**Etoricoxib was noninferior to diclofenac for cardiovascular outcomes in osteoarthritis and rheumatoid arthritis**


**Clinical impact ratings:** GIM/FP/GP ★★★★★✩ Hospitalists ★★★★★✩ Cardiology ★★★★★✩ Hematol/Thrombo ★★★★★✩ Rheumatology ★★★★★✩

**Question**

In patients with osteoarthritis or rheumatoid arthritis, is etoricoxib noninferior to diclofenac for cardiovascular (CV) outcomes?

**Methods**

Design: Randomized controlled noninferiority trial (Multinational Etoricoxib and Diclofenac Arthritis Long-term [MEDAL] Programme) was a prespecified pooled analysis of data from 3 randomized controlled trials: MEDAL, Etoricoxib versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness [EDGE], and EDGE II.

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, outcome assessors, monitoring committee, and statisticians).*

Follow-up period: Mean 18 months.

Setting: 1380 sites in 46 countries.

Patients: 34 701 patients (mean age 63 y, 74% women) who had osteoarthritis of the knee, hip, hand, or spine (≥4 of 7 of the American Rheumatism Association 1987 revised criteria; n = 9787); needed chronic paracetamol (acetaminophen) as first-line therapy.

Intervention: Etoricoxib, 60 or 90 mg/d (n = 17 412), or diclofenac, 75 mg twice/d or 50 mg 3 times/d (n = 17 289). Low-dose aspirin (≤100 mg/d), proton-pump inhibitors, or misoprostol were recommended in certain high-risk patients.

**Outcomes**

Composite endpoint of the first venous or arterial thrombotic CV events (myocardial infarction, unstable angina, pectoris, intracardiac thrombus, resuscitated cardiac arrest, thrombotic stroke, cerebrovascular thrombosis, transient ischemic attack, peripheral venous thrombosis, pulmonary embolism, peripheral arterial thrombosis, and death). Secondary outcomes included confirmed arterial events, Anti-Platelet Trialists’ Collaboration (APTC) endpoint (myocardial infarction, stroke, or vascular death), upper and lower gastrointestinal clinical events (GCEs), and complicated events (perforation, obstruction, and witnessed ulcer or significant bleeding).

**Patient follow-up:** 96% (per-protocol analyses [used for the primary analysis]) and 100% (intention-to-treat analysis).

**Etoricoxib vs diclofenac in osteoarthritis or rheumatoid arthritis at mean 18 months†**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Analysis</th>
<th>Event rate per 100 patient-y</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Etoricoxib</td>
<td>Diclofenac</td>
<td></td>
</tr>
<tr>
<td>Primary composite thrombotic</td>
<td>Per protocol</td>
<td>1.2</td>
<td>1.0 (0.8 to 1.1)‡</td>
</tr>
<tr>
<td>cardiovascular endpoint</td>
<td>Intention to treat</td>
<td>1.3</td>
<td>1.1 (0.9 to 1.2)</td>
</tr>
<tr>
<td>Upper GCEs</td>
<td>Intention to treat</td>
<td>0.7</td>
<td>0.7 (0.6 to 0.8)</td>
</tr>
</tbody>
</table>

†GCE = gastrointestinal clinical event. CI defined in Glossary.

‡Criterion for noninferiority was met because the upper limit of the 95% CI of the hazard ratio was < 1.3.

**Commentary**

Selective cyclooxygenase-2 (COX-2) inhibitors were introduced as an alternative to traditional NSAIDs because of their reduced propensity to induce gastrointestinal bleeding. Confidence in selective COX-2 inhibitors was shaken when increases in myocardial infarction and cerebral thrombosis were shown in patients receiving these drugs (1). However, these adverse effects were noted in comparative trials of COX-2-treated and placebo-treated patients, a design with ethical difficulties.

Cannon and colleagues observed the efficacy and incidence of adverse CV and gastrointestinal events in patients receiving etoricoxib or diclofenac. This large-scale and immaculately designed and executed trial showed that the incidence of major CV events was similar in both groups. The incidence of major gastrointestinal problems was higher in the diclofenac group. This outcome suggests that enthusiasm for selective COX-2 inhibitors may be well founded, but it is unwise to rush to judgment. This trial compared 1 COX-2 inhibitor and 1 NSAID; experience indicates that the outcome might not be the same in all drugs in these classes. Furthermore, although the sample size was large, patients were heterogeneous. The results are clear-cut overall, but they do not necessarily help physicians faced with individual patients. The trial groups included patients with osteoarthritis or rheumatoid arthritis. Rheumatoid arthritis is a risk factor for CV disease (2), as are possibly corticosteroids, which about 16% of patients were receiving. We have not progressed in knowing which patients are most at risk for major CV problems. Hypertension and fluid retention necessitated stopping higher-dose etoricoxib slightly more frequently than diclofenac. Those seeking further reassurance may be better served by an improved analysis of risk factors in susceptible patients than by large-scale and time-consuming trials on a similar scale (3).

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**References**