health
Department:
Health
REPUBLIC OF SOUTH AFRICA

South Africa National Essential Medicine List
Hospital level (Adult) Medication Review Process
Component: Musculoskeletal System

MEDICINE REVIEW:

1. Executive Summary

Date: 15/01/2018
Medicine (INN): NSAIDs, oral: Diclofenac, naproxen, meloxicam, piroxicam
Medicine (ATC): M01A: M01AB05, M01AE52, M01AC06, M01AC01
Indication (ICD10 code): Osteoarthritis (M13-, M16-, M17-, M18-, M19-), Rheumatoid arthritis (M05-,M06-,M08-,M09-)
Patient population: The focus of this review will be on the pain management of osteoarthritis and/or rheumatoid arthritis. These have been described as the most common arthritic conditions in adults. (1) Both are progressive joint disorders, characterized by joint degradation that result in extreme pain and may cause disability and a reduction in quality of life.
Prevalence of condition: More than 1.5 billion people worldwide suffer from chronic pain. Arthritic conditions are one of the primary sources of chronic pain and the prevalence of these conditions are increasing with an aging population. (2) Osteoarthritis alone affects over 250 million people worldwide, imposing a substantial burden on society. (1) In the United Kingdom, more than 17 million prescriptions are written for anti-inflammatory and analgesic drugs annually. (3)
Level of Care: Primary healthcare and hospital level (adults)
Prescriber Level: Nursing staff and doctors
Current standard of Care: Ibuprofen, oral (M01AE01) 400 mg 8hourly
Efficacy estimates: Unable to establish
Motivator/reviewer name(s): Dr R Griesel, Dr H Gunter
PTC affiliation: Dr R Griesel - Red Cross Children's Hospital**;** Dr H Gunter **-** Red Cross Children's Hospital**.**

2. Name of author(s)/motivator(s)

Primary reviewer: Dr R Griesel
Secondary reviewer: Dr H Gunter

3. Author affiliation and conflict of interest details

Dr R Griesel: Red Cross Children's Hospital, Adult Hospital Level Committee member (2017-2019) – No conflicts of interest to declare.
Dr H Gunter: Groote Schuur Hospital, Adult Hospital Level Committee co-opted member (2019-2020) – No conflicts of interest to declare.

4. Introduction/ Background

Pain is a common reason for patients to visit a health care facility. The number of patients seeking treatment for pain is anticipated to rise as the population ages and the prevalence of chronic conditions increase. Prescribing pain medication for the elderly requires a skilled and knowledgeable physician to navigate through the numerous variables that make the elderly a heterogeneous and complex population to treat.

Safety is a core concern in prescribing effective pain management, especially for chronic conditions such as osteo- and rheumatoid arthritis that require long-term treatment. Hence, there is consensus among recommendations that paracetamol should be the first-line analgesic agent due to its favorable side effect and safety profile, despite several meta-analyses having shown that it is less effective in pain relief than anti-inflammatory drugs. (4,5)

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective drugs, (6,7) but their use is associated with a broad spectrum of adverse reactions involving the liver, kidney, cardiovascular system, skin, and gut. (8) Gastrointestinal (GI) adverse effects are the most common and cover a wide clinical spectrum ranging from dyspepsia, heartburn, and abdominal discomfort, to more serious events such as peptic ulcer disease with life-threatening complications of bleeding and perforation. (9,10) Therefore, the dilemma for the prescribing physician is to maintain the anti-inflammatory and analgesic benefits while reducing or preventing the untoward adverse effects. The occurrence of GI complications depends on the presence and number of risk factors, and age is the most frequent and relevant of these. Thus, patients at risk of upper GI complications should have preventative strategies in place, which include the use of the lowest effective, tolerated dose of NSAID for the shortest duration of time possible, and co-therapy with a gastro-protective drug (11,12)

During the last few years, great attention has been focused on the adverse cardiovascular effects of COX-2 selective NSAIDs (coxibs), which prompted a re-evaluation of the cardiovascular and global safety profile of traditional (non-selective) NSAIDs (tNSAIDs). The increased cardiovascular risk of coxibs has been well documented in randomized controlled trials (RCTs) and observational studies. While this risk may

be different according to dose and patient baseline cardiovascular clinical conditions, more recent evidence suggests that at least some, if not all, tNSAIDs may also increase that risk. (13-15) The renovascular effects of NSAIDs are also well known. Current evidence suggests that tNSAIDs and coxibs have a similar incidence of these adverse effects, but with molecule-specific quantitative differences between the various drugs. (16)

This medicines review will assess the most recently available evidence in the safety assessment of tNSAIDs. The aim will firstly be to determine the relative safety differences between ibuprofen as compared with diclofenac, naproxen, meloxicam, and piroxicam. An assessment of efficacy and cost will also be considered in the final recommendation.

5. Purpose/Objective i.e. PICO

P *Adult population with arthritic conditions (osteoarthritis, rheumatoid arthritis)*
I *Diclofenac, Naproxen, Meloxicam, Piroxicam*
C *Ibuprofen*
O *Safety outcomes – cardiovascular, GI, tolerability*
Efficacy outcomes – pain, physical functioning, patient global assessment of disease

6. Methods:

a. Data sources

Pubmed and Cochrane

b. Search strategy

((((((((("piroxicam"[MeSH Terms] OR "piroxicam"[All Fields]) OR ("meloxicam"[Supplementary Concept] OR "meloxicam"[All Fields])) OR ("diclofenac"[MeSH Terms] OR "diclofenac"[All Fields])) OR ("naproxen"[MeSH Terms] OR "naproxen"[All Fields])) OR ("ibuprofen"[MeSH Terms] OR "ibuprofen"[All Fields])) OR (non-steroidal[All Fields] AND ("anti-inflammatory agents"[Pharmacological Action] OR "anti-inflammatory agents"[MeSH Terms] OR ("anti-inflammatory"[All Fields] AND "agents"[All Fields]) OR "anti-inflammatory agents"[All Fields] OR ("anti"[All Fields] AND "inflammatory"[All Fields] AND "drugs"[All Fields]) OR "anti inflammatory drugs"[All Fields]))) OR ("anti-inflammatory agents, non-steroidal"[Pharmacological Action] OR "anti-inflammatory agents, non-steroidal"[MeSH Terms] OR ("anti-inflammatory"[All Fields] AND "agents"[All Fields] AND "non-steroidal"[All Fields]) OR "non-steroidal anti-inflammatory agents"[All Fields] OR "nsaids"[All Fields])) AND ((gastrointestinal[All Fields] OR renal[All Fields]) OR ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields]))) AND (("adverse effects"[Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields]) OR ("safety"[MeSH Terms] OR "safety"[All Fields]))) NOT ("celecoxib"[MeSH Terms] OR "celecoxib"[All Fields])) NOT ("aspirin"[MeSH Terms] OR "aspirin"[All Fields]) AND ((Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "2007/12/22"[PDat] : "2017/12/18"[PDat] AND "humans"[MeSH Terms])

((comparative[All Fields] AND efficacy[All Fields]) OR efficacy[All Fields]) AND ((non-selective[All Fields] AND ("anti-inflammatory agents, non-steroidal"[Pharmacological Action] OR "anti-inflammatory agents, non-steroidal"[MeSH Terms] OR ("anti-inflammatory"[All Fields] AND "agents"[All Fields] AND "non-steroidal"[All Fields]) OR "non-steroidal anti-inflammatory agents"[All Fields] OR "nsaids"[All Fields])) OR (traditional[All Fields] AND ("anti-inflammatory agents, non-steroidal"[Pharmacological Action] OR "anti-inflammatory agents, non-steroidal"[MeSH Terms] OR ("anti-inflammatory"[All Fields] AND "agents"[All Fields] AND "non-steroidal"[All Fields]) OR "non-steroidal anti-inflammatory agents"[All Fields] OR "nsaids"[All Fields]))) AND (Meta-Analysis[ptyp] OR systematic[sb])

12 x systematic reviews and meta-analyses of RCTs were identified
9 x systematic reviews of observational studies identified
1 x RCT not included in above systematic reviews and meta-analyses

c. Excluded studies:

Table 1: Excluded studies/systematic review/meta-analyses and reasons for their exclusion

Author, date	Type of study	Reason for exclusion
Zhang, 2017(17)	Systematic review and meta-analysis	Search results were restricted to cross-sectional, cohort and case-control studies in the English language
Odom, 2014(18)	Meta-regression based on 2 systematic reviews	Systematic reviews of NSAID observational studies
McGettigan, 2011(15)	Systematic review	The search was restricted to population based controlled observational studies
Ungprasert, 2015(19)	Systematic review and meta-analysis	The search was restricted to observational (case-control and cohort) studies
Gunter, 2017(20)	Meta-analysis	Focused on coxibs

Ungprasert, 2015(21)	Systematic review and meta-analysis	The search was restricted to observational (case-control and cohort) studies
Bally, 2017(22)	Bayesian meta-analysis	The search was restricted to observational studies and systematic reviews of non-randomised studies
Lui, 2014(23)	Systematic review and meta-analysis	The search was restricted to observational (case-control and cohort) studies
Castellsague, 2012(24)	Systematic review and meta-analysis	The search was restricted to observational (case-control and cohort) studies
Song, 2016(25)	Bayesian network meta-analyses of RCTs	Comparators of naproxen were coxibs only
Smith, 2016(26)	Systematic analytic review	NSAID efficacy was assessed as class effect compared to opioids
Bjordal, 2004(27)	Meta-analysis of RCTs	NSAID efficacy was assessed as class effect

d. Evidence synthesis

Previous reviews

There have been 2 previous reviews done by members of this committee. The first from May 2015, reviewed the evidence for adverse effects from NSAIDs and highlighted a systematic review of population-based controlled observational studies by McGettigan et al, (15) as well as a meta-analyses of individual participant data from RCTs by the Coxib and tNSAID trialists' collaboration.(28) The conclusion from this review was that there were measurable differences in side-effect profiles of NSAIDs, but that these were not sufficiently large enough to justify formulary changes. (Appendix 1) A further assessment from November 2015 looked at safety concerns among naproxen, meloxicam and piroxicam in the management of arthritis. This review concluded that ibuprofen, meloxicam, naproxen and piroxicam all have comparable efficacy in terms of analgesia, but that naproxen appears to be the safest regarding cardiovascular side-effects and heart failure. It does however state that the results of the PRECISION trial (29) had not been released, and that these would have a significant impact. Furthermore, the review concluded that from the available evidence, piroxicam shows a trend towards lower cardiovascular risk, similar to naproxen, with limited data showing moderate cardiovascular risk associated with meloxicam when compared to ibuprofen. (Appendix 2)

Following on these prior reports, further assessment of newly released systematic reviews, meta-analyses, and RCTs related to the topic were done.

Current review

A comprehensive systematic review and meta-analysis of RCTs performed by Richy et al, (30) looking specifically at the efficacy and safety profile of piroxicam as compared to other tNSAIDs, found adequate data to support a similar to more favourable profile of piroxicam. (Table 2) However, the study lacked data on cardiovascular safety assessment of tNSAIDs. Piroxicam was shown to be significantly better at global improvement against naproxen, but not the other tNSAIDs. Furthermore, meloxicam did appear to have a better safety profile regarding GI side effects than piroxicam. A network meta-analysis by Trelle et al, calculated the cardiovascular safety of NSAIDs. (31) Looking particularly at the primary outcome of myocardial infarction (MI) and the secondary outcomes of stroke, death from cardiovascular disease, and death from any cause, they concluded that: although uncertainty remains, little evidence exists to suggest that any of the investigated drugs are safe in cardiovascular terms. However, naproxen seemed to be less harmful, particularly regarding the MI outcome and death from cardiovascular disease. (Table 2) A systematic review of meta-analyses of RCTs performed by Salvo et al (32) is summarized in Table 2. The important findings from this systematic review include: first, cardiovascular safety was not a primary focus in original trials assessing tNSAIDs. Second, a great deal of important safety information on traditional NSAIDs can be gathered from Coxib trials where they are used as the comparator drugs. Third, from the incidence estimates of cardiovascular and GI events among tNSAIDs (used as comparator drugs in most situations), ibuprofen appears to have the most favourable cardiovascular profile, and for the combined GI outcome of perforation, ulcer, and bleeding, meloxicam appears to have the most favourable profile. (Tables 2, 3, and 4)

The meta-analyses of individual participant data from RCTs by the Coxib and tNSAID trialists' collaboration (28) helped to characterize and quantify the vascular and GI hazards of coxibs and tNSAIDs. (Table 2) It showed that high-dose diclofenac has vascular risks similar to the coxibs, but also raises the possibility that high-dose ibuprofen has similar vascular effects. High-dose naproxen seems to be associated with less vascular hazard, however this result should be interpreted with caution. First, we do not know whether this would be true in patients treated with aspirin, in whom naproxen will not result in any additional inhibition of COX-1 and might actually interfere with the antiplatelet effect of low-dose aspirin. Second, the effects of lower naproxen doses, such as those typically used in over-the-counter preparations (e.g., 220 mg twice a day), are uncertain since they would be less likely to mimic the aspirin-like effect of 500 mg twice a day. Third, the apparent advantage of naproxen regimens might not be preserved after longer-term use. Finally, naproxen substantially increases the risk of upper GI complications (although such bleeds are less likely than vascular events to result in disability and such hazards could be mitigated with proton-pump inhibitors). Although NSAIDs increase vascular and GI risks to a varying extent, this study indicates that the effects of different regimens in particular patients can be predicted, which could help in guiding decisions about the clinical management of inflammatory

disorders.

A more recent systematic review and network meta-analysis by Van Walsem et al, (33) compared the relative benefit-risk of diclofenac to other tNSAIDs and coxibs in patients with osteoarthritis and rheumatoid arthritis. Findings from this study are summarized in Table 2. Regarding efficacy, diclofenac 150 mg/day was likely to be more effective (95% CrI includes 0 but the point estimate is favourable and there is a ≥ 85% probability that treatment is better than the comparator) in alleviating pain than celecoxib and ibuprofen (both scales: VAS and Likert), naproxen (VAS), and etoricoxib (VAS 12 weeks). Diclofenac 100 mg/day was comparable (if the 95% CrI includes 0 (probability treatment is better than comparator >15% and <85%) to all other interventions for pain relief. Regarding safety all active treatments demonstrated similar incidence of cardiovascular outcomes (Anti-Platelet Trialists' Collaboration (APTC) and major cardiovascular events). Diclofenac was associated with a lower incidence of major upper GI events compared to naproxen and ibuprofen, comparable to celecoxib, and higher than etoricoxib. Risk of withdrawals due to any cause was lower for diclofenac than ibuprofen, similar to naproxen and celecoxib, and higher than etoricoxib. Patients treated with diclofenac had a similar risk of withdrawals due to an adverse event to ibuprofen and naproxen and higher risk compared to celecoxib and etoricoxib. Overall the study highlighted the potential efficacy benefit of diclofenac, as well as the lower incidence of upper GI event when compared with tNSAIDs.

The eagerly awaited results of the PRECISION trial (29) were published in late 2016. The main aim of this trial was to assess cardiovascular, GI, renal, and other outcomes with celecoxib as compared with two tNSAIDs (ibuprofen and naproxen). Although the primary objective included the comparison of celecoxib to tNSAIDs, information regarding the comparison of safety for ibuprofen and naproxen can also be deducted from the trial. Ibuprofen and naproxen appeared to have no statistically significant differences regarding all major outcomes in the study. (Table 6 and Figure 6) Particularly regarding the APTC outcome, ibuprofen was found to be non-inferior to naproxen. However, a noteworthy finding was that the rate of nonfatal MI was higher in the ibuprofen group than in the naproxen group (HR, 1.39; 95% CI, 1.01 to 1.91; P = 0.04). The authors concluded from this study that moderate doses of celecoxib showed non-inferiority as compared to naproxen and ibuprofen, with regard to the primary APTC cardiovascular outcome. Celecoxib treatment also resulted in lower rates of GI events than did either comparator drug and in lower rates of renal adverse events than did ibuprofen.

