Te Awakairangi Health NETWORK

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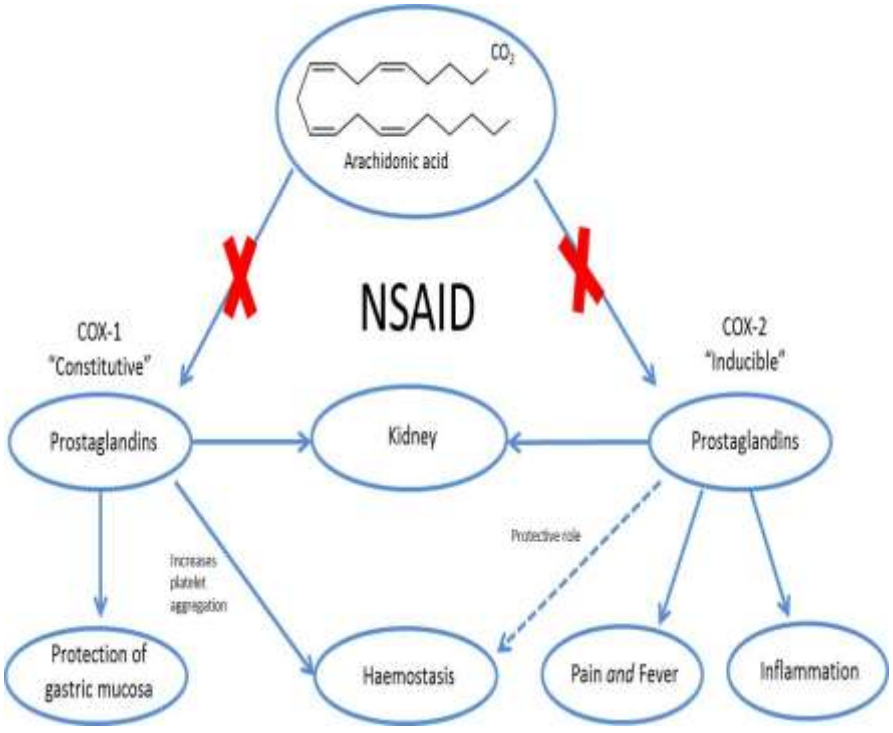
NSAIDs – time to review

There is a comprehensive body of evidence emerging, despite their popularity and availability over-the-counter, that the clinical efficacy of NSAIDs does not come without a *potential risk of significant cardiovascular harm.* Most NSAIDs (non-selective or 'traditional' and COX-2 selective) are associated with an increased risk of cardiovascular events such as stroke or myocardial infarction (MI).[1-4] A recent meta-analysis (May 2013) reviewing the cardiovascular safety of NSAIDs provides further evidence that some NSAIDs such as diclofenac carry more risk than others.[1]

Key Messages:

- ✓ **Use lowest effective dose for shortest possible time -** higher daily doses of NSAIDs are associated with an increased risk of MI, stroke and death from cardiovascular disorders - for patients with a past history of an MI, even short term use can be associated with increased cardiovascular harm[4]
- ✓ **Choose a NSAID with lowest risk of cardiovascular harm** - now substantial evidence that NSAIDs that inhibit COX-2, without complete inhibition of COX-1, incur the greatest risk (see insert below)
- ✓ **Exercise particular caution when prescribing diclofenac -** evidence suggests diclofenac has a significant risk of cardiovascular harm
- ✓ **Always consider an individual patient's Cardiovascular Risk factors before prescribing NSAIDs** (i.e hypertension, hyperlipidaemia, diabetes mellitus, smoking, age)[5-9]

Understanding the mechanism of action of NSAIDs



COX-1 verses COX-2 What is the difference?

The extent to which an NSAID inhibits respective cyclooxygenase isoforms enzymes may be indicative of risk of cardiovascular harm.

X COX-2 Inhibition, in the absence of inhibition of platelet aggregation through complete COX-1 inhibition, may lead to a thrombogenic environment.

✓ In addition, COX-2 has a protective role in thrombogenesis, hypertension and atherogenesis[2].

FOR CARDIOVASCULAR SAFETY - choose NSAIDS with lowest cardiovascular risk

Of all the non-selective NSAIDs, naproxen (at any dose) or low dose ibuprofen (1,200 mg/day) are considered to have the most favourable thrombotic cardiovascular safety profiles [7]

Diclofenac: a cause for concern?

Across the literature, diclofenac has consistently been associated with a cardiovascular risk similar to that of selective COX-2 inhibitors. Diclofenac completely inhibits COX-2, but has only ~ 70% inhibition of COX-1 at therapeutic concentrations. The greater risk appears to be in patients taking dicofenac for *long periods* and at *greater than 100mg/daily*. By comparison, naproxen consistently demonstrates a lower CV risk profile and completely inhibits both isoenzymes. Currently regulatory bodies across the globe are reviewing diclofenac containing medicines.

Updated Information for Healthcare Professionals overseas (UK & Europe)

New contraindications and warnings were issued in the UK (July 2013)[7] after the Europe-wide review of cardiovascular safety and the recently published meta-analysis of clinical data (May 2013).[1]

Now contraindicated in any patient with established • Ischaemic heart disease • Peripheral arterial disease • Cerebrovascular disease • Congestive heart failure (NYHA classification II-IV) Patients with these conditions should be switched to alternative treatment at next routine appointment	Treatment should only be initiated after careful consideration of significant risk factors for cardiovascular events (e.g hypertension, hyperlipidaemia, diabetes mellitus, smoking)	From now on diclofenac should be considered to have the same cardiovascular precautions as for selective COX-2 inhibitors (e.g celecoxib)

Current Information for Healthcare Professionals (NZ)

Medsafe® in New Zealand has chosen to take a more conservative approach issuing a Trans Transman Early Warning System Alert on diclofenac and the risk of cardiovascular events (July 2013). [9]

• Overall benefit to risk of harm balance remains positive. • Not possible to clearly differentiate cardiovascular risk between different non-steroidal anti-inflammatory drugs (NSAIDs). • Use the lowest effective dose for the shortest possible duration. • Diclofenac should not be used in patients with a recent myocardial infarction history (within the last 6 to 12 months)	• Periodically review patients on long-term diclofenac for effectiveness, adverse effects and development of cardiovascular risk factors. • Relevant risk factors for cardiovascular events associated with diclofenac (and other NSAIDs) include hypertension, hyperlipidaemia, diabetes, ischaemic heart disease and smoking.	• Discuss the risks and benefits of NSAID treatment with patients before commencing therapy. • Report any adverse reactions to the Centre of Adverse Reactions Monitoring (CARM).

References

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2. McGettigan P, Henry D. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines in low-middle and high income countries. Plos Med 2013;10:e 1001388
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4. Olsen AM, Fosbol EL, Lindhardsen Jj et al. Long term cardiovascular risk of non-steroidal anti-inflammatory drug use according to time passed after first-time myocardial infarction: a nationwide cohort study. Circulation 2012;126:1955-63
5. PRAC recommends the same cardiovascular precautions for diclofenac as for selective COX-2 inhibitors
6. http://www.ema.europa.eu/ema/index.jsp?curl=pages and events/news/2013/06
7. Diclofenac: new contraindications and warnings after a Europe-wide review of cardiovascular safety. MHRA Drug Safety Update 13th June 2013 Vol 6 Issue 11
8. 9 years since Vioxx: NSAIDs still a concern. NPS Direct 09 May 2013 www.nps.org.au

9. Diclofenac (Voltaren) and risk of cardiovascular events (heart and stroke) Trans-Tasman Early Warning System – Alert Communication
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