Expert Discussion of the Latest Trial Results: Summary Remarks

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On March 18, 2006, Dr. Gregg W. Stone, Professor of Medicine at Columbia University Medical Center and Chairman of the Cardiovascular Research Foundation in New York, led an expert panel discussion of new data presented at the American College of Cardiology on management of patients with acute coronary syndromes. Following is a summary of the transcript of Dr. Stone's introduction to this panel discussion, starting with an overview of the ACUITY trial, of which Dr. Stone is the lead investigator.

The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial was a 13,819-patient international study to determine what the optimal pharmacologic adjunctive strategy should be in patients with acute coronary syndromes (ACS) undergoing an early invasive strategy.[1] Multiple studies have now shown that the optimal way to manage moderate- and high-risk patients with ACS (unstable angina or non–ST-segment elevation myocardial infarction) is with an early invasive strategy. That is, rapid utilization of the cardiac catheterization laboratory in order to define the coronary anatomy and then triage the patient to the most appropriate therapy, either percutaneous or surgical revascularization or medical therapy. The Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) registry has tracked adherence to Class IA/B American Heart Association/American College of Cardiology (AHA/ACC) guideline recommendations and outcomes in more than 100,000 high-risk ACS patients in the United States. These subjects presented with ischemic symptoms at rest within 24 hours before presentation, as well as with high-risk features, such as ST-segment depression, transient ST-segment elevation, and/or positive cardiac markers (elevated troponin I or T and/or creatine kinase MB levels greater than the upper limit of normal for participating institutions). Data from CRUSADE provide invaluable information on how these patients are currently treated. Approximately 67% of patients are brought to the catheterization laboratory during the index hospitalization (at a median time of < 24 hours), with 50% undergoing coronary angiography within 48 hours of admission. Forty-two percent undergo a percutaneous coronary intervention (PCI), 10% undergo coronary artery bypass surgery, and the remainder are treated medically.

These background clinical data are important when we put the results of clinical trials dealing with this population of patients into proper perspective. However, despite the integration of newer therapies including stents,

glycoprotein (GP) IIb/IIIa inhibitors, and thienopyridines, the rates of adverse ischemic and hemorrhagic events still remain unacceptably high.

In the ACUITY trial, we built on the background that an early invasive strategy in moderate and high-risk ACS patients is the preferred approach, and we attempted to identify the optimal antithrombin medication in these patients treated with all other current Class I indications including the use of aspirin, clopidogrel, and GP IIb/IIIa inhibitors started either upstream or deferred until the PCI is performed.

Conventional antithrombin treatment during PCI in patients with ACS includes unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). The most commonly employed LMWH used in the catheterization laboratory is enoxaparin. Recent studies that have compared the safety and efficacy of UFH to LMWH, including the Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) clinical trial, the Aggrastat to Zocar (A to Z) trial, and Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein Inhibitors (SYNERGY), have collectively shown approximate similar overall outcomes when they are used either prior to or in the catheterization laboratory in the ACS patient. In ACUITY, we looked specifically at a relatively new agent, the synthetic direct thrombin inhibitor bivalirudin.

Bivalirudin has many attractive mechanistic, pharmacokinetic, and pharmacodynamic properties that make it an attractive alternative to either UFH or LMWH when used in patients either as a primary medical therapy or in the cardiac catheterization laboratory in patients undergoing PCI (Table 1). Bivalirudin has a short half-life of approximately 25 minutes, is very specific in targeting only thrombin, is equally active against both clot-bound as well as serum thrombin, does not cause heparin-induced thrombocytopenia, and does not activate platelets, in contradistinction to UFH.

By activating platelets, UFH used alone may lead to an increase in ischemic complication rates in patients undergoing PCI. Although it may be necessary to employ GP IIb/IIIa inhibitors with UFH to reduce ischemic complication rates, this leads to an increase in hemorrhagic complications and thrombocytopenia. Bivalirudin actually blocks platelet activation by thrombin, the most potent endogenous platelet activator, and so in that regard, when added to aspirin and clopidogrel, it may be particularly effective in preventing thrombotic complications.

