Landmark Review
The MEDAL Programme

Cardiovascular outcomes: diclofenac and etoricoxib in arthritis

About the commentators -

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Arthritis is a growing problem for New Zealanders. Arthritis New Zealand estimates that more than 500,000 adults (around 1 in 6) are currently living with arthritis, and this is expected to increase to around 720,000 (or 1 in 5) by 2020. [1]

Much of the increase is expected to occur as a consequence of demographic ageing. Currently over three quarters of those aged 75 or older have osteoarthritis (OA), whereas the overall prevalence is around 8%.[1] The profile is similar for rheumatoid arthritis (RA), with a general prevalence of 3%, compared to 23% of over-75 year-olds. [1] Rising BMI in the New Zealand population is also a contributing factor, with between 17–18% of all cases considered to be attributable to obesity. [1]

The prevalence, financial costs and burden of disease resulting from arthritis are similar to those arising from other major disease areas including cardiovascular disease and cancers. [2] In New Zealand, overall costs run to several billion dollars each year, with indirect costs such as loss of productivity and informal care outweighing direct costs by a factor of 3 to 1. [1]

Early diagnosis and effective treatment can result in long-term health benefits for patients and decrease overall costs to the community. [2] However it is estimated that a large proportion of people with arthritis remain untreated. [2]

About the MEDAL programme

The MEDAL programme is comprised of 3 large-scale randomised, controlled trials. 34,701 patients with rheumatoid arthritis (n = 9,787) or osteoarthritis (n = 24,913) from 1,380 sites in 46 countries participated in the trials, for a mean treatment duration of 18 months. [3]

The objective of the trials was to compare the risk of thrombotic cardiovascular events with etoricoxib or diclofenac during the long-term treatment of rheumatoid or osteoarthritis.

Background

Use of long-term nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with rheumatoid or osteoarthritis has been limited due to the risk of damage to the gastrointestinal (GI) tract. Agents which selectively inhibit cyclo-oxygenase-2 (COX-2 selective inhibitors) were developed in order to reduce the risk of GI injury, but have been associated with an increased risk of thrombotic cardiovascular events in placebo-controlled trials. [3]

The MEDAL programme was designed to provide the first data from long-term controlled trials which assessed the risk of thrombotic cardiovascular events with a traditional NSAID in comparison to a new COX-2 selective inhibitor. In an attempt to reflect the general population with arthritis, the patients recruited into the trial included those with a range of pre-existing cardiovascular and gastrointestinal risk-factors. [3]

Registered uses of diclofenac and etoricoxib

Diclofenac (75-150mg/day) is indicated for treatment of inflammatory and degenerative forms of rheumatism including rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism.[4] It is fully funded for inflammatory arthritis (including osteoarthritis with an inflammatory component) in patients who are stabilised and well controlled on the medication.

Etoricoxib (60-120 mg/day) is indicated for treatment of acute and chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis, management of ankylosing spondylitis, treatment of acute gouty arthritis, relief of acute pain and chronic musculoskeletal pain.[5] Etoricoxib is not reimbursed on the pharmaceutical schedule.

For more information on indications see **www.medsafe.govt.nz**

For funding criteria see **www.pharmac.govt.nz**

Trial Design

The MEDAL programme presents the pooled results of 3 large-scale randomised, controlled, clinical trials comparing etoricoxib and diclofenac. (Fig. 1)

Patients meeting the entry criteria (Fig. 2) were randomly assigned on a 1:1 basis to treatment with etoricoxib or diclofenac, using a matching placebo design to ensure blinding.

Evaluations were conducted at 4-monthly intervals. Overall arthritis disease status was reported using a 5-point patient-rated global assessment scale. Thrombotic cardiovascular events and upper and lower GI events were identified through active surveillance of reported adverse events. All events were adjudicated by an independent, blinded committee.

The primary endpoint was first occurrence of all thrombotic cardiovascular events, with secondary outcomes measuring subsets of cardiovascular events including arterial and APTC (Anti-Platelet Trialists Collaboration) events. Other outcomes included discontinuations resulting from hypertension, oedema, renal dysfunction, GI adverse events, hepatic events or liver function test abnormalities.

Study population

34,701 patients, with a mean age of 63 years were randomised to treatment. Baseline characteristics were similar for both groups. 74% of participants were women.

Co-morbidities included diabetes (11%), dyslipidaemia (29%), hypertension (47%), established atherosclerotic disease (12%) and established atherosclerotic disease with 2 or more cardiovascular risk factors (38%). At baseline, 35% of subjects were using low-dose aspirin. (Fig 3)

Mean duration of treatment was 18.2 and 17.7 months for patients treated with etoricoxib and diclofenac respectively. Over 60% of subjects received treatment for ≥ 12 months, and 37% for ≥ 24 months.