Finally, the most recently published network meta-analyses on efficacy and safety of diclofenac in osteoarthritis, was performed on unpublished legacy trials. (34) A significant limitation of this study is that the amount of data on naproxen, piroxicam, indomethacin, and paracetamol in combination with dextropropoxyphene were few, and the number of patients in those treatment arms too small for reliable comparisons with diclofenac. Although the study does mainly focus on efficacy comparisons between diclofenac and ibuprofen, some useful insights were raised about safety comparisons between the two drugs. Results suggested that diclofenac was comparable (probability that diclofenac is better than the comparator is >15% and <85%) to ibuprofen in terms of safety and tolerability. Withdrawal rates due to all causes with diclofenac at both doses were comparable to those with ibuprofen (at 1200 and 2400mg/day). The authors conclude by stating that the present network meta-analyses results reassure that the older unpublished blinded trials have similar results compared to more recently published trials and also contributes to increase the transparency of clinical trials performed with diclofenac further back in the past.

Table 2: Summary of included studies/systematic review/meta-analyses

Author, date	*Type of study*	*N*	*Population*	*Comparators*	*Primary outcome*	*Effect sizes*	*Comments*
Richy et al, 2009 (30)	Meta-analyses of RCTs	75 RCTs were included in the meta-analysis. A total of 33, 286 patients were exposed to either piroxicam or other NSAIDs.	Any prospective, randomised, parallel-group, controlled trial assessing the relative (comparative trial) efficacy of piroxicam at conventional therapeutic doses (10–40 mg) administered orally for more than 7 days in patients suffering of a variety of acute or chronic conditions, including pain, ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, was included in the analysis. Most of them had osteoarthritis (45%), followed by rheumatoid arthritis (21%), acute pain conditions (17%), chronic pain (10%), and other conditions (7%).	Naproxen and tenoxicam were the most widely used comparator drugs, followed by indomethacin, etodolac, diclofenac, meloxicam, ibuprofen, salycilates and nabumetone.	Trials had to report formal assessments of pain, articular swelling, mobility, global efficacy and tolerance stratified in global, GI and skin. GI outcomes included all clinically significant events (dyspepsia, persistent stomach pain, vomiting, perforation, ulcer, and bleeding), and distinct analyses were carried out for minor events (nausea, vomiting, constipation, diarrhea, gastric pain, and dyspepsia) and major events (GI bleeding, perforation, obstruction and symptomatic, endoscopically confirmed, ulcer). The last RCT involving piroxicam was performed just before the appreciation of the cardiovascular adverse effects associated with NSAID (both coxibs and traditional) use. Therefore no RCT provided cardiovascular data to be included in the meta-analysis.	Regarding global efficacy, 81 comparative assessments of piroxicam versus 9 different NSAIDs, accounting for 14, 332 patients were included. Piroxicam showed an efficacy similar to that of the other NSAIDs, although it appeared to be better than that of naproxen OR= 1.37 (1.05; 1.77). Studies featuring pain as an outcome reported a non-significant difference whatever the metric used was dichotomous OR= 0.99 (0.80; 1.23) or continuous (effect size) ES = 0.06 (−0.02; 0.13) (p = 0.16). Studies featuring mobility or stiffness reported a non-significant difference whatever the metric used was dichotomous OR= 1.05 (0.80; 1.38) or continuous ES = 0.02 (−0.14; 0.18) (p = 0.82). Studies featuring articular swelling reported a non-significant difference when dichotomous outcomes were used OR = 0.81 (0.48; 1.37) while a significantly better efficacy of piroxicam over the other NSAIDs was calculated when continuous metrics were used ES = 0.26 (0.07; 0.44) (p = 0.008). The global OR for improvement, as judged by the patients, was 1.12 (0.98; 1.28). Here again, a significant higher efficacy of piroxicam over naproxen was found OR= 1.41 (1.02; 1.93). As far as safety is concerned, 68 comparative assessments of piroxicam versus 9 different NSAIDs, accounting for 28, 626 patients were included (Figure 1), providing OR for any clinically documented side-effect when exposed to piroxicam against any other NSAID of OR= 0.83 (0.73; 0.95). In this setting, piroxicam appeared to be significantly safer than indomethacin [OR = 0.53 (0.43; 0.64)], naproxen [OR = 0.74 (0.65; 0.85)], and salicylates [OR = 0.36 (0.17; 0.75)]. Regarding overall GI safety and for the whole dataset, piroxicam was significantly safer than other NSAIDs [OR = 0.74 (0.59;	The following covariates significantly and positively impacted the reported relative efficacy of piroxicam: low comparator doses, chronic conditions, studies lasting 2–4 weeks, higher methodological quality of the included studies. The following covariates significantly and positively impacted the reported relative safety of piroxicam: high comparator doses (global safety), standard (i.e. 20 mg) doses of piroxicam and comparator (global safety, GI safety), short term studies (<2 weeks). The main limitations of RCTs included in this study are that most studies were short-term (<3 months) and that description of some side effects was not well defined or pre-specified in some trials. At the publication of this meta-analysis no RCTs had reported data concerning the cardiovascular safety of piroxicam.

						0.93)], particularly indomethacin [OR = 0.46 (0.36; 0.58)], naproxen [OR = 0.66 (0.53; 0.82)], and salicylates [OR = 0.45 (0.27; 0.78)] while meloxicam appeared to be the only NSAID GI safer than piroxicam [OR = 1.49 (1.05; 2.13)] (Figure 2). The risk of major GI adverse events (GI bleeding, perforation, obstruction and symptomatic ulcer) between piroxicam and the other NSAIDs fell short of statistical significance [OR = 1.33 (0.96; 1.84)]. In the individual comparison, piroxicam only showed a statistically higher risk of major GI adverse effects when compared to meloxicam [OR = 2.37 (1.13; 4.97)]. Skin safety was investigated and reported to be similar between piroxicam and all the other NSAIDs [(OR = 1.01 (0.68; 1.51)].	
Trelle et al, 2011 (31)	Network meta-analysis	31 RCTs evaluating 7 different NSAIDs were included in the analyses. In total, 116, 429 patients with 117, 218 patient years of follow-up were covered in the analysis of the primary outcome.	Large scale RCTs comparing any NSAID for any medical condition were included. To be included, trials required at least two arms with at least 100 patient years of follow-up. In the case of trials with several arms, they included only arms with at least 100 patient years of follow-up. They excluded trials in patients with cancer. For an intervention to be included in the analyses, at least 10 patients allocated to the intervention had to have had a MI in all eligible trials combined.	Comparing any NSAID with other NSAID, paracetamol or placebo.	The prespecified primary outcome was fatal or non-fatal MI. Secondary outcomes were haemorrhagic or ischaemic fatal or non-fatal stroke; cardiovascular death, defined as any death due to cardiovascular causes (for example, MI, low output failure, fatal arrhythmia, pulmonary embolism, stroke), and death of unknown cause; death from any cause; and the Antiplatelet Trialists' Collaboration (APTC) composite outcome of non-fatal MI, non-fatal stroke, or cardiovascular death.	29 trials with 554 accumulated events contributed to the analysis of MI. For 3 of the preparations (naproxen, diclofenac, and etoricoxib) evidence was lacking for an increased risk of MI compared with placebo. (Figure 3) Estimated RR were greater than 1.3 for ibuprofen (1.61, 95% CI 0.50 to 5.77). 26 trials with 377 accumulated events contributed to the analysis of stroke. All drugs seemed to be associated with an increased risk compared with placebo. (Figure 3) Estimated rate ratios were greater than 1.3 for naproxen (1.76, 0.91 to 3.33), ibuprofen (3.36, 1.00 to 11.60), diclofenac (2.86, 1.09 to 8.36). 26 trials with 312 accumulated events contributed to the analysis of cardiovascular death. All drugs except naproxen showed some evidence for an increased risk of cardiovascular death compared with placebo. (Figure 3) 28 trials with 676 accumulated events contributed to the analysis on overall mortality. All the drugs seemed to be associated with increased risks of death from any cause compared with placebo. (Figure 3) 30 trials with 1091 accumulated	Although the analyses covered more than 100, 000 patient years of follow-up, the number of events for most outcomes was low and the estimates of RR imprecise, as indicated by wide CIs. There were several limitations to the study. First, they were unable to consider all NSAIDs in the analysis: large scale RCTs are lacking for most of the older drugs and even for some newer ones. Second, the quality of the analysis was limited by the quality of the underlying data. Although the methodological quality of included trials was generally satisfactory, the quality of reporting was often less than optimal and there were discrepancies fond in the reported number of events between different sources of information for major trials. Third, several trials lacked independent adjudication of events, therefore bias in either direction cannot be excluded, including bias towards the null owing to non-differential misclassification of events or assessor bias in trials without independent adjudication. Finally, regimens used in clinical practice might differ from the regimens used in the included clinical trials. Intermittent usage seems to be more common in clinical practice than the chronic long-term usage in the trials, resulting in less intense drug use.

						events contributed to the analysis on the APTC composite outcome. All drugs seemed to be associated with increased risks of the composite of non-fatal MI, non-fatal stroke, or cardiovascular death compared with placebo. (Figure 3)	
Salvo et al, 2011 (32)	A Systematic review of meta-analyses	A total of 29 meta-analyses were included in the review. Of the 29 meta-analyses selected, 17 reported on cardiovascular events, 11 on GI events, and 1 on both. The number of RCTs included in various meta-analyses ranged from 2 to 72, and the number of patients from 117 to 34, 688 (120.6 –25, 836 person-years when reported).	The meta-analyses included RCTs that evaluated NSAIDs in either one or several indications (7 and 23 meta-analyses, respectively). The most frequently studied indications for the use of NSAIDs were osteoarthritis (23 meta-analyses), rheumatoid arthritis (20 meta-analyses), and chronic low back pain (3 meta-analyses).	The drugs investigated in the retained meta-analyses were rofecoxib (9), celecoxib (7), etoricoxib (7), valdecoxib (5), meloxicam (5), lumiracoxib (4), aspirin (2), parecoxib/ valdecoxib combined, etodolac, and nabumetone (1 each). The relevant comparators for meloxicam were placebo, diclofenac, naproxen, and piroxicam.	Estimates of cumulative incidence (%) and/or incidence rates (% person-years) for GI and cardiovascular events are shown.	There were no cardiovascular events incidence estimates reported for meloxicam in the study. Regarding incidence estimates for GI events meloxicam had a cumulative incidence rate for the combined outcome of perforation, ulcer, and bleeding (PUB) of 0.13 – 0.16%. For upper GI bleeding the cumulative incidence rate for meloxicam was 0.18%. Incidence estimates for the reference drugs are summarized in Tables 3 and 4.	According to the QUOROM (Quality of Reports of Meta-Analyses) checklist, the methodological quality of the included trials was generally good, although in three of the meta-analyses the methods employed were not sufficiently detailed. The RCTs performed to evaluate the safety profile of meloxicam in the retrieved meta-analyses were relatively short term (most were 4 weeks, and none was >26 weeks) as compared with those performed for coxibs (as long as 4 years). Another limitation is that the same RCT could have been included in different meta-analyses (indeed, approximately half of all reports cited were individual papers). Therefore, the estimates from different meta-analyses are unlikely to be fully independent. Substantially more data were available for coxibs than for tNSAIDs; also, almost no information regarding cardiovascular adverse events was associated with tNSAIDs, whereas a great amount of such data was available for coxibs. Conversely, no information was available regarding GI events for celecoxib, lumiracoxib, or parecoxib.

Coxib and traditional NSAID trialists' collaboration, 2011 (28)	Meta-analyses of individual participant data	Data from comparisons of coxibs versus placebo were available in 184 trials (88, 367 participants, 52, 466 person-years), and coxibs versus tNSAID in 113 trials (diclofenac in 33 trials, 61, 572 participants, 90, 644 person-years; ibuprofen in 22 trials, 22, 225 participants, 11 668 person-years; naproxen in 48 trials, 48, 706 participants, 31 631 person-years; and other tNSAID in 14 trials, 6, 192 participants, 928 person-years).	In trials providing individual participant data, the mean age at randomization was 61 years, about two thirds were female, and 79% were white. Few patients had a history of atherosclerosis (9%), of diabetes (9%), or of upper gastrointestinal peptic ulcer (7%). Overall, the indication for treatment with an NSAID was rheumatoid arthritis or osteoarthritis in around four-fifths of participants, but in trials of a coxib versus placebo the indication was the prevention of colorectal adenomata or of Alzheimer's disease in around a quarter of participants.	Comparison of an NSAID versus placebo (or open control) or one NSAID regimen versus another NSAID regimen	The main objective was to characterize and quantify the cardiovascular and GI risks of particular NSAID regimens among different types of patients, particularly those at increased risk of vascular disease. The primary vascular outcome was major vascular events, defined as non-fatal MI, non-fatal stroke, or death from a vascular cause; subsidiary vascular outcomes included major coronary events (non-fatal MI or death from coronary disease); stroke (subdivided into haemorrhagic, ischaemic, or unknown types), and hospitalization for heart failure. Deaths were subdivided into vascular, non-vascular, and unknown causes. The primary GI out come was upper GI complications, defined as an upper GI perforation, obstruction, or bleed.	Compared with placebo (or, in a few cases, allocation to no NSAID treatment), the risk of major vascular events was increased with diclofenac (1.41, 1.12–1.78, p=0.0036) chiefly due to an increase in the risk of major coronary events (1.70, 1.19–2.41, p=0.0032). Ibuprofen also significantly increased major coronary events (2.22, 1.10–4.48, p=0.0253), but not major vascular events (1.44, 0.89–2.33, p=0.14). High-dose naproxen was not associated with any significant excess risk of major vascular events (0.93, 0.69–1.27), and nor was there an increase in major coronary events (0.84, 0.52–1.35). There was no evidence that any NSAID significantly increased the risk of stroke. The risk of hospitalization due to heart failure was roughly doubled by all NSAID regimens studied (diclofenac 1.85, 1.17–2.94, p=0.0088; ibuprofen 2.49, 1.19–5.20, p=0.0155; naproxen 1.87, 1.10–3.16, p=0.0197) Risk of vascular death was significantly increased with diclofenac (1.65, 0.95–2.85, p=0.0187), non-significantly increased by ibuprofen (1.90, 0.56–6.41, p=0.17), but not increased by naproxen (1.08, 0.48–2.47, p=0.80). The risk of death from any cause was not significant for diclofenac (1.20, 0.94–1.54, p=0.15), and nor were there significant excesses of death from any cause for ibuprofen (1.61, 0.90–2.88, p=0.11) or naproxen (1.03, 0.71–1.49, p=0.88). Compared with placebo, there was an increased risk of upper GI complications (most of which were bleeds) in association with allocation to diclofenac (1.89, 1.16–3.09, p=0.0106), ibuprofen (3.97, 2.22–7.10, p<0.0001), and naproxen (4.22, 2.71–6.56, p<0.0001)	This meta-analysis is unaffected by selection and other biases inherent in observational studies, showed clearly that the vascular risks of diclofenac, and possibly ibuprofen, are similar to coxibs, but that naproxen is not associated with an increased risk of major vascular events. The potential for bias has been minimized in this meta-analysis by obtaining access to detailed individual data from most trials recording vascular and GI outcomes. Most events occurred in a small number of recent trials that used secure randomization methods and treatment blinding, sensitivity analyses indicated that the results were not materially influenced by uncertainties about the quality of older trials. The tNSAID regimens studied were all high-dose, with little variation between trials. Since vascular hazard is probably related to the degree of COX-2 inhibition, which increases with dose, such dose dependency seems likely. A key objective was to quantify the hazards of NSAIDs in patients with an increased risk of vascular disease. Among those at low risk of vascular disease (the majority of participants in these trials), the predicted absolute risks of major vascular events were small irrespective of the particular regimen chosen. For high-risk individuals (about 40% of whom were taking aspirin), for every 1000 patients allocated to a year of treatment with a coxib regimen or high-dose diclofenac regimen, about seven or eight more would have a major vascular event, of which two would be fatal. (Figure 4) High-dose ibuprofen may be associated with a similar risk, but is also likely to yield a higher risk of upper GI complications than either a coxib or diclofenac. (Figure 4)
Van Walsem, 2015 (33)	Systematic literature review with Bayesian network meta-analyses (RCTs with study	176 studies included 146, 524 patients assigned to one of the interventions of interest, acetaminophen, or placebo. The size of	The majority of studies included patients with osteoarthritis (n = 124) and a smaller number of studies investigated an rheumatoid arthritis population (n = 38) or a	95 studies were placebo controlled while 80 studies compared active treatments only (any of the interventions compared to each	Efficacy outcomes: pain relief measured by visual analogue scale (VAS), Western Ontario McMaster Universities Arthritis Index (WOMAC) VAS, or WOMAC Likert scale; physical functioning measured by WOMAC	<u>Pain relief:</u> The efficacy analysis was based on the labeled doses for treatment of osteoarthritis and rheumatoid arthritis for each treatment option. All drugs were significantly better than placebo for all efficacy	Most studies reported a randomised (n = 174), double-blind (n = 160), and multi-centre study design (n = 128). 2 non-randomised studies in which patients served as their own control were included. Studies supporting a crossover design, in which

