May aspirin be replaced in the treatment of myocardial infarction?

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Acute myocardial infarction is usually the result of a thrombotic coronary occlusion secondary to vulnerable plaque rupture. Plaque vulnerability depends on the size and consistency of the atheromatous core, the fibrous cap thickness, and the existence of ongoing inflammation with activated macrophages and T-lymphocytes\(^{1,2}\). It has been shown that plaques with a lipid core occupying more than 40% of the plaque area and with a thin fibrous cap are particularly prone to rupture. Plaques causing little coronary obstruction have similar characteristics\(^3\). Thus a critical coronary stenosis is not always, as was long considered, the primary pathogenic factor of acute myocardial infarction. Plaque rupture and endothelial denudation activate platelet aggregation and promote the initiation of the coagulation cascade with the resulting formation of an intracoronary thrombus rich in platelets and fibrin.

Prognosis following a plaque rupture is largely determined by the thrombogenic substrate, which is strongly dependent on platelet aggregability and other factors. Different abnormalities of platelet function have been described in the setting of acute myocardial infarction\(^{1,4}\) including decreased platelet prostacyclin binding and increased thromboxane A\(_2\) biosynthesis. As a result of the interaction between platelets and the atheromatous 'gruel' after rupture, arachinodate is released from the platelet membrane. The cyclooxygenase and thromboxane synthetase enzymes convert this precursor to thromboxane A\(_2\) to play an important role in platelet aggregation. Platelet hyperactivity, as assessed by measures of spontaneous platelet aggregation, has been shown to be associated with impaired prognosis after myocardial infarction\(^5\).

Since acute myocardial infarction is mostly due to rupture of a vulnerable plaque with superimposed occlusive thrombus the aim of treatment is to restore infarct-related artery patency before necrosis is completed (before 6 h after symptoms onset). Recanalization of the occluded artery may be rapidly achieved by intravenous fibrinolysis or primary angioplasty (PTCA). Both therapies, however, require the use of other concomitant drugs to minimize the risk of reclosure, i.e. antiaggregants. The additional anti-thrombotic treatment that usually includes aspirin may increase the occurrence of bleeding, especially gastrointestinal and cerebrovascular. There are four major groups of antiplatelet compounds\(^6\): (1) drugs that inhibit cyclooxygenase. Aspirin is a reference standard of this group, in which triflusal is also included. In this issue of the journal Cruz-Fernández et al.\(^7\) present the results of the TIM (triflusal in myocardial infarction trial) study. This study was designed to compare the safety and efficacy of triflusal vs aspirin in patients with acute myocardial infarction. (2) Agents that interfere with ADP-mediated platelet reactions such as ticlopidine and clopidogrel. (3) Thrombin inhibitors such as hirudin. (4) GPIIb/IIIa receptor antagonists such as abciximab. ISIS 2\(^8\) has provided conclusive evidence of the benefits of aspirin in acute myocardial infarction. Patients who received low doses of aspirin compared with placebo had a 33% reduction in risk of cardiovascular mortality at 5 weeks and a 50% reduction in non-fatal reinfarction. Over the past years, other trials\(^{9,10}\) have also demonstrated the importance of aspirin in the management of acute coronary syndromes. The beneficial effect of aspirin is mainly related to decreased platelet aggregation due to irreversible blockade of platelet cyclooxygenase which is required for thromboxane A\(_2\) synthesis. Low dose aspirin is considered the antiplatelet regimen of choice for long-term oral treatment of patients with ischaemic heart disease, especially in the acute phase of coronary syndromes and for secondary prevention of myocardial infarction. However, aspirin has the disadvantage of non-selectively inhibiting all cyclooxygenase isoforms at a comparable molar potency. Furthermore, although aspirin blocks the synthesis of thromboxane \(A_2\), one of many agonists that can cause platelet aggregation, it does not inhibit platelet adhesion or platelet secretion in parallel with inhibition of thromboxane \(A_2\) formation\(^6\). Thus, from this perspective aspirin is a weak inhibitor of platelet aggregation induced by triggers such as subendothelial collagen or thrombin. Lastly, in patients with severe atherosclerosis there is no selective sparing of vascular prostacyclin production at anti-thrombotic doses. Thus it seems clear that alternative drugs to aspirin may be useful and particularly important for patients with aspirin resistance, intolerance or allergy.

Direct thrombin inhibitors and glycoprotein \(\text{GPIIb/IIIa receptor antagonists are superior to}

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aspirin in platelet-dependent unstable angina and prevent reocclusion after PTCA, but are currently only available for intravenous administration. Several trials with oral agents have been terminated prematurely due to excessive bleeding or lack of superiority over conventional antiplatelet treatment[11].

The only currently available alternative to aspirin in the setting of acute myocardial infarction and secondary prevention of coronary artery disease, are drugs that act via cyclooxygenase product formation, such as triflusul[12] and compounds that interfere with ADP mediated platelet reduction, such as ticlopidine and clopidogrel[6]. A recent trial comparing aspirin and clopidogrel[6] in post myocardial infarction patients found no benefit in efficacy from clopidogrel, although a modest benefit was seen in the overall group of ischaemic patients.

