Are Stenting and Glycoprotein IIb/IIIa Blockade of Good Value in Primary Percutaneous Coronary Intervention?

Jason H. Cole, MD; William S. Weintraub, MD

Therapy for ST-elevation acute myocardial infarction (STEMI) has undergone remarkable change over the past decade, and more evolution is doubtless in store. First, it has become relatively clear that primary angioplasty provides a real, if small, benefit over thrombolytic therapy. More recently, clinical trial data have shown that coronary stenting, initially thought to be unsafe in the thrombotic setting of an STEMI, is indeed safe and provides for a reduction in early events and repeat revascularization, although there was lingering concern over possible increased mortality with stenting compared with balloon angioplasty. Finally, some have argued recently that glycoprotein IIb/IIIa inhibitors also provide a benefit over conventional anticoagulation regimens.

A major study addressing optimal adjunctive therapy with primary angioplasty was the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, which used a 2-by-2 factorial design to independently evaluate the effectiveness of adding coronary stents or the glycoprotein (GP) IIb/IIIa inhibitor abciximab to standard balloon percutaneous coronary angioplasty (PTCA) in the setting of an acute MI. Considering stenting versus PTCA, there were no significant differences in initial hospital outcomes or in death, recurrent MI, and stroke at 1 year. Stenting, however, was associated with a significant 6.4% absolute risk reduction in rate of rehospitalization. In contrast, abciximab use was associated with a decrease in initial hospital length of stay but also with a significant increase in rehospitalization. However, there were no significant 1-year differences in death, MI, or stroke associated with abciximab use.

In this issue of Circulation, Bakhai et al provide the results of the cost-effectiveness component of the CADILLAC trial, analyzing the 1703 patients who were enrolled at US centers. In their analysis, initial hospital costs were greater by $1384/patient for the stent group. However, by 1-year follow-up, this difference had fallen to $169/patient because of increased rehospitalization and revascularization in the nonstent group. The authors express this difference in standard terms of quality-adjusted life years (QALY), which is a composite expression of the benefit purchased with healthcare dollars spent on stents. In these terms, stents yielded a cost-effectiveness ratio of $11 237/QALY, which is well within the limits of what is generally considered to be cost-effective. On the other hand, because abciximab appeared to marginally improve clinical outcomes and lessen time to discharge during initial hospitalization, costs were only $413/patient greater for the treatment versus the nontreatment group. In this case, however, there was more rehospitalization in the experimental group, leading to a 1-year follow-up difference of $1244/patient for treatment with abciximab. The increase in hospitalization, combined with the finding of no significant mortality difference between the groups, meant that in the authors’ primary analysis, standard anticoagulation dominated abciximab use. In other words, the GP IIb/IIIa antagonist provided less overall benefit at greater cost.

Should these cost-effectiveness data impact clinical decision-making? For the question of stenting, the answer almost certainly seems to be yes. There has been evidence that stenting may be safe and effective in acute MI since the late 1990s, but the debate has continued. One concerning study was Stent Primary Angioplasty for Myocardial Infarction (Stent-PAMI), which showed a trend toward increased death rate at 1 year in patients treated with stent versus balloon (1.8% versus 0.9%, P=0.39). This finding affected the cost-effectiveness calculation for the study, which in sensitivity analysis showed balloon treatment to be a dominant strategy unless the mortality benefit to PTCA alone was under 0.3%. As alluded to by the authors of the present study, it is unclear why CADILLAC shows different 1-year mortality trends than did Stent-PAMI, with possibilities including random chance, improvements in stent design, or experience of investigators. Nonetheless, the clinical results of CADILLAC for stenting in the setting of STEMI are reassuring. It is also instructive that conclusions regarding cost-effectiveness are highly dependent on assumptions made for mortality, even in studies that are not adequately powered...
to evaluate it. Nonetheless, the economic results for stenting in CADILLAC remain impressive because cost-effectiveness for stenting over PTCA alone was under $50,000/QALY in 86% of bootstrap simulations. Finally, the mean aggregate 1-year cost for PTCA versus stent was $18,690 versus $18,859. As the authors point out, if the cost of stents continues to decrease, a reduction of $200 in price would make primary stenting in acute MI a dominant strategy. A simpler way to think about the economic analysis of CADILLAC is that the clinical benefit could be achieved without a significant increase in cost. The impact of drug-eluting stents, both clinical and economic, in the setting of STEMI remains to be elucidated.

