Platelet glycoprotein IIb/IIIa inhibition during percutaneous coronary revascularization: what more needs to be proven?

The adoption of new technologies into the practice of interventional cardiology often follows a stereotypical course. Concepts for which there is an intuitively sensible rationale may be rapidly accepted, particularly if there is a readily observable ‘advantage’ over existing techniques and risks appear low. Directional atherectomy, for example, was developed according to the hypothesis that ‘debulking’ of atherosclerotic plaque would provide a more controlled procedural result and less restenosis compared with balloon angioplasty[1]. Angiographic outcome was usually superior to that with the balloon and complication rates were perceived to be low, and directional atherectomy came to be employed in up to 20% of interventional procedures within the United States[2]. Even after randomized trials demonstrated no benefit to this technique with regard to the incidence of restenosis and a clear excess risk of periprocedural complications[2,3], use of directional atherectomy was not markedly diminished[4] until this technique was supplanted by coronary stenting. Similarly, although enthusiasm for stenting was initially tempered by technical difficulties with early designs, subacute thrombosis, and anticoagulation-associated bleeding, this technique enjoyed explosive growth once the major risks were eliminated by high-pressure deployment and enhanced antiplatelet therapy. Relatively small randomized trials demonstrated the efficacy of stenting in reducing rates of target vessel revascularization and angiographic restenosis in select subgroups of patients and coronary lesion morphologies[5,6], yet the technique was applied broadly to patients for whom the benefits had not yet been shown. Thus, a pattern has emerged of clinical acceptance, at times overwhelmingly, of new device technologies for which the theoretical rationale is appealing, the immediate angiographic results gratifying, and the risks perceived as minimal or unimportant. Rigorous supportive randomized trial results may be limited or non-existent, with extrapolation to patient and lesion subsets or clinical settings for which little objective data has yet been generated.

The clinical application of glycoprotein IIb/IIIa receptor blockade has followed a somewhat different course. Regulatory approval of the first of this class of agents, abciximab, was based upon controlled trial data[7] demonstrating important reductions in the risks of periprocedural myocardial infarction and urgent repeat revascularization among a larger number of patients than had ever been studied in a device trial. The magnitude of benefit with abciximab was at least as large as that observed for any device, and bleeding risk with this agent was comparable to that associated with contemporaneous anticoagulation regimens for stent implantation. Since that first study, subsequent large-scale trials have shown consistent clinical benefit from abciximab, with reductions of up to 50–60% in the risk of acute ischaemic complications among a broad spectrum of patients undergoing percutaneous revascularization[8–10]. Moreover, excess haemorrhagic risk initially associated with this agent has been abrogated by reduction and weight-adjustment of heparin dosing and early vascular sheath removal[8]. The cost of abciximab is comparable to that of new device technologies. Nevertheless, although the proportion of interventional procedures during which abciximab is employed has progressively increased over the last 3 years, estimated rates of 30–40% within the United States and 5–10% in Europe remain substantially lower than those for stents. Moreover, patterns of abciximab use tend to contrast with those of devices; rather than extrapolating application to broad patient populations on the basis of limited trial data, clinicians often attempt to identify subgroups of patients within the trials in whom to focus therapy with glycoprotein IIb/IIIa inhibitors. As a consequence, many patients receive these agents not as the planned therapeutic strategy initiated immediately prior to revascularization as was tested in the trials, but in an unproven fashion as ‘bailout’ therapy for complications during the interventional procedure.

The EPISTENT Trial

The recent EPISTENT trial assessed the role of abciximab with coronary stenting[11,12], currently the
dominant means of percutaneous coronary revascularization. In EPISTENT, 2399 patients undergoing elective or urgent coronary intervention were randomized to receive stenting plus placebo, stenting plus abciximab, or balloon angioplasty plus abciximab (the ‘reference standard’ from previous trials). Stents were implanted according to contemporary techniques of high-pressure inflation (median 16 atmospheres), with post-procedural administration of aspirin and ticlopidine.

The primary end-point analysis at 30 days confirmed that the efficacy of abciximab in reducing acute ischaemic complications during elective stenting was comparable to that with non-stent technologies in previous trials (Table 1), with a 51% decrease in the risk of death, myocardial infarction, or urgent revascularization. By 6 months follow-up, the benefits of stenting had become apparent, as had the complementarity of these two strategies (Table 1). The treatment effect of abciximab in reducing acute ischaemic complications was durable, with suppression of the composite end-point of death or myocardial infarction by over 50% with abciximab and stenting. Moreover, the 6-month results validated the efficacy of stenting in reducing repeat target vessel revascularization rates in a diverse group of patients and coronary lesions. As compared with balloon angioplasty (with abciximab), stenting without or with abciximab reduced the incidence of revascularization procedures by 31–44%.