Triflusul is an antiplatelet agent structurally related to salicylates, but does not derive from acetyl-salicylic acid (aspirin). Antiplatelet properties of triflusul and its active 3-hydroxy-4trifluoro-methylbenzoic acid (HTB) metabolite are primarily mediated by specific inhibition of platelet arachinodic acid metabolism through inhibition of cyclooxygenase[12]. Therefore the production of thromboxone A2, a main contributor of platelet aggregation, is suppressed, as in aspirin. HTB, the triflusul main metabolite, is a reversible cyclooxygenase inhibitor with a prolonged elimination half life. In addition, triflusul and HTB have properties of phosphodiesterase inhibition. This blockade increases platelet and endothelial cyclic adenosine monophosphate (AMPc) concentrations and limits intracellular calcium mobilisation. Thus, although triflusul is a weak inhibitor of platelet cyclooxygenase, the addition effect of its metabolite may contribute to the efficacy of triflusul. As a result, platelet aggregation and secretion are impaired, improving the antithrombotic activity by acting at two different levels of the process. Experimental studies have also shown that triflusul and HTB have an inhibitory effect on cardiovascular inflammatory mediators at a dosage similar to an antiplatelet effect[14]; this may have important clinical implications. In the last 10 years several clinical trials have tested the efficacy of triflusul in different cardiovascular processes (PTCA, unstable angina, post coronary bypass surgery, peripheral occlusive arterial disease, cerebrovascular disease). All these studies have proven a clinical efficacy greater than placebo and/or similar to aspirin but with fewer side effects, especially haemorrhagic complications[12].

Based on these results, triflusul appeared to be a useful alternative to aspirin in the management of acute myocardial infarction, and clinical trials like the TIM trial were ready to run[7]. This double-blind randomized sequential, parallel study was conducted in patients with confirmed acute myocardial infarction (ST ascent or Q wave) randomized to 600 mg of triflusul or 300 mg of aspirin. The treatment was started within 24 h of symptom onset, with a follow-up of 35 days. The baseline characteristics and concomitant treatment were similar in the two arms with over 1000 patients in each arm from 29 centres in Spain, Italy and Portugal. The number of patients taking beta-blockers and ACE inhibitors in this study is lower than in other European countries. However, the majority of patients were treated with antiplatelet drugs (100%) heparin (88%) and fibrinolytic agents (more than 70%).

The primary end-point was the combined incidence of death, non-fatal reinfarction or non-fatal cerebrovascular events in the first 35 days after myocardial infarction. The secondary end-points were death, non-fatal reinfarction, non-fatal cerebrovascular events and the need for urgent revascularization. Although patients in the triflusul arm showed a 12% lower risk of a primary end-point, the difference was not statistically significant. However, the incidence of non-fatal cerebrovascular events was lower in the triflusul (0.48%) than in the aspirin (1.31%) arm. This 63% reduction represents a reduction of nine cerebrovascular events per 1000 patients treated in absolute terms. This difference was mainly due to a reduction in non-fatal cerebral haemorrhage (six patients in aspirin group to none in triflusul group).

The difference in non-fatal cerebrovascular events seems due to a lower incidence of cerebrovascular events in the triflusul-treated group than to an increase in cerebrovascular events in the aspirin-treated group. The incidence of these events in the aspirin arm was of 1.3%, in the normal range of cerebrovascular complications according to other trials of aspirin.

Although aspirin is the standard antiplatelet drug in the management of acute ischaemic syndromes in clinical practice the incidence of haemorrhagic complications especially cerebrovascular bleeding, remains a concern. The TIM trial[7] shows that efficacy of treatment in the 35 days after myocardial infarction is maintained with triflusul with a significant reduction in cerebrovascular bleedings and with a non-significant but clinically relevant trend towards fewer bleedings from any site. Thus, triflusul may be an excellent option in the acute phase of myocardial infarction, especially in patients at risk of haemorrhage or aspirin resistance, intolerance, or allergy. Further studies comparing the efficacy of triflusul with other antiplatelet agents, such as ticlopidine and clopidogrel in different subsets of patients with acute ischaemic syndromes, studying efficacy,
side effects and cost-effectiveness are needed before triptilus can be considered a candidate for routine therapy in myocardial infarction. The TIM trial may offer an alternative to aspirin, a challenge which will certainly stimulate further research in this field.

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References


QT dispersion in ischaemic heart disease

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Almost a century after Einthoven’s invention of the string galvanometer, the surface electrocardiograph retains its central place in cardiological diagnosis. In seeking to extract yet more information from the standard 12 lead ECG, much attention has been given in recent years to the measurement of QT dispersion. The QT interval reflects the duration of depolarization and repolarization of the ventricular myocardium. Abnormal prolongation of the QT interval (congenital or acquired) predisposes to ventricular tachycardia. The QT interval relates directly to the duration of depolarization and repolarization of the ventricular myocardium. Abnormal QT dispersion (measured as the difference between the longest and the shortest QT duration in the 12 ECG leads) reflects inhomogeneous repolarization of ventricular muscle which may provide a substrate for serious ventricular arrhythmias. In the context of ischaemic heart disease, researchers have explored the measurement of QT dispersion as a potential marker of arrhythmic risk, of myocardial ischaemia and of myocardial viability. In none of these applications has the technique so far established a place in routine clinical practice, though some progress has been made in our understanding of the measurement and significance of QT dispersion.

In population studies, QT dispersion has been reported to be an independent predictor of long-term cardiovascular mortality in subjects with known cardiovascular disease at entry. In patients with acute myocardial infarction, measurement of QT dispersion has shown little promise as a predictor of long-term mortality risk for individuals. However, the link between myocardial ischaemia and increased QT dispersion has been elegantly demonstrated in angina patients subjected to atrial pacing.

In this issue, Ikonomidis and colleagues report a study of the relationship between QT dispersion and myocardial viability, as detected by dobutamine stress echocardiography, in patients with past myocardial infarction. They also looked for associations between these phenomena, the patency of the infarct-related artery and the occurrence of ventricular arrhythmias during dobutamine infusion. A low dose dobutamine infusion protocol was chosen (maximum 20 μg·kg⁻¹·min⁻¹ in most patients) to reduce the likelihood of inducing ischaemia during the test; in