Drug Updates

Number 94 December 2004

This *Heartbeat* will discuss recent drug safety issues associated with cardiovascular risk. These include the increased risk of using Bextra for pain management, the lack of benefit with atenolol for blood pressure and the greater benefit vs risk of using clopidogrel in patients with acute coronary syndrome (ACS).

Bextra Associated with ↑CV Risk

Valdecoxib (Bextra, by Pfizer), a cyclooxygenase-2 (COX-2) selective nonsteroidal anti-inflammatory drug (NSAID), is the latest "designer" NSAID to be associated with increased cardiovascular risk, according to an alert in the December 10 issue of MedWatch, the FDA's safety information and adverse event reporting program.

The FDA has announced that the use of valdecoxib for pain management is contraindicated in patients recovering from CABG surgery. The contraindication was based on the results of a recently completed Pfizer study involving more than 1,500 post–CABG surgery patients showing that administration of valdecoxib increased the risk of MI, CVA, deep vein thrombosis, and pulmonary embolism compared with placebo.

The FDA also has revised the safety labeling for valdecoxib to include a "boxed warning" advising of the risk of serious skin reactions associated with its use. According to the FDA, the risk of severe skin reactions appears to be greater with valdecoxib than with other COX-2 inhibitors and traditional NSAIDs. While these adverse skin reactions are most likely to occur in the first two weeks of therapy with valdecoxib, they may occur at any time. Patients with a history of allergic reactions to sulfa may be at increased risk. Valdecoxib should be discontinued immediately if skin rash, mucosal lesions, or other signs of allergic reaction occur.

Rofecoxib (Vioxx, by Merck), another COX-2 designer NSAID, was removed from the market in September because of safety concerns associated with increased CV risk. This would suggest that all COX-2 inhibitors, which have the same mechanism that inhibits inflammation and makes the drugs easier on the stomach but also shifts the thrombotic balance to a more pro-thrombotic state, may increase CV thrombotic events.

Another recent observational study, to be published in the December Annals of Internal Medicine, though inconclusive, suggests that celecoxib (Celebrex, by Pfizer) may be safer than Vioxx. The FDA has promised to convene a panel early next year to re-examine all the COX-2 drugs.

Conclusion: The connection between heart disease and COX-2 inhibitors remains unclear. Avoid COX-2 inhibitors in any patients with known or high risk of heart disease unless they have a significant risk of gastrointestinal problems. At this time Celebrex would appear the safest choice.

Atenolol May Not Be a Wise Choice for HBP

A recent systematic review of the effect of the widely used beta-blocker atenolol on CV morbidity and mortality in hypertensive patients identified four studies that compared atenolol to placebo or no treatment, and five studies that compared it to other antihypertensive medications.[1] Despite noteworthy differences in BP reduction, there were no outcome differences between atenolol and placebo in 6825 patients with a mean follow-up of 4.6 years on all-cause mortality, CV, or MI risk. The risk of stroke, however, trended lower with atenolol when compared with placebo. When atenolol was compared with other antihypertensives in 17,671 patients who were followed up for a mean of 4.6 years, there were minimal differences in BP lowering between

treatment arms, but CV mortality and stroke rates were significantly higher with atenolol.

Conclusion: Atenolol is probably not an appropriate drug for hypertensive patients with some CV risk, i.e. diabetics, etc. This is not thought to be a class effect, as there are significant improved outcomes with metropolol and carvedilol. Atenolol is hydrophilic and thus has some difficulty penetrating the CNS, which likely influences the drug's ability to prevent ventricular fibrillation by altering CNS processes linked to it.

Dual Anti-platelet Therapy Should Be Initiated Early In ACS: Benefits Outweigh Risks Even For CABG Patients

The question of timing in the use of clopidigrel (Plavix, by Bristol Myers Squibb) in patients with acute coronary syndromes (ACS) has focused on balancing the benefit of early treatment with a potential increased risk of bleeding. Should you treat early (as was done in all the clinical trials showing benefit) or wait until coronary visualization has defined anatomy and then direct clopidigrel treatment to medical or percutaneous coronary intervention (PCI) patients, avoiding those who need to undergo CABG to minimize the bleeding risk?

"It's really a case of the tail wagging the dog if you withhold early clopidogrel to try to avoid any increased risk of bleeding, because you also miss an opportunity for prevention of cardiovascular events. For every 1000 patients treated early with clopidogrel, an additional 10-12 major cardiac events would be prevented at the expense of creating one TIMI minor-moderate bleed in people going on to CABG," says Dr. Christopher Cannon, Associate Professor of Medicine, Harvard Medical School, Cardiovascular Division Brigham and Women's Hospital.

A recent study[2] broke down this risk in those who underwent CABG in the CURE trial and concluded, "The benefits versus risks of early and long-term clopidigrel therapy (freedom from CV death, MI, stroke, or life-threatening bleeding) are similar to those undergoing revascularization CABG or PCI) and in the study population as a whole. Overall the benefits of starting clopidigrel on admission appear to outweigh the risks, even among those who proceed to CABG during hospitalization."