Conclusions regarding the use of abciximab are a little more unsettled. Our current understanding of vascular biology gives much reason to believe that GP IIb/IIIa receptor inhibitors would improve clinical outcomes in the setting of stenting or primary angioplasty. It is clear that platelets are fundamental in the pathophysiology of MI, and activated GP IIb/IIIa receptors crosslink fibrinogen, leading to platelet aggregation. Prior studies, including the Randomized Efficacy of Stenting Over PTCA (RESEARCH) trial, have included small numbers of patients undergoing primary angioplasty for MI, and results have indicated a trend toward reduced composite end points in both cases. Encouraging results were also reported for the Absorbable Biodegradable Polymer-Drug Eluting Stent (ABSORB) trial, which showed a decrease in death, reinfarction, and urgent target-vessel revascularization (TVR) at 30 days. It is important to recognize, however, that the data for GP IIb/IIIa use in the setting of primary stenting have remained somewhat limited, and these agents have not been uniformly successful in trials involving patients with the acute coronary syndrome. In fact, the most prominent failure of these agents may have occurred with abciximab in the GUSTO IV–ACS (Global Utilization of Streptokinase and tPA for Occluded arteries) trial. Given these conflicting findings, there was great anticipation of the recent reporting of the primary results of the CADILLAC study. Although these results demonstrated improved outcomes, as measured by death, recurrent MI, and urgent TVR at 30 days, the results did not persist at 12 months. Thus, in the setting of limited clinical efficacy, the economic analysis is actually much less important. In this setting, it is difficult to make any recommendation for abciximab. The authors suggest that there may be a decrease in initial hospital cost with the use of the GP IIb/IIIa antagonist, but this result is driven by the fact that the abciximab group was discharged from the hospital earlier, a goal that was explicitly reinforced by a protocol that pushed for early discharge in this group. At 1 year, there was no significant cost benefit, and one could only be found by performing sensitivity analysis accepting the nonsignificant 0.6% absolute reduction in mortality. Thus, the economic analysis of CADILLAC may provide the foundation for sound decision-making: routine stenting with primary angioplasty but no routine IIb/IIIa antagonist.

Cost-effectiveness analyses are performed from a perspective—that is, from the point of view of payers, providers, or society. The US Public Health Service recommends performing cost-effectiveness analysis from the point of view of society, to thus reflect the benefits and costs of a new therapy to society as a whole. It is not entirely clear what perspective the authors of the CADILLAC economic analysis have chosen for their analysis. They allude to the perspective of both society and individual payers when they describe their use of statistical tools that “most closely [approximate] the perspective of a typical third-party payer or health-care system.” As others have pointed out, a focus on “downstream costs” from a societal perspective is currently thought to provide the clearest picture for healthcare policy makers. However, another theme that is critically important in the understanding of healthcare economics is that a global perspective does not provide the same answers for everyone in the healthcare system. Implicit in cost-effectiveness analysis is the principle that clinical benefit can be “purchased” by the costs associated with a therapy. Benefits will accrue to patients, their families, and possibly their employers. The cost of this benefit may be felt quite differently by providers on the one hand and third-party payers on the other. The clearest example of this phenomenon in the CADILLAC analysis relates to the possible benefit seen with abciximab therapy during the index hospitalization. The combination of abciximab therapy and a strategy of early discharge decreased hospital stay by about a half day on average, allowing hospitals to recoup a significant proportion of the initial cost of the drug by decreasing length of stay. This information may be of great importance to a hospital that is reimbursed a flat fee by a third-party payer. The hospital may be able to provide a clinical benefit to its patients with only a low level of cost. If downstream costs are higher with abciximab at 1 year as a result of more hospitalizations, the hospital may benefit while payers will have increased costs.

The same principle of perspective may ultimately be of even greater importance with the question of stenting. Compared with balloon PTCA, the use of stents costs about $1400 more up front during the index hospitalization, but over the course of a year, the stent provides clinical benefit to patients, with fewer hospitalizations and fewer revascularizations. As discussed, stenting seems so beneficial because these clinical benefits also produce lower costs—the patient receives better and less expensive care. Such benefits are easily realized by a system in which all costs are borne by the same source—eg, a single payer government system or a comprehensive managed care organization. In other settings, however, costs have been shifted significantly. The hospital in which the index hospitalization takes place may have absorbed significant costs in order to provide an overall benefit to the “system” later on. If the initial treating physician is under pressure to “control costs,” he or she could conceivably not use a stent, even though, from the perspective of total costs, the stent comes almost free to the healthcare system. It will be important to keep this principle in mind as cost-effectiveness calculations are performed to address the emerging question of the economic impact of drug-eluting stents.

Considering these challenges in economic analysis, how does the consideration of cost and benefit improve clinical decision-making regarding the use of stents and GP IIb/IIIa...
antagonists in acute STEMI? The progression of understanding over the past few years has been clear, as follows: from no stents in primary angioplasty, to expensive stents, to stents whose costs are ultimately recouped within a year. In the current environment, one is tempted to say that a stent not only provides clinical benefit, it can almost be implanted for free. For GP IIb/IIIa receptor antagonist use, we must be careful. Until we can define a clear benefit in patient outcomes beyond 30 days, the use of these agents will not provide a level of benefit within the currently accepted bounds of cost-effectiveness. A final lesson from this study is that our healthcare system should seek to align incentives so that patients, providers, and payers can all seek value—that is, good care that it is worth what we pay for it.

References

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