Parecoxib, Valdecoxib, and Cardiovascular Risk

Curt D. Furberg, MD, PhD; Bruce M. Psaty, MD, PhD; Garret A. FitzGerald, MD

Selective inhibitors of cyclooxygenase (COX)-2\(^1\) depress prostacyclin (PGI\(_2\)) but not COX-1–derived thromboxane A\(_2\). The effects of thromboxane A\(_2\) would be exaggerated during treatment with COX-2 inhibitors, potentially predisposing patients to heart attack and stroke.\(^2\)

A randomized controlled trial in patients undergoing coronary artery bypass graft (CABG) surgery and receiving either placebo or 40 mg parecoxib (Dynastat; Pfizer), the intravenously administered prodrug of valdecoxib (Bextra; Pfizer), followed by oral valdecoxib 40 mg BID for 14 days, revealed a cluster of cardiovascular events.\(^3\) In a second study, one group received parecoxib/valdecoxib, another intravenous placebo followed by valdecoxib (20 mg BID for 10 days), and the third placebo alone. Despite the reduction in dose and duration of therapy, a cluster of events was again apparent. Data from the second trial are in the new label for valdecoxib.\(^4\)

The Table represents the incidence of coronary and cerebrovascular events in the two trials individually and combined in a meta-analysis.\(^5\) The two active treatment arms of the unpublished trial were combined and compared with placebo. Although the treatment–placebo difference did not reach conventional levels of statistical significance for the individual trials, valdecoxib in the combined analysis was associated with a 3-fold higher risk of cardiovascular events than placebo. There was no statistical evidence of heterogeneity.

Parecoxib is only known to afford pain relief by its rapid transformation to valdecoxib in vivo, and valdecoxib has selectivity for inhibition of COX-2 in vitro that approximates that of rofecoxib. A PGI\(_2\)-based mechanism would be facilitated by the presence of hemostatic activation, such as CABG surgery. Aside from clinical context, the hazard likely is related to the actual selectivity attained in vivo and to drug dose, half-life, and duration of treatment. It is currently unclear to what degree such risk extends to patients treated chronically with lower doses for arthritis because studies of sufficient size and duration to characterize the potential cardiovascular risk in such populations have not been reported.

Although valdecoxib has been contraindicated in patients undergoing CABG, the cardiovascular risks of valdecoxib in other patients have not been studied adequately. In the absence of evidence of safety, it is prudent to avoid the use of valdecoxib altogether or use it only as a drug of last resort. The recent emergence of a cardiovascular hazard with a third, structurally distinct COX-2 inhibitor—celecoxib—provides compelling evidence that these adverse coronary and cerebrovascular events represent a class effect, as originally predicted.\(^1\) A black-box warning that alerts practitioners to the potential cardiovascular hazards, especially in patients at moderate to high risk, seems timely for all COX-2 inhibitors. The circumstances under which COX-2 inhibitors can be safely administered for extended periods to patients at low risk of cardiovascular disease remain to be defined.

### References