Of particular interest were results among the 20% of patients in EPISTENT with diabetes mellitus. Long-term outcome among diabetics following percutaneous coronary revascularization has previously been shown to be inferior to that among non-diabetics, with higher rates of death, myocardial infarction, and repeat revascularization. In EPISTENT, rates of acute ischaemic end-points at 30 days and 6 months tended to be higher among diabetic compared with non-diabetic patients in either the stenting plus placebo or angioplasty plus abciximab treatment groups, but event rates were virtually the same among those with and without diabetes with the combination of stenting plus abciximab. More striking was the influence of these therapies on late revascularization rates. Diabetic patients randomized to placebo plus stenting had a substantially higher incidence of target vessel revascularization at 6 months than did their non-diabetic counterparts (16.6% vs 9.0%, respectively) and stenting alone (with placebo) in diabetics did not reduce the incidence of this end-point compared with angioplasty (with abciximab) (16.6% vs 18.4%, respectively, \( P = \text{ns} \)). Repeat target vessel revascularization rates following stent implantation were significantly reduced by 51%, however, by treatment with abciximab among patients with diabetes mellitus, completely neutralizing the excess risk for this end-point among diabetic vs non-diabetic patients. Findings of an angiographic substudy were concordant with the clinical results.

Most recently, 1-year follow-up results of EPISTENT have shown a significant 60% reduction in mortality by the combination of stenting and abciximab compared with either therapy alone. Among diabetic patients, in whom placebo-group mortality at 1 year was over twice that of non-diabetic patients, death rates were reduced by over 75% with stenting plus abciximab to a level equivalent to that among non-diabetics.

### EPISTENT in Perspective

The EPISTENT trial clearly establishes the important complementarity of combining an improved mechanical technique for percutaneous coronary revascularization with potent pharmacological therapy.

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**Table 1 Major clinical end-points in the EPISTENT Trial**

<table>
<thead>
<tr>
<th></th>
<th>Stent + Placebo</th>
<th>Stent + Abciximab</th>
<th>Angioplasty + Abciximab</th>
<th>( P )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30 days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, MI, urgent revascularization</td>
<td>10.8</td>
<td>5.3</td>
<td>(&lt; 0.001)</td>
<td>6.9</td>
</tr>
<tr>
<td>Death</td>
<td>0.6</td>
<td>0.3</td>
<td>0.268</td>
<td>0.8</td>
</tr>
<tr>
<td>MI</td>
<td>9.6</td>
<td>4.5</td>
<td>(&lt; 0.001)</td>
<td>5.3</td>
</tr>
<tr>
<td>Urgent revascularization</td>
<td>2.1</td>
<td>1.3</td>
<td>0.190</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>6 months</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Death or MI</td>
<td>11.4</td>
<td>5.6</td>
<td>(&lt; 0.001)</td>
<td>7.8</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>10.6</td>
<td>8.7</td>
<td>0.215</td>
<td>15.4</td>
</tr>
</tbody>
</table>

Variables expressed as percent of total.
*Compared with stent + placebo.
Data from\(^{[11,12]}\).
MI = myocardial infarction.
to suppress platelet thrombosis. Together, these two approaches allow coronary intervention to be performed with extraordinarily low rates of short- and long-term ischaemic events and neutralize the high-risk status of many subsets of patients, including diabetics or those with unstable angina. These results contribute to a cohesive body of randomized trial data showing unequivocal clinical benefit with abciximab in the setting of percutaneous coronary revascularization. Yet the majority of patients worldwide continue to undergo coronary intervention without adjunctive glycoprotein IIb/IIIa blockade. What are potential arguments for withholding this therapy?

'I don’t see these complication rates in my interventional practice’

Perceived differences in ischaemic complication rates between clinical practice and randomized trials usually reflect systematic vs non-systematic ascertainment of adverse end-points. Trials in which myocardial enzyme determinations were obtained per protocolized schedule in all patients have typically shown rates of periprocedural myocardial infarction to be in the range of 8–12%[2,7–9,11,16], in contrast to rates of 2–5% in trials where enzymes were measured only in patients suspected of having an event[6,17–20]. It should also be recognized that investigators at clinical sites involved in randomized interventional trials tend to be experienced operators performing high procedural volumes; thus, outcomes in these patients may in fact reflect the ‘best case’ scenario.

