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Cardiovascular complications of specific COX-2 inhibitors

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAID) are the most commonly used drugs throughout the world. The mechanism of their activity has been discovered, and a decrease in prostaglandin production due to inhibition of the cyclooxygenase enzyme complex is believed to be the major mechanism of their anti-inflammatory activity. Discovery of two isoforms of cyclooxygenase, COX-1 and COX-2 was a base for synthesis of new group of NSAID, the COX-2 inhibitors. The drugs have been found to have significant anti-inflammatory properties and to be relatively low harmful for the gastrointestinal system.

The discovery of enhanced cardiovascular risk of rofecoxib resulted in the withdrawal of the drug and initiated an extensive discussion on the cardiovascular safety of COX-2 inhibitors.

The evaluation of the cardiovascular and general safety of COX-2 inhibitor is a complex process; the drugs are widely used by patients with rheumatoid arthritis or osteoarthritis, i.e. older patients already at higher risk of cardiovascular events due to age, inflammation, immobilization and other factors. It is also of importance that the COX-2 inhibitors like non-specific NSAID have very different chemical structure and several side-effects may be related to the other parts of the drug molecule than that responsible for COX-2 inhibition. The open question is to which extend the cardiovascular risk is associated with the individual drug molecule or is a class effect. Studies like CLASS, VIGOR, APPROV and MEDAL evaluated the safety of such coxibs as celecoxib, etoricoxib, parecoxib and valdecoxib. The studies were performed within various protocols and in various groups of patients (with low or high cardiovascular risk). In some studies, low doses of aspirin were added to the coxib.

The mechanism of the increased risk of cardiovascular events in patients on COX-2 medication is a subject of discussion. Such mechanisms as pro-thrombotic activity (due to inhibition of prostacyclin synthesis), induction of hypertension, peripheral edema, renal impairment or competition with aldosterone for cytochrome enzymes have been suggested. On the other hand, some studies indicate for the endothelial improvement and beneficial effect of coxibs on lipid metabolism as the contradictory mechanisms.

In general, some enhanced risk of the COX-2 inhibitors should be considered in clinical practice but benefits like low risk of gastrointestinal bleeding should be taken into consideration as well.