Abciximab in Coronary Intervention for Acute Myocardial Infarction and Stable Ischemic Heart Disease: Early Investment for Growing Benefit

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ABSTRACT: Background. At 30 days, it is recognized that 12-hour periprocedural abciximab infusion protects against reinfarction and the need for revascularization in percutaneous coronary intervention (PCI) in acute myocardial infarction (MI). However, it is controversial whether the benefit to patients continues or fades away subsequently. We investigate whether abciximab provides a persistent advantage in terms of life-years gained in large trials of abciximab in PCI. Methods and Results. We identified four eligible randomized, controlled studies of PCI and adjunctive abciximab therapy in acute MI enrolling a total of 3,183 patients. Using the published time course of survival, we calculated the life-years gained at a series of time points over the following year. The weighted mean value and standard error for life-years gained at 1 year was 0.0034 ± 0.0005. For abciximab-treated patients, life-years gained increases non-linearly for the first 90 days (gain = \( y = 0.0032 + 0.0016t - 3E^{0.5}; R^2 = 0.998; p < 0.05 \) for non-linear term) then linearly thereafter (gain = \( y = 0.004t - 0.0005; R^2 = 0.9998 \)). The “number needed to treat” to gain 1 life-year is twenty-fold lower at the 1-year time point than at the 60-day time point. Conclusion. When viewed across trials, benefit to the patient in terms of gain in life-years grows, rather than shrinks, with the passage of months. Initially, growth is significantly greater than linear, suggesting that a single periprocedural infusion continues to help prevent events from occurring up to 3 months post procedure. Evaluation of benefit at early time points may therefore underestimate the benefit of abciximab.

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Key Words: abciximab; percutaneous intervention; stenting; survival; life-years gained

Does the administration of the antiplatelet antibody fragment abciximab in the critical phase of reperfusion during percutaneous coronary intervention (PCI) really continue to protect against cardiovascular events beyond its 12-hour dosing period? In major trials, at 30 days, there is a significant reduction in the combined endpoints of target vessel revascularization (TVR), reinfarction and death; yet, whether this translates into a significant difference in later survival is controversial. The RAPPORT trial reported no increase in the endpoint of survival from abciximab, either at 30 days or at 6 months, and suggested that risks of abciximab, such as hemorrhage, may even outweigh the benefits. ISAR 2 also found no survival benefit from abciximab at 5 years. In fact, only one trial, ACE, has demonstrated a significant survival benefit for abciximab-treated patients at 1 year post procedure, although the survival curves of other trials show trends toward divergence at later time points and a recent meta-analysis of three trials confirms a strong and persistent impact of abciximab on survival after acute myocardial infarction (MI).

To patients, the important benefit is additional years of life gained. The number of “life-years gained” per dose of abciximab at any given subsequent time point can be readily calculated from survival curves as the area between the survival curves up to that time point. In this study, we examined the way in which any benefits of abciximab administration evolved with time. Specifically, we looked for quantitative evidence that the benefit to the patient in life-years gained faded away with time after the first month, which is what has been suspected from qualitative inspection of the data.

Methods

Search strategy. The trials included in this study were identified on the Medline database. Key words for searching were: abciximab, Reopro, acute myocardial infarction, ischemic heart disease, reperfusion, survival and mortality.

Inclusion criteria. We identified four randomized, controlled trials comparing the use of abciximab versus placebo or abciximab versus no abciximab as an adjunct to catheter-based reperfusion for acute MI. Studies were required to report follow up for a minimum of 1 year. All the included studies reported survival data in the form of Kaplan-Meier curves. We excluded studies that focused on specific patient groups such as diabetics, studies that only provided data for event-free survival, studies investigating the use of abciximab without catheter-based reperfusion, and finally, studies comparing abciximab with other interventions such as clopidogrel or thrombolysis.