	duration ≥ 2 weeks for efficacy outcomes and ≥ 4 weeks for safety and tolerability outcomes were included).	the studies varied, with the number of patients randomised to each treatment ranging from 12 to 6, 769. The trial duration ranged from 2 to 104 weeks, while most studies lasted 12 weeks (n = 56) or 6 weeks (n = 31).	combined osteoarthritis/ rheumatoid arthritis population (n = 14). Nineteen studies allowed the use of gastro-protective agents during the study, if needed by patients, and 38 studies specifically prohibited their use. The age of the enrolled patients ranged from 17 to 75 years. Most studies included a predominantly female population and two included women only. Disease duration ranged between 1 and 21 years.	other, placebo, or paracetamol 4, 000 mg/day).	VAS or WOMAC Likert scale; patient global assessment of disease severity measured on a VAS or 5-point Likert scale; all outcomes reported at 6 or 12 weeks, within a 2-week range. Safety and tolerability outcomes: APTC events; major cardiovascular events (stroke, MI, peripheral arterial thrombosis, peripheral venous thrombosis, pulmonary embolism, and cardiovascular-related death); major upper GI events (perforation, obstruction, and gastric and/or duodenal ulcer (includes bleeding ulcers)); withdrawal due to any cause, due to lack of efficacy, or due to adverse events, as reported at the longest follow-up time point.	outcomes. Diclofenac 150 mg/day was likely to be more effective in alleviating pain than celecoxib and ibuprofen (both scales: VAS and Likert), naproxen (VAS), and etoricoxib (VAS 12 weeks). Its efficacy was similar compared to etoricoxib (VAS) and naproxen (Likert) at 6 weeks. Diclofenac 100 mg/day was comparable to all other interventions for pain relief. For physical functioning, diclofenac 150mg/day seemed to be similar to celecoxib and ibuprofen on VAS at 6 and 12 weeks and seemed favourable to celecoxib and naproxen on Likert at 6 weeks. Diclofenac 100 mg/day was comparable to the rest of the treatments for physical functioning VAS at 6 weeks and Likert at 12 weeks. The safety results were based on all available data for the doses (that is, diclofenac 75 to 200 mg/day, naproxen 500 to 1,500 mg/day, ibuprofen 1,200 to 2,400 mg/day). <u>APTC:</u> Diclofenac was associated with a similar risk of an APTC event as all other interventions, with an RR of 1.1 (0.7-1.8) versus celecoxib, 0.9 (0.4-2.0) versus naproxen, 1.0 (0.9-1.2) versus etoricoxib, and 0.9 (0.5-1.6) versus ibuprofen. (Figure 5) <u>Major cardiovascular events:</u> As demonstrated in Figure 5, diclofenac was associated with a similar risk of major cardiovascular events as all other interventions, with an RR of 1.2 (0.8-1.8) versus celecoxib, 0.9 (0.4-1.9) versus naproxen, 1.1 (0.9-1.3) versus etoricoxib, and 1.1 (0.7-1.9) versus ibuprofen. The probability of diclofenac being a safer treatment (that is, reducing the number of events) was low (<25%) for all pairwise comparisons, with the exception of naproxen (62%). <u>Major upper GI events:</u> Diclofenac was associated with a	patients switched from placebo to active treatment or different dosages of the active substance were included. However, if no washout period between crossover was observed, data on efficacy and safety outcomes after crossover were not used. The methodological and reporting quality of the included trials was assessed with the Oxford quality scoring system for RCTs. The risk of bias was assessed on the following aspects: randomization according to an appropriate method, allocation concealment of patients and investigators, and complete and non-selective reporting of study withdrawals and dropouts. Inherent limitations were related to the quality and availability of data, the potential for within-study bias, and publication bias. Although the studies included were of satisfactory quality, there are limitations to the evidence base, mainly related to the low number of events. Another potential limitation is that studies often use different methods for handling missing data due to dropouts, including last observation carried forward, baseline observation carried forward, multiple imputation, available data, and others. These differences can lead to differences in reported outcomes. The results of the key benefits and risks for diclofenac 150mg/day versus the other treatments of interest are summarized in Table 5.

						lower risk for major upper GI events than both naproxen and ibuprofen, with a RR of 0.3 (0.2-0.6) versus naproxen and 0.5 (0.3-0.9) versus ibuprofen. Diclofenac was associated with a comparable risk of major upper GI events compared to celecoxib (RR 1.4 (0.8-2.3)). (Figure 5) Withdrawal due to any reason: As demonstrated in Figure 5, diclofenac was associated with a lower risk of withdrawal due to any reason than placebo, ibuprofen, and acetaminophen, with an RR of 0.7 (0.6-0.8), 0.7 (0.6-0.9) and 0.8 (0.6-1.0), respectively. The risk was similar for diclofenac compared to celecoxib and naproxen, with an RR of 1.1 (1.0-1.3) and 1.0 (0.8-1.2), respectively. Withdrawal due to adverse events: Diclofenac was comparable to naproxen (RR 1.1 (0.9-1.4)), ibuprofen (0.9 (0.7-1.2)), and acetaminophen (0.9 (0.6-1.4)). The risk was higher for diclofenac compared to placebo (RR 1.6 (1.3-1.9)), celecoxib (1.4 (1.2-1.8)), and etoricoxib (1.7 (1.4-2.2)). (Figure 5)	
Nissen et al, 2016 (29)	The PRECISION trial was a randomized, multicenter, double blind, non-inferiority trial.	A total of 24, 222 patients underwent randomization at 926 centers in 13 countries between October 23, 2006, and June 30, 2014, and 141 were excluded from the analysis (106 were determined to be fraudulently enrolled, and 35 enrolled more than once), leaving 24, 081 participants who could be included in the analysis. There were 8, 072 patients assigned to the celecoxib group (mean [±SD] daily dose, 209±37 mg), 7,	Enrolled patients who were 18 years of age or older and who, as determined by the patient and physician, required daily treatment with NSAIDs for arthritis pain; patients whose arthritis pain was managed adequately with acetaminophen were not eligible. A key inclusion criterion was established cardiovascular disease or an increased risk of the development of cardiovascular disease.	Patients were randomly assigned, in a 1:1:1 ratio, to receive celecoxib (100 mg twice a day), ibuprofen (600 mg three times a day), or naproxen (375 mg twice a day) with matching placebo. Esomeprazole (20 to 40 mg) was provided to all patients for gastric protection. Investigators were encouraged to provide cardiovascular preventive management in accordance with local standards and guidelines. Patients who were taking low-dose aspirin (≤325 mg daily) were permitted	The primary composite outcome, in a time-to-event analysis, was the first occurrence of an adverse event that met APTC criteria. A secondary composite outcome, major adverse cardiovascular events, included the components of the primary outcome plus coronary revascularization or hospitalization for unstable angina or transient ischemic attack. Secondary outcomes also included clinically significant GI events. Tertiary outcomes included clinically significant renal events, iron deficiency anemia of GI origin, and hospitalization for heart failure or hypertension. An assessment of the intensity of arthritis pain with the use of the VAS was a non-adjudicated secondary outcome.	The mean durations of treatment and follow-up, respectively, were 20.3±16.0 and 34.1±13.4 months for all patients. During this 10-year trial, 68.8% of patients stopped taking the study drug, and 27.4% of patients discontinued follow-up; 2.5% of patients died. In the intention-to-treat population the primary APTC outcome occurred in 201 in the naproxen group (2.5%), and 218 in the ibuprofen group (2.7%). The hazard ratio for ibuprofen versus naproxen was 1.08 (95% CI, 0.90 -1.31; P = 0.02 for non-inferiority). All results from the trial are summarized in Table 6 and Figure 6. The rate of nonfatal MI was higher in	The PRECISION trial had some limitations. Adherence and retention were lower than in most trials that assess cardiovascular outcomes. The current results reflect the relative safety of only these three drugs and cannot provide insight into the effects of the more than two dozen other marketed NSAIDs, particularly because each of these drugs may have a unique safety profile.

		969 assigned to the naproxen group (852±103 mg), and 8, 040 assigned to the ibuprofen group (2, 045±246 mg).		to continue this therapy. The characteristics of the patients at baseline were similar among the treatment groups.		the ibuprofen group than in the naproxen group (hazard ratio, 1.39; 95% CI, 1.01-1.91; P = 0.04). The hazard ratio for GI events in the ibuprofen group versus the naproxen group was 1.08 (95% CI, 0.85-1.39; P = 0.53). In the assessment of pain with the use of the VAS scale, a significant but small benefit was found for naproxen relative to celecoxib or ibuprofen; the change in VAS score from baseline was −9.3±0.26mm for celecoxib, −9.5±0.26 for ibuprofen, and −10.2±0.26 for naproxen (P<0.001 for naproxen versus celecoxib, P = 0.01 for naproxen versus ibuprofen)	
Guyot, 2017 (34)	Network Meta-analyses	A list of all legacy clinical trials conducted by Novartis was reviewed to identify RCTs of diclofenac with planned treatment duration of at least 4 weeks for the treatment of osteoarthritis. 19 trials were selected for the study. All 19 RCTs, except one, were double-blind trials. In addition, 15 of the 19 RCTs were multicenter trials, whereas four were single-centre trials. The average number of intention-to-treat patients per arm was 107. Two studies randomised over 300 patients per treatment arm. Five studies randomised ≤30 patients per treatment arm.	The mean weighted average proportion of men was 32% (range: 0–49%). Most studies included patients of either sex, except one, which included only female patients. The average age of patients across all studies ranged between 47 and 67 years (mean: 61years). The mean disease duration ranged from 0.3 to 12.6 years, with a weighted mean average of 7.4 years.	All RCTs in osteoarthritis that compared diclofenac versus placebo or other analgesic comparators with data on efficacy and/or safety were included. The most common comparators were ibuprofen (1200/2400 mg/day) and naproxen (500/750/1000 mg/day). Other less common comparators, such as piroxicam (20 mg/day), indomethacin (75 mg/day) and paracetamol (1950 mg/day) in combination with dex-tropropoxyphene (195 mg/day) were also included in a few RCTs. The clinical outcome data for diclofenac (efficacy, tolerability and safety) compared with ibuprofen, the only comparator with enough data for robust comparisons, are presented in detail. In addition, diclofenac (75 and 200 mg/day), naproxen, and other NSAIDs (piroxicam, indomethacin,	VAS and Likert pain scale scores, VAS and Likert scale patients' global assessment (PGA), and VAS and Likert scale investigators' global assessments (IGA) were considered for analyzing efficacy outcomes. Efficacy endpoints were assessed at 2, 4, and 12 weeks for VAS pain, at 4 and 12 weeks for PGA VAS, and at 4 weeks for IGA VAS. In addition safety (any adverse events and serious adverse events) and tolerability (withdrawals due to all causes, lack of efficacy, and adverse events) parameters were included in the analysis.	The study focused on efficacy outcomes in comparing diclofenac to ibuprofen. The overall efficacy outcomes of the present network meta-analyses indicate that diclofenac 150 mg/day was more efficacious than ibuprofen 1200mg/day and likely to be more favourable than ibuprofen 2400mg/day in relieving pain. Similarly, while comparing lower doses, diclofenac 100 mg/day was more efficacious than ibuprofen 1200 mg/day. This low dose of diclofenac was comparable to ibuprofen 2400 mg/day based on PGA and pain relief at 4 and 12 weeks, but it was likely to be unfavourable for pain relief at 2 weeks. The most frequent adverse events were GI disorders (e.g. peptic ulcer disease, gastritis, regional enteritis, or ulcerative colitis), nervous system disorders, respiratory, thoracic and mediastinal disorders, general disorders and administration site conditions, renal and urinary disorders, musculoskeletal and connective tissue disorders, infections and infestations, and cardiac disorders. No relevant differences were detected between diclofenac and ibuprofen. The summary results of the key benefits and risks of diclofenac 150 and 100 mg/day versus ibuprofen are	The systematic literature review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The main limitations of the present study were related to missing data for some of the planned comparisons, and the limited amount of data from these largely unpublished legacy studies. There was enough data for robust efficacy comparisons between diclofenac and ibuprofen, but the amount of data on naproxen, piroxicam, indomethacin, and paracetamolin combination with dextropropoxyphene were limited, and the number of patients in those treatment arms was too small for reliable comparisons with diclofenac. Therefore, the detailed presentation of the results had to be limited to comparison between diclofenac and ibuprofen.

				paracetamol and dextropropoxy-phene) were included in a few retrieved studies, but the number of patients was too small for reliable comparisons with diclofenac (100 and 150mg/day).		summarized in Tables 7 and 8, respectively.	
Stam, 2012 (36)	Mixed treatment comparison of randomised controlled trials with a double blind period. Only full-published reports were considered; letters and abstracts were excluded.	Overall 29 studies (of which 28 were reported in 25 publications) were included in the analysis. Overall, the analysis included over 18,000 patients.	All patients suffered from OA (knee and/or hip as the primary affected joint) for more than 3.5 years, with an average duration of 8.7 years. Baseline scores of pain and physical functioning were comparable across the trials as well.	The interventions included acetaminophen 4000mg/day, ibuprofen 2400mg/day, naproxen 1000mg/day, diclofenac 150mg/day, celecoxib 100, 200 or 400 mg/day, etoricoxib 30 and 60 mg/day. The duration of the intervention was at least 2 weeks. Comparators included: Acetaminophen, a non selective NSAID or a COX-2 selective NSAID at mentioned dosage or placebo.	In accordance with recommendations of OMERACT (Outcome Measures in Rheumatology Clinical Trials) the outcome measures included were: pain, physical function and patient global assessment [12]. The outcomes pain and physical function were required to be assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scales.	All interventions, with the exception of acetaminophen and celecoxib 100 mg, were more efficacious than placebo. Naproxen 1000mg, ibuprofen 2400mg, diclofenac 150mg and celecoxib 200mg resulted in at least small improvements (>90% probability of ES ≥0.2) over placebo. (Table 10) Of the tNSAIDs diclofenac 150mg does appear to have the greatest effect size and highest probability of having a moderate improvement compared to placebo. In terms of physical function, naproxen 1000mg, ibuprofen 2400mg, diclofenac 150mg, celecoxib 200mg, and lumiracoxib all offered at least small improvements (ES ≥0.2) over placebo (Table 11). Among the tNSAIDs diclofenac 150mg showed the greatest effect size and had the greatest probability of a moderate improvement relative to placebo. Regarding PGADS, diclofenac 150mg was comparable to etoricoxib 60mg and superior to other tNSAIDs (Table 12).	None
Da Costa, 2017 (37)	Network meta-analysis	76 randomised clinical trials investigating seven different NSAIDs and paracetamol were described and included in the analysis. 23 nodes were included in the network meta-analysis.	Large-scale randomised controlled trials of patients with knee or hip osteoarthritis, comparing any of the following interventions: NSAIDs, paracetamol (acetaminophen), or placebo, for the treatment of osteoarthritis pain. Across the trials, the mean age of patients ranged from 58 to 71 years, the percentage of female patients ranged from 49% to 90%, and the median follow-up was 12	The interventions with the most randomly assigned patients were celecoxib 200 mg/day (11 507 patients) and naproxen 1000 mg/day (7997 patients), whereas the interventions with the fewest randomly assigned patients were diclofenac 70 mg/day (104 patients) and etoricoxib 90 mg/day (112 patients).	The prespecified primary outcome was pain. The secondary outcome was physical function	Pooled effect sizes suggested that all interventions, irrespective of dose, improved osteoarthritic pain symptoms when compared with placebo. Diclofenac 150mg was the only tNSAID that showed sufficient statistical evidence to support a minimum clinically important effect (i.e. the probability that the difference from placebo is at or below the prespecified threshold of -0.37 was at least 95%) (Figure 7) Diclofenac 150mg was ranked the highest among the tNSAIDs assessed, with a 100% probability to reach the minimum clinically important	Methodological quality of included trials was assessed using a slightly adapted version of the risk of bias approach of the Cochrane Collaboration. 99% of the trials were judged to have a low risk of bias for blinding of patients, 74% for blinding of therapists, 25% for incomplete outcome data, and 18% for concealment of allocation. None of the trials was thought to have a high risk of bias for any of the methodological quality items assessed, except for incomplete outcome data, since 58 (76%) of the 76 trials analysed had excluded at least one of the randomly assigned patients from their analysis. 52 (68%) of the 76 trials analysed reported the use of last-observation-carried-forward for

			weeks (range 1–56 weeks). In total, 58 451 patients were included in the primary analysis of osteoarthritis pain.			difference. (Figure 8) Regarding improved physical functioning, diclofenac 150mg was the only tNSAID with enough evidence to support a minimum clinically important treatment effect.	imputation of missing data, four (5%) did not need to use imputation, and 20 (26%) did not do an intention-to-treat analysis. None of the trials reported the use of multiple imputation. 70 (92%) of the trials analysed received financial funding from a commercial body; source of funding was unclear for the other six (8%; table).

