

## EDITORIAL COMMENT

# Intracoronary Glycoprotein IIb/IIIa Inhibitors

## From Questioning the Logic to Weighing the Data\*

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Initially, the administration of intracoronary (IC) rather than intravenous (IV) glycoprotein IIb/IIIa inhibitors was met with skepticism. It had been widely believed that the entire pool of circulating platelets had to be inhibited, and at least 80% to 90% of platelet glycoprotein IIb/IIIa receptors bound by drugs (1). Drug doses resulting in >90% receptor binding did not improve clinical benefit; doses with <80% binding were thought to paradoxically increase thrombotic events (2).

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In 1999, 6 years after the approval of abciximab, the earliest case reports of its IC administration described the dissolution of intracoronary thrombus (3,4). (It is important to remember that studies of IC glycoprotein IIb/IIIa inhibitors have involved the IC administration of only the bolus dose(s); the standard dose and duration of infusion has generally still been given IV.) The safety of this approach was suggested by a study of 611 patients who received IC abciximab, with only 1 adverse reaction, an allergic reaction manifested by hypotension, bronchospasm, and tachycardia (5). The possible superiority of IC glycoprotein IIb/IIIa inhibitors was later suggested in a study of 403 acute coronary syndrome patients; those receiving IC abciximab had a statistically significant, 50% reduction in major adverse cardiovascular events (MACE) compared with those receiving it IV (6). In another nonrandomized study of 173 percutaneous coronary intervention patients, death or myocardial infarction (MI) was lower with IC abciximab when

compared with IV (5.9% vs. 13.9%,  $p = 0.04$ ) (7). Further evidence in support of IC abciximab came from a randomized trial of 154 ST-segment elevation MI patients; myocardial perfusion was improved and infarct size was reduced with IC rather than IV abciximab (8). In 137 patients randomized to IV versus IC abciximab, there was no difference in final TIMI (Thrombolysis In Myocardial Infarction) flow grade, but there was a smaller troponin rise in the IC group (9). One-year MACE was not different between the groups.

All the available glycoprotein IIb/IIIa inhibitors have been studied using IC administration. With eptifibatid, there were initial safety concerns because of its low pH (5.35 vs. 7.2 with abciximab). However, in a study of MI patients (10,11), IC eptifibatid appeared to be safe, and over one-half the patients had normal myocardial perfusion at the end of the procedure. A later study (12) of 376 percutaneous coronary intervention patients who received a bolus of IC eptifibatid without an infusion raised the possibility that an IC bolus alone might decrease bleeding complications while still reducing MACE.

Intracoronary tirofiban has also been studied. An open-label, randomized study (13) of 118 acute coronary syndrome patients demonstrated that tirofiban administered IC rather than IV was associated with lower MACE at 14 days, although the benefit was not sustained at 30 days. In another study (14), 54 ST-segment elevation MI patients were randomized to IV or IC tirofiban; patients receiving IC tirofiban had better TIMI flow grades and greater ST-segment resolution.

The specific mechanisms by which IC glycoprotein IIb/IIIa inhibitors may confer greater benefit are now being explored. A higher local concentration might disrupt platelet cross-linking to a greater extent, augmenting thrombus disaggregation (15,16). Intracoronary eptifibatid achieved greater glycoprotein IIb/IIIa receptor occupancy on platelets sampled from the coronary sinus in MI patients than did IV administration (17). Microvascular function was also improved. It is easiest to conceive of why IC glycoprotein IIb/IIIa inhibitors might be superior when there is reduced coronary artery blood flow in which platelet-rich thrombi are present.

If one accepts the potential superiority of IC glycoprotein IIb/IIIa inhibitors, it is not surprising that their administration via a catheter within the coronary artery might be associated with even greater benefit. When giving a medication through a guiding catheter, it often refluxes into the aorta or, with guiding catheters situated in the left main coronary artery, preferentially flows to the vascular bed with greater flow rather than the vascular bed of interest. Slow flow or no-reflow further reduces drug delivery to the site of interest when given through the guiding catheter. Thus, infusion through the lumen of an over-the-wire balloon, an aspiration catheter, or a specialized catheter for local drug delivery may be preferred (18). In a study comparing IC adenosine administered through a microcatheter with IV administration, IC administration had a greater effect on fractional flow reserve (19). Local drug

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delivery may lead to a several-fold increased concentration of the medication and, therefore, might increase its efficacy (20). In 45 acute MI patients with TIMI flow grades 0 to 1, IC abciximab, when compared with IV abciximab, given via a dual lumen catheter distal to the occlusion was associated with improved myocardial blush grade, ST-segment resolution, and smaller infarct size on scintigraphy (21). The study by Prati et al. (22) lends additional support to the potential superiority of administration of abciximab well into the coronary artery, using optical coherence tomography to document a greater reduction in intracoronary thrombus when abciximab was administered IC via the ClearwayRX Therapeutic Perfusion Catheter (Atrium Medical Corp., Hudson, New Hampshire) rather than via the guiding catheter. To deliver the drug, the porous balloon on the catheter is inflated to 2 to 4 atm. Inflation to "low pressures" is believed to allow drug administration not only into the coronary lumen but also along and perhaps into the wall of the coronary artery, with a lesser potential for vessel wall injury.

The study had important limitations. It is small and had a surrogate primary end point. Many patients were randomized but not included in the final analysis. How this porous drug delivery balloon compares with other simpler, better studied and less expensive IC drug delivery methods is unknown.

Many important questions remain about the IC administration of glycoprotein IIb/IIIa inhibitors. Nonetheless, this and other recent studies are reshaping our understanding of glycoprotein IIb/IIIa inhibitors and support the role of local administration. Large randomized trials supporting the routine administration of IC glycoprotein IIb/IIIa inhibitors are needed; several such studies are underway. Until all these studies are completed, the best route for glycoprotein IIb/IIIa inhibitor administration remains unknown.

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