

Editorial

Taming platelets in coronary stenting: ticlopidine out, clopidogrel in?

The use of intracoronary stents has revolutionised percutaneous myocardial revascularisation by reducing the need for urgent surgical intervention and decreasing long term restenosis rates to approximately 15%.¹⁻⁴ The early use of these devices was complicated by high rates of acute and subacute thrombosis requiring intensive anticoagulation regimens, which were only partially effective at reducing their incidence.⁵ The importance of the platelet, rather than the coagulation cascade, in the pathogenesis of these complications was confirmed when Schömig *et al* reported an 82% reduction in myocardial infarctions with a combination of aspirin and ticlopidine compared to heparin, phenprocoumon, and aspirin in patients receiving coronary artery stents.⁶ Since that time aspirin and ticlopidine have been widely used following stent insertion for four weeks to six months, with reported composite end points of death, myocardial infarction, and revascularisation, of 0-1.9% in the first 30 days.⁶⁻⁸

Ticlopidine

The rationale for combining aspirin and ticlopidine is derived from their different mechanisms of action, which may potentiate one another. Aspirin produces permanent inhibition of the cyclo-oxygenase pathway thus reducing production of thromboxane A₂, prostaglandin E₂, and prostacyclin. Ticlopidine inhibits ADP induced platelet aggregation by selective, irreversible, and competitive binding to the type 2 purinergic ADP receptor. In vivo studies on platelet function have demonstrated that the combination of aspirin and ticlopidine has a greater effect on platelet aggregation than either agent alone.^{9, 10} It is still unclear, however, whether this dual effect translates into a significant clinical benefit for all coronary stent patients, as several non-randomised studies have reported that aspirin or ticlopidine alone may be adequate to prevent acute stent thrombosis.^{8, 11, 12} It must be emphasised that these studies optimised stent deployment using ultrasound guidance and high pressure balloon dilatation, which are not routine practice in the UK and there is still a general unease about coronary stenting using aspirin alone.

The success of this antiplatelet combination has been tempered to some extent by the frequent side effects of ticlopidine. Severe neutropenia is the most serious of these and occurs in 0.7-1.2%⁴ of patients with up to six months of continuous treatment and 4% of patients with five years¹³ of treatment. In most patients, this complication is reversible with cessation of ticlopidine, but a recent study reported that eight of 19 patients with ticlopidine induced neutropenia died as a result of sepsis despite aggressive treatment with granulocyte colony stimulating factor.¹⁴ Furthermore, the incidence of other side effects such as skin rashes, gastrointestinal disturbance, and renal dysfunction is reported to be 7% in patients on a six week course,⁴ and 22% in those taking ticlopidine for five years.¹³ The clear message from these studies is that if ticlopidine is to be used it should be for as short a time as possible.

Clopidogrel

The recently presented preliminary data from the CLASSICS trial (clopidogrel aspirin stent international co-operative study; American College of Cardiology, New Orleans, USA, 1999) suggest that clopidogrel can be used as an effective alternative to ticlopidine (fig 1). Clopidogrel is a thienopyridine analogue of ticlopidine with a similar mechanism of action. Experimental studies have suggested that a dose of 75 mg clopidogrel is equivalent, in terms of platelet aggregation inhibition, to 500 mg of ticlopidine and may be even more effective in preventing high shear mediated stent thrombosis.¹⁵

The CLASSICS study examined three groups of 335 patients undergoing coronary artery stenting and compared aspirin and two different clopidogrel regimens with aspirin and ticlopidine (fig 1). The study was not powered to detect differences in major adverse cardiac events but was designed to examine the safety, in terms of side effects, of the aspirin and clopidogrel combination. The CAPRIE trial (clopidogrel versus aspirin in patients at risk of ischaemic events)¹⁶ in 19 000 patients showed that clopidogrel alone is as well tolerated as aspirin, but the safety of the aspirin-clopidogrel combination had not been tested. In the CLASSICS trial, the combined results from the two clopidogrel groups with 325 mg of aspirin produced significantly fewer complications than 325 mg aspirin and 250 mg ticlopidine bid (4.56% *v* 9.12%; *p* = 0.005). Of note was the finding that the loading dose produced no more complications than the standard dose of 75 mg of