Analysis of life-years gained. From the Kaplan-Meier curves for percentage of survivors or percentage of deaths over time, we determined the absolute difference in survival...
between abximab and placebo/control at 15- and 30-day intervals for 1 year from the time of abximab administration. We calculated the cumulative segmental area at each time point to give a curve of life-years gained over time. In order to make the data comparable between trials, we multiplied the life-years gained at each time point by a weighting factor for each trial, which was calculated as the sample size, n, divided by the total sum of the sample sizes (3,183). This effectively normalized the data so that they could be combined into a mean weighted life-years gained curve for all the studies. The curve of life-years gained over time visibly appeared to change from non-linear to linear at the 3-month time point. Two separate regression analyses were therefore performed, one for the curve from 0–3 months and one for 3 months to 1 year. Successively higher-order polynomials were tried until the highest-power term was no longer significantly different from zero. R2 represents the goodness of fit of the equation to the data.

Results

**Trial characteristics.** A total of four trials were included. The trials cover a range of patient inclusion criteria and have different study sizes, as listed in Table 2 of the Appendix.

**Cumulative benefit over time.** For each trial, from the raw survival curves (Figure 2, left panels), the cumulative survival benefit was calculated at each time point (middle panel). To allow the pattern of evolution of this benefit to be compared across trials, we multiplied each data point by a weighting factor based on the sample size of each trial (right panels).

**Time course of development of benefit.** Putting together the shapes of the time courses of life-years gained from the different trials, we observed an apparently curvilinear increase with time. To test for the presence of non-linearity, we performed both linear and non-linear regression analysis and demonstrate that percent age life-years gained increases non-linearly for the first 90 days (gain = y = 0.003t^2 + 0.0016t - 3E-10; R^2 = 0.998; p < 0.05 for non-linear term) then linearly thereafter (gain = y = 0.004t - 0.0005; R^2 = 0.9998) (Figure 2).

**Numbers needed to treat: dramatic impact of follow-up duration.** The non-linearity of the life-years-gained curves is reflected in the large change in “number needed to treat” (NNTs) over time. Over 1 year, the NNT to gain 1 life-year after an acute MI is reduced twenty-fold (Table 1).

**Discussion**

In this study, we found that survival benefit from abximab as an adjunct to stenting for acute MI does not wane away after 30 days. The net benefit from the patient’s point of view, life-years gained, increases as the period of observation lengthens, non-linearly for the first 90 days, then linearly thereafter.

A similar analysis has been performed for defibrillator implantation, demonstrating that the gain in patient lifespan increases non-linearly over time following implantation and that the benefits of a “front-loaded” intervention, with high initial costs and risks, are strongly dependent upon follow-up duration. Abciximab infusion over 12 hours as an adjunctive treatment to catheter-based reperfusion is even more front-loaded, with the costs incurred exclusively in the first few hours. Where absolute risk differences may be controversially small or variable between trials when viewed at isolated time points during follow up, it is all the more important to calculate the gain in survival as a function of time and to view the results across trials to minimize the effects of inevitable random variation.

**Potential mechanisms.** The initial benefit of abximab appears not only to arise from an improvement in infarct-

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**Table 1. Numbers needed to treat to gain 1 life-year with abximab therapy.**

<table>
<thead>
<tr>
<th>Time Point (days)</th>
<th>NNT to Gain 1 Life Year, by Giving Abciximab in Acute MI (weighted mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>6521 ± 3746</td>
</tr>
<tr>
<td>120</td>
<td>1515 ± 420</td>
</tr>
<tr>
<td>180</td>
<td>810 ± 176</td>
</tr>
<tr>
<td>240</td>
<td>502 ± 73</td>
</tr>
<tr>
<td>300</td>
<td>379 ± 49</td>
</tr>
<tr>
<td>360</td>
<td>311 ± 44</td>
</tr>
</tbody>
</table>

NNT = number needed to treat; SE = standard error

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**Table 2. Trial characteristics.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Clinical Setting</th>
<th>n</th>
<th>F/U (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMIIRAL Montalescot et al, 2001</td>
<td>RCT, DB</td>
<td>PCI for acute STEMI (symptoms &lt; 12 hours’ duration)</td>
<td>300</td>
<td>3</td>
</tr>
<tr>
<td>ACE trial Antoniucci et al, 2004</td>
<td>RCT</td>
<td>PCI for acute MI (broad inclusion criteria with high-risk patients - “real life”)</td>
<td>400</td>
<td>1</td>
</tr>
<tr>
<td>ISAR-2 Ndrepepa et al, 2004</td>
<td>RCT</td>
<td>PCI for acute MI (&lt; 48 hours’ duration)</td>
<td>401</td>
<td>5</td>
</tr>
<tr>
<td>CADILLAC Tcheng et al, 2003</td>
<td>RCT</td>
<td>PCI for acute MI, symptoms &lt; 12 hours duration, exclusion of high-risk patients.</td>
<td>2,082</td>
<td>1</td>
</tr>
</tbody>
</table>