Table 3

Table 3 Incid ıtes of selected cardiovascular (CV) events for reference nonsteroidal anti-inflammatory drugs (NSAIDs)

	MI		IS		Stroke		FS		CeV		ThE		HF	
Drugs	*N*	Rate, % (range)	*N*	Rate, % (range)	*N*	Rate, % (range)	*N*	Rate, % (range)	*N*	Rate, % (range)	*N*	Rate, % (range)	*N*	Rate, % (range)
Celecoxib														
Cumulative	—	—	—	—	—	—	—	—	—	—	—	—	1	0.19
Rofecoxib														
Cumulative	1	0.08	—	—	—	—	—	—	—	—	—	—	1	0.60
Diclofenac														
Cumulative	3	(0.20–0.74)	1	0.20	—	—	—	—	3	(0.29–0.48)	2	(0.22–0.81)	—	—
Incidence rate	3	(0.22–0.49)	1	0.22	1	0.45	—	—	2	(0.32–0.45)	1	0.89	—	—
Ibuprofen														
Cumulative	2	(0.00–0.19)	1	0.00	—	—	—	—	2	(0.00–0.24)	1	0.00	—	—
Incidence rate	2	(0.00–0.41)	1	0.00	1	0.31	—	—	1	0.00	1	0.00	—	—
Nabumetone														
Cumulative	1	0.39	—	—	—	—	—	—	1	0.00	—	—	—	—
Naproxen														
Cumulative	6	(0.10–0.33)	2	(0.00–0.20)	3	(0.09–0.24)	2	(0.00–0.04)	4	(0.13–0.28)	4	(0.00–0.91)	—	—
Incidence rate	3	(0.27–0.51)	1	0.00	2	(0.36–0.51)	1	0.25	1	0.12	1	0.81	—	—
Piroxicam														
Cumulative	—	—	—	—	—	—	—	—	—	—	1	0.08	—	—

CeV, cerebrovascular event; FS, fatal stroke; HF, heart failure; IS, ischemic stroke; MI, myocardial infarction; ThE, thromboembolic event.

Assessment of Efficacy

As seen above, safety outcomes for specific tNSAIDs are conflicting and lack consistency. To assist in making an informed decision, efficacy will also be reviewed in detail. The effectiveness of NSAIDs is overwhelming when compared to placebo; however, the relative effectiveness of individual NSAIDs when compared with each other is controversial. The Oxford League Table (Table 9) has been suggested as a good tool for assessing the relative efficacy of analgesics. (35) The efficacy of analgesics is expressed as the number needed to treat (NNT): the number of patients who need to receive the active drug for one to achieve at least 50% relief of pain compared with placebo over a 4 to 6 hour treatment period. Information from the table was from systematic reviews of randomized, double blind, single-dose studies in patients with moderate to severe pain in postoperative dental, orthopedic, gynecological and general surgical pain. From the table it is clear that ibuprofen 800mg is superior to other tNSAIDs, with diclofenac 100mg and piroxicam 40mg close seconds. Naproxen 440mg follows lower down with a NNT of 2.3 (CI 2.0 – 2.9). Limitations of the Oxford League Table are the assumption that different pain models are comparable, and that benefit and harm can be extrapolated from one model to another. For example, a drug that is well suited to one pain setting may have a different effect or no effect at all in another. A further drawback is the small size of some trials used to combine the data. Small trials with few patients cannot accurately estimate the magnitude of the analgesic effect, e.g. ibuprofen 800 mg (which is at the top of the league table with an impressive NNT of 1.6 and only 76 patients involved in the comparative trials).

Stam et al. performed a mixed treatment comparison of RCTs, which assessed the efficacy of coxibs and tNSAIDs among patients with osteoarthritis. (36) The outcomes of interest were pain, physical function and patient global assessment of disease. Among the tNSAIDs, diclofenac 150mg appeared to show the greatest effect size and had the greatest probability of a moderate improvement relative to placebo. (Tables 10, 11, and 12) Furthermore, a network meta-analysis by Da Costa et al, assessed the effectiveness of NSAIDs for the treatment of pain in knee and hip osteoarthritis. (37) Among the tNSAIDs assessed for pain, diclofenac 150mg had the highest probability that the difference to placebo is at or below a prespecified minimum clinically important effect for pain reduction of at least 95%. (Figure 7) Regarding improved physical functioning; diclofenac 150mg was the only tNSAID with enough evidence to support a minimum clinically important treatment effect. All involved trials were deemed to have a low risk of bias for blinding of patients. Effect estimates did not change in sensitivity analyses with two additional statistical models and accounting for methodological quality criteria in meta-regression analysis. The authors concluded that diclofenac 150mg/day is the most effective NSAID available at present, in terms of improving both pain and physical function in patients with osteoarthritis. (Figure 8)

Table 4

Table 4 Incidence estimates of selected gastrointestinal (GI) events for reference nonsteroidal anti-inflammatory drugs (NSAIDs) (only cumulative incidence is provided)

	UGIB		GIB		PUBs	
Drugs	*N*	Rate, % (range)	*N*	Rate, % (range)	*N*	Rate, % (range)
Celecoxib	—	—	—	—	1	0.00
Diclofenac	2	(0.04–0.56)	—	—	6	(0.13–1.12)
Etodolac	—	—	—	—	1	0.42
Ibuprofen	1	0.00	—	—	3	(0.55–2.16)
Nabumetone	—	—	—	—	1	0.00
Naproxen	1	0.59	1	2.04	4	(0.37–3.00)
Piroxicam	1	0.21	—	—	4	(0.37–1.16)

GIB, gastrointestinal bleeding; PUB, perforation, ulcer, and bleeding; UGIB, upper gastrointestinal bleeding.

In light of the findings by Van Walsem et al, (33) Guyot et al, (34) The Oxford League Table, (35) Stam et al, (36) and Da Costa et al, (37) diclofenac 150mg per day appears to be the most efficacious tNSAID for pain relief, physical function and patient global disease assessment improvement. However, a review from 2013 by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) found that the effects of systemic diclofenac on the heart and circulation are similar to those of coxibs. The risk of arterial thromboembolic events especially in patients with underlying heart or circulatory conditions or with certain cardiovascular risk factors, applies particularly when diclofenac is used at a high dose and for long-term treatment. (38) The PRAC therefore recommended an amendment to the product information for diclofenac to include an updated contraindication in patients with established congestive heart failure, ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease. In addition, patients with certain cardiovascular risk factors (such as hypertension, hyperlipidaemia, diabetes mellitus, or smoking) should only use diclofenac after careful consideration and therefore the warnings should also be updated to reflect this. Moreover, the general rule that NSAIDs should be used at the lowest dose for the shortest duration possible should be consistently implemented. Their conclusions were that the benefit-risk balance for diclofenac remains favourable subject to the agreed restrictions, warnings, other changes to the product information, and additional risk minimisation measures. (39)

In February 2014, the US Food and Drug Administration (FDA) convened an advisory committee meeting to discuss the accumulated data relating to the cardiovascular risk of NSAIDs and the potential implications on the class prescription labelling. (40) Their recommendations included: (1) the current data does not support the conclusion that naproxen has a lower risk of thrombotic events than other NSAIDs, (2) there is no latency period for the risk of cardiovascular thrombotic events, and (3) there are some patient populations at increased risk for events. They concluded that: "With the information available today, there is insufficient evidence to conclude from a population perspective that there are differences between the major marketed NSAIDs in regard to their potential for cardiovascular events." Using a ratio of relative risks of major vascular events from the Coxib and traditional NSAID Trialists' Collaboration publication, they concluded that diclofenac's risk is higher than naproxen's, but that other comparisons were not significant. (Table 13)

Table 5

Table 3 Relative benefits and risks of diclofenac

	Outcome	Unit	Assessment time point	Placebo	Celecoxib	Naproxen	Etoricoxib	Ibuprofen	Acetaminophen
Benefits	Pain (VAS)	ΔCFB (mm)	6 weeks	−13.5 (−16.7, −10.4)	−4.7 (−8.0, −1.4)	−3.4 (−7.0, 0.1)	−0.1 (−4.3, 4.0)	−3.2 (−7.9, 1.5)	−9.1 (−13.5, −4.7)
		ΔCFB (mm)	12 weeks	−12.3 (−17.3, −7.4)	−5.1 (−10.2, −0.1)	−3.3 (−8.6, 1.8)	−3.3 (−9.1, 2.5)	−4.5 (−11.5, 2.4)	−8.0 (−16.6, 0.5)
	Physical functioning (VAS)	ΔCFB (mm)	6 weeks	−7.7 (−11.9, −3.4)	0.2 (−4.1, 4.6)	2.8 (−1.7, 7.4)	2.4 (−2.4, 7.3)	1.2 (−4.5, 6.9)	−5.4 (−12.4, 1.8)
		ΔCFB (mm)	12 weeks	−4.5 (−12.4, 3.1)	2.3 (−5.7, 10.5)	6.0 (−2.2, 14.1)	5.8 (−2.9, 14.3)	3.3 (−5.9, 12.3)	−7.2 (−14.5, 0.3)
	PGA VAS	ΔCFB (mm)	6 weeks	−15.3 (−25.4, −5.2)	−5.7 (−16.1, 4.7)	−6.3 (−17.1, 4.5)	−5.9 (−18.0, 6.0)	−3.7 (−14.7, 7.4)	NA
Risks	APTC	Rate ratio	Duration of study	NA	1.1 (0.7, 1.8)	0.9 (0.4, 2.0)	1.0 (0.9, 1.2)	0.9 (0.5, 1.6)	NA
	Major CV event	Rate ratio	Duration of study	NA	1.2 (0.8, 1.8)	0.9 (0.4, 1.9)	1.1 (0.9, 1.3)	1.1 (0.7, 1.9)	NA
	Major GI event	Rate ratio	Duration of study	NA	1.4 (0.8, 2.3)	0.3 (0.2, 0.6)	1.5 (1.3, 1.9)	0.5 (0.3, 0.9)	NA
	Withdrawal due to any reason	Rate ratio	Duration of study	0.7 (0.6, 0.8)	1.1 (1.0, 1.3)	1.0 (0.8, 1.2)	1.2 (1.0, 1.5)	0.7 (0.6, 0.9)	0.8 (0.6, 1.0)
	Withdrawal due to adverse events	Rate ratio	Duration of study	1.6 (1.3, 1.9)	1.4 (1.2, 1.8)	1.1 (0.9, 1.4)	1.7 (1.3, 2.2)	0.9 (0.7, 1.2)	0.9 (0.6, 1.4)
	Withdrawal due to lack of efficacy	Rate ratio	Duration of study	0.4 (0.3, 0.4)	0.8 (0.7, 1.0)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	0.7 (0.5, 0.9)	0.6 (0.4, 0.8)

Mean and 95% credible intervals are presented; negative ΔCFB and rate ratios <1 favour diclofenac. Benefits were assessed using diclofenac 150 mg/day, naproxen 1,000 mg/day, ibuprofen 2,400 mg/day, celecoxib 200 mg/day, and etoricoxib 60 mg/day. Risks were assessed using dose ranges of the interventions of interest (diclofenac 75 to 200 mg/day, naproxen 500 to 1,500 mg/day, ibuprofen 1,200 to 2,400 mg/day, celecoxib 100 to 800 mg/day, or etoricoxib 30 to 90 mg/day). VAS, visual analogue scale; ΔCFB, difference in change from baseline; PGA, patient global assessment; APTC, Antiplatelets Trialists' Collaboration; CV, cardiovascular; GI, gastrointestinal.

Table 6

Table 2. Adjudicated Outcomes in the Intention-to-Treat Population.

Outcome	Celecoxib Group (N=8072)	Naproxen Group (N=7969)	Ibuprofen Group (N=8040)	Celecoxib vs. Naproxen*		Celecoxib vs. Ibuprofen*	
				Adjusted Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)	P Value
	number of patients (percent)						
Primary APTC end point†	188 (2.3)	201 (2.5)	218 (2.7)	0.93 (0.76–1.13)	0.45	0.85 (0.70–1.04)	0.12
Major adverse cardiovascular events‡	337 (4.2)	346 (4.3)	384 (4.8)	0.97 (0.83–1.12)	0.64	0.87 (0.75–1.01)	0.06
Composite of serious gastrointestinal events	86 (1.1)	119 (1.5)	130 (1.6)	0.71 (0.54–0.93)	0.01	0.65 (0.50–0.85)	0.002
Clinically significant gastrointestinal events§	55 (0.7)	56 (0.7)	72 (0.9)	0.97 (0.67–1.40)	0.86	0.76 (0.53–1.08)	0.12
Iron-deficiency anemia of gastrointestinal origin§	33 (0.4)	69 (0.9)	64 (0.8)	0.47 (0.31–0.71)	<0.001	0.51 (0.33–0.77)	0.002
Renal events	57 (0.7)	71 (0.9)	92 (1.1)	0.79 (0.56–1.12)	0.19	0.61 (0.44–0.85)	0.004
Hospitalization for congestive heart failure	45 (0.6)	48 (0.6)	46 (0.6)	0.92 (0.62–1.39)	0.70	0.98 (0.65–1.47)	0.91
Hospitalization for hypertension	24 (0.3)	34 (0.4)	40 (0.5)	0.69 (0.41–1.17)	0.17	0.60 (0.36–0.99)	0.04
Death from any cause	132 (1.6)	163 (2.0)	142 (1.8)	0.80 (0.63–1.00)	0.052	0.92 (0.73–1.17)	0.49
Components of composite end points							
Death from cardiovascular causes	68 (0.8)	86 (1.1)	80 (1.0)	0.78 (0.57–1.07)	0.13	0.84 (0.61–1.16)	0.30
Nonfatal myocardial infarction	76 (0.9)	66 (0.8)	92 (1.1)	1.14 (0.82–1.59)	0.43	0.82 (0.61–1.11)	0.21
Nonfatal stroke	51 (0.6)	57 (0.7)	53 (0.7)	0.88 (0.61–1.30)	0.52	0.95 (0.65–1.40)	0.81
Hospitalization for unstable angina	55 (0.7)	64 (0.8)	65 (0.8)	0.86 (0.60–1.23)	0.40	0.84 (0.59–1.21)	0.35
Revascularization	174 (2.2)	161 (2.0)	198 (2.5)	1.07 (0.87–1.33)	0.52	0.87 (0.71–1.07)	0.18
Hospitalization for TIA	18 (0.2)	18 (0.2)	27 (0.3)	0.99 (0.51–1.90)	0.97	0.66 (0.37–1.20)	0.18

Table 7

Relative benefits and risks of diclofenac 150 mg compared to placebo, and ibuprofen 1200 mg and 2400 mg.