In addition, the pharmacokinetics of bivalirudin are extraordinarily linear, providing a reliable dose-response effect, and are less affected by other acute phase serum reactants than is the case with heparin. This leads to a predictable antithrombotic effect with bivalirudin, and, as a result, minimizes the incidence of bleeding complications. Monitoring on bivalirudin serum concentrations or biologic activity with either the activated partial thromboplastin time (aPTT) or activated clotting time (ACT) tests is not necessary, and was not performed in ACUITY.

Table 1
Bivalirudin as an Alternative to UFH/LMWH

- Advantages of the direct thrombin inhibitor bivalirudin
  - No requirement for antithrombin III
  - Effective on clot-bound thrombin
  - Inhibits thrombin-mediated platelet activation
  - No interactions with PF-4
  - Plasma half-life 25 min
  - No requirement for anticoagulant monitoring
- Clinical results with bivalirudin in PCI
  - Similar protection from ischemic events as UFH + GP IIb/IIIa inhibitors, with markedly reduced bleeding[2]
- Not previously tested in contemporary ACS patients

UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; PF-4, platelet factor 4; PCI, percutaneous coronary intervention; GP, glycoprotein; ACS, acute coronary syndrome.
Adapted with permission from Lincoff AM et al.[2]

Until now, bivalirudin had only been studied extensively in patients undergoing PCI. In the Randomized Evaluation in Percutaneous coronary intervention Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial of more than 6000 randomized patients in a placebo-controlled blinded trial, patients receiving bivalirudin with the provisional or bailout use of GP IIb/IIIa inhibitors (which was required in only 7% of patients) were compared to those receiving UFH with a GP IIb/IIIa inhibitor.[2] A significant reduction of major and minor bleeding complications and thrombocytopenia without any significant difference in ischemic complications was observed with bivalirudin compared to UFH plus GP IIb/IIIa inhibition.

The REPLACE-2 trial subjects had either stable chronic coronary artery disease or mild unstable ischemic syndromes. Patients with unstable angina requiring IIb/IIIa inhibitors and those with visible thrombus were excluded from randomization. Patients were also excluded if they had been treated with UFH within 6 hours (unless activated partial thromboplastin time was $\leq$ 50 seconds or activated clotting time was $\leq$ 175 seconds) or with

LMWH within 8 hours, bivalirudin within 24 hours, abciximab within 7 days, or eptifibatide or tirofiban within 12 hours before randomization.

In ACUITY, which was performed at 450 centers in 17 countries around the world, 13,819 patients were randomized to 3 different study arms: UFH or enoxaparin + GP IIb/IIIa inhibition, bivalirudin + GP IIb/IIIa inhibition, or bivalirudin + provisional GP IIb/IIIa inhibition (Figures 1 and 2). The control arm was a heparin, either UFH or enoxaparin at operator choice, plus a GP IIb/IIIa inhibitor in all patients. To further define the utility of upstream GP IIb/IIIa inhibitors, the 2 arms employing use of a GP IIb/IIIa inhibitor (either with a heparin or with bivalirudin) were further sub-randomized to either

Figure 1. *ACUITY Study Design: First Randomization. *Stratified by pre-angiography thienopyridine use or administration. NSTEMI, Non–ST-Elevation Myocardial Infarction; UFH, unfractionated heparin; GP, glycoprotein; ACS, acute coronary syndrome; R, randomized; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACUITY, Acute Catheterization and Urgent Intervention Thrombotic Strategy.*