'The end-points of these trials are not relevant’

It certainly cannot be argued that prevention of death is not a relevant goal of any therapy for ischaemic heart disease. Importantly, although the mortality reduction by abciximab appears to be optimized with coronary stenting, all of the abciximab trials have shown trends toward suppression in mortality rates at long-term follow-up, particularly among higher risk patients[10,21–23]. Similarly, few would suggest that reduction in emergency revascularization procedures is not a worthwhile objective. The controversial issue is generally that of the clinical importance of periprocedural non-Q wave myocardial infarctions following percutaneous coronary revascularization. Yet nearly every study which has examined the impact of periprocedural enzyme release over an adequate period has demonstrated that patients who experience myocardial infarctions during and after coronary intervention are at significantly greater risk for late cardiac death than those who do not[24–29]. An increased risk of late events has been observed even among patients with ‘small’ CK-MB elevations[27–29] although the extent of mortality risk appears proportional to the degree of enzyme elevation. Taken together, these data provide compelling evidence that CK-MB enzyme release following coronary intervention is a clinically relevant event, and that prevention of periprocedural myocardial necrosis is linked to long-term reduction in cardiac mortality.

‘GP IIb/IIIa inhibitors are only needed in high risk patients’

The treatment effect of this class of agents certainly seems accentuated among patients with high-risk features such as unstable angina[30], diabetes mellitus[12], bail-out stents[31], or troponin elevations[32]. Nevertheless, no patient subgroup has been identified who do not benefit from abciximab therapy during coronary intervention. Moreover, the magnitude of clinical benefit in ‘low-risk’ patients has been commensurate with or superior to that derived from other accepted therapies in this setting.

‘Abciximab costs too much’

It is probable that abciximab would be employed during virtually all interventional procedures if it were as inexpensive as aspirin. The cost of abciximab, at ~$1400 per patient-dose, is more than that for epifibatide or tirofiban, but these reversible agents have not yet shown the same magnitude of efficacy as abciximab in randomized trials[16,20]. While a detailed comparison of the different glycoprotein IIb/IIIa inhibitors is beyond the scope of this discussion, theoretical mechanistic considerations support the apparent differences in efficacy. Thus, until appropriate comparative trials are completed, abciximab must be regarded as the agent of choice for optimal outcome during coronary intervention.

A relevant perspective on the economic issue is that the per patient cost of stents is at least equivalent to and often greater than that of abciximab. Moreover, as with stents, the acquisition cost of abciximab does not reflect the true economic cost of the drug. From a hospital standpoint, cost savings derived from reduction in ischaemic events offset much of the acquisition cost. From the societal standpoint, long-term reductions in ischaemic events result in additional cost savings, particularly among high-risk subgroups of
patients, which further contribute to the economic attractiveness of this therapy. From any perspective, it is unrealistic to expect new therapies to be cost neutral or cost saving, and the appropriateness of allocating resources should be based upon cost-effectiveness relative to other therapies employed in practice. In this regard, the cost-effectiveness of abciximab during percutaneous coronary revascularization appears quite favourable, in the range of other accepted interventions such as coronary artery bypass surgery for left main coronary disease.

Conclusions

Abciximab markedly diminishes important ischaemic events, including death, among essentially all patients undergoing percutaneous coronary revascularization. The strength of evidence and the magnitude of treatment effect with this agent is at least equivalent to or better than that of many other widely accepted and utilized therapies, yet a sizeable proportion of eligible patients do not receive this agent. The question therefore becomes — what more needs to be proven to effect broad application of this therapy to the large population of patients for whom it is indicated? It is unlikely that additional placebo-controlled trial data will be forthcoming, as it seems no longer ethically appropriate to randomize patients, particularly those with high-risk characteristics, to placebo in this setting. Future studies will instead be directed at assessing the combination of glycoprotein IIb/IIIa inhibitors with new antithrombin and other anti-platelet agents, refining the role of these drugs in the acute ischaemic syndromes, and evaluating long-term oral therapy. While the economic costs of abciximab are unquestionably relevant, a re-evaluation of this treatment in the context of others supported by our health care systems is indicated, so that this highly effective therapy may be appropriately extended to all patients who would derive clinical benefit.

A. M. LINCOFF
E. J. TOPOL
The Cleveland Clinic Foundation,
Cleveland, Ohio, U.S.A.

References