	Outcome	Assessment time point	Placebo	Ibuprofen 1200 mg	Ibuprofen 2400 mg
Benefits ΔCFB (mm)	Pain (VAS)	2 weeks	−16.7 (−23.3; −10.2)	NA	−1.3 (−4.3; 1.7)
		4 weeks	−12.4 (−19.7; −5.0)	−9.6 (−16.9; −2.4)	−1.6 (−6.5; 3.6)
		12 weeks	−8.8 (−18.3; 0.6)	−6.0 (−10.8; −1.2)	−3.1 (−8.1; 1.8)
	PGA (VAS)	4 weeks	−12.3 (−18.1; −6.6)	−8.5 (−12.7; −4.4)	−1.6 (−4.8; 1.4)
		12 weeks	−4.9 (−13.9; 4.0)	−4.0 (−8.6; 0.6)	−2.7 (−7.5; 2.1)
	IGA VAS	4 weeks	−10.7 (−17.4; −4.0)	NA	−1.2 (−3.9; 1.6)
Risks Rate ratio	Serious adverse events	Duration of study	0.45 (0.01; 6.08)	0.65 (0.18; 1.97)	1.37 (0.69; 2.92)
	Withdrawal due to all causes	Duration of study	0.63 (0.47; 0.84)	0.99 (0.72; 1.34)	1.04 (0.83; 1.31)
	Withdrawal due to lack of efficacy	Duration of study	0.37 (0.24; 0.56)	0.74 (0.39; 1.35)	0.63 (0.43; 0.93)
	Withdrawal due to adverse events	Duration of study	2.29 (1.27; 4.32)	1.13 (0.69; 1.81)	1.45 (0.96; 2.25)

Mean and 95% credible intervals are presented; negative ΔCFBs favour diclofenac, rate ratios <1 favour diclofenac.
ΔCFB, difference in change from baseline; IGA, investigator global assessment; NA, not available; PGA, patient global assessment; VAS, visual analogue scale.

Table 8

Relative benefits and risks of diclofenac 100 mg compared to placebo, and ibuprofen 1200 mg and 2400 mg.

	Outcome	Assessment time point	Placebo	Ibuprofen 1200 mg	Ibuprofen 2400 mg
Benefits ΔCFB (mm)	Pain (VAS)	2 weeks	−10.5 (−16.2; −4.9)	NA	5.0 (−4.4; 14.2)
		4 weeks	−7.2 (−14.0; −0.4)	−4.5 (−12.9; 4.0)	3.5 (−5.4; 12.8)
		12 weeks	−7.5 (−14.3; −0.8)	−4.7 (−10.8; 1.4)	−1.9 (−10.2; 6.5)
	PGA (VAS)	4 weeks	−9.4 (−14.4; −4.5)	−5.6 (−10.8; −0.5)	1.2 (−4.8; 7.3)
		12 weeks	−5.0 (−11.3; 1.4)	−4.1 (−9.8; 1.7)	−2.7 (−10.6; 5.2)
	IGA VAS	4 weeks	−6.5 (−11.5; −1.4)	NA	3.1 (−5.7; 11.9)
Risks Rate ratio	Serious adverse events	Duration of study	0.77 (0.21; 3.03)	1.13 (0.05; 69.69)	2.41 (0.12; 133.67)
	Withdrawal due to all causes	Duration of study	0.54 (0.39; 0.75)	0.85 (0.57; 1.26)	0.90 (0.58; 1.36)
	Withdrawal due to lack of efficacy	Duration of study	0.24 (0.14; 0.40)	0.48 (0.23; 1.00)	0.41 (0.20; 0.83)
	Withdrawal due to adverse events	Duration of study	1.96 (1.00; 4.10)	0.96 (0.47; 2.01)	1.24 (0.55; 2.89)

Mean and 95% credible intervals are presented; negative ΔCFBs favour diclofenac, rate ratios <1 favour diclofenac.
ΔCFB, difference in change from baseline; IGA, investigator global assessment; NA, not available; PGA, patient global assessment; VAS, visual analogue scale.

Table 9

Table 1. Oxford League Table.

Analgesic	Number of patients in comparison	Percent with at least 50% pain relief	NNT	Lower confidence interval	Higher confidence interval
Valdecoxib 40 mg	473	73	1.6	1.4	1.8
Ibuprofen 800	76	100	1.6	1.3	2.2
Ketorolac 20	69	57	1.8	1.4	2.5
Ketorolac 60 (intramuscular)	116	56	1.8	1.5	2.3
Rofecoxib 50	1900	63	1.9	1.8	2.1
Diclofenac 100	411	67	1.9	1.6	2.2
Piroxicam 40	30	80	1.9	1.2	4.3
Lumiracoxib 400 mg	252	56	2.1	1.7	2.5
Paracetamol 1000 + Codeine 60	197	57	2.2	1.7	2.9
Oxycodone IR 5 + Paracetamol 500	150	60	2.2	1.7	3.2
Diclofenac 50	738	63	2.3	2.0	2.7
Naproxen 440	257	50	2.3	2.0	2.9
Oxycodone IR 15	60	73	2.3	1.5	4.9
Ibuprofen 600	203	79	2.4	2.0	4.2
Ibuprofen 400	4703	56	2.4	2.3	2.6
Aspirin 1200	279	61	2.4	1.9	3.2
Bromfenac 50	247	53	2.4	2.0	3.3
Bromfenac 100	95	62	2.6	1.8	4.9
Oxycodone IR 10 + Paracetamol 650	315	66	2.6	2.0	3.5
Ketorolac 10	790	50	2.6	2.3	3.1
Ibuprofen 200	1414	45	2.7	2.5	3.1
Oxycodone IR 10+Paracetamol 1000	83	67	2.7	1.7	5.6
Piroxicam 20	280	63	2.7	2.1	3.8
Diclofenac 25	204	54	2.8	2.1	4.3
Dextropropoxyphene 130	50	40	2.8	1.8	6.5
Pethidine 100 (intramuscular)	364	54	2.9	2.3	3.9
Tramadol 150	561	48	2.9	2.4	3.6
Morphine 10 (intramuscular)	946	50	2.9	2.6	3.6
Naproxen 550	169	46	3.0	2.2	4.8
Naproxen 220/250	183	58	3.1	2.2	5.2
Ketorolac 30 (intramuscular)	359	53	3.4	2.5	4.9
Paracetamol 500	561	61	3.5	2.2	13.3
Paracetamol 1500	138	65	3.7	2.3	9.5
Paracetamol 1000	2759	46	3.8	3.4	4.4
Oxycodone IR 5 + Paracetamol 1000	78	55	3.8	2.1	20.0
Paracetamol 600/650 + Codeine 60	1123	42	4.2	3.4	5.3
Ibuprofen 100	396	31	4.3	3.2	6.3
Paracetamol 650 + Dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate)	963	38	4.4	3.5	5.6
Aspirin 600/650	5061	38	4.4	4.0	4.9
Tramadol 100	882	30	4.8	3.8	6.1
Tramadol 75	563	32	5.3	3.9	8.2
Aspirin 650 + Codeine 60	598	25	5.3	4.1	7.4
Oxycodone IR 5 + Paracetamol 325	149	24	5.5	3.4	14.0
Tramadol 50	770	19	8.3	6.0	13.0
Codeine 60	1305	15	16.7	11.0	48.0
Placebo	>10,000	18	N/A	N/A	N/A

Adapted with permission from Bandolier (http://www.jr2.ox.ac.uk/bandolier/index.html).

Table 10

Table 5a. Pain: Treatment Effects Relative to Placebo

		95% CrI		Probability that Treatment Shows Small, Moderate or Large Improvement Relative to Placebo*		
Treatment (mg)	**ES****	**Low**	**High**	**Small**	**Moderate**	**Large**
acetaminophen 4000	-0.09	-0.25	0.08	0.08	0.00	0
nsNSAIDs						
naproxen 1000	-0.39	-0.53	-0.26	>0.99	0.06	0.00
ibuprofen 2400	-0.41	-0.63	-0.18	0.96	0.20	0.00
diclofenac 150	-0.49	-0.67	-0.31	>0.99	0.47	0.00
COX-2 selective NSAIDs						
celecoxib 100	-0.11	-0.31	0.10	0.18	0.00	0.00
celecoxib 200	-0.34	-0.41	-0.27	>0.99	0.00	0.00
celecoxib 400	-0.27	-0.45	-0.10	0.81	0.01	0.00
lumiracoxib 100	-0.30	-0.46	-0.14	0.89	0.01	0.00
lumiracoxib 200	-0.27	-0.44	-0.10	0.80	0.00	0.00
lumiracoxib 400	-0.29	-0.46	-0.13	0.87	0.01	0.00
etoricoxib 30	-0.66	-0.83	-0.49	>0.99	0.97	0.05
etoricoxib 60	-0.62	-0.78	-0.45	>0.99	0.92	0.02

*Small (ES ≥ 0.2), moderate (ES ≥ 0.5) or large (ES ≥ 0.8).
**Negative effect sizes indicate improvement.

Table 11

Table 6a. Physical Function: Treatment Effects Relative to Placebo

		95% CrI		Probability that Treatment Shows Small, Moderate or Large Improvement Relative to Placebo*		
Treatment (mg)	**ES****	**Low**	**High**	**Small**	**Moderate**	**Large**
acetaminophen 4000	-0.04	-0.20	0.13	0.03	0	0
nsNSAIDs						
naproxen 1000	-0.37	-0.51	-0.23	0.99	0.04	0.00
ibuprofen 2400	-0.41	-0.64	-0.18	0.96	0.22	0.00
diclofenac 150	-0.52	-0.70	-0.33	>0.99	0.58	0.00
COX-2 selective NSAIDs						
celecoxib 100	-0.15	-0.35	0.06	0.30	0.00	0.00
celecoxib 200	-0.34	-0.42	-0.27	>0.99	0.00	0.00
celecoxib 400	-0.26	-0.43	-0.09	0.74	0.00	0.00
lumiracoxib 100	-0.32	-0.48	-0.15	0.92	0.02	0.00
lumiracoxib 200	-0.35	-0.52	-0.17	0.95	0.04	0.00
lumiracoxib 400	-0.36	-0.53	-0.20	0.97	0.05	0.00
etoricoxib 30	-0.61	-0.76	-0.46	>0.99	0.93	0.01
etoricoxib 60	-0.64	-0.83	-0.46	>0.99	0.93	0.05

*Small (ES ≥ 0.2), moderate (ES ≥ 0.5) or large (ES ≥ 0.8).
**Negative effect sizes indicate improvement.

Table 12

Table 7a. PGADS: Treatment Effects Relative to Placebo

Comparator (mg)	Difference in CFB*	95% CrI Low	95% CrI High	Probability that Treatment Shows Clinical Improvement Over Placebo (≥ 10 mm VAS)
nsNSAIDs				
naproxen 1000	-12.9	-17.7	-8.2	0.89
ibuprofen 2400	-9.0	-13.1	-5.0	0.31
diclofenac 150	-16.2	-20.6	-11.7	>0.99
COX-2 selective NSAIDs				
celecoxib 200	-14.7	-17.3	-12.1	>0.99
lumiracoxib 100	-11.9	-19.6	-4.3	0.68
lumiracoxib 200	-11.8	-19.6	-4.2	0.66
lumiracoxib 400	-13.9	-21.5	-6.1	0.85
etoricoxib 30	-14.2	-16.8	-11.6	>0.99
etoricoxib 60	-16.2	-19.8	-12.7	>0.99

*Negative effect sizes indicate improvement.

Table 13

Table 1 Calculated ratios of relative risk (RRR) (95 % confidence interval) for major vascular events with non-selective NSAIDs from the CNT collaboration meta-analysis [14]

NSAID Comparators	RRR (
Ibuprofen vs. naproxen	1.55 (0.88–2.74)
Ibuprofen vs. diclofenac	1.02 (0.60–1.74)
Diclofenac vs. naproxen	1.52 (1.03–2.22)

CI confidence interval, *CNT* Coxib and traditional NSAID Trialists', *NSAIDs* non-steroidal anti-inflammatory drugs, *RRR* ratios of relative risk

e. Evidence quality:

All studies included in this review followed rigorous guidelines for the systematic review process and meta-analyses. Details on these are highlighted in the comment section of Table 2. Most importantly the findings are based on RCTs and represent the highest level of evidence.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	A multitude of publications (Van Walsem et al, (33) Guyot et al, (34) The Oxford League Table, (35) Stam et al, (36) and Da Costa et al (37)) highlight the efficacy benefit of diclofenac 150mg regarding improvement of pain, physical functioning, and patient global assessment of disease severity.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [ ] Harms outweigh benefits [ ] Benefits = harms or Uncertain [x]	See recommendation and rationale below.

<table>
<tr>
<td>THERAPEUTIC INTERCHANGE</td>
<td>Therapeutic alternatives available:

Yes [x] No [ ]

List the members of the group.
Diclofenac, naproxen

List specific exclusion from the group:
Coxibs
Indomethacin
Lornoxicam
Meloxicam
Piroxicam</td>
<td><u>Rationale for therapeutic alternatives included:</u>
As mentioned, the therapeutic alternatives included in this review are diclofenac, naproxen. The rational for assessing these medicines are: they are available in South Africa and have the most available evidence to assess their safety.
References: Relevant references are mentioned in the review.

<u>Rationale for exclusion from the group:</u>
The coxibs were excluded from this review due to cost. Indomethacin and lornoxicam did not have enough evidence available regarding safety assessment to be included. Meloxicam and piroxicam – cardiovascular saftey has not been adequately assessed.
References: n/a</td>
</tr>
<tr>
<td>VALUES & PREFERENCES / ACCEPTABILITY</td>
<td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [x]

Is the option acceptable to key stakeholders?
Yes [ ] No [ ] Uncertain [x]</td>
<td></td>
</tr>
<tr>
<td>RESOURCE USE</td>
<td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [x]</td>
<td>Cost of medicines/ day:
<table>
<tr><th>Medicine (oral formulation)</th><th>Cost/daily dose (ZAR)</th></tr>
<tr><td>Diclofenac, 75-150 mg/day</td><td>0.24 to 0.48*</td></tr>
<tr><td>Naproxen, 500-1000 mg/day</td><td>1.54 to 3.07**</td></tr>
<tr><td>Ibuprofen, 200-400 mg 8 hrly</td><td>0.38 to 0.66*</td></tr>
</table>
* Contract circular: HP09-2017SD (diclofenac 25mg, 500 tabs – 0.0802/tablet; weighted average price: ibuprofen 200 mg – R 0.127/tablet; 400 mg – R0.219/tablet)
** 60% of SEP (average price for 250 mg tab – R0.384): SEP database 16 March 2018

Additional resources: MSH drug price indicator, 2015 (adjusted to 2017 using SEPA)
• Diclofenac, 25 mg tab (S.Africa:DDP): $0.0050 = R 0.0663
• Diclofenac, 50 mg tab (S.Africa:DDP):$0.0127 = R 0.168
• Naproxen 250 mg tab (Peru:DDP): $0.0216 = R 0.286
• Naproxen 500 mg tab (Peru:DDP): $0.0308 = R0.408
• Ibuprofen 200 mg tab (S.Africa:DDP): $0.0069 = R0.0915
• Ibuprofen 400 mg tab (Peru:DDP): $0.0123= R0.163
References:
International medical products price guide, 2015
https://www.msh.org/resources/international-medical-products-price-guide
SEP adjustments (2016:4.8% ; 2017:5.70%; 2018: 1.26%)
OANDA average exchange rate (2018-01-01 to 2018-03-04) - www.oanda.com</td>
</tr>
<tr>
<td>EQUITY</td>
<td>Would there be an impact on health inequity?

Yes [ ] No [x] Uncertain [ ]</td>
<td>N/A</td>
</tr>
<tr>
<td>FEASIBILITY</td>
<td>Is the implementation of this recommendation feasible?
Yes [x] No [ ] Uncertain [ ]</td>
<td>N/A</td>
</tr>
</table>

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
			X		

Recommendation: Following this report on the efficacy and safety of tNSAIDs, the Adult Hospital Level Committee reccomended that diclofenac 150mg be considered for patients. There does not seem to be an NSAID that completely relinquishes a cardiovascular side effect profile. NSAID use should be instituted with great caution in those at risk of cardiovascular events. On review of the risk benefit profiles of various NSAIDs, therapeutic alternatives that may be considered include naproxen and ibuprofen.