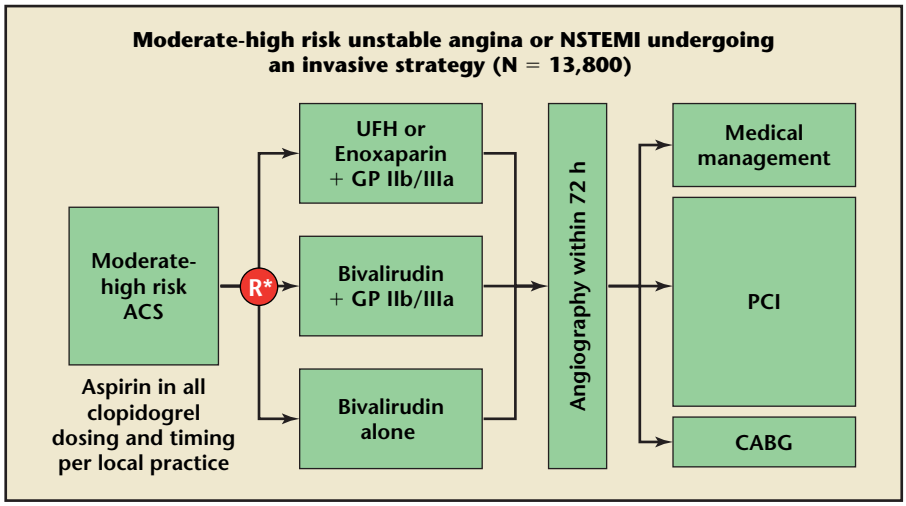


Figure 2. *ACUITY Study Design: Second Randomization. NSTEMI, Non–ST-Elevation Myocardial Infarction; UFH, unfractionated heparin; R, randomized; GP, glycoprotein; pts, patients; CCL, cardiac catheterization laboratory; PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; ACUITY, Acute Catheterization and Urgent Intervention Thrombotic Strategy.*

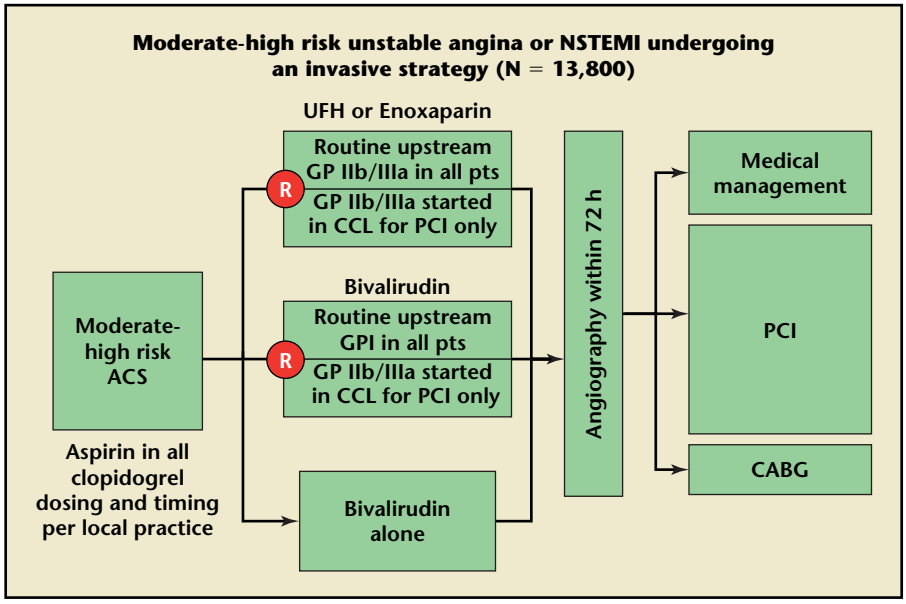


Table 2
Study Medications: Antithrombin Agents Started Before Angiography

	UF Heparin U/kg	Enoxaparin mg/kg	Bivalirudin mg/kg
Bolus	60	1.0 sc bid	0.1 IV
Infusion/h	12*		0.25 IV
PCI	ACT 200-250s	0.30 IV bolus† 0.75 IV bolus‡	0.50 bolus IV 1.75/h infusion IV§
CABG	Per institution	Per institution	Per institution‖
Medical management	None¶	None¶	None¶

* Target aPTT 50-75 seconds.
† If last enoxaparin dose ≥ 8 h − < 16 h before PCI.
‡ If maintenance dose discontinued or ≥ 16 h from last dose.
§ Discontinued at end of PCI with option to continue at 0.25 mg/kg for 4-12 h if GP IIb/IIIa inhibitor not used.
‖ Bivalirudin option for off-pump same as PCI dose. For on-pump bivalirudin discontinued 2 h before.
¶ Option to continue with pre-PCI antithrombotic regimen at physician discretion.
UF, unfractionated; PCI, percutaneous coronary intervention; ACT, activated clotting time; CABG, coronary artery bypass graft; IV, intravenous; aPTT, activated partial thromboplastin time.

upstream use of GP IIb/IIIa inhibitors in the emergency department or as soon as entry into the study, or to use that was deferred until selective administration at the time of PCI in the cath lab (Table 2). Both of these IIb/IIIa inhibitor use strategies are Class I in the guidelines, as no large-scale study had previously examined which was superior.