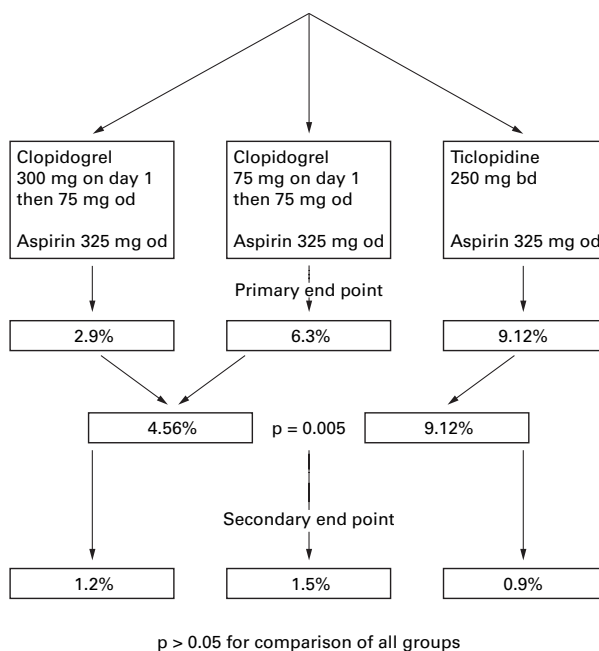


Figure 1 Design and results of the CLASSICS trial: 335 patients in each group were treated for 28 days. Primary end point: cluster of major bleeding, neutropenia, thrombocytopenia, and other early discontinuation for non-cardiac cause. Secondary end point: cluster of major cardiac events (myocardial infarction, sudden death, subacute thrombosis).

clopidogrel. The analysis of the secondary end point of major adverse cardiac events produced a non-significant difference between the groups with an event rate in the aspirin and ticlopidine group of 0.9% and in the aspirin and clopidogrel loading group of 1.2%. Even though the numbers are small and there is a lack of any good comparative efficacy data, the event rate of approximately 1% in both groups does compare favourably with other studies of coronary stenting.⁶⁻⁸

Clopidogrel also has the advantage of being less expensive than ticlopidine: a one month course at 75 mg daily costs approximately £30 (US\$48) whereas a similar course of ticlopidine at 250 mg bid costs approximately £90 (US\$144).

Conclusions

Given the favourable side effect profile, the lower cost, and likely equivalence to ticlopidine in coronary stenting, the time has probably come for clopidogrel and aspirin to become the first choice regimen for post-stent patients. Ticlopidine would then be reserved for those who cannot tolerate clopidogrel. For those who require hard evidence-based guidelines, however, the jury is still out.

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Editorial

Should we ever treat the echo rather than the patient?

It is not unusual to find a Doppler derived peak gradient of 40 mm Hg across a Björk-Shiley valve in the aortic position. However, in the case reported below¹ further investigation led to the identification of thrombus, and the patient underwent reoperation despite being asymptomatic. Should this case affect our management of mechanical valves?

Most centres perform routine postoperative echocardiography. This is useful to compare with future studies as a new paraprothestic leak may be a sign of endocarditis, and a major change in forward flow pattern may support the clinical suspicion of obstruction. However, published guidelines²⁻³ do not recommend further studies unless the patient has symptoms or there is clinical suspicion of valve dysfunction. According to these guidelines, the study ultimately leading to surgery in this patient need not have been performed. We do not know if this would have mattered. The patient might have remained asymptomatic. Alternatively, the thrombosis could have progressed leading to symptomatic severe obstruction, an embolic event or even death.

