GP IIb/IIIa inhibition: Time to drop the infusion?

October 11, 2006 Shelley Wood

Brooklyn, NY - A bolus-only dose of GP IIb/IIIa inhibitors may be enough to prevent thrombotic complications while reducing bleeding risk in the modern PCI era, perhaps even leveling the playing field with bivalirudin, a new analysis suggests [**2**]. According to **Dr Jonathan D Marmur** (State University of New York Health Science Center, Brooklyn), lead author of a new analysis of the **Evaluation of 7E3 for the Prevention of Ischemic Complications** (EPIC) trial, the findings should be reassuring for interventional cardiologists who have already stopped using a GP IIb/IIIa infusion following the bolus dose in patients undergoing PCI.

The paper has been published online on the *American Heart Journal* website [**2**].

Due to concerns about the higher bleeding seen with GP IIb/IIIa inhibition compared with bivalirudin in the **REPLACE-2** study, many operators have switched to bivalirudin, despite earlier signs of a higher MI rate with the newer drug, Marmur explained to **heart*wire***. The problem, he says, is that GP IIb/IIIa infusion is based on "horrendously outdated data" derived in the prestent era. With the advent of stents, concerns about abrupt artery closure disappeared, as did fears of later MI, eliminating the need for ongoing GP IIb/IIIa inhibitors.

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"Recent observations, which have in some ways been driven by the bivalirudin experience, are that the bleeding complications related to coronary interventions are actually much more dangerous and deleterious to the patients' outcomes than physicians previously believed," Marmur commented. "So what's happening is that the interventional community is radically shifting away from IIb/IIIas toward bivalirudin, and the market share is very dramatically

changed. But what I've always argued is that if you look closely at the REPLACE-2 study, what they really compared was an apple vs an orange in that they gave bivalirudin essentially as a bolus . . . whereas in the GP IIb/IIIa arm, they gave the FDA-approved dose: they ran [abciximab or eptifibatide] for 12 to 24 hours, because that's what's in the package insert."

He continued: "My sense is that if you get away from the infusions with GP IIb/IIIas, you can replicate the REPLACE-2 results for bivalirudin. In other words, duration matters. And also, because you're giving GP IIb/IIIas, you actually get, in my opinion, the best of both worlds, because you also limit the MI rate."

Early EPIC outcomes

Marmur and colleagues examined early outcomes in EPIC, using the rationale that stents now decrease the incidence of acute closure but potentially increase periprocedural bleeding concerns. In EPIC, published 12 years ago, 2099 patients were randomized to placebo, abciximab bolus, or abciximab bolus plus infusion. At six hours after randomization, the primary composite end point of death, MI, or urgent revascularization was significantly reduced in the abciximab-bolus group as compared with placebo; the authors also report a nonsignificant reduction in MI using abciximab-only compared with placebo. Previous studies have found a higher rate of major bleeding in the bolus-plus-infusion arm of EPIC, compared with the bolus-only arm, the authors note.

Early outcomes: Composite rate of death, MI, urgent intervention

Time postrandomization	Placebo	Bolus	p	Bolus+infusion	p vs placebo
6 h	5.3	2.9	0.22	2.4	0.005
12 h	6.65	4.7	0.129	4.2	0.047

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"In EPIC, the bolus-only actually gave you a good outcome at 6 to 12 hours," Marmur commented. "It shouldn't be such a mental stretch for people to realize once the stent has gone in, the ballgame is over, so you don't need the infusion."

Moreover, when a high loading dose (600 mg) of clopidogrel is used, it typically takes effect at around the six-hour mark if not before, Marmur noted, well within the protective window of the GP IIb/IIIa-inhibitor bolus dose.

A focus on combination therapy
Management of multiple risk factors calls for multiple therapeutic interventions. However, the question of which combination should be aimed at which

Cost implications come with a price

Marmur says many high-volume interventional cardiologists have now cut out the GP IIb/IIIa infusion entirely. "It's obvious to a lot of people that these infusions are probably idiotic and possibly dangerous, so a lot of people have just dropped them."

He and others have called on the major GP IIb/IIIa-inhibitor manufacturers to do a trial of bolus only, but he predicts such a trial will never happen. "The reasons are primarily financial," Marmur explains, because the bolus portion of the drug is so cheap. At his own institution, the pharmacy can divide the FDA-approved bolus and infusion dose into five bolus-only doses at a cost of around $60 to $70 per patient.