The patient characteristics were well matched among the 3 arms studied. Interestingly, in the control arm, in which the choice of heparin was up to the discretion of the investigator, there was equal utilization of UFH and enoxaparin. Although the selection of heparin was not randomized, there were no major differences in outcomes between UFH and enoxaparin. In the bivalirudin plus provisional GP IIb/IIIa arm, only about 9% of patients were treated with a GP IIb/IIIa inhibitor, and only 6.5% of use was for breakthrough ischemia (Figures 3 and 4).

Three 30-day primary outcomes were pre-specified: composite ischemia (death, myocardial infarction, or

Figure 3. *Primary Endpoint Measures (Intent to Treat Analysis). UFH, unfractionated heparin; GP, glycoprotein; NI, non-inferior; Sup, superior.*

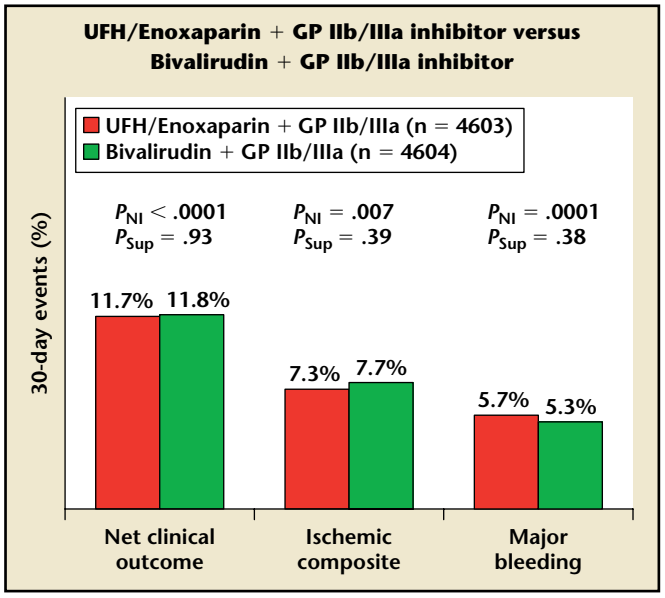


Figure 4. *Primary Endpoint Measures (Intent to Treat Analysis). UFH, unfractionated heparin; GP, glycoprotein; NI, non-inferior; Sup, superior.*

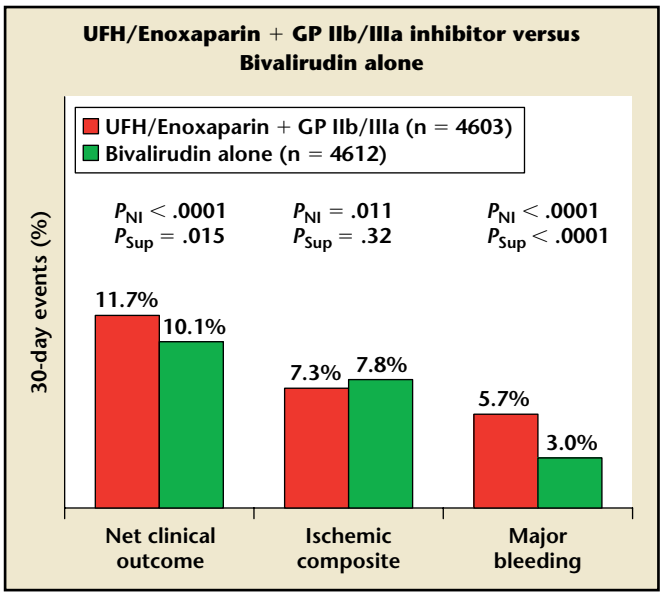


Table 3
UFH/Enoxaparin + GP IIb/IIIa Versus Bivalirudin Alone: Net Clinical Outcome Composite

