Figure 3. Increasing Lipid-Poor apoA-1 as an Acceptor for Cholesterol Efflux via ABCA1.

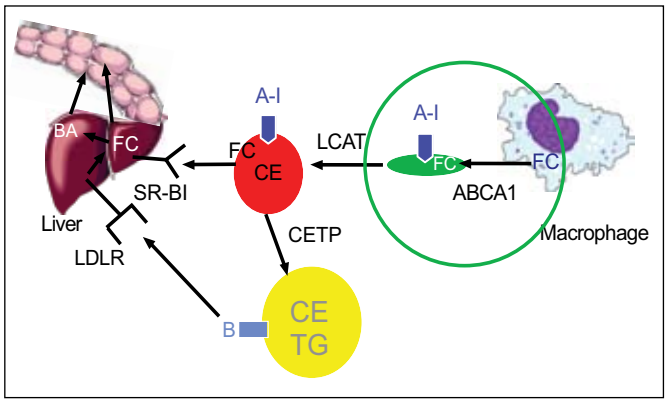


Figure 4. Niacin May Reduce Hepatic Uptake of HDL apoA-1.

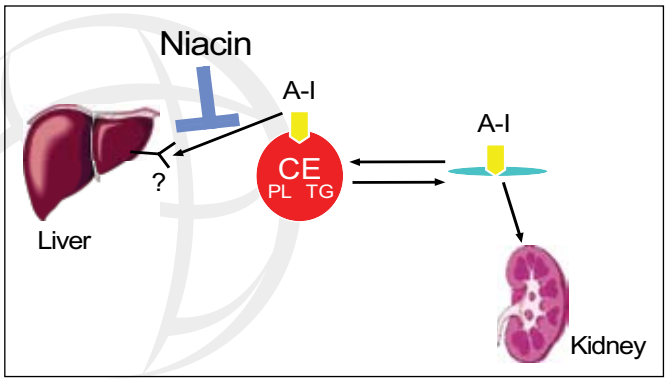
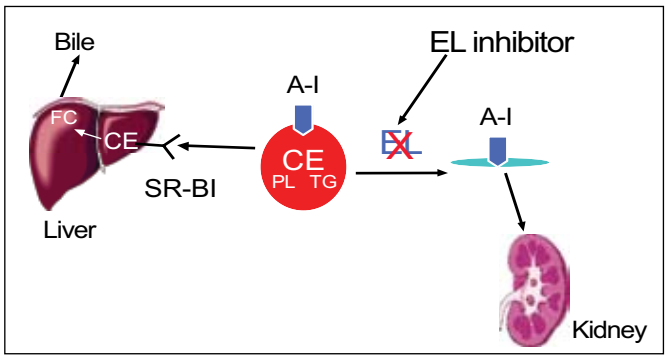


Figure 5. Endothelial Lipase: Target for Pharmacologic Inhibition to Raise HDL?



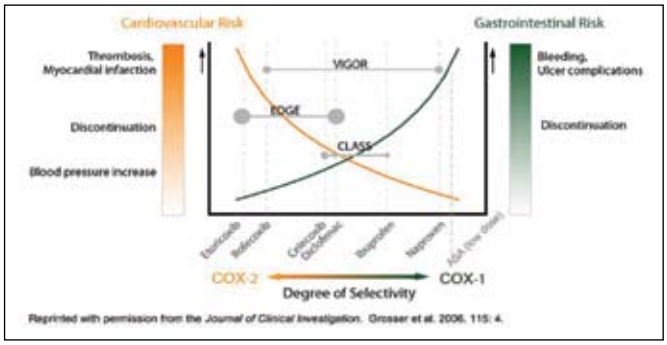
"As we turn more to function and away from HDL cholesterol as a key biomarker of efficacy, we're going to desperately need better measures and biomarkers of HDL function and reverse cholesterol transport in humans. I think for the field this is critically important," concluded Dr. Rader.

NSAIDS in Cardiovascular Disease

Thirty million people worldwide take non-steroidal anti-inflammatory drugs (NSAIDS) for the treatment of chronic pain and inflammation. In light of the cardiovascular (and renal) risks associated with NSAIDS, can clinicians safely use these drugs in their practices?

The spectrum of biological effects with NSAIDS depends on the selectivity of cyclooxygenase (COX) inhibition. COX-1 inhibitors pose gastrointestinal (GI) toxicity but may have antithrombotic effects. COX-2 inhibitors may have less GI toxicity but can have prothrombotic potential, which seems to differ across individual drugs within the coxib class (Figure 1). Cardiovascular risk may be dose-related and possibly duration-related, said Debabrata Mukherjee, MD, of the Gill Heart Institute, University of Kentucky, Lexington.

Figure 1. Implications of Relative Degrees of Selectivity.