In an accompanying editorial, **Dr Tim A Fischell** (Borgess Heart Center, Kalamazoo, MI) agrees that it may be time to "reexamine to concept of bolus-only GP IIb/IIIa-inhibitor use," particularly now that operators are more aggressively loading thienopyridine therapy [**2**].

"The bivalirudin regimen, in general, is also less expensive than a double bolus plus infusion using eptifibatide or bolus plus infusion dosing of abciximab," Fischell writes. "A bolus-only technique with IIb/IIIa inhibitors, combined with lower-dose, weight-adjusted unfractionated heparin, may have the same advantages as bivalirudin (ie, reduction in non-Q-wave MI, no prolonged infusion, and low bleeding risk), but with even lower costs."

But what might be good for patients may not be good for drug makers, Marmur points out. "This has tremendous cost implications, there's no question," he told **heart*wire***. "That's part of the problem: it's so cheap the companies don't want to do it, because they can't make money from it. I've even met with them and I've said, you should make the drug bolus-only and charge us 10 times more—we'll all use it. But they're scared to do it because it's a big investment to do another $50 million trial against bivalirudin."

The bolus and the bathwater

In the absence of a trial proving the safety and efficacy of a bolus-only dose, however, Marmur believes many people will drop the GP IIb/IIIas altogether, except as a bailout drug after bivalirudin. "I think the survival of this agent is on the line; GP IIb/IIIas are being abandoned in droves—it's a big problem. What I think is happening is we're throwing the baby with the bathwater: the baby is the bolus, the bathwater is the infusion. And really what I'd like to do is protect the patient against the intraprocedural events with the IIb/IIIa bolus, and then get rid of it."

I don't use infusions and I never will.

Marmur and colleagues have another paper in press—a retrospective, single-center study showing a bolus-only GP IIb/IIIa strategy to be associated with rates of in-hospital death, MI, repeat revascularization, and major/minor bleeding that are lower than those reported with unfractionated heparin with planned GP IIb/IIIa inhibitors and bivalirudin

with provisional GP IIb/IIIa inhibition reported in the REPLACE-2 trial. Still, the old EPIC data may end up being the only prospective, randomized trial data to shed any light on the bolus-only issue.

"I think EPIC gives some support to a bolus-only strategy, so that's a major randomized trial showing that the bolus-only arm shows some benefit," Marmur told **heart*wire***.

Commenting on the study for **heart*wire***, **Dr A Michael Lincoff** (Cleveland Clinic, OH), lead investigator for the REPLACE-2 trial, said he was "not sure" what conclusions could be drawn from Marmur et al's study.

"We've known all along that the big difference between the bolus compared with the bolus-and-infusion arms in EPIC was the 'catch-up' of events with bolus only. That may or may not be the case with stents and thienopyridine pretreatment—it's entirely speculative," Lincoff observed. "This current analysis really doesn't tell us anything new. It would be difficult now to do a more contemporary trial of bolus only, as the sample size would be very large and the design likely one of noninferiority, so it is unlikely that we will ever have definitive data regarding whether or not bolus-only therapy is efficacious. Short of definitive data, we are left with only speculation driven by indirect and largely inappropriate comparisons against bolus plus infusion GP IIb/IIIa or against bivalirudin."

Marmur, for his part, believes his study should at least provide reassurance for operators who have reached their own conclusions about GP IIb/IIIa infusions. "I think it's important that people realize that there's some support in the community for those people who at least don't use these infusions. I don't use infusions and I never will."

Sources

1. Marmur JD Mitre CA, Barnathan E, Cavusoglu E. Benefit of bolus-only platelet glycoprotein IIb/IIIa inhibition during percutaneous coronary intervention: insights from the very early outcomes in the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial. *Am Heart J* 2006; DOI 10.1016/j.ahj.2006.04.035. Available at: http://journals.elsevierhealth.com/periodicals/ymhj/inpress.
2. Fischell TA. "Bolus-only" glycoprotein IIb/IIIa inhibitor use for elective percutaneous coronary intervention: Maybe less is more? *Am Heart J* 2006; DOI: 10.1016/j.ahj.2006.06.029. Available at: http://journals.elsevierhealth.com/periodicals/ymhj/inpress.

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