Actual Treatment (n)	Bivalirudin Alone (%)	UFH/Enoxaparin + GP IIb/IIIa (%)	Relative Risk (95% CI)	*P*	P_{int}
PCI (5170)	11.6	13.3	0.87 (0.75-1.00)	.09	
CABG (1048)	10.6	18.2	0.97 (0.75-1.26)	.84	.59
Medical (2989)	5.1	6.5	0.78 (0.58-1.04)	.09	
Randomization to angio/interv tertiles					
Early (< 3.0 h)	8.3	9.8	0.85 (0.67-1.06)	.15	
Intermediate (3.0-19.7 h)	9.2	9.4	0.98 (0.78-1.23)	.86	.62
Late (≥ 19.7 h)	12.5	14.4	0.87 (0.73-1.05)	.14	
A-thrombin crossover					
No prior AT (3290)	9.1	10.0	0.91 (0.73-1.12)	.36	
Consistent Rx (5519)	6.7	7.1	0.94 (0.80-1.10)	.46	.56
Crossover (3211)	10.6	12.6	0.84 (0.65-1.10)	.21	

UFH, unfractionated heparin; GP, glycoprotein; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

unplanned revascularization for ischemia), major bleeding unrelated to bypass graft surgery, and the net clinical outcome endpoint (the composite of ischemia plus major bleeding) (Table 3). It was anticipated that ischemic and bleeding events would be reduced with the substitution of bivalirudin for heparin used in combination with a GP IIb/IIIa; however, this outcome did not occur. There were actually very similar rates in both adverse ischemic endpoints after cardiac catheterization and major bleeding, and thus the net clinical benefit outcome endpoint was also similar between the 2 groups. Bivalirudin monotherapy, however, resulted in a statistically significant improvement in freedom from the composite of death, myocardial infarction, unplanned revascularization for ischemia, and major bleeding at 30 days. This was achieved with similar (non-inferior) protection from adverse ischemic events, with bivalirudin monotherapy compared to a heparin plus GP IIb/IIIa inhibitors, with a nearly 50% reduction in significant bleeding. This reduction in significant bleeding was observed both when measured by the ACUITY scale and by the Thrombolysis in Myocardial Infarction (TIMI) major bleeding scale. ACUITY scale and TIMI minor bleeding were also both markedly reduced by bivalirudin monotherapy compared to control. In addition, the need for blood transfusions was significantly reduced with bivalirudin monotherapy (Table 4).

Numerous subgroups were examined to look for an interaction among baseline demographics, risk characteristics, and other variables on the ability of bivalirudin monotherapy to reduce major bleeding while still suppressing composite ischemic complications as effectively as heparin plus IIb/IIIa inhibitors. Approximately 15 subgroups were examined, including age, gender, renal insufficiency, diabetes, geographic location, troponin positivity, TIMI unstable angina risk score; presence of ST-segment deviations at rest; pre-treatment with clopidogrel; antithrombin crossovers (eg, prior heparin to bivalirudin); and GP IIb/IIIa use upstream versus deferred. There was no interaction with any of these variables on outcomes with bivalirudin for major bleeding (ie, bivalirudin monotherapy compared to heparin plus IIb/IIIa as inhibitors reduced major bleeding in all subgroups examined). Nor were there any significant interactions for the endpoint of composite ischemia, except for a borderline effect ($P = .054$) for the administration of a thienopyridine before angiography or PCI.

