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NSAID Trials and the Choice of Comparators — Questions of Public Health Importance

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Under ideal conditions, large clinical trials would be designed so that they satisfied the marketing needs of the pharmaceutical manufacturers that generally sponsor them and, at the same time, answered important clinical questions that may have a major influence on public health. In practice, however, alternative choices in trial design often favor one of these two goals. The choice of the reference treatment in active-comparator studies is an excellent example.

For nonsteroidal antiinflammatory drugs (NSAIDs), which all relieve arthritis pain, the question of greatest interest in randomized trials involves the incidence of adverse events. The more selective cyclooxygenase-2 (COX-2) inhibitors were developed in the hope that they would pose a lower risk of gastrointestinal bleeding than traditional NSAIDs. Although an early trial of the COX-2 inhibitor rofecoxib showed a relative gastrointestinal benefit, it also suggested that the risk of myocardial infarction was about five times as high with rofecoxib

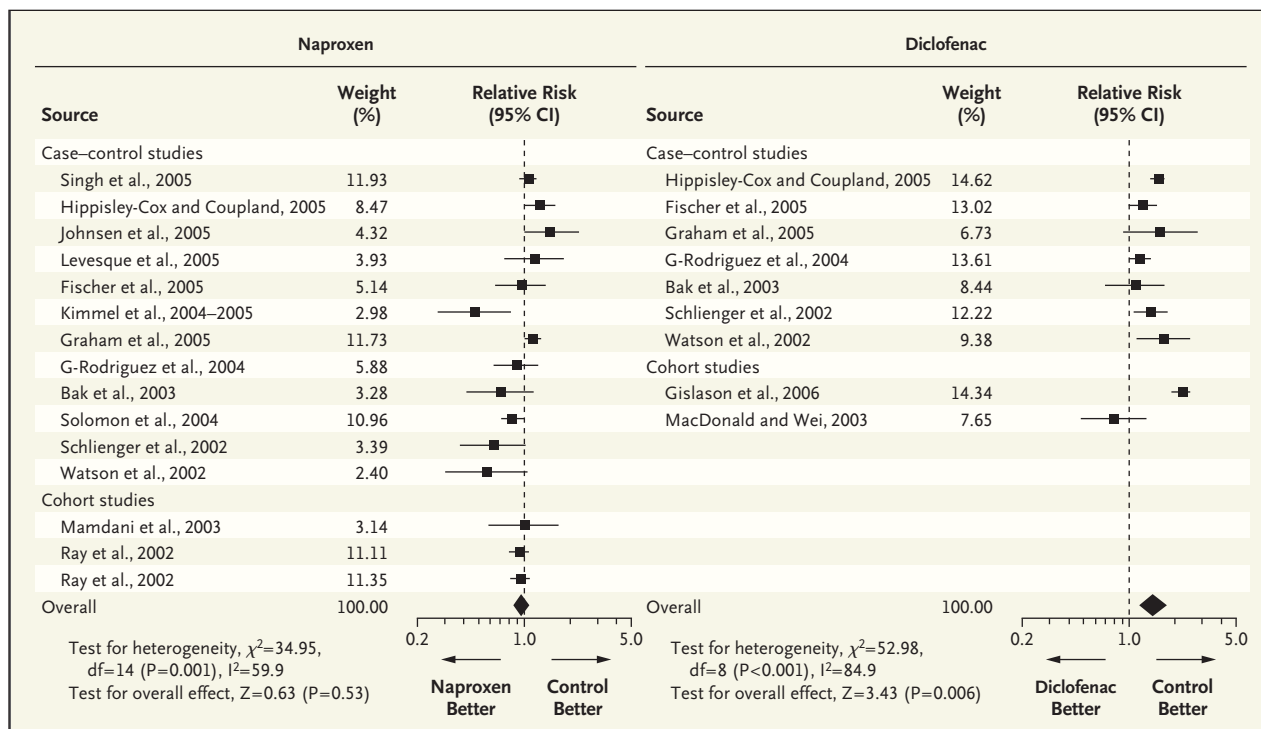
as with naproxen. Subsequently, placebo-controlled trials of rofecoxib, celecoxib, and valdecoxib documented an increased risk of cardiovascular disease.

In the recently reported Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program, 24,913 subjects with osteoarthritis and 9787 with rheumatoid arthritis were randomly assigned to receive etoricoxib or diclofenac and were followed for an average of 18 months.¹ The pain-relief efficacy was similar for the two drugs. In the intention-to-treat analysis, etoricoxib was not associated with a significantly higher risk of thrombotic cardiovascular events than was diclofenac (hazard ratio, 1.05; 95% confidence interval [CI], 0.93 to 1.19). Complicated upper gastrointestinal events — which included perforation, obstruction, documented ulcer, and significant bleeding — did not differ between the two treatment groups (0.30 event per 100 person-years with etoricoxib vs. 0.32 per 100 person-years with diclofenac). The MEDAL report provides relatively

precise estimates of the risk-benefit trade-off for the choice between diclofenac and etoricoxib.

Diclofenac, though not the most frequently used NSAID in the United States, was chosen as the comparator, according to the MEDAL report, because it is “the most widely prescribed NSAID in the world.”¹ However, its relative COX-2 selectivity is similar to that of celecoxib. The potential for cardiovascular complications associated with COX-2 inhibition was recognized as early as 1999. So even before the MEDAL trial began, one might have hypothesized that diclofenac would increase the risk of cardiovascular events.

Recent observational data (see figure) and clinical-trial evidence support this hypothesis. In a meta-analysis of 121 placebo-controlled trials, the COX-2 inhibitors were associated with an increased risk of vascular events (relative risk, 1.42; 95% CI, 1.13 to 1.76).³ In 26 trials that included diclofenac as the active comparison treatment, the risk was, if anything, slightly lower with the “new” COX-2 inhibitors (relative risk, 0.92; 95%



Point Estimates and Summary Relative Risks of Cardiovascular Events Associated with Naproxen and Diclofenac.

The control was nonuse or remote use of antiinflammatory drugs. Adapted with permission from McGettigan and Henry.²

CI, 0.81 to 1.05). In contrast, in the 42 trials that used naproxen as the comparison treatment, COX-2 inhibitors were associated with an increased risk (relative risk, 1.57; 95% CI, 1.21 to 2.03).³ These data suggest that as compared with naproxen, diclofenac may increase the risk of vascular events by about 70%.

In other words, the comparison drug in the MEDAL trial appears to have cardiovascular toxicity similar to that of other COX-2 inhibitors. To address the most important clinical question, the comparison group should receive the best available active treatment. Indeed, in February 2005, the Arthritis and Drug Safety and Risk Management Advisory Committees of the Food and

Drug Administration (FDA) recommended naproxen, not diclofenac, as the “preferred comparator” for large trials of COX-2 inhibitors. This public recommendation by an independent group not only helps to set the standard for future trials but also aids in the interpretation of completed trials.

The withdrawal from the market of two COX-2 inhibitors, rofecoxib and valdecoxib, because of cardiovascular toxicity has inspired greater scrutiny of this whole class of drugs. One side effect of these withdrawals may be the size and scope of the MEDAL program, which is more typical of post-marketing phase 4 trials than preapproval phase 3 trials. When the FDA reviews the evi-

dence with regard to etoricoxib, it will have an unusual abundance of data available. But the question of etoricoxib’s approvability, which will depend on a finding about whether it is “safe and effective for the intended use,” is a narrow one.

This determination is distinct from the key clinical question: What is the gastrointestinal and cardiovascular safety of etoricoxib as compared with that of traditional NSAIDs? Etoricoxib is likely to be associated with a higher rate of cardiovascular events than naproxen, but the relative gastrointestinal safety of the two drugs remains unknown. Is the combination of naproxen and a proton-pump inhibitor as safe as or safer than etoricoxib

for the gastrointestinal tract? The MEDAL program missed the opportunity to address these important clinical and public health questions.

In recent years, similar questions have remained unanswered after trials comparing some new cardiovascular drugs with other active treatments; in several trials of antihypertensive therapy, for instance, organizers selected the beta-blocker atenolol as the comparator, although low-dose diuretics are the most effective antihypertensive agents in preventing cardiovascular disease.⁴

The Institute of Medicine's committee on drug safety recently proposed a public-private partnership to help define key public health questions that merit investment in large, long-term phase 4 trials.⁵ This partnership would not only identify the studies of greatest public health importance but also recommend the best design features, including, when appropriate, the comparison treatment. Under this model, the public designation of a phase 4 trial as a key study through an independent and unbiased process might provide sponsors with an incentive to evaluate their drugs in a manner that highlights their potential clinical value and not their anticipated marketing potential. Such a designation might also engender in them a sense of responsibility for funding studies designed to answer pressing clinical questions.

Would industry support such trials? Some companies might well give priority to their social obligations. Others might not, especially if participation would conflict with their responsibility

Sponsors need incentives to evaluate drugs in a manner that highlights potential clinical value, not marketing potential.

to shareholders to devote resources to studies that would be likely to show their products to the best advantage.

In view of this tension between marketing needs and public health questions, some commentators have called for a national commitment to publicly supported studies of the risks and benefits of drugs. In the absence of such funding, perhaps Congress could provide the FDA with the authority to dictate the design and conduct of occasional phase 4 trials.⁵ But funding is not the sole problem. In the United States, the long tradition of leaving to the pharmaceutical industry the task of evaluating the efficacy and safe-

ty of its products has permitted manufacturers to make study-design choices that largely determine the shape of the answers eventually provided by the trials. The identification, design, and prioritization of large phase 4 drug trials of potential public health importance represent a major medical, social, and scientific effort that currently lacks a champion in the United States.

Dr. Weiss reports receiving consulting fees from Wyeth.

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