Rationale: This medicine review included numerous systematic reviews and meta-analyses of RCTs which assessed the efficacy and safety of tNSAIDs and coxibs.. Diclofenac 150mg daily does appear to be the most efficacious tNSAID, however its cardiovascular risks are similar to the coxibs as presented by the Coxib and tNSAID trialists' collaboration. The recently published network meta-analysis by Van Walsem et al. mitigates these risks and highlights a similar cardiovascular risk profile to ibuprofen and an improved GI safety profile (as compared to ibuprofen). Ibuprofen at high doses (2400mg daily) has been shown to have a comparable efficacy to diclofenac 150mg daily, however it was also shown to increase major coronary events (the Coxib and tNSAID trialists' collaboration) and stroke (Trelle et al). Ibuprofen also had an increased rate of non-fatal MI as compared to naproxen in the PRECISION trial. Naproxen does appear to lack efficacy when compared to other tNSAIDs (The Oxford League Table and Stam et al). Naproxen does have the more favourable cardiovascular profile, as highlighted in the studies by Trelle et al. and the Coxib and tNSAID trialists' collaboration, however these findings were diminished by an FDA advisory committee meeting and by the Coxib and tNSAID trialists' collaboration themselves. Finally, the tNSAIDs meloxicam and piroxicam have not had adequate assessment of their cardiovascular safety profiles and cannot be successfully compared to diclofenac, ibuprofen, and naproxen.

Conclusion: Evidence from this review supports the increased risk of cardiovascular and gastrointestinal adverse events associated with use of all the traditional NSAIDS diclofenac, ibuprofen and naproxen. If clinically indicated, the choice of NSAID should be based on the individual risk profile of the patient. Risks for developing cardiovascular and/or gastrointestinal adverse events could be minimised by using the lowest tolerated dose for the shortest possible duration of treatment time. Diclofenac 150mg, as appearing to be more efficacious with a similar cardiovascular and improved gastrointestinal safety profile compared to ibuprofen, is recommended. Therapeutic alternatives of ibuprofen and naproxen could be considered.
Level of Evidence: I Systematic review and meta-analyses, RCTs, Expert opinion

Review indicator:

Evidence of efficacy	Evidence of harm/safety	Price reduction
X	x	x

VEN status:

Vital	Essential	Necessary
	x	

NEMLC MEETINGS OF 12 APRIL 2018 AND 5 DECEMBER 2019:
NEMLC ratified the medicine review and accepted the proposal as recommended by the Adult Hospital Committee - diclofenac, naproxen and ibuprofen be considered as a therapeutic class and further recommended that all three agents be advertised in the tablet tender as a therapeutic group.

Monitoring and evaluation considerations: None

Research priorities: None

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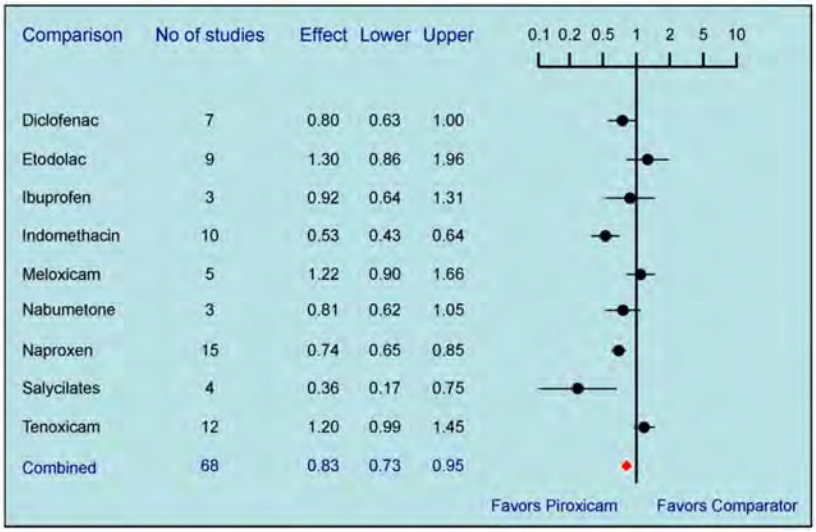
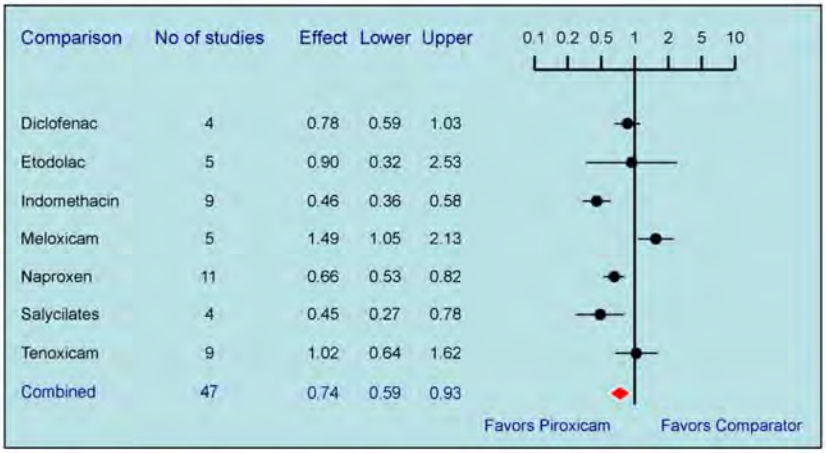
FIGURES

Figure 1



Forest plot showing the global safety (dichotomous outcomes) of piroxicam against other NSAIDs. For each comparator NSAID, the odds ratio (red diamond) is shown. The size of the diamond represents the weight that the corresponding studies (whose number is in brackets) exert in the meta-analysis (Mantel–Haenszel weight). The pooled (combined) estimate is given at the bottom.

Figure 2



Forest plot showing the GI safety (all the events, dichotomous outcomes) of piroxicam against other NSAIDs. For each comparator NSAID, the odds ratio (red diamond) is shown. The size of the diamond represents the weight that the corresponding studies (whose number is in brackets) exert in the meta-analysis (Mantel–Haenszel weight). The pooled (combined) estimate is given at the bottom.

Figure 3

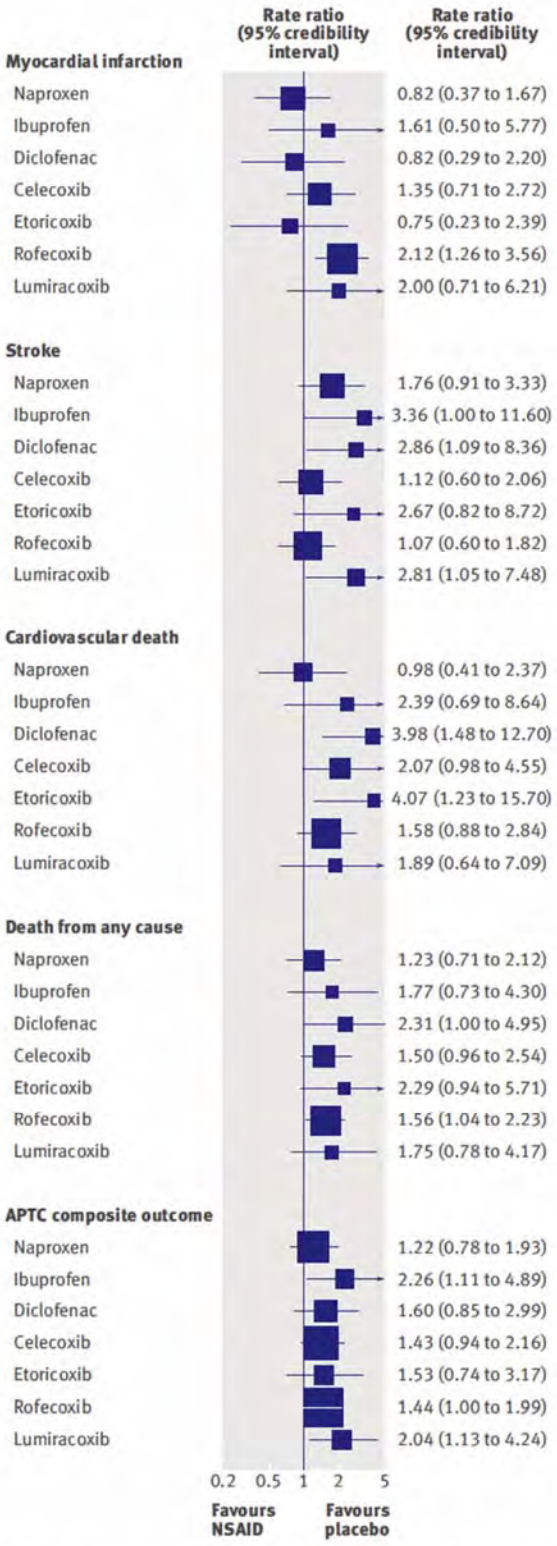


Fig 2| Estimates of rate ratios for non-steroidal anti-inflammatory drugs compared with placebo. NSAID=non-steroidal anti-inflammatory drug; APTC=Antiplatelet Trialists' Collaboration

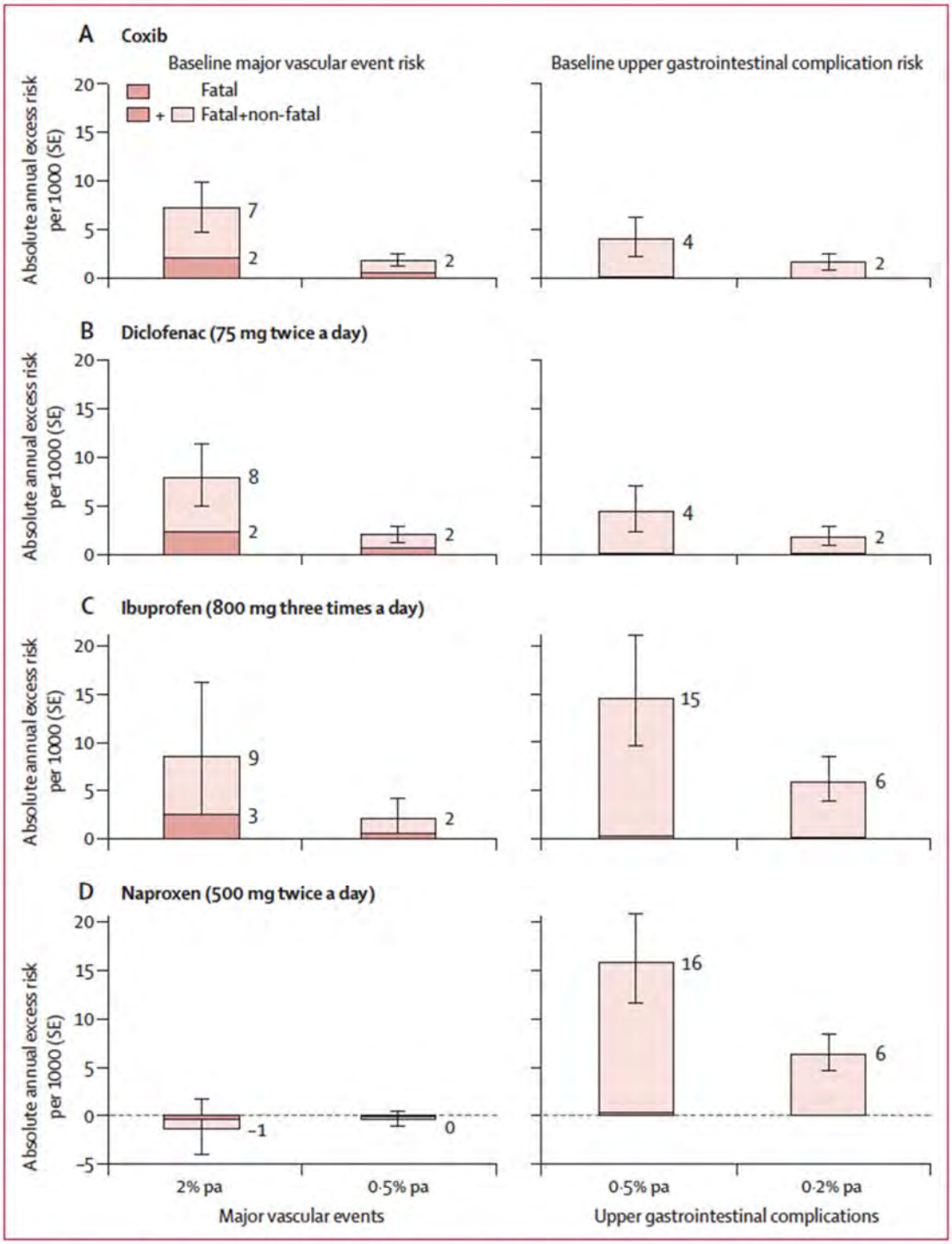


Figure 5: **Annual absolute effects per 1000 of coxibs and tNSAIDs at different baseline risks of major vascular events and upper gastrointestinal complications**

For each category of drug (coxib, diclofenac, ibuprofen, and naproxen), the predicted annual absolute risks of major vascular events (±1 SE) are shown (left) for patients with predicted risk of 2·0% or 0·5% per annum of a major vascular event. For comparison, predicted annual absolute risks of upper gastrointestinal complications (±1 SE) are shown for patients with predicted risks of 0·5% or 0·2% per annum (right). Absolute annual risks for placebo-allocated patients are assumed to be those of a hypothetical patient after all appropriate forms of prophylactic treatment (eg, antihypertensive therapy, statin therapy, proton-pump inhibitors) have been instituted.

Figure 4

Figure 5

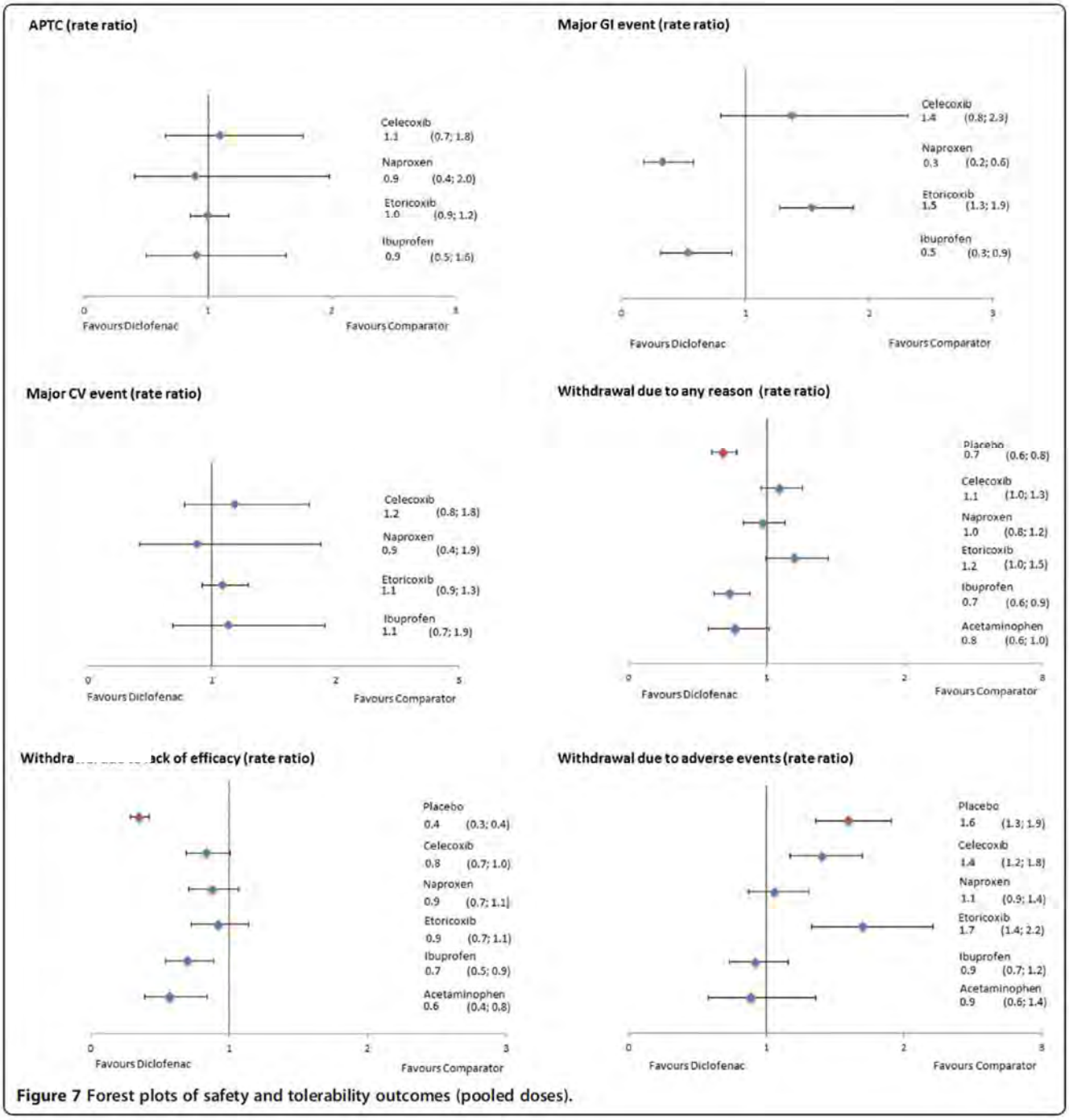


Figure 7 Forest plots of safety and tolerability outcomes (pooled doses).