In patients who received clopidogrel before going to the cath lab, there was a very similar incidence of ischemia with the bivalirudin monotherapy arm and the reference heparin plus GP IIb/IIIa inhibitor arm. In fact, the point estimate trended slightly to benefit bivalirudin monotherapy for a reduction of ischemic endpoints, with a marked reduction in major bleeding (Figure 5). On the other hand, in the patients who did not receive a thienopyridine prior to going to the cath lab, ischemic events were slightly more common in the bivalirudin monotherapy group compared with heparin and GP IIb/IIIa inhibitors, although there still was a marked reduction in major bleeding with bivalirudin monotherapy alone. Given the borderline .054 *P* value, uncorrected for

Table 4
Bleeding Endpoints (Non-CABG)

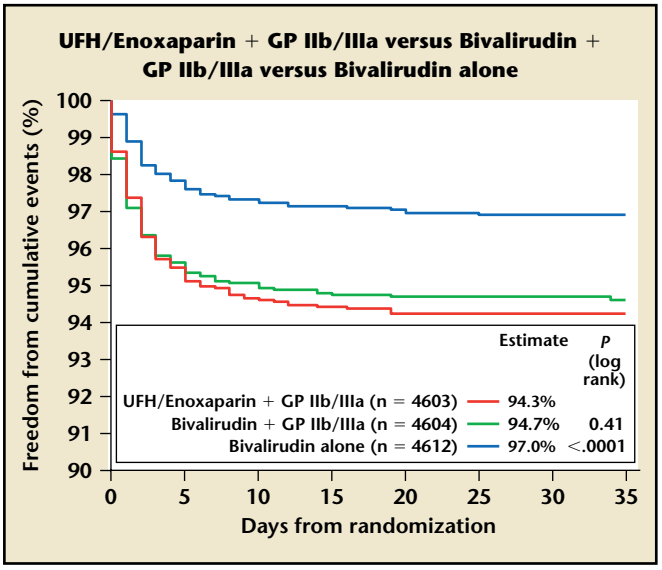
	UFH/Enoxaparin + GP IIb/IIIa (n = 4603)	Bivalirudin + GP IIb/IIIa (n = 4604)	Bivalirudin Alone (n = 4612)	P_1 Value	P_2 Value
ACUITY Scale					
Any	23.9%	23.7%	14.2%	.88	< .001
Major	5.7%	5.3%	3.0%	.38	< .001
Minor	21.6%	21.7%	12.8%	.84	< .001
TIMI Scale					
Any	6.6%	6.4%	3.9%	.67	< .001
Major	1.8%	1.6%	0.9%	.42	< .001
Minor	6.4%	6.1%	3.7%	.52	< .001
Blood transfusion	2.7%	2.6%	1.6%	.70	< .001

P_1 = Bivalirudin + GP IIb/IIIa inhibitor vs UFH/Enoxaparin + GP IIb/IIIa inhibitor; P_2 = Bivalirudin alone versus UFH/Enoxaparin + GP IIb/IIIa inhibitor. CABG, coronary artery bypass graft; UFH, unfractionated heparin; GP, glycoprotein; ACUITY, Acute Catheterization and Urgent Intervention Thrombotic Strategy; TIMI, Thrombolysis In Myocardial Infarction.

multiple comparisons, caution must be used when interpreting whether this interaction effect is real. However, the outcomes of patients with ACS who are managed with bivalirudin monotherapy may be optimized if they receive a thienopyridine prior to going to the cardiac catheterization laboratory, in keeping with the recommendations of the Clopidogrel in Unstable Angina to Prevent Recurring Events (CURE) and Clopidogrel for the Reduction of Events During Observation (CREDO) trials.

The results of the ACUITY trial should be put into perspective in view of other important trials that have been reported or published recently. The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 (ISAR-REACT 2) trial, a multicentered investigation, studied approximately 2000 patients undergoing PCI with unstable angina in whom upstream IIb/IIIa inhibitors were not used.[3] Patients undergoing PCI were pretreated with a 600-mg loading dose of clopidogrel at least 2 hours prior to the procedure and were then randomized to abciximab (usual bolus and infusion dose) (n = 1012) or placebo (n = 1010) on a background of UFH therapy. Abciximab reduced adverse ischemic events in this population. This reduction of the composite endpoint of death, myocardial infarction, or urgent target vessel revascularization due to myocardial ischemia within 30 days benefit was restricted to patients who were troponin positive (Tables 5 and 6).