Thrombosis of mechanical valves in the aortic position is exceptionally rare.⁴ It is therefore unlikely that many lives would be saved by routine echocardiography in all patients.

On the contrary, it is more likely that lives would be endangered as a result of replacing valves unnecessarily on the suspicion of obstruction incorrectly diagnosed from the echocardiogram; surgery based largely or exclusively on gradient alone has occurred anecdotally. In this case report the echocardiogram was clearly abnormal. The disk probably opened incompletely and the peak gradient had doubled compared with previous studies and was well above the published 95% upper limit of 30 mm Hg (Chambers JB, unpublished data, 1990)⁵⁻⁶ for a valve of this size and type. However, a peak gradient of 40 mm Hg¹ could be normal for a 23 mm or smaller Björk-Shiley valve (Chambers JB, unpublished data, 1990).⁵⁻⁶ For a 19 mm St Jude or Carbo-medics valve a peak gradient as high as 60 mm Hg could be normal.⁷⁻⁸ Thus, an apparently high individual velocity or derived gradient requires careful interpretation in relation to the valve type and size, to previous studies in the same patient, and in the context of left ventricular function and symptoms before clinical management is changed.

The risk of mechanical thrombosis is so close to 0⁴ that if a patient is well the valve can usually be assumed to be normal. The present case¹ is a rare exception and routine echocardiography of asymptomatic patients with clinically normal mechanical valves is not necessary.

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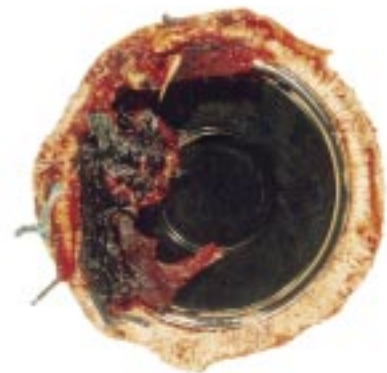
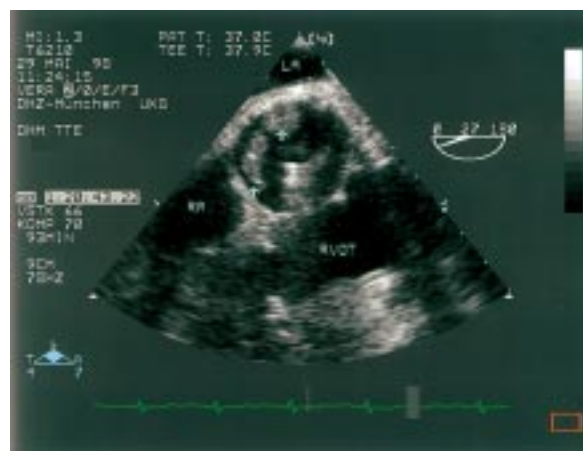
IMAGES IN CARDIOLOGY

Thrombosis of an aortic valve prosthesis

A 66 year old woman had undergone aortic valve replacement (Björk-Shiley standard prosthesis, size 27) 23 years earlier because of severe aortic stenosis. She had since been asymptomatic and all outpatient examinations showed normal prosthetic function. She had recently undergone surgery for haemorrhoids, which required anticoagulation to be interrupted and bridged by once daily subcutaneous injections of low molecular heparin. A peak pressure gradient of 40 mm Hg was measured across the prosthesis on transthoracic Doppler echocardiography. Based on a similar heart rate, this was double that of a

previous examination; therefore, obstruction of the prosthetic valve was suspected.

Transoesophageal echocardiography showed thrombotic material adjacent to the prosthesis. A cross sectional view through the aortic root revealed thrombi (arrowed) localised at the prosthetic ring protruding into the lumen. A long axis view of the ascending aorta showed flow exclusively across the major orifice by colour Doppler (not shown). The thrombotic prosthesis was excised and replaced with a bileaflet aortic valve prosthesis; her recovery was uneventful.



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