality rate was halved from 8.4% with a TIMI flow 0 at 90-minute angiogram to 4% in those with angiographic TIMI flow 3. Similarly, in a meta-analysis of 4,607 patients,[5] mortality was 9.2% with TIMI grade 0/1 flow but 6.6% with TIMI grade 2 flow, and only 3.7% with TIMI grade 3 flow. Furthermore, five- and 10-year follow-up suggests a continued benefit in patients with initial (i.e. at the time of the infarct) TIMI grade 3 flow.[6]

It is clearly important to achieve sustained arterial patency. Thrombolytic therapy alone is unable to produce or maintain adequate patency, with only a third to a half of patients achieving TIMI grade 3 flow;[7] the reocclusion rate is 30% by three months.[8] Patients with reoccluded arteries have a higher event rate at one year compared with those whose arteries were patent at three months (83% versus 63%, respectively); by three years the event rate is 73% versus 33%.[7]

The role of antiplatelet agents

Blocked coronary arteries are the result of thrombotic occlusion following a plaque event, and arterial thrombus is initiated by platelet activation and platelet propagation. It therefore seems straightforward to address this through the use of adjunctive antiplatelet agents. The benefit of additional antiplatelet therapy has been confirmed with the use of aspirin, which has been shown to improve survival additive to using a thrombolytic and to reduce the rate of angiographic reocclusion by 22%.[8]

Aspirin, while beneficial, acts on only one of a number of pathways that are important in the platelet activation process. It inhibits cyclo-oxygenase and thereby reduces the production of prostaglandin and thromboxane (TX) A2 from arachidonic aid. Despite effective inhibition of cyclo-oxygenase, platelet activation can still occur through TXA2-independent pathways, leading to the aggregation of platelets and the formation of thrombin. Intravenous antiplatelet agents, the glycoprotein (GP) IIb/IIIa inhibitors, have been shown to be beneficial when primary angioplasty is being undertaken in the setting of acute MI.[9]

Trying to target the thrombolytic process with a potent oral additional antiplatelet agents to improve clot dissolution and therefore facilitate TIMI grade 3 flow is therefore worthwhile. The antiplatelet agent, clopidogrel, inhibits the binding of adenosine diphosphate (ADP) to its platelet membrane receptors, thereby blocking the activation of the GP IIb/IIIa receptor, its binding to fibrinogen and further platelet aggregation. It has a number of advantages: it is an oral agent, it is additive to aspirin due to its action through alternative pathways, and it is already used in clinical practice.

Table 1. CLARITY: primary efficacy and angiographic outcomes

Outcome	Placebo	Clopidogrel	Odds ratio	P value
Primary end point (%)*	21.7	15.0	0.64	<0.001
- TIMI flow grade 0/1	18.4	11.7	0.59	<0.001
- MI	3.6	2.5	0.70	0.08
- death	2.2	2.6	1.17	0.49
Angiographic end points (%)				
- TIMI flow grade 3	60.8	67.8	1.36	<0.001
- TIMI myocardial perfusion 3	51.2	55.8	1.21	0.008
- thrombus	50.8	43.0	0.73	<0.001

*The primary efficacy end point was a composite of an occluded infarct-related artery (defined by a TIMI flow grade of 0 or 1) on angiography or death or recurrent MI before angiography

The synergistic potential for aspirin and clopidogrel has been confirmed in other, less acute manifestations of atherothrombotic disease, such as unstable angina and non-ST-elevation MI (i.e. acute coronary syndromes). The impact of the combination of antiplatelet therapies in these patients was investigated in the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial,[10] which showed that aspirin plus clopidogrel reduced the relative risk of cardiovascular death, non-fatal MI, or stroke by 20% compared with aspirin plus placebo (p< 0.001), without significantly increasing the risk of bleeding – a major concern with all antiplatelet/antithrombotic treatments.

Given our knowledge of the common underlying (platelet-initiated thrombus) causes of acute coronary syndromes and MI (the two most significant manifestations along the spectrum of arterial stenosis/occlusion), and the complementary modes of action of aspirin and clopidogrel, it is reasonable to suggest that dual antiplatelet therapy could have a role in the management of acute MI and should be tested.