Figure 5. *Major Bleeding Endpoint. UFH, unfractionated heparin; GP, glycoprotein.*



The ISAR-REACT 2 trial confirms the benefit of GP IIb/IIIa inhibitors in the "hot" ACS patient undergoing PCI observed years ago in the Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment (CAPTURE) trial. In the ACUITY trial, troponin-positive patients treated with bivalirudin monotherapy had similar protection from ischemic events compared to a heparin agent plus GP IIb/IIIa inhibitors but a marked reduction in major bleeding. This occurred despite the lower doses of heparin used in ACUITY compared to the ISAR-REACT 2 Trial.

Second, the specific Factor Xa inhibitor fondaparinux was investigated in 2 trials in patients with ACS/non–ST-segment elevation myocardial infarction (Organization to Assess Strategies for Ischaemic Syndromes [OASIS] 5)[4] and

Table 5
ACUITY Trial: Primary Results

	UFH/Enoxaparin + GP IIb/IIIa	Bivalirudin + GP IIb/IIIa		Bivalirudin Alone	
Observed	**Rate (%)**	**Rate (%)**	***P* Value**	**Rate (%)**	***P* Value**
Endpoint					
Net clinical outcome	11.7	11.8	< .001 NI	10.1	.015 Sup
Ischemic events	7.3	7.7	.007 NI	7.8	.011 NI
Major bleeding	5.7	5.3	.001 NI	3.0	< .001 Sup

ACUITY, Acute Catheterization and Urgent Intervention Thrombotic Strategy; UFH, unfractionated heparin; GP, glycoprotein; NI, non-inferiority; Sup, superiority.

ST-segment elevation myocardial infarction undergoing either thrombolytic therapy or primary angioplasty (OASIS 6).[5] Among more than 20,000 patients enrolled in OASIS 5 with non–ST elevation ACSs, treatment with fondaparinux was non-inferior for the primary composite endpoint of death, myocardial infarction, or refractory ischemia at day 9 compared with treatment with enoxaparin, and bleeding was significantly reduced. Longer-term follow-up revealed a reduction in mortality with fondaparinux at 6 months (5.8% vs 6.5% with enoxaparin, $P = .05$). However, patients stayed on the study drugs more than 5 days in OASIS 5, and only 63% and 34% underwent cardiac catheterization and PCI respectively. Moreover, an increase in catheter thrombus formation in the PCI cohort was noted and of concern. In OASIS 6, which evaluated the effect of fondaparinux versus UFH in patients with ST–segment-elevation myocardial infarction, the benefit was confined to patients who did not undergo primary PCI. The rates of coronary complications were increased with fondaparinux compared to heparin in the primary PCI cohort, notably related to guide catheter thrombosis. Thus, fondaparinux is an excellent alternative to heparin in patients managed conservatively, but PCI requires an agent with antithrombin activity, such as bivalirudin.

The most important clinical implication of ACUITY is that an upstream bivalirudin monotherapy strategy (started in the emergency room after patient presentation) appears to be a significant advance in the treatment of moderate- and high-risk patients with ACS undergoing angiography within 72 hours of admission. By preserving the anti-ischemic effect of heparin and GP IIb/IIIa inhibitors while significantly reducing major and minor bleeding, bivalirudin monotherapy significantly enhances event-free survival in these high-risk patients. Bivalirudin monotherapy is also the simplest of the pharmacologic regimens to administer because it is delivered as an intravenous bolus plus infusion similar to UFH, without a need for serial assessments of antithrombotic activity (ACT, aPTT), and is discontinued at the end of the catheterization or PCI procedure without the need for a prolonged postprocedural infusion of a GP IIb/IIIa inhibitor. ■

Table 6
Clinical Implications

- In patients with moderate-high risk ACS undergoing an early invasive strategy with use of GP IIb/IIIa inhibitors
  - Bivalirudin is an acceptable substitute for either unfractionated heparin or enoxaparin
- However, compared to either UFH/enoxaparin with GP IIb/IIIa inhibition *or* bivalirudin with GP IIb/IIIa inhibition
  - A bivalirudin alone strategy results in significantly greater net clinical benefit and enhanced survival free from adverse events at 30 days

ACS, acute coronary syndrome; GP, glycoprotein; UFH, unfractionated heparin.

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