RCT = randomized, controlled trial; DB = double-blind; F/U = follow up; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction; IHD = ischemic heart disease; MI = myocardial infarction

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**Table 3. Percentage of patients treated with stent placement and clopidogrel or ticlopidine in addition to abciximab or placebo.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>% Stents</th>
<th>% Other Agents</th>
<th>Placebo/Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMIIRAL</td>
<td>78</td>
<td>100</td>
<td>100 (ticlopidine)</td>
<td>100 (ticlopidine)</td>
</tr>
<tr>
<td>ACE</td>
<td>200</td>
<td>99</td>
<td>0</td>
<td>100 (ticlopidine)</td>
</tr>
<tr>
<td>ISAR-2</td>
<td>201</td>
<td>100</td>
<td>100 (ticlopidine)</td>
<td>100 (ticlopidine)</td>
</tr>
<tr>
<td>CADILLAC</td>
<td>1052</td>
<td>55.7</td>
<td>100 (ticlopidine)</td>
<td>100 (ticlopidine)</td>
</tr>
</tbody>
</table>
related artery patency, but also from increased microvascular blood flow with improved regional perfusion and recovery of left ventricular function. Scintigraphic data demonstrate more effective myocardial reperfusion with abciximab, with a reduction in infarct size and severity and improved left ventricular function, consistent with improved myocardial salvage leading to better short and long-term clinical outcomes. However, it is possible that the long-lived benefits of abciximab are mediated by its durable anti-inflammatory actions on non-target vessel lesions. In support of this, abciximab has been demonstrated to inhibit leucocyte migration across endothelial cell barriers and also has been implicated in the stabilization of atherosclerotic plaques through prevention of vascular smooth-muscle cell apoptosis. An alternative explanation may be that abciximab acts not only on circulating platelets, but also on platelets residing within the reticulo-endothelial system. This store of abciximab-treated platelets then continues to manifest antithrombotic properties gradually over time.

**Clinical and economic implications.** The CADILLAC trial in 2003 performed a cost-effectiveness analysis of catheter-based reperfusion therapy with and without abciximab. Abciximab was associated with a 1-year cost of $1,200 per patient. Because the trial found an early increase in mortality at 1 month, but no significant long-term survival benefit at 6 months, the net cost-effectiveness remained uncertain. It may be that this difference is related to the higher use of percutaneous coronary...
transluminal angioplasty alone, rather than stenting in the CADILLAC trial, leading to a higher restenosis rate at 6–12 months. The study concluded that the cost-effectiveness of abciximab is dependent upon its effect on long-term outcomes. Our study builds on this by demonstrating that the observed clinical benefit of intervention with abciximab is highly dependent upon the duration of follow up. Through incorporating the dimension of time into our analysis of survival, we demonstrate that a single abciximab infusion for 12 hours continues to have an increasingly beneficial effect on both prevention of cardiovascular events and mortality.

If absolute survivals are compared at too early a stage during the follow-up period, i.e., in the shallow portion of the life-years gained curve, it is possible to seriously underestimate, or even completely miss, survival advantage conferred by abciximab. Evaluation of life-years gained over an extended period of time is helpful in judging the clinical benefits of abciximab therapy. Examination of multiple trials also attenuates the relative impact of random variability ‘noise’ within individual trials, which cause curves that are tending to diverge to do so at different times in different studies; these essentially random fluctuations in a single trial do not tell us anything useful about the time course of effects of an intervention.