Dr Keith Fox and colleagues analyzed data from the 12,562 patients randomized in the **CURE,** (**C**lopidogrel in **U**nstable angina to prevent **R**ecurrent Ischemic **E**vents) trial. This was a large-scale, randomized, double-blind, placebo-controlled trial, comparing clopidogrel with placebo in patients presenting with an ACS without ST-segment elevation. All patients received aspirin daily. The clopidogrel patients were loaded with 300mg and then received 75mg daily. The authors stratified 12,562 CURE patients as follows:

- 2072 (16.5%) underwent CABG: 1061 placebo and 1011 clopidogrel patients
- 2658 (21.2%) underwent PCI: 1345 placebo and 1313 clopidogrel patients.
- 985 patients received medical therapy without revascularization.

There was a 1% absolute increase in the incidence of major bleeding in the clopidogrel group and no increase in patients with life-threatening bleeding or hemorrhagic stroke. In addition, the excess bleeding that occurred was in the mild to moderate category, and there was no significant life-threatening bleeding.

The other key part of this paper demonstrates **the benefit of clopidogrel treatment: a *~20% reduction in events,*** which is an exact match for the increase in moderate bleeding in the patients who received clopidogrel within 5 days of CABG. "So, for the CABG patients it's an even trade between moderate bleeding and death, MI, or stroke. This puts into perspective the benefit you get for that moderate increase in bleeding." Most of the benefit seen in CABG patients during initial hospitalization is pre-op. The biggest benefit in terms of events prevented in treating these very high-risk patients is gained early during the most unstable period.

Review of other Pertinent Data[3]:

PCI-CURE demonstrated the early effects of clopidogrel in PCI patients: 30% reduction in death or recurrent ischemic events over the first 24 hours. In a pre-specified subgroup analysis, patients who received clopidogrel at least 6 hours before PCI experienced a relative risk reduction of 38.6% for this

endpoint, compared with no reduction with treatment less than 6 hours before PCI.[4]

Stenting vs balloon angioplasty: Data presented at the ACC by Shamir Mehta MD demonstrate a 44% reduction in CV death or MI out to one year in patients who had undergone balloon angioplasty, showing that both the early and late benefits of clopidogrel treatment occur in places other than stent sites, i.e., all other blockages and vulnerable plaques throughout the coronary tree.

CREDO showed the benefit of an early loading dose: patients who were treated 6-24 hours prior to catheterization had a 38% reduction in death, MI, or urgent target vessel revascularization, similar to what was seen in PCI-CURE, suggesting that patients need to be at steady-state level to get the maximal benefit of the agent. The number needed to treat to prevent 1 patient from having a death, MI, or stroke in CREDO was 33, compared to 25 in PCI-CURE, showing a dramatic improvement in clinical outcome.[5]

The diffuseness of disease: It is this "hidden disease" – the presence of vulnerable plaques throughout the coronary tree – that is the target of long-term treatment with high-dose statins, aspirin, ACE inhibitors, and now clopidogrel, showing benefit out through a year in these studies.[6]

ISAR-REACT demonstrated the benefit of a 600 mg loading dose of clopidogrel in a low-risk, elective PCI patients randomized to abciximab or placebo. All patients were pretreated 7 hours prior to PCI with the 600 mg clopidogrel load, and the addition of the GP IIb/IIIa inhibitor did nothing to prevent events. Note that a steady state is required – loading "on the table" is not adequate for good platelet inhibition.[7]

Bleeding risks: The good news is that it looks like we can reduce the risk of bleeding when lowering the dose of aspirin to 75-100 mg. Interestingly, using low-dose aspirin plus clopidogrel is associated a lower risk of bleeding than using 325 mg of aspirin.[8]

Conclusion: There will be a relatively small risk of increased bleeding with early treatment with clopidogrel in the ACS group as a whole, but a large benefit in terms of prevention of major cardiac events. Furthermore, the downside risk can be minimized more than 95% of the time by delaying CABG for 5 days. **Early antiplatelet therapy—> 6 hr to get post PCI benefit—with clopidogrel, starting with a 300mg loading dose followed by 75mg/day and aspirin 81mg/day is indicated in all ACS patients in order to maximize overall benefit –prevention of 10-12 major cardiac events vs 1 TIMI minor bleed post CABG.**

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[1] Carlberg B et al. Atenolol in hypertension. *Lancet* 2004; 364: 1684-89.

[2] Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. *Circulation* September 7 2004; 110 (10): 1202-8.

[3] Highlights from a commentary by Dr Christopher Cannon on www.theheart.org November 12 2004.

[4] Mehta SR et al for the CURE Trial Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; 358 (9281): 527-33.

[5] Steinhubl SR et al for the CREDO Investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; 288 (19): 2411-20. Erratum in: JAMA 2003; 289 (8): 987.

[6] Asakura M, Ueda Y, Yamaguchi O, et al. Extensive development of vulnerable plaques as a pan-coronary process in patients with myocardial infarction: an angioscopic study. *J Am Coll Cardiol* 2001; 37 (5): 1284-8.

[7] Kastrati A, et al for the ISAR_REACT investigators. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med* 2004; 350 (3): 232-8.

[8] Peters RJ, Mehta SR, Fox KA, et al for the CURE Trial Investigators. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* 2003; 108 (14): 1682-7.