For more information on the MEDAL trial design and patient demographics see the American Heart Journal, Aug 2006, Vol 152, No2, 237-245

Fig. 1 Study Medications

MEDAL (n = 23,504)	Etoricoxib 60mg/day (OD)* Etoricoxib 90mg/day (OD)* Diclofenac 150mg/day (BID)
EDGE (n = 7,111)	Etoricoxib 90mg/day (OD) Diclofenac 150mg/day (TID)
EDGE II (n = 4,086)	Etoricoxib 90mg/day (OD) Diclofenac 150mg/day (BID)

*The first 4333 patients recruited with OA, and all RA patients received etoricoxib 60mg/day, the remainder received 90mg/day.

Fig. 2 Entry Criteria

- Male or female aged ≥ 50
- Rheumatoid or osteoarthritis
- Requiring chronic treatment with NSAID

Patients with a history of myocardial infarction, coronary artery bypass graft surgery or percutaneous coronary interventions ≥ 6 months prior to enrolment were eligible for the study.

Specialist Opinion - Dr Andrew Harrison

COX-2 selective inhibitors were developed to provide the anti-inflammatory benefits of traditional NSAIDs without the gastrointestinal and anti-platelet side effects. Large long term placebo controlled trials of rofecoxib [6] and celecoxib [7] confirmed the suspicion that prolonged COX-2 inhibition increases the risk of thrombotic cardiovascular events. As a result, rofecoxib was withdrawn from the market. Observational studies have indicated that some traditional NSAIDs may also increase the risk of cardiovascular disease [8], but there have been no placebo-controlled RCTs to confirm this.

Etoricoxib (Arcoxia) is a COX-2 selective inhibitor that is available in New Zealand, but still awaiting FDA approval in the USA. Diclofenac is the most commonly used NSAID in New Zealand and worldwide. The Multinational Etoricoxib and Diclofenac Long-term (MEDAL) program was prospectively undertaken to pool the data from three studies in order to compare the adverse cardiovascular, renovascular and gastrointestinal effects of etoricoxib and diclofenac in arthritis patients [3].

Fig. 3 Adjunctive Medications

Low dose aspirin (≤ 100mg/day) prophylaxis

- Recommended for patients with pre-existing cardiovascular, peripheral arterial, or cerebrovascular disease
- Encouraged for patients with diabetes

Anti-ulcer prophylaxis

(proton pump inhibitors or misoprostol)

- Recommended for patients with high risk of upper GI events (patients with: age >65 years; history of upper GI ulcer or haemorrhage; corticosteroid, receiving anticoagulant or antiplatelet therapy.)

Specialist Opinion - Dr Terry Macedo

The most significant features that make the MEDAL program design a landmark study included:

1. It was a large scale randomised clinical trial over a significantly long follow-up period with a study period of 3 years and average patient treatment time of 18 months.
2. Etoricoxib at usual therapeutic doses was compared with Diclofenac at usual therapeutic doses
3. A "real life" trial that included patients with previous cardiovascular events, with patients with cardiovascular risk factors, and patients on aspirin (35% at baseline).

Outcome measures and results

Thrombotic cardiovascular events

Overall rates (per 100 patient years) for thrombotic cardiovascular events were similar for etoricoxib (1.24) and diclofenac (1.30), hazard ratio (HR) 0.95 (95% CI 0.81-1.11).

There was also no difference in risk for etoricoxib or diclofenac-treated patients with regard to the secondary outcome measures of arterial thrombotic events or APTC events. (Fig. 4.)

Fig. 4 Incidence of thrombotic cardiovascular events

	Treatment	n	n/PYR	Rate (95% CI)*	HR (95% CI)
Thrombotic events					
Per-protocol	Etoricoxib	16 819	320/25 836	1·24 (1·11–1·38)	0·95 (0·81–1·11)
	Diclofenac	16 483	323/24 766	1·30 (1·17–1·45)	
Arterial thrombotic events					
Per-protocol	Etoricoxib	16 819	272/25 839	1·05 (0·93–1·19)	0·96 (0·81–1·13)
	Diclofenac	16 483	272/24 771	1·10 (0·97–1·24)	
APTC events					
Per-protocol	Etoricoxib	16 819	216/25 851	0·84 (0·73–0·95)	0·96 (0·79–1·16)
	Diclofenac	16 483	216/24 787	0·87 (0·76–1·00)	