Figure 6

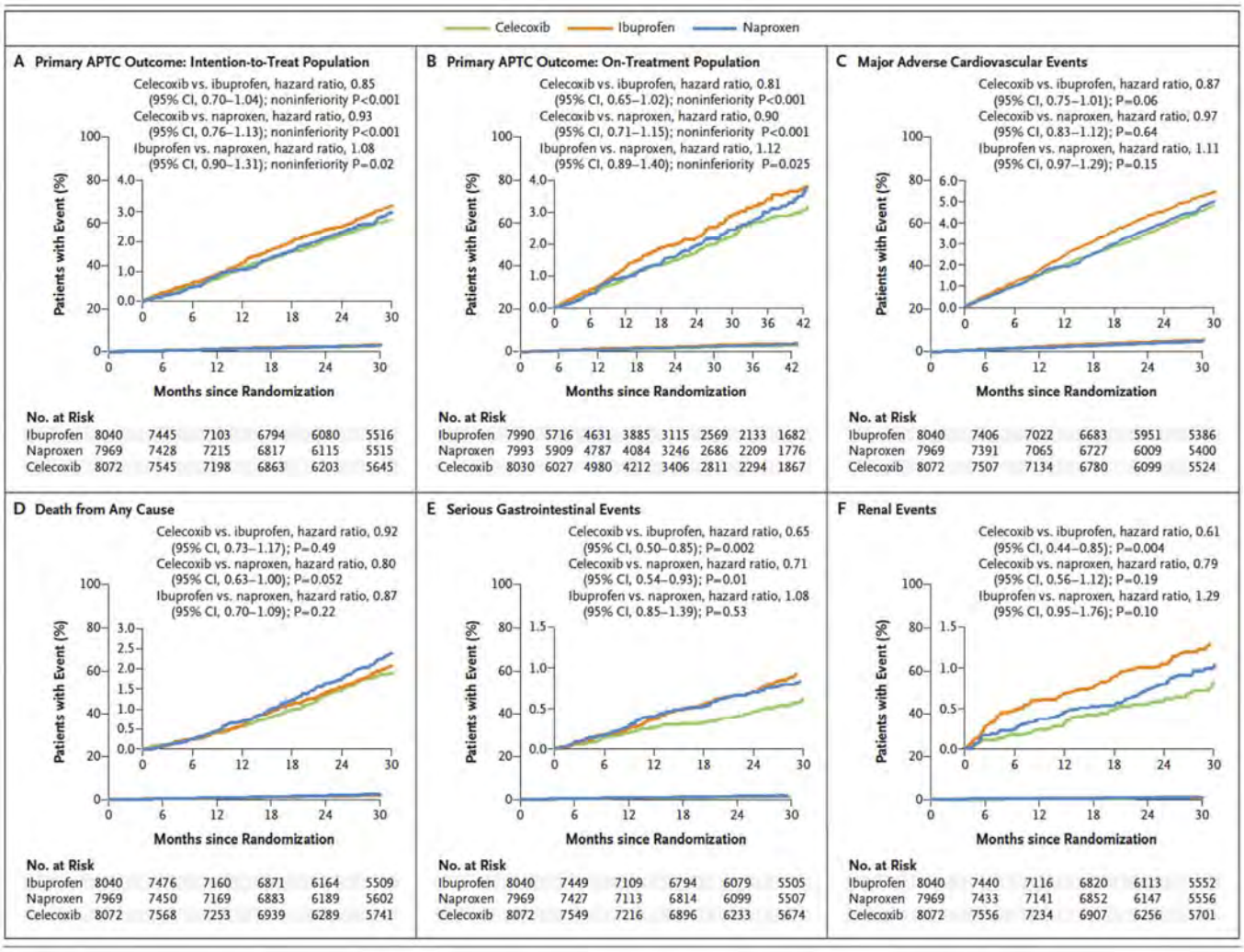
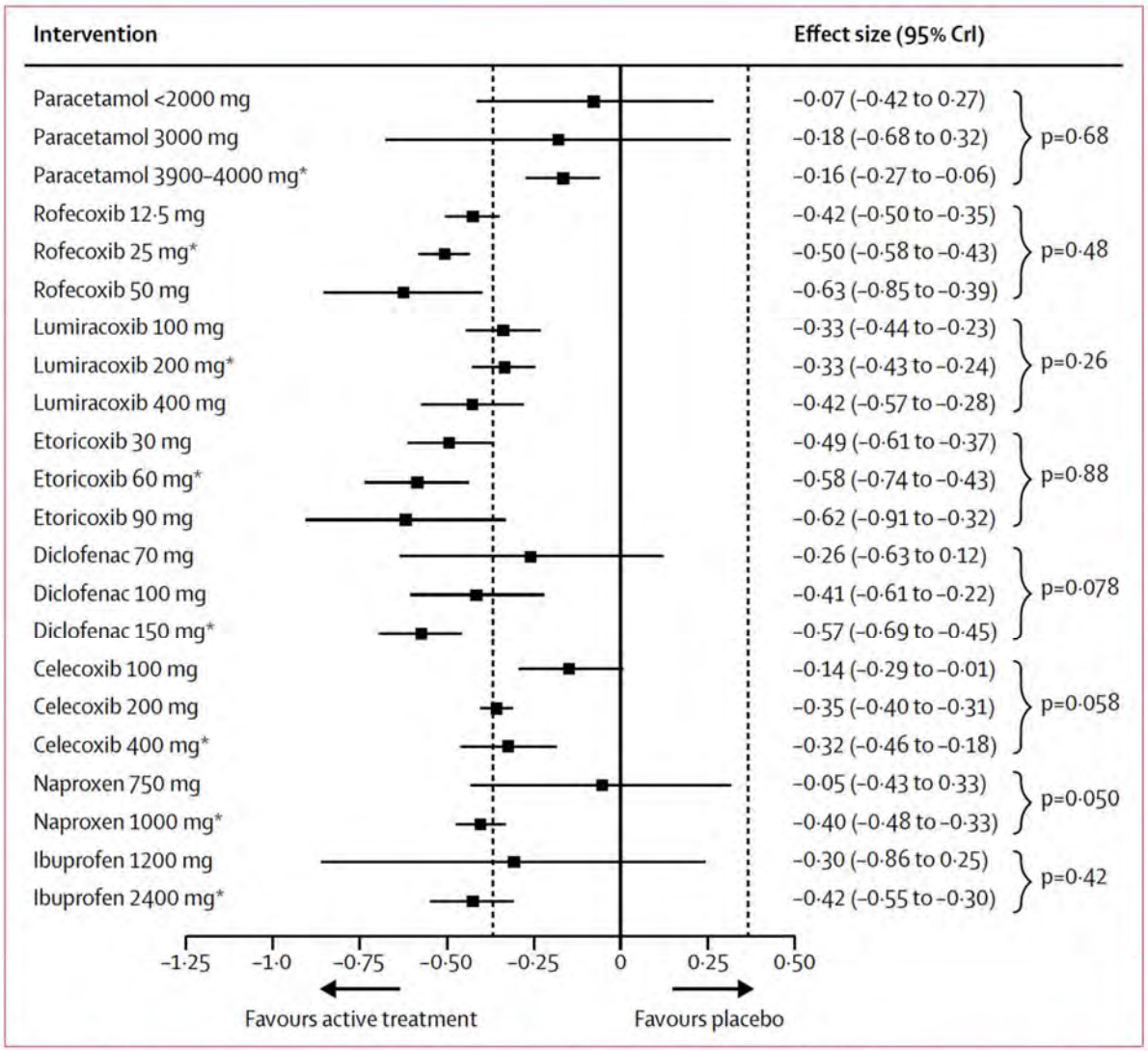

Celecoxib
Ibuprofen
Naproxen
A Primary APTC Outcome: Intention-to-Treat Population
Celecoxib vs. ibuprofen, hazard ratio, 0.85 (95% CI, 0.70–1.04); noninferiority P<0.001
Celecoxib vs. naproxen, hazard ratio, 0.93 (95% CI, 0.76–1.13); noninferiority P<0.001
Ibuprofen vs. naproxen, hazard ratio, 1.08 (95% CI, 0.90–1.31); noninferiority P=0.02
Patients with Event (%)
Months since Randomization
No. at Risk
Ibuprofen 8040 7445 7103 6794 6080 5516
Naproxen 7969 7428 7215 6817 6115 5515
Celecoxib 8072 7545 7198 6863 6203 5645
B Primary APTC Outcome: On-Treatment Population
Celecoxib vs. ibuprofen, hazard ratio, 0.81 (95% CI, 0.65–1.02); noninferiority P<0.001
Celecoxib vs. naproxen, hazard ratio, 0.90 (95% CI, 0.71–1.15); noninferiority P<0.001
Ibuprofen vs. naproxen, hazard ratio, 1.12 (95% CI, 0.89–1.40); noninferiority P=0.025
Patients with Event (%)
Months since Randomization
No. at Risk
Ibuprofen 7990 5716 4631 3885 3115 2569 2133 1682
Naproxen 7993 5909 4787 4084 3246 2686 2209 1776
Celecoxib 8030 6027 4980 4212 3406 2811 2294 1867
C Major Adverse Cardiovascular Events
Celecoxib vs. ibuprofen, hazard ratio, 0.87 (95% CI, 0.75–1.01); P=0.06
Celecoxib vs. naproxen, hazard ratio, 0.97 (95% CI, 0.83–1.12); P=0.64
Ibuprofen vs. naproxen, hazard ratio, 1.11 (95% CI, 0.97–1.29); P=0.15
Patients with Event (%)
Months since Randomization
No. at Risk
Ibuprofen 8040 7406 7022 6683 5951 5386
Naproxen 7969 7391 7065 6727 6009 5400
Celecoxib 8072 7507 7134 6780 6099 5524
D Death from Any Cause
Celecoxib vs. ibuprofen, hazard ratio, 0.92 (95% CI, 0.73–1.17); P=0.49
Celecoxib vs. naproxen, hazard ratio, 0.80 (95% CI, 0.63–1.00); P=0.052
Ibuprofen vs. naproxen, hazard ratio, 0.87 (95% CI, 0.70–1.09); P=0.22
Patients with Event (%)
Months since Randomization
No. at Risk
Ibuprofen 8040 7476 7160 6871 6164 5509
Naproxen 7969 7450 7169 6883 6189 5602
Celecoxib 8072 7568 7253 6939 6289 5741
E Serious Gastrointestinal Events
Celecoxib vs. ibuprofen, hazard ratio, 0.65 (95% CI, 0.50–0.85); P=0.002
Celecoxib vs. naproxen, hazard ratio, 0.71 (95% CI, 0.54–0.93); P=0.01
Ibuprofen vs. naproxen, hazard ratio, 1.08 (95% CI, 0.85–1.39); P=0.53
Patients with Event (%)
Months since Randomization
No. at Risk
Ibuprofen 8040 7449 7109 6794 6079 5505
Naproxen 7969 7427 7113 6814 6099 5507
Celecoxib 8072 7549 7216 6896 6233 5674
F Renal Events
Celecoxib vs. ibuprofen, hazard ratio, 0.61 (95% CI, 0.44–0.85); P=0.004
Celecoxib vs. naproxen, hazard ratio, 0.79 (95% CI, 0.56–1.12); P=0.19
Ibuprofen vs. naproxen, hazard ratio, 1.29 (95% CI, 0.95–1.76); P=0.10
Patients with Event (%)
Months since Randomization
No. at Risk
Ibuprofen 8040 7440 7116 6820 6113 5552
Naproxen 7969 7433 7141 6852 6147 5556
Celecoxib 8072 7556 7234 6907 6256 5701

Figure 7



Estimates of the treatment effects on pain for different daily doses of NSAIDs and paracetamol compared with placebo

Between trial-heterogeneity τ^2=0·012 (95% CrI 0·008–0·018). Analysis considers data from all timepoints as available. Area between dashed lines shows the treatment effect estimates below the minimum clinically important difference. Two-sided p values are derived from tests of linear dose–effect. NSAID=non-steroidal anti-inflammatory drug. CrI=credibility interval. *Maximum approved daily dose..

Figure 8

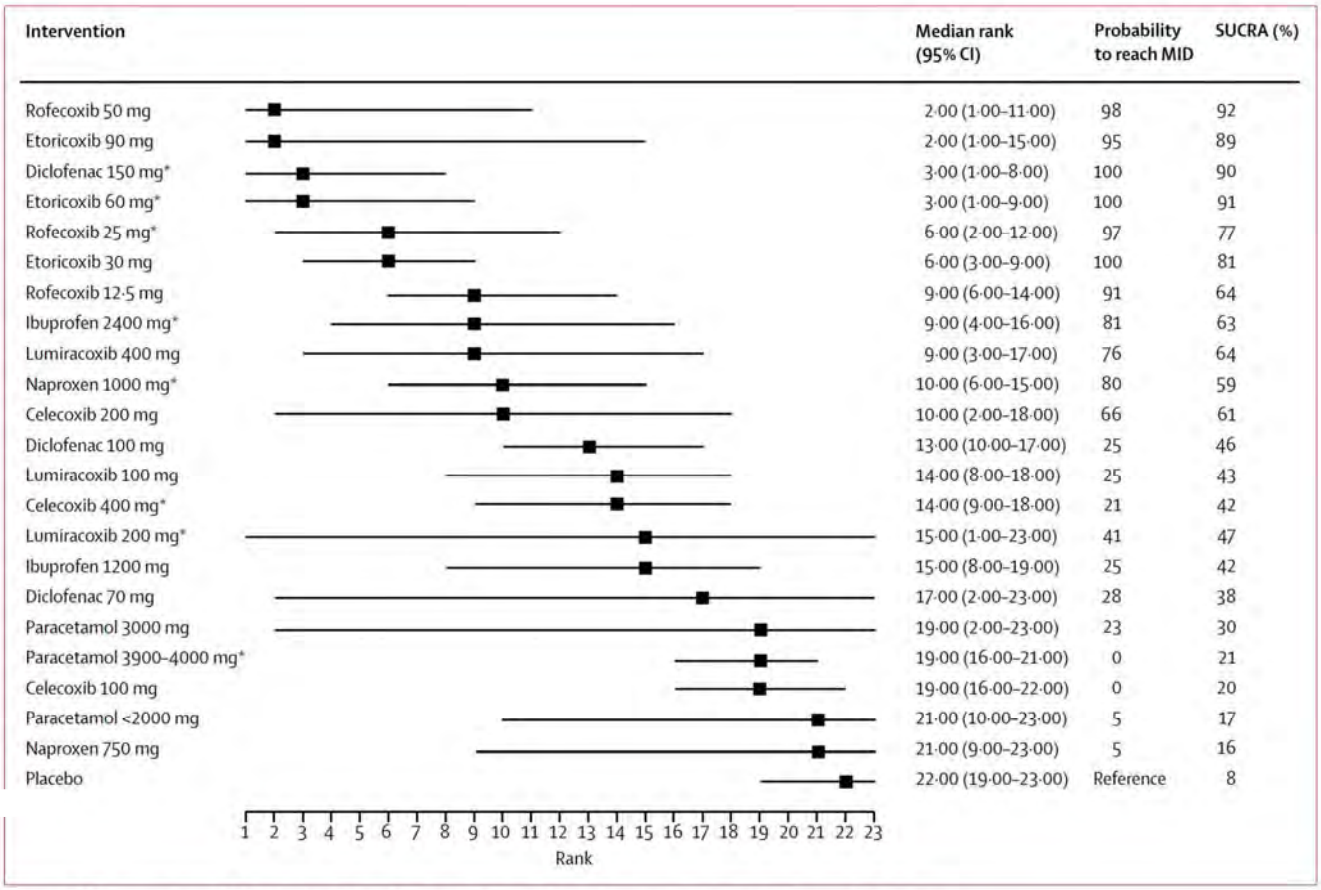


Figure 3: **Median rank, probability of reaching MID, and SUCRA values of competing interventions and daily doses**
MID=minumum clinically important difference. SUCRA=surface under the cumulative ranking curve. CrI=credibility interval. *Maximum daily dose.

