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## **ROUTINE UPSTREAM INITIATION VS DEFERRED SELECTIVE USE OF GLYCOPROTEIN IIB/IIIA INHIBITORS IN ACUTE CORONARY SYNDROMES: THE ACUITY TIMING TRIAL**

In patients with moderate- and high-risk acute coronary syndromes (ACS) who undergo an early, invasive treatment strategy, current guidelines recommend administration of platelet glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibitors, either upstream to all patients prior to angiography or deferred for selective use in the catheterization laboratory just prior to angioplasty. The preferred approach is undetermined.

The objective of this study was to determine the optimal strategy for the use of Gp IIb/IIIa inhibitors in patients with moderate- and high-risk ACS undergoing an early, invasive treatment strategy.

This prospective, randomized, open-label trial with 30-day clinical follow-up included four hundred fifty academic and community-based institutions in 17 countries. The study involved a total of 9207 patients with moderate- and high-risk ACS undergoing an invasive treatment strategy. Patients were randomly assigned to receive either routine upstream (n=4605) or deferred selective (n=4602) Gp IIb/IIIa inhibitor administration, respectively. The primary outcome was assessment of noninferiority of deferred Gp IIb/IIIa inhibitor use compared with upstream administration for the prevention of composite ischemic events (death, myocardial infarction or unplanned revascularization for ischemia) at 30 days, using a 1-sided alpha level of .025. Major secondary end points included noninferiority or superiority of major bleeding and net clinical outcomes (composite ischemia or major bleeding).

Glycoprotein IIb/IIIa inhibitors were used more frequently (98.3% vs. 55.7%, respectively) and for a significantly longer duration (median, 18.3 vs. 13.1 hours;  $P < .001$ ) in patients in the upstream group compared with the deferred group. Composite ischemia at 30 days occurred in 7.9% of patients assigned to deferred use compared with 7.1% of patients assigned to upstream administration (relative risk, 1.12; 95% confidence interval, 0.97-1.29;  $P = .044$  for noninferiority;  $P = .13$  for superiority); as such, the criterion for noninferiority was not met. Deferred use compared with upstream use resulted in reduced 30-day rates of major bleeding (4.9% vs. 6.1%, respectively;  $P < .001$  for noninferiority;  $P = .009$  for superiority) and similar rates of net clinical outcomes (11.7% vs. 11.7%;  $P < .001$  for noninferiority;  $P = .93$  for superiority).

Among patients with moderate- and high-risk ACS undergoing an invasive treatment strategy, deferring the routine upstream use of Gp IIb/IIIa inhibitors for selective administration in the cardiac catheterization laboratory only to patients undergoing percutaneous coronary intervention resulted in a numerical increase in composite ischemia that, while not statistically significant, did not meet the criterion for noninferiority. This finding was offset by a significant reduction in major bleeding.

*Stone GW, Bertrand ME, Moses JW, Ohman EM, Lincoff AM, Ware JH, et al. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY Timing trial. JAMA. 2007 Feb 14;297(6):591-602.*

**Comment:**

The ACUITY timing trial asks whether we can further reduce ischemic events by starting glycoprotein IIb/IIIa inhibitors earlier—when first the patient presents with an abnormal EKG or abnormal enzymes suggesting heart attack. The use of these potent platelet inhibitors has been shown effective in cath labs to reduce composite ischemic event rates. But is it better to start glycoprotein inhibitors early or is it better to wait until the cath lab?

The working hypothesis was that waiting to administer glycoprotein IIb/IIIa inhibitors until the cath lab is not inferior to giving the glycoprotein right away. In fact, the study suggested there could be some slight advantage to using glycoprotein IIb/IIIa inhibitors early, but there was also more bleeding in the early, upstream group compared to the deferred group—which offset any advantage of giving it upstream. When bleeding complications were added to the composite ischemic endpoint, the two strategies yielded identical results: 11.7 percent of patients in both the upstream and deferred groups experienced death, MI and unplanned revascularization (bypass—another angioplasty).

The take-home message is that glycoprotein IIb/IIIa inhibitors are beneficial in high-risk ACS patients—especially those patients who have positive enzymes and ischemic ECG changes. This is true whether you start glycoprotein IIb/IIIa inhibitors upstream or in the cath lab. Upstream use comes at the price of bleeding, however, which may offset any benefit.

Experience and the literature show that patients with major bleeding after angioplasty are significantly impacted long-term (whether related to bleeding itself or some other coagulation problem) those patients do less well in the long-term than those who don't bleed. Of course that is a concern.

The trial did not show a large difference in the timing of administering the inhibitor. One group waited 18.3 hours, the other, 13.4 hours. A five-hour difference is not a lot of time. Both were less than 24 hours. Is five hours worth the potential bleeding? The unanswered question is how fast you need to get them into the cath lab to begin with. We know an early invasive strategy with these types of high-risk patients do better than those treated medically.

— **I. Chavez MD**, Senior Consulting Cardiologist, Minneapolis Heart Institute.

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