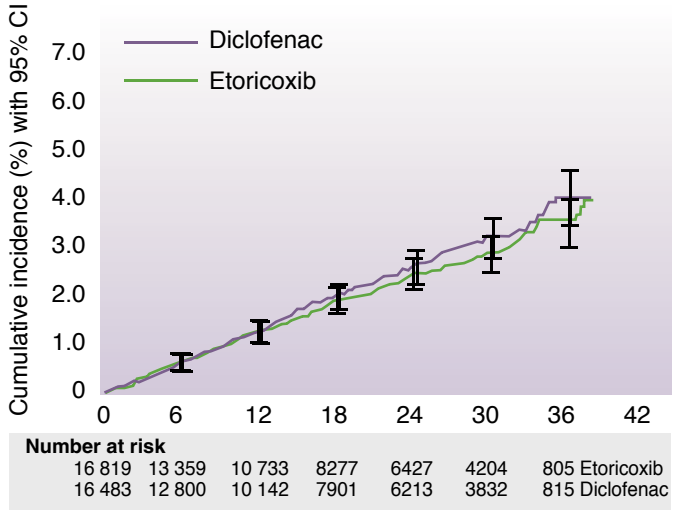
PYR=patient-years at risk. *Per 100 PYR.
APTC = Anti-platelet trialists collaboration

Subgroup analyses showed no significant effect of study, baseline cardiovascular risk, low-dose aspirin use or etoricoxib dose on hazard ratio.

Myocardial infarction was the most common thrombotic event, with rates of 0.43 and 0.49 (per 100 patient years) in the etoricoxib and diclofenac groups respectively. Fatal thrombotic events did not differ between the groups (0.17 per 100 patient years).

Analysis of the cumulative incidence of thrombotic events over 36 months suggested that the risk-ratio remained constant over time. (Fig 5).

Fig 5. Cumulative incidence of thrombotic cardiovascular events (per-protocol analysis)



Other events

Overall rates of upper gastrointestinal events were lower in patients treated with etoricoxib compared to diclofenac (0.67 vs 0.97 per 100 patient years; HR 0.69; 0.57-0.93). However rates of complicated upper GI events were not different (0.30 vs 0.32).

Discontinuations as a result of hypertension were significantly greater in etoricoxib-treated patients.

Results from the MEDAL study suggested some tolerability differences for etoricoxib 90mg/day compared to 60mg/day.

Rates of congestive heart failure were not different with etoricoxib 60mg/day vs diclofenac, but were higher with etoricoxib 90mg (not significant).

Patients treated with 90mg etoricoxib, but not those receiving 60mg/day, were significantly more likely to discontinue treatment due to oedema than those receiving diclofenac.

Efficacy analysis

Changes in patient-rated global assessment of disease status were similar for etoricoxib (-0.67 ± 1.02) and diclofenac (-0.61 ± 1.02).

Discontinuations for lack of efficacy were also similar for etoricoxib (9%) and diclofenac (9.8%).

Conclusions

In conclusion the study found that rates of thrombotic cardiovascular events were similar during long-term use of etoricoxib or diclofenac.

Dr Andrew Harrison (continued)

Over the three year study period there was no significant difference in the cumulative risk of thrombotic cardiovascular events in the etoricoxib group versus the diclofenac group, either overall or for any of the diagnostic subgroups such as cardiovascular death, cardiac, cerebrovascular or peripheral vascular disease. Comparison of pre-specified subgroups including age, sex, diabetes, established atherosclerotic cardiovascular disease, low-dose aspirin use at baseline, OA versus RA or dose of etoricoxib did not reveal any significance differences in risk of cardiovascular events. Discontinuations due to oedema (up to 1%) and hypertension (2 -2.5%) were higher in the etoricoxib groups, but there was no difference in discontinuations due to renal dysfunction or the incidence of congestive heart failure in any of the study protocols. Discontinuations due to gastrointestinal and hepatic adverse events were significantly lower in the etoricoxib group in all the MEDAL studies.

The studies are limited by the lack of a placebo arm, although this would be impractical in patients with arthritis. The MEDAL program does not provide evidence of a lack of association between etoricoxib and cardiovascular adverse events, but it does indicate that risk of thrombotic cardiovascular events associated with etoricoxib is no greater than with diclofenac. Practically speaking, if in a given patient the risk-benefit analysis favours the use of diclofenac, the practitioner should be equally prepared to prescribe etoricoxib. If gastrointestinal tolerability is a particular issue, and renovascular and economic factors are of lesser concern, the equation would be tipped in favour of etoricoxib.

Dr Terry Macedo (continued)

The most important result is that the risk of all thrombotic cardiovascular events was the same for Etoricoxib and Diclofenac. Diclofenac has been in widespread use for many years and it is reassuring that the newer Etoricoxib does not have an increased CV risk compared to an NSAID that we are all very familiar with. However, observational population/cohort studies have suggested that the conventional NSAIDs carry an increased CV risk. Overall this risk is similar to the Coxibs. While this gives reason to be cautious with the use of both Coxibs and conventional NSAIDs in patients with higher cardiovascular risk, the problem is not novel or new, and is not peculiar to the Coxibs.