Looking into the future. Patients may well want us to consider a longer time window than simply 1 year when planning treatment for them. Three, 5 or even 10 years may be preferable durations. However, only two of the trials for acute MI, ADMIRAL and ISAR-2, have a follow-up period extending much beyond 1 year. Over the 3 years of follow up for ADMIRAL, the survival curves continue to diverge such that the life-years gained at 3 years is seven times that at 6 months. ISAR 2, the acute MI trial with the longest period of follow up of 5 years, showed that by 3 years, the life-years gained is five times that at 6 months. However, from this point, the survival curves change direction so that by 5 years, there appears to be no gain in life-years from abciximab. Whether this is a consistent intrinsic phenomenon of this therapy, or instead a manifestation of random noise, will remain unknown until we have more evidence from other trials with longer follow-up periods, but it seems biologically implausible that an adverse effect of a single administration of an agent could manifest consistently at such a late time point.

Comparison with other antiplatelet and antithrombotic agents. There is considerable heterogeneity between trials in the use of thienopyridines (Table 3). In nearly all the trials studied, aspirin and heparin formed a background treatment in addition to the test treatments of balloon angioplasty ± stent placement ± abciximab, and in three trials, ticlodipine was given to all patients. To determine whether treatment with these other antiplatelet agents has a beneficial effect upon life-years gained, even in the absence of abciximab, further analysis of trials that directly compare abciximab with thienopyridines in a randomized, controlled manner is required.

Currently, the data regarding newer, small-molecule glycoprotein IIb/IIIa inhibitors, such as tirofiban and eptifibatide, are less extensive than for abciximab. The TARGET trial in 2001 reported that abciximab conferred significantly greater protection against cardiovascular events and mortality at 30 days post percutaneous intervention compared to tirofiban, however, subsequent follow up at 6 months and 1 year has failed to confirm this superiority in the long term.16 The average treatment cost of a bolus and infusion of abciximab is €840 compared to €455 for eptifibatide and €450 for tirofiban, perhaps reflecting differences in their half-lives. The benefit in terms of life-years gained from abciximab relative to the other glycoprotein IIb/IIIa inhibitors and other antiplatelet agents might be the subject of future scrutiny in order for accurate cost-benefit analysis to take place.

Study limitations. Our life-years gained analysis was performed on results made public to the scientific community from randomized, controlled trials. Some potentially relevant trials did not meet our inclusion criteria, for example, the duration of follow up was shorter than 1 year. Others, such as RAPPORT,1 did not make public the time course of total survival and did not agree to disclose such data for the purposes of this study, therefore, we were unable to include them in our analysis of life-years gained. However, our examination of a meta-analysis of eight abciximab trials indicates that even if we had access to such data, our conclusions would be similar with a non-linear increase in life-years gained for the first 60 days. This meta-analysis in 2001 included all existing trials for abciximab in PCI, regardless of indication (acute MI and stable IHD) and covered two studies that we did not, RAPPORT and ERASER.19 At the maximum follow-up duration reported of 6 months, the life-years gained was still nine times greater than at 1 month.

Life-years gained analysis, by definition, excludes all endpoints other than survival. It may be argued that exclusion of
secondary endpoints such as MI or TVR limits the power of this method to assess the full incremental benefit of abciximab for patient health. However, wide variability in secondary or combined endpoints recorded by different trials impedes calculations, such as “event-free” life-years gained, which are based upon these outcomes. Similarly, heterogeneity between trials in the use of conjunctive antiplatelet agents and in follow-up duration introduces discrepancies in the weight of evidence from different trials, which is difficult to quantify. It is important to note that we did not have access to patient life-expectancy data, so we are unable to assess directly whether the use of abciximab in PCI can increase or decrease life-expectancy of individual patients. Additionally, we are unable to comment on the quality of the additional life-years gained, as we did not have access to data regarding patient quality of life or other surrogate measures such as ventricular ejection fraction or adjunctive pharmacotherapy. Finally, we are unable to make assertions as to the molecular mechanisms underlying the long-lived actions of abciximab using the type of data we have collected in this study.

Conclusions

There is no sign of a decay in the life-years gained from abciximab infusion at the time of stenting up to 90 days post procedure for acute MI. In fact, the cumulative benefit to patients increases non-linearly for the first 90 days and linearly thereafter, so that at 1 year, the life-years gained are twenty times that at 2 months. For treatments such as abciximab, where benefit outlives both the course of therapy and its associated expense, it is important not to calculate the benefit too early in the follow-up period. Life-years gained analysis is thus the most appropriate method of evaluating the survival advantage of a front-loaded intervention whose benefits continue to accrue over time.

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References


Abciximab in PCI