CLARITY

The large multinational CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction 28) study was undertaken to investigate this hypothesis and the results were published last year.[11] The trial involved 3,491 patients at 319 centres in 23 countries, in patients up to 75 years old presenting within 12 hours of onset of an ST-elevation MI. All patients received standard fibrinolytic therapy, heparin if appropriate and aspirin; half of the group was randomised and approximately half received clopidogrel (300 mg loading dose, followed by 75 mg daily) while the other half received placebo. The study treatment lasted until the patient underwent scheduled angiography (within eight days) or until hospital discharge, if that was sooner. Treatment could be continued thereafter at the investigator's discretion. The primary end point was the combination of angiographic (TIMI flow) and clinical end points. Results are shown in table 1.

The addition of clopidogrel was associated with improved artery patency: the percentage of patients with a TIMI grade 0/1 flow was reduced from 18% with placebo to 12% with clopidogrel, while the proportion of patients with a TIMI grade 3 flow increased from 61% to 68%, respectively. As a result, combination antiplatelet therapy with aspirin and clopidogrel reduced the absolute risk of the primary end point (coronary artery occlusion, recurrent MI or death) by 6.7 percentage points (36% odds reduction; p<0.001). The efficacy benefits were maintained after hospital discharge such that by 30 days, the combination was associated with a 20% odds reduction in the composite end point of cardiovascular death, recurrent MI, or urgent revascularisation (p=0.03). As in the CURE study, there was no significant difference between the clopidogrel and placebo groups in bleeding rates.

COMMIT

A second recently published study on the clinical impact of combined antiplatelet therapy in acute MI also suggests benefit.[11] In this China-based study of more than 45,000 patients admitted to hospital within 24 hours, half were randomly allocated to clopidogrel and half to matched placebo in addition to aspirin. Treatment continued until hospital discharge. Those given clopidogrel suffered a 9% reduction in death, re-infarction or stroke relative to the placebo group (9.2% versus 10.1%, respectively, p=0.002); and a 7% reduction in death (7.5% versus 8.1%, respectively, p=0.03). While the absolute reductions appear small they are significant and do equate to nine fewer events per 1,000 patients for two weeks of treatment, although cost benefit both in terms of actual financial cost and patient side effects will need to be addressed. In this context there appeared to be no excess of bleeding in the treated group.

Conclusion

Effective opening of the infarct-related artery is of paramount importance in the acute management of MI patients. Thrombolytic therapy is the standard pharmaceutical approach, with adjunctive aspirin also playing a significant role. CLARITY has indicated that future research should focus on combination antiplatelet therapy, together with ongoing efforts to educate the public about the implications of recognising chest pain and seeking rapid, urgent medical assistance. We now need to consider whether this is a safe, effective, additional therapeutic option to paramedics giving pre-hospital thrombolytics, as well as to those receiving in-hospital lytics. Use of additional antiplatelet treatment, based on these data, should also be considered by those drawing up national and international guidelines.

Conflict of interest

AG receives research grants and is a member of the speaker's panel for Sanofi-Aventis and Bristol-Myers Squibb who both market clopidogrel. He was UK principal investigator on the CLARITY study.

Key messages

- The short- and long-term success of treatment depends on immediately reinstating optimal blood flow, using blood-clot dissolving therapies such as fibrinolytics and antiplatelet agents
- Although it is the single most effective pharmaceutical strategy, thrombolysis is not effective in all patients, with only 60% attaining the important TIMI grade 3 flow rate. Further thrombolytics do not prevent future re-occlusion
- Aspirin and clopidogrel target different pathways of the platelet activation process. Their synergistic potential has already been proven in the long-term care of patients with acute coronary syndromes (unstable angina and non-ST elevation MI)
- The CLARITY-TIMI 28 study now provides evidence that dual antiplatelet therapy could have an important role in the acute management of patients with ST-elevation MI

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