Parecoxib, Valdecoxib, and Cardiovascular Risk

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elective inhibitors of cyclooxygenase (COX)-2\(^1\) de-
press 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 cor-
nary 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 cere-
brovascular events in the two trials individually and com-
bined 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the unpublished trial were combined and compared with placebo.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 conven-
tional 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 facili-
tated 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
cronically 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 cere-
brovascular 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.

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coronary artery bypass