ACUITY/ACUITY Timing

The central issue examined by the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) Trial, according to principal investigator Gregg W. Stone, MD, Columbia University Medical Center and the Cardiovascular Research Foundation, was "how best to anticoagulate patients with acute coronary syndromes (ACS)."

ACUITY was a two part study; a main study evaluating optimum anticoagulation strategies, with a sub-study (ACUITY-TIMING) that looked at timing of anticoagulation therapy.

The main ACUITY study asked 2 key questions:

Is heparin (unfractionated heparin [UH] or enoxaparin) or bivalirudin the more effective anticoagulant in non-ST elevation unstable coronary syndrome?

Will bivalirudin plus a glycoprotein IIb/IIIa inhibitor (GPI) be more effective than enoxaparin and a GPI in preventing ischemic complications in patients with unstable angina—while slightly decreasing or at least not increasing major bleeding?

In ACUITY-Timing the question of when to initiate anticoagulation was addressed. Is it better to start GPIs "upstream," at the time of patient presentation, or initiate GPI therapy selectively in patients triaged to PCI after angiography?

Dr. Stone noted that advocates of "upstream" therapy contend that some patients experience MI and death while awaiting revascularization—an outcome that a GPI might prevent. Those who support waiting to initiate therapy "would maintain that MI or death doesn't happen very often," Dr. Stone observed, "and that major bleeding might occur while on anticoagulants."

ACUITY enrolled more than 13,000 patients with a median age of 63 years, 30% of them women. Patients were randomized to three study arms: (1) UH or enoxaparin plus GPI; (2) bivalirudin plus GPI, or (3) bivalirudin alone. (In the bivalirudin alone arm, GPIs could be used when needed for "bailout" if sub-optimal clinical results were encountered.) The study's mean follow-up period was 1 year.

Aspirin was also administered, and clopidogrel was recommended but not mandated.

ACUITY-Timing data was generated by a second randomization. ACUITY patients (n=9200) with moderate to high risk ACS randomized to either the heparin or bivalirudin arms were subsequently randomized to two further arms: (1) upstream GPI vs. (2) no upstream GPI with GPI used selectively in patients triaged to PCI.

ACUITY's primary endpoints were: (1) A composite of death, MI, unplanned revascularization for ischemia, and major bleeding at 30 days; (2) a composite of death, MI, and unplanned revascularization at 30 days, and (3) major bleeding at 30 days

Among patients with acute coronary syndromes, treatment with bivalirudin alone was associated with reduction in MI, unplanned revascularization, major bleeding, or mortality at 30 days, as compared with UH/enoxaparin plus GPI, driven primarily by a reduction in bleeding. Additionally, Dr. Stone noted that "bivalirudin plus a GPI and bivalirudin alone were not inferior to heparin plus a GPI."

For the ACUITY-Timing sub-study, delayed GPIs in patients with ACS was associated with less major bleeding at 30 days compared with upstream GPI administration. The difference between

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rates of major bleeding was statistically significant—6.1% for upstream GPI vs. 4.9% for deferred GPI (p=0.009). Ischemic endpoints did not meet non-inferiority criteria (7.1% for upstream vs 7.9% for delayed). No difference in mortality was seen (1.3% upstream vs. 1.5% delayed) or MI (4.9% vs 5.0%), but unplanned revascularization for ischemia was slightly lower in the upstream group (2.1% vs 2.8%, p=0.03 for superiority). Among patients who went on to PCI (n=5,170), the composite ischemic endpoint was significantly lower in the upstream therapy group (8.0% vs 9.5%, p=0.05).

Among ACS patients, upstream GPI therapy was non-inferior for the net clinical benefit endpoint, compared with delayed GPI administration—but did not meet the criteria for non-inferiority for the ischemic endpoint.

Overall, ACUITY suggests that bivalirudin monotherapy reduces bleeding without a significant increase in events, compared with heparin + GPI. Meanwhile, ACUITY-Timing suggests that while upstream GPI is associated with fewer ischemic events, there was no difference in net clinical outcome between the two strategies.

"The bottom line is that bivalirudin monotherapy is as good as UFH or enoxaparin plus a IIb/IIIa blocker but with far less bleeding," said Dr. Stone. "Bivalirudin monotherapy will facilitate care tremendously."

However, session moderator Matthew Wolff, MD, Chief, Cardiovascular Medicine, University of Wisconsin, noted that ACUITY was a complex trial. "Results here become difficult to interpret," he said. "In ACUITY Timing, for example, only five hours separated the upstream and delayed use of GPI, which is not enough for meaningful comparison."

Dr. Wolff indicated that seeing all the data will be important. "Once the data is published we can assess various questions and caveats on dosages and timing this study raises."

REACH Registry

The REACH (Reduction of Atherothrombosis for Continued Health) study was specifically designed to determine the "real world" risk of a major adverse cardiac events (MACE) in patients with either established atherothrombotic disease or those who were at a high risk for this condition. It is the largest and most geographically extensive registry of its kind, with more than 68,000 patients in 44 countries, covering 6 regions and including 5,000 physician investigators. Patients were recruited based on a history of coronary artery disease (CAD), cerebrovascular disease (CVD) or peripheral vascular disease (PVD), or at least three risk factors for atherothrombosis, including diabetes, cigarette smoking, uncontrolled high blood pressure or uncontrolled high cholesterol levels at entry to study.

Patients with atherothrombotic disease, even in stable form, have a surprisingly high risk of death or major cardiovascular events, according to data from the registry. Within a year, one in eight patients will die, have a heart attack or stroke, or be hospitalized for a complication of vascular obstruction. The risk is even greater for patients with widespread disease burden.

At one year follow-up, investigators observed an overall MACE rate of 13%; noting that patients with peripheral arterial disease were at substantially higher risk, experiencing a one year MACE rate of 22%. In addition there was an incremental increase in risk in those with widespread atherothrombotic disease. In patients with atherothrombotic disease in one location only, the MACE rate was 13%, whereas in those with the disease in three locations, the MACE risk climbed to 28%.

"I find these event rates to be high, given that we are dealing with a stable outpatient population treated with contemporary therapy," said Dr. Gabriel Steg, professor of cardiology at Hôpital Bichat-Claude Bernard, Paris, on behalf of the REACH Reigstry's Scientific Council. "The REACH data shows that it is critical that we stop viewing atherothrombosis as a disease of a specific medical specialty – cardiology, neurology, or vascular disease – instead we must view it as a 'global' disease."