National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Pain

Adverse effects of NSAIDS

Observational data[1],[2] has pointed to differences in the incidence of cardiovascular adverse events associated with various non-steroidal anti-inflammatory agents (NSAIDs). In particular, there are concerns about the risks associated with diclophenac relative to ibuprofen and naproxen. In a pair-wise comparison, the relative risk ratio for naproxen was lower than for ibuprofen (RRR = 0.92, 99% CI 0.87 to 0.99). Diclophenac versus ibuprofen: 1.13 (99% CI 1.03 to 1.24.)

Table 4. Selected pair-wise comparisons of individual drugs.

Drug Tested	Reference Drug in the Comparison				
	Rofecoxib	Diclofenac	Ibuprofen	Naproxen	Celecoxib
Etoricoxib	1.29 (0.86, 1.93), $n=3$ studies	1.36 (0.89, 2.09), $n=3$ studies	**1.68** (1.14, 2.49), $n=3$ studies	**1.75** (1.16, 2.64), $n=3$ studies	
Etodolac		0.95 (0.78, 1.16), $n=5$ studies	1.04 (0.88, 1.24), $n=7$ studies	1.10 (0.96, 1.26), $n=7$ studies	
Diclofenac	1.0 (0.89, 1.12), $n=18$ studies		**1.13** (1.03, 1.24), $n=27$ studies	**1.22** (1.11, 1.35), $n=25$ studies	**1.15** (1.02, 1.30), $n=19$ studies
Naproxen			**0.92** (0.87, 0.99), $n=12$ studies	—	0.96 (0.81, 1.13), $n=21$ studies
Meloxicam				**1.11** (1.0, 1.23), $n=6$ studies	
Indomethacin				**1.23** (1.10, 1.39), $n=15$ studies	

Values are pooled RRRs and 99% CIs. Bold indicates significant difference at $p<0.0033$ (the Bonferroni-adjusted threshold p-value: $n=15$ comparisons; alpha = 0.05).
doi:10.1371/journal.pmed.1001098.t004

Table 5. Results of sensitivity analyses on selected pair-wise comparisons.

Comparison	RRR	RR_{CD}	P_{C1}	P_{C0}	RRR_{adj}	Percent Bias
Etoricoxib versus naproxen	1.75	11.00	0.25	0.10	1.00	75.00
Etoricoxib versus ibuprofen	1.68	9.40	0.25	0.10	1.00	68.48
Indomethacin versus naproxen	1.23	2.80	0.25	0.10	1.00	22.88
Diclofenac versus naproxen	1.22	2.70	0.25	0.10	1.00	21.79
Diclofenac versus celecoxib	1.15	2.10	0.25	0.10	1.00	14.86
Diclofenac versus ibuprofen	1.13	1.95	0.25	0.10	1.00	13.01
Naproxen versus ibuprofen	0.92	0.50	0.25	0.10	1.00	−7.89

RR_{CD} is the association between confounder and disease outcome. P_{C1} is the prevalence of confounder in the exposed. P_{C0} is the prevalence of confounder in the unexposed. RRR_{adj} is the "true", or fully adjusted, RRR. Percent bias is the percentage change to the RRR that would be introduced by a hypothetical confounding variable under the assumptions in the table.
doi:10.1371/journal.pmed.1001098.t005

While these effects are clearly discernible, the problems of biases associated with studies of this nature are well known and always difficult to quantify.

[1] McGettigan P, Henry D (2011) Cardiovascular Risk with Non-Steroidal Anti-Inflammatory Drugs: Systematic Review of Population-Based Controlled Observational Studies. PLoS Med 8(9): e1001098. doi:10.1371/journal.pmed.1001098

[2] McGettigan P, Henry D (2013) Use of nonsteroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. PLoS Med 10: e1001388. doi:10.1371/journal.pmed.1001388

An individual patient meta-analysis[3] assists with this by pooling larger numbers of patients from RCTs, but still suffers from the external validity issues related to careful patient selection. The results of this are best seen in this figure from the report:

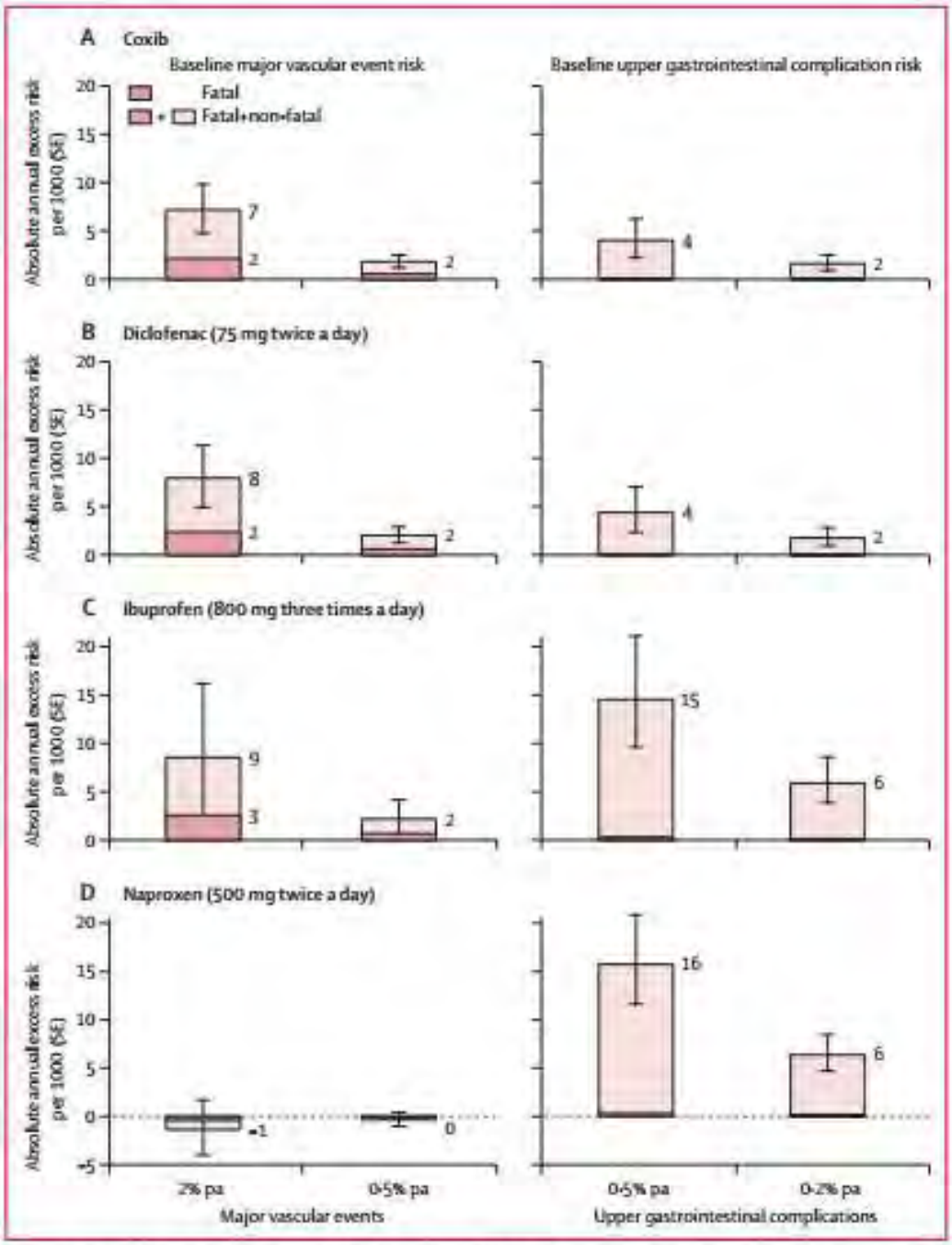


Figure 5: **Annual absolute effects per 1000 of coxibs and tNSAIDs at different baseline risks of major vascular events and upper gastrointestinal complications**

For each category of drug (coxib, diclofenac, ibuprofen, and naproxen), the predicted annual absolute risks of major vascular events (±1 SE) are shown (left) for patients with predicted risk of 2·0% or 0·5% per annum of a major vascular event. For comparison, predicted annual absolute risks of upper gastrointestinal complications (±1 SE) are shown for patients with predicted risks of 0·5% or 0·2% per annum (right). Absolute annual risks for

[3] Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-infl ammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet2013; 382: 769–79.

Although this figure illustrates the balance between CVS and vascular events, it is still not clear what the actual patient impact of a vascular event versus a GIT complication would be; short of translating this into QALYs, this remains difficult to balance.

A further issue concerns duration of therapy; although not formally addressed, it is likely that the CVS effects of short term use are much lower than pertaining to long duration use in high risk patients (e.g. those with rheumatoid arthritis or osteoarthritis.)

Conclusion: It is clear that there are measurable differences in side-effect profiles of NSIADs; whether these are sufficiently large to justify formulary changes is less certain.

National Essential Medicine List Medication Review Process
Adult Hospital level
Component: Musculoskeletal disorders

Date: 26 November 2015

Medication: Naproxen, meloxicam and piroxicam in arthritis

Introduction:
Inflammatory arthritis results in structural damage to joints, which results in persistent pain in these patients. The management of pain is an important aspect of the management of arthritis. Comorbidities are highly prevalent in this group of patients, so considering the safety of various analgesics with this in mind is important.

Search strategy and article selection:

A search of the Cochrane database identified 1 relevant review (updated 2012). The review assessed the efficacy and safety of pharmacological pain treatment in inflammatory arthritis with gastrointestinal or liver comorbidities, or both. [i]

Meloxicam in arthritis:

1. PubMed: ("Arthritis"[Mesh] AND "meloxicam"[Supplementary Concept]) AND "Treatment Outcome"[Mesh] AND ((Clinical Trial[ptyp] OR Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp]) AND "humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms])
   Results: 17. Two studies rejected: 1 did not match the drug under review, 1 did not match the disease state under review.

2. Google scholar: the following terms were used: ‘meloxicam’, ‘cardiovascular safety’, ‘gastrointestinal safety’ and ‘meta analysis’.

3. Bandolier website: the following term was used “meloxicam”.
   Results: 1 – “Nabumetone & meloxicam gastrointestinal safety”; that summarized the meta-analysis by Schoenfeld et al (1999).

Naproxen in arthritis:

1. PubMed: "Arthritis"[Mesh] AND "Naproxen"[Mesh] AND ("safety"[MeSH Terms] OR "safety"[All Fields]) AND ((Controlled Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Multicenter Study[ptyp] OR Observational Study[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms])
   Results: 85. Studies were excluded because: they did not match the drug under review; they compared treatment combinations not under review. Studies that were only available in abstract form were excluded.

2. An article identified from a report on the PRECISION trial identified one further meta-analysis from Lancet that was considered eligible for inclusion in this review[ii]. The

primary vascular outcome was major vascular events (non-fatal myocardial infarctions, non-fatal stroke, or death from a vascular cause). Other vascular outcomes included major coronary events (non-fatal myocardial infarction or death from coronary disease), stroke, and hospitalization for heart failure. The primary gastrointestinal outcome was upper gastrointestinal complications (upper gastrointestinal perforation, obstruction or bleed).

3. Bandolier website: the following term was used "naproxen".
   Results: 2 – "The Oxford League table of analgesic efficacy"; "NSAIDs and adverse effects" and" Myocardial infarction: aspirin, NSAIDs, and COXIBs".

Piroxicam in arthritis:

1. PubMed: ("Arthritis"[Mesh] AND "piroxicam"[Supplementary Concept]) AND "Treatment Outcome"[Mesh] AND ((Clinical Trial[ptyp] OR Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp]) AND "humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms])
   Results: 18. Studies were excluded as they did not match the medicine or the formulation under review; the comparator medicine was not standard of care; study determined non-pharmacological outcomes or studies compared duration therapy.

2. Google scholar: the following terms were used: 'piroxicam', 'meta-analysis' and 'safety'.

3. Bandolier website: the following term was used "piroxicam".
   Results: 2 – "The Oxford League table of analgesic efficacy"; "NSAIDs and adverse effects".

Comparable doses

Comparative doses were derived from the WHO defined daily doses index[iii]:

Medicine	**WHO ATC DDD**
Meloxicam	15 mg
Naproxen	500 mg
Piroxicam	20 mg
Ibuprofen	1200 mg
Diclofenac	100 mg

Evidence synthesis:

The SELECT[iv] and MELISSA[v] trials, and the study by Yocum *et al*[vi] , were sponsored by Boehringer Ingelheim GmbH, manufacturers of Mobic® (meloxicam). There was no mention of the method of randomization in these trials. These trials indicated adverse events using the Adverse Reaction Terminology List/Coding Thesaurus Of the World Health Organization, although they are presented in different formats in each study. The MELISSA trial had an increased attrition rate with the meloxicam group due to lack of efficacy. The McGettigan study is a systematic review only[vii]. The manufacturer-funded meta-analyses [viii,ix] suggesting a lower risk of gastro-intestinal complications with meloxicam, were of low-quality; as details of the quality and individual results of the included RCTs were not reported.

Effectiveness

1. Naproxen

Compared with oral acetaminophen naproxen had significantly better effect sizes for pain at 3 months (0.20, 95% CI 0.03 to 0.37), in the treatment for osteoarthritis of the knee. However when compared to celecoxib, there was no difference in effect size (0.05, 95% CI -0.08 to 0.17) The Oxford League table of analgesic efficacy[x] shows a NNT of 2.5 for ibuprofen 400 mg compared to a NNT of 2.7 for naproxen 400-550 mg and a NNT of 3.4 for naproxen 200/220 mg.

2. Meloxicam

To date, no RCTs of meloxicam have been included in Cochrane reviews. The double-blinded RCTs that were identified comparing melxicam to other NSAIDs were generally comparable in terms of efficacy, except in 2 RCTs [v, vi] (where attrition was greater in the meloxicam group due to lack of efficacy).

RCT	Study design	Study comparators	Effect	Comments
Hawkey et al (1998) [v] (MELISSA TRIAL)	Double-blnd, randomised, RCT; n=9323, over 28 days.	Meloxicam 7.5mg (n=4635) vs diclofenac 100mg slow release (n=4688) in osteoarthritic patients.	**Efficacy:** - Diclofenac more efficacious than meloxicam (assessed by VAS scale) statistically significant but not clinically significant (differences were small & did not reach pre-determined levels of clinical significance) -Significantly more patients discontinued meloxicam because of lack of efficacy (80/4635 vs 49/4688; p < 0.01). **Safety:** -Fewer GI adverse events with meloxicam(13%) vs. diclofenac (19%; p < 0.001).; with less dyspepsia (p < 0.001), nausea & vomiting (p < 0.05), abdominal pain (p < 0.001) & diarrhoea (p < 0.001). -Patient days of hospitalization was 5 vs 121 for meