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Summing the risk of NSAID therapy

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Reports concluding that chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) increases the likelihood of cardiovascular adverse events have led patients and clinicians to reduce use. It is intriguing to recollect that the cardiotoxicity of NSAIDs (both cyclo-oxygenase-2 [COX-2] selective inhibitors and non-selective dual inhibitors have been implicated) would not have been revealed if not for the push to market novel drugs developed to reduce the well-documented gastrointestinal complications of this widely used class. While weighing risks and benefits of interventions is an essential component of clinical decisionmaking, it has become increasingly complex to decide in whom the use of any NSAID—with or without a gastroprotective agent, and with or without concomitant aspirin—is appropriate. In view of the multiplicity, and in many cases rarity, of adverse events, it is unlikely that a single mega-trial will adequately address the numerous safety and effectiveness issues. In the meantime, careful

synthesis of the literature—not complete reliance on single studies that address one outcome—is required to inform decisionmaking. This stepwise approach is crucial, because appropriate selection of an NSAID should be driven by assessment of an individual's cardiovascular and gastrointestinal risk, or both, rather than by a drug's reported rate of adverse events in heterogeneous populations (table).¹

The importance of individualised risk assessment and its role on a single NSAID-related safety outcome is exemplified in the study by Frances Chan and colleagues in today's *Lancet*.³ They report that the twice-daily addition of a proton-pump inhibitor to twice daily celecoxib lowered the 13-month recurrence of ulcer bleeding to 0% in the combined treatment group compared with 8.9% with celecoxib alone (95% CI for the difference, 4.1–13.7). The trial enrolled individuals at highest risk of a gastrointestinal complication: those with previous gastrointestinal bleeding. While the complete absence of recurrent events for those on combination therapy, even in the face of aspirin therapy, is surprising, the finding provides clear guidance for those individuals at greatest gastrointestinal risk who require an NSAID. The incremental risk-reduction of a proton-pump inhibitor in the setting of aspirin and a COX-2 inhibitor is consistent with the trials comparing etoricoxib and diclofenac.⁴ The MEDAL programme combined data from three trials and the findings contrast with those from several studies showing no significant gastrointestinal safety benefit of COX-2 inhibitors plus aspirin over a traditional NSAID-aspirin combination.^{5,6}

	No or low NSAID gastrointestinal risk	NSAID gastrointestinal risk
No cardiovascular risk (without aspirin)	Nonselective NSAID (cost consideration)	COX-2 selective inhibitor or non-selective NSAID+proton-pump inhibitor COX-2 selective inhibitor+proton-pump inhibitor for those with prior gastrointestinal bleeding
Cardiovascular risk (with aspirin)	Naproxen* Addition of proton-pump inhibitor if gastrointestinal risk of aspirin/NSAID combination warrants gastroprotection	Proton-pump inhibitor irrespective of NSAID Naproxen if CV risk outweighs gastrointestinal risk COX-2 selective inhibitor+proton-pump inhibitor for those with previous gastrointestinal bleeding

*Non-selective or selective (low-dose) inhibitor without established aspirin interaction if naproxen is ineffective.²
Misoprostol at full dose (200 µg four times a day) may be substituted for proton-pump inhibitor. Adapted from reference 1.

Table: Clinicians guide to anti-inflammatory therapy in 2007

This new information supporting the gastrointestinal advantage of a combination of a COX-2 and proton-pump inhibitor should not be interpreted without careful consideration of competing risks from the cardiovascular perspective. For individuals with documented cardiovascular risks, the selection of an NSAID is not straightforward. Recent position statements,⁷ supported by collective but not conclusive data,⁸ suggest that naproxen is differentiated from other selective and non-selective agents that may increase cardiovascular risk. For those with competing cardiovascular and gastrointestinal risks, the tradeoffs between reducing gastrointestinal adverse events (COX-2 inhibitor instead of a non-selective NSAID) must be explicitly weighed against concerns about cardiovascular side-effects (naproxen instead of other agents).

In addition to individual patients' characteristics, attention to dose, administration, and duration of NSAID use should also be considered. Chan and colleagues used celecoxib 200 mg twice daily, a dose with established cardiovascular risk.⁹ There is no published evidence that concomitant aspirin lessens the increased cardiovascular risk observed with COX-2 selective inhibitors.^{9,10} A once daily 400 mg and 200 mg dose of celecoxib seems to not share this hazard,^{11,12} at least in patients with average cardiovascular risk. On examination of the existing data, NSAID adverse effects should not be attributed simply by drug classification (ie, COX-2 selective inhibitor or non-selective inhibitors), but instead by the dose and duration of COX-2 inhibition. While the ongoing PRECISION trial, in which naproxen, ibuprofen, and celecoxib are being compared, will be informative, the lack of a placebo control arm and the years of data collection necessary require timely decisions be made with available data.¹³

Comment about costs is warranted, because it may not be feasible to recommend the "safest" regimen in every circumstance. The cost-effectiveness of risk-reducing therapies is intimately related to the patients' underlying risk.¹⁴ For those at highest gastrointestinal risk, the use of a proton-pump inhibitor and a low-dose COX-2 inhibitor seems cost effective for those without high cardiovascular risk. In those patients in whom the cardiovascular risk parallels or exceeds gastrointestinal concerns, naproxen with a proton-pump inhibitor is recommended when non-NSAID approaches fail.

The choice of NSAID remains confusing and controversial in a setting of several important unanswered

questions. As important pieces are added to the puzzle, it remains critical to sum the risks using all the parts.

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