It is more valuable and appropriate to consider the individual patient's cardiovascular risk profile in deciding on the use of a Coxib or conventional NSAID, rather than applying the same level of caution across the whole arthritis population. For example if the calculated 5 year cardiovascular event risk is <= 5%, a RR of 1.2-1.4 results in only a small absolute increased CV risk. If a patient starts with a 20% 5 year CV risk, the absolute increase in risk is clearly much larger.

It should be remembered that the 2 main reasons for choosing a Coxib are efficacy in treating arthritis pain, and gastrointestinal safety. The greatest advantage of a Coxib is the reduced (though not eliminated) risk of upper gastrointestinal ulcers and their complications. The strongest indication for a Coxib is in the patient with a low cardiovascular risk but a high upper gastrointestinal risk. Even age alone (>65 years) is a significant risk factor (RR 2-3.5) for clinical upper GI events. Coxibs do not appear to have any advantage in lower gastrointestinal risk such as Inflammatory Bowel Disease.

As the efficacy of conventional NSAIDs and Coxibs varies between patients in an unpredictable manner, a Coxib should even be considered for a patient with low gastrointestinal risk if it is as or more effective than a conventional NSAID.

Fig 6. Incidence of thrombotic cardiovascular events by type

	Etoricoxib (N=16 819, 25 836 PY)*		Diclofenac (N=16 483, 24 766 PY)		HR (95% CI)
	n (%)†	Rate‡	n (%)†	Rate‡	
Patients with fatal thrombotic cardiovascular events	43 (0·26)	0·17 (0·12–0·22)	43 (0·26)	0·17 (0·13–0·23)	0·96 (0·63–1·46)
Patients with cardiac events	183 (1·09)	0·71 (0·61–0·82)	194 (1·18)	0·78 (0·68–0·90)	0·90 (0·74–1·10)
Patients with cerebrovascular events	89 (0·53)	0·34 (0·28–0·42)	79 (0·48)	0·32 (0·25–0·40)	1·08 (0·80–1·46)
Patients with peripheral vascular events	53 (0·32)	0·20 (0·15–0·27)	55 (0·33)	0·22 (0·17–0·29)	0·92 (0·63–1·35)

Patients with several events were listed for each of their specific diagnoses. PY=patient-years. *Etoricoxib combined 60mg and 90mg. †Crude incidence (n/Nx100); ‡Events per 100 patient-years.

Note: for sub-categories of event incidence see full MEDAL study publication[3]

Specialist Opinion - Dr John Petrie

The importance of the MEDAL Study is in the resolution of clinical concern as to the relative safety of standard non-steroidal anti-inflammatory drugs (NSAIDs) and the newer cyclo-oxygenase-2 inhibitors (Coxibs). A carefully planned, non-inferiority design consisting of a large number of patients studied over an 18 month period, MEDAL demonstrates no difference in terms of cardiovascular events between Etoricoxib and Diclofenac. Few trials of NSAIDs have extended beyond six months of treatment exposure, and even less have recruited patients with the co-existent medical problems that are so typical of the population at large. No previous trial has studied such a large number of rigorously defined osteoarthritis and rheumatoid arthritis patients with a primary end point not of efficacy, but of cardiovascular toxicity. MEDAL repeats, supports and extends the findings of the cardiovascular toxicity arm of the TARGET Study [9], which demonstrated no difference between Lumaricoxib and Naproxen or Ibuprofen. There is now a strong evidence base that should promote confidence in the use of Coxibs in the treatment of an increasingly important social burden; the pain of arthritis.

It is easy to overlook the consequences of pain relief when contemplating randomised control trials of drugs in such large populations with non-target end points. That both NSAIDs and Coxibs work well in most cases is taken for granted. The value of such relief to individuals is invariably underestimated when practitioners operate in an environment of fear of adverse outcomes, no matter how small any purported increase in absolute risk may be. Media reports highlighting the published studies of placebo-controlled studies of Coxibs in colonic polyposis [6,7] claim proof of increased cardiovascular toxicity. It is an unexplained paradox that aspirin demonstrates the same increase in cardiovascular risk in the same population[10] raising more questions about the patient group than warranting media hype and regulatory authority disapprobation. Pharmaco-epidemiological studies [11] do reveal an increase in relative risk of both NSAID and Coxibs in patients with active arthritis, but selection bias cannot exclude the inflammatory process of arthritis as the risk factor.

There are potential risks with NSAID and Coxibs, including hypertension, peripheral oedema and renal impairment. However, these can usually be identified in individual patients by clinical monitoring. The reduced gastrointestinal toxicity of Etoricoxib (and the Coxibs in general) is well established. Coxibs are of particular value in patients in the older age group, those with previous gastrointestinal toxicity and those who are also on steroids. MEDAL, along with the cardiovascular toxicity arm of the TARGET trial, should encourage practitioners to recommend the use of Coxibs in this patient group for whom relief of pain can significantly improve quality of life.

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