James Brophy, MD, of Westmount, Canada, who explored the post-marketing data on NSAIDS, described an important meta-analysis published last year (*Br Med J.* 2006;332:1302-8) in which the relative risk for cardiovascular events for all COX-2 inhibitors was increased by 42% compared with placebo. Individual differences were difficult to show. "There are 121 randomized controlled trials," he remarked, "but we still have outstanding questions."

Observational studies help to fill this gap. The largest studies all show increased cardiovascular risks with rofecoxib (Vioxx®) (14% to 80%), but results are

Continued on page 33

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.

Continued from page 14

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.

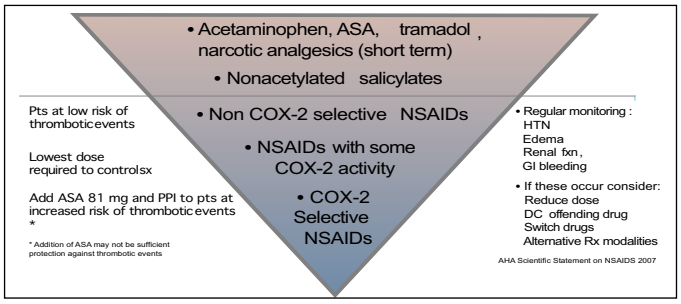
Managing the Cardiac Patients Who Needs NSAIDS

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.



NSAIDS and the Kidney: What is the Danger?

Michael E. Farkouh, MD, Mt. Sinai Heart Clinical Trials Unit, New York, emphasized that dose-dependent renal effects also occur in up to 5% of patients following long-term use of NSAIDS. In light of the coxib controversy, concerns over renal toxicity are increasing, he said.

Problems include acute renal failure, hypertension, congestive heart failure, fluid and electrolyte abnormalities, nephritic syndrome, and papillary necrosis. Patients most at risk include those with age-related decline in glomerular filtration rate, hypovolemia, loop diuretic use, heart failure, cirrhosis and nephrosis.

Risk for acute renal failure with NSAIDS varies by the preparation, according to a recent epidemiologic study (*Am J Epidemiol*. 2006;164:881-9). Naproxen and rofecoxib carry the highest adjusted relative risk over non-exposure (about 2.3 fold); celecoxib's risk is 1.5 and meloxicam's risk is nearly 1.3. Multiple studies have demonstrated that adverse renal effects with rofecoxib are dose-related.

Another significant problem is the aggravation of hypertension with NSAIDS. When patients require treatment with both antihypertensive agents and NSAIDS, Dr. Farkouh advised, "Don't disregard the blood pressure effects of these drugs and make sure your office measures blood pressure reliably." He recommended using lower doses of the NSAID (nonselective or coxib), titrating the antihypertensive, reducing salt intake, questioning patients about over-the-counter NSAID use, and considering aspirin or a non-opioid analgesic instead.

In contrast to current agents, a new agent, lumiracoxib (Prexige®), has a greatly improved renal safety profile and, especially at low doses, is associated with less heart failure compared with other agents, Dr. Farkouh said.

Continued from page 24

low-saturated fat sources and plant proteins), vegetables and fruits should be consumed in abundance, and processed foods should be minimized.

Steven M. Haffner, MD, University of Texas Health Science Center, San Antonio, posed three "key questions" regarding the metabolic syndrome: 1) Does the presence of impaired fasting glucose suggest the need for intensification of cardiovascular risk factor management? 2) Is pharmacologic treatment of impaired fasting glucose and/or impaired glucose tolerance justified to prevent or delay type 2 diabetes? 3) Does therapy for prevention or delay of diabetes decrease cardiovascular disease?

Unfortunately, the answers to these questions, at this point, are "ambiguous," he said. The increase in coronary heart disease risk is "modest" in the setting of impaired fasting glucose, therefore, intensification of risk factor management in this population is not formally recommended. Treatment for impaired fasting glucose or impaired glucose tolerance is only recommended in very-high-risk subjects who have more than a 10% per year risk of developing diabetes. Finally, there is little evidence that preventing diabetes will also prevent cardiovascular disease.

Furthermore, added Lynda Powell, PhD, of Rush University Medical Center, Chicago, it is difficult to motivate patients to make even those changes that clearly prevent cardiovascular disease. "For every 100 patients treated, we achieve success in terms of blood pressure control in only 33, lipid lowering in only 17, and weight loss in only 10 patients," she observed.

Clinicians can help motivate patients toward healthier lifestyles by focusing on one change at a time, keeping the message very simple and repeating it often, she said. They should also emphasize the immediate benefits of change, rather than the long-term goals. The immediate benefits of walking, for example, are the opportunity to breathe fresh air, undisturbed, and reflect on life and thus reduce stress. In addition, she advocates a "coping peer" program that uses fellow patients as a support system for lifestyle modification.