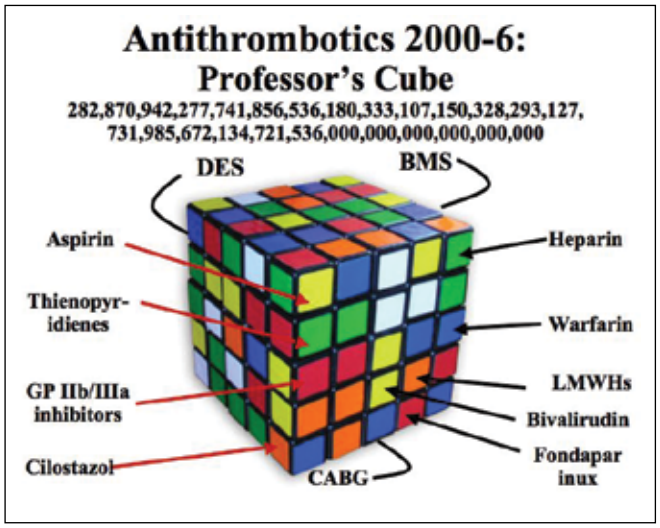
MD CONFERENCE EXPRESS

Update on Antithrombotic Therapy

Figure 1. Antithrombotics 2000-2006.



With the introduction of several new antiplatelet and anticoagulant agents that have multiple actions and interactions, selection of the optimal antithrombotic has become quite complex (Figure 1). "We now think of thrombosis as an assembly line where treatment interventions impact hundreds of pathways simultaneously," said Robert Califf, MD, of Duke University, Durham, North Carolina.

James J. Ferguson, MD, Baylor College of Medicine, Houston, described how he integrates low-molecular-weight heparin (LMWH) into his practice. He noted that for medical management, enoxaparin is superior to unfractionated heparin (UFH) because it is more reliable, easier to use, and safe and effective in transitioning to the catheterization laboratory. Concerns remain, however, about bleeding risks, use in patients with renal dysfunction, and lack of reversibility. In invasive management, the lack of monitoring and uncertainty about prior dosing is problematic, intravenous use is off-label, and the addition of UFH may increase bleeding risk.

For procedural anticoagulation during percutaneous intervention (PCI) in the absence of a recent subcutaneous dose, the recommended dose of enoxaparin is 0.75 to 1.0 mg/kg IV in the absence of concomitant GPIIb/IIIa inhibitors. When GPIIb/IIIa inhibitors are being used the recommended dose is 0.5 to 0.75 mg/kg IV. In patients with acute myocardial infarction (MI) treated with fibrinolytic therapy, enoxaparin is clinically superior to UFH although the risk of bleeding is slightly increased. A critical feature in this setting is dose adjustment in the elderly and in patients with renal failure.

Direct Xa Inhibitors

Lars Wallentin, MD, Uppsala University Hospital, Uppsala, Sweden, described recent results with the subcutaneous direct Xa inhibitor fondaparinux in 20,078 patients with non-ST-elevation acute coronary syndromes (nSTE-ACS) enrolled in the OASIS-5 trial. Patients assigned to fondaparinux 2.5 mg/day had a 13% reduction in death, MI, refractory ischemia, or major bleeding at 6 months ($p < .00001$) compared with those randomized to enoxaparin 1 mg/kg BID. Major bleeding was also reduced (approximately 50%). Dr. Wallentin added that because of the reduction in bleeding risk fondaparinux will play a

prominent role in the medical management of nSTE-ACS in the new European guidelines. However, in patients undergoing PCI, some distally-acting anticoagulant (eg, unfractionated heparin) appears to be necessary to reduce the risk of procedural thrombosis, based on findings from OASIS-5 that demonstrated an increase in catheter thrombus formation in the fondaparinux arm.

Oral direct Xa inhibitors will be important antithrombotics of the future, he predicted. Apixiban and rivaroxaban are already in phase 2-3 trials for deep-vein thrombosis (DVT) prevention and stroke prevention in AF, and several drugs are in phase 2 and 3 studies in ACS.

Direct Thrombin Inhibitors

Thrombin plays a central role in thrombosis and given the complexity of its role and structure, agents that directly inhibit thrombin appear to have different features. As a group, compared with UFH, the DTIs are "both encouraging and disappointing," Dr. Califf observed. In ACS, their effects are confined to reducing non-fatal MI, *not* mortality. In the PCI setting, he said, bivalirudin is a "reasonable concept," since it reduces the risk of bleeding compared with standard therapy with heparin + GP IIb/IIIa inhibitors, but it is not as effective in reducing non-fatal MI.

In patients with low-to-intermediate-risk of ischemic complications, bivalirudin is rational as a "stand alone" anticoagulant, particularly in patients with an elevated bleeding risk. Newer IV and oral DTIs are now entering late-stage clinical trials (Table 1).

Table 1. Direct Thrombin Inhibitors in Human Trials.

Compound	Binding	Route	Indications in Trials	Stage
Lepirudin	Bivalent	IV/SC	HIT-HITTS	Marketed
Argatroban	Univalent	IV	HIT/HITTS	Marketed
Desirudin	Bivalent	IV/SC	VTE	Approved
Bivalirudin	Bivalent	IV	PCI, ACS, CABG, HIT	Marketed
Flovagatran	Univalent	IV	Renal dialysis	Phase 2
AZD0837	Univalent	Oral	AF, VTE	Phase 2
Dabigatran	Univalent	Oral	AF, VTE, ACS	Phase 3
SSR182289A	Univalent	Oral	Unspecified	Phase 2
3DP-4815	Univalent	Oral	Unspecified	Phase 1-2
Aptamers	Univalent	IV	CABG	Phase 1
GW 473178	Antibody	IV	Unspecified	Phase 1

GP IIb/IIIa Inhibitors

GP IIb/IIIa inhibitors have been used for over a decade and are among the best studied agents in medicine. However, as new antithrombotics emerge, the role of older, established drugs needs to be periodically reevaluated, said Robert P. Giugliano, MD, Brigham & Women's Hospital, Boston.

Their primary role is in patients planning to undergo PCI. In patients with ST-elevation myocardial infarction (STEMI), prior meta-analyses have shown inconsistent results, but the most recent long-term individual patient data from three European studies demonstrated a durable reduction in death and MI with abciximab compared to placebo. In patients with STEMI, attention has now turned to the question of optimal timing of initiation of therapy (early in the emergency department vs later in the catheterization laboratory).

In patients with nSTE-ACS, current guidelines recommend GP IIb/IIIa inhibitors for high-risk patients and for those who are planning to undergo an early invasive strategy, since these agents have been demonstrated to reduce ischemic complications prior to and during PCI. However, with newer and potentially safer antithrombotics being developed, the benefits of GP IIb/IIIa inhibitors in reducing ischemic complications must be balanced with the increased risk of bleeding, especially in women and the elderly, Dr. Giugliano said. Recent studies have suggested that excessive dosing of antithrombotics may increase the rate of bleeding; adjusting for renal dysfunction is important to avoid this complication.

Adenosine Diphosphate Inhibitors

Clopidogrel has become an essential agent in the PCI setting. A loading dose should be used for rapid onset, and doses > 300 mg appear to have a role in overcoming some of the problems with clopidogrel—delay in efficacy, variability of response, and metabolic interferences. For example, a loading dose of 600-900 mg has been shown to have a better effect on platelet aggregation, but whether this translates clinically remains to be proven. Metabolism and drug-drug interactions are other avenues of research,

including an examination of polymorphisms that may dictate response to the drug. New ADP receptor antagonists in development, including prasugrel (a more potent oral thienopyridine), AZD 6140 (a reversible PGY_{12} inhibitor), and cangrelor (a short-acting intravenous thienopyridine), are expected to improve upon the current deficiencies with clopidogrel, said Philippe-Gabriel Steg, MD, of the University of Paris.

Novel Targets for Antithrombotic Therapy

Robert A. Harrington, MD, Duke University, Durham, North Carolina, looked to the future, observing that novel agents will change the field tremendously. Aptamers are single-stranded nucleic acids that adopt a specific shape, enabling them to bind with high affinity and specificity to target proteins. RNA aptamers are being developed as highly specific anticoagulants with rapid onset/offset and an available antidote. New platelet surface receptors, such as the thrombin receptor antagonist SCH 530348, can achieve very high platelet blockade with a low risk of bleeding. Also at ACC, Moliterno, et al presented findings from a multinational randomized study of SCH 530348 in PCI, showing very high rates of platelet aggregation, low rates of bleeding (similar to placebo), and a 4.0% rate of 60-day death or MI at the highest dose, compared with 7.3% for placebo (p=0.20). Should randomized controlled trials of these and other novel targets and agents confirm these promising initial findings, clinicians will have more effective, and safer, options for preventing thrombosis.

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inconsistent for celecoxib (Celebrex®), particularly in standard doses. Patients without previous myocardial infarction (MI) have a 23% increased risk with rofecoxib but no increased risk with celecoxib; in patients with previous MI, however, risk is increased by 59% with rofecoxib and by 40% with celecoxib.

Dr. Mukherjee agreed. "The totality of the data suggests that celecoxib is not worse than the older NSAIDS though there is a signal of risk at higher doses," he said. "The black box warning is for *all* the coxibs. If you need an NSAID, naproxen may be the least toxic."

Unresolved questions might be answered by the Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen (PRECISION) trial, which will assess the relative cardiovascular safety of three of the most commonly used pain relievers. The study will enroll patients with arthritis and either coronary heart disease or multiple risk factors for heart disease, and follow them for the occurrence of cardiovascular events.

Managing the Cardiac Patients Who Needs NSAIDS

Elliott Antman, MD, of the Brigham and Women's Hospital, Boston, said that in his practice he uses NSAIDS only as necessary and in patients at the lowest cardiovascular risk, in the lowest possible doses, using the lowest risk agents and the shortest duration of treatment. In patients deemed to have no risk for substance abuse, short-term narcotics may actually be a better choice, he added.

In a study reported at the American Heart Association 2006, Gibson, et al showed that among patients suffering an ST-segment-elevation MI, the adjusted risk for death or MI was increased by 29% in patients who were taking NSAIDS within the prior week. Dr. Antman advised clinicians to be sure their MI patients were not continued on NSAIDS when admitted.

He commented, "COX-2-selective NSAIDS should not be the first line but the last line of treatment today," advising clinicians to closely monitor patients should they prescribe NSAIDS (Figure 2).

Figure 2. Pharmacologic Therapy for Musculoskeletal Symptoms in Patients with Known CVD or Risk Factors for IHD.