

## **CARDIOVASCULAR COMPLICATIONS RELATED TO COX-2 INHIBITORS**

### **Introduction**

The potential association of cardiovascular complications with the use of selective COX-2 inhibitors (coxibs) has been of continued interest to clinicians and has been the subject of several recent studies publications in medical journals as well as two previous ACR *Hotlines* ("Update: Safety Issues Related to NSAIDs and COX-2 Inhibitors" released in April 2002, available at <http://www.rheumatology.org/publications/hotline/o4o2cox2.asp>, and "Selective COX-2 Inhibitors as Risk Factors for Cardiovascular Events" released August 2001, available at <http://www.rheumatology.org/publications/hotline/o8o1acox2.asp>).

Substantial media coverage of data from a poster on "Risk of Acute Myocardial Infarction and Sudden Cardiac Death with Use of COX-2 Selective and Non-Selective NSAIDs" presented at the 20th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, August 22–25, 2004 in Bordeaux, France, has renewed interest in this topic. This study was funded by an FDA contract with Kaiser Permanente.

### **Summary Information**

#### *Acute Myocardial Infarction*

The poster, which was presented by David Graham, MD, and colleagues, assessed the risk of acute myocardial infarction and sudden cardiac death among nearly 1.4 million members of Kaiser Permanente of California who were treated with coxibs or traditional NSAIDs between 1/99 and 12/01. Low dose aspirin and over-the-counter NSAID use were not captured in the electronic medical records, but were quite similar between rofecoxib and celecoxib users when assessed by survey. There were a total of 8,199 acute cardiac events in the study cohort (6,675 acute MI, and 1,524 cases of sudden cardiac death, or SCD). Using a nested case-control design and controlling for other cardiovascular risk factors, each case (persons with a cardiovascular outcome) was matched with four controls. The main data of interest are presented below.

**Table 1. The relative risk of acute cardiac events (either AMI or sudden death)**

Private NSAID use	Adjusted OR (95% CI)
Remote use	1.00
Recent use	1.14 (1.06–1.22)
Current use	
-Celecoxib	0.86 (0.69–1.07)
-Rofecoxib <25 mg	1.29 (0.93–1.79)
-Rofecoxib >25 mg	3.15 (1.14–8.75)
-Ibuprofen	1.09 (0.99–1.21)
-Naproxen	1.18 (1.04–1.35)
-Other NSAIDs	1.16 (1.04–1.30)

From this data, the authors conclude that rofecoxib > 25mg/day was associated with a 3-fold elevated risk of AMI or SCD. There was no increased risk for celecoxib. As the authors acknowledge, the very small number of cases and controls using high dose rofecoxib (10 cases and 8 controls among 26,748 total patients treated with rofecoxib) create a wide confidence interval. However, these data are consistent with another recent observational database study of a large Medicare population [1]. In this study, researchers at Harvard Medical School conducted a case-control study that included 10,895 cases and 43,580 controls. Rofecoxib at any dosage was associated with an elevated risk of AMI compared with celecoxib (RR = 1.24, 95% CI 1.05–1.46). Rofecoxib > 25 mg/day was associated with a relative risk of 1.70 (95% CI 1.07–2.71) compared with high dose celecoxib. The risk was highest in the first 90 days after starting rofecoxib and was not elevated after the first three months.

### **Hypertension**

The Phase III trials with rofecoxib suggested a possible increase in blood pressure that has been investigated by two subsequent studies. One trial randomized over 1000 patients with OA with known hypertension to rofecoxib 25 mg or celecoxib 200 mg per day [2]. The primary endpoint of this study was clinically significant changes in systolic and diastolic blood pressure. By the end of the six week trial, 14.9% of patients randomized to rofecoxib met the pre-specified definition of systolic hypertension (an increase in systolic BP by 20 mm Hg to a level of at least 140 mm Hg) versus 6.9% for celecoxib ( $p < 0.01$ ). There were similar trends in diastolic blood pressure but these did not meet the statistical significance threshold. An observational study among Medicare beneficiaries without prior hypertension also found an increased risk of new blood pressure elevations requiring anti-hypertensive treatment for patients using rofecoxib compared with celecoxib (odds ratio = 1.6, 95% CI 1.2–2.1) or a traditional NSAID (OR = 1.4, 95% CI 1.1–1.9) [3].

### **Congestive Heart Failure**

A recent observational study from Ontario raised important concerns about rofecoxib in elderly patients with respect to CHF [4]. This study included over 100,000 patients over 65 and compared with risk of an admission for CHF among patients using coxibs, traditional NSAIDs or neither. Compared with patients using no NSAID, patients taking rofecoxib at any dosage had an adjusted relative risk of CHF admission of 1.8 (95% CI 1.5–2.2). Those taking a traditional NSAID also had an increased risk of CHF (RR 1.4, 95% CI 1.0–1.9). However, celecoxib users were at no increased risk (RR 1.0, 95% CI 0.8–1.3).

### **The Bottom Line**

1. The VIGOR RCT [5] and analyses of several observational datasets have found an increased risk of acute myocardial infarction with the use of rofecoxib at dosages above 25 mg per day. More studies are needed to define the magnitude and duration of this increased risk.
2. Data from several sources are consistent in finding an increased risk of hypertension and congestive heart failure in patients taking rofecoxib.
3. When using any coxib or traditional NSAID, clinicians need to be aware of potential adverse events including AMI, hypertension, and CHF. Clinicians need to weigh such risks against anticipated benefits, and consider issues such as dose, risk factors, and comorbid conditions.

This HOTLINE is being provided to inform readers of these recent studies. Readers are reminded that some of these data have been presented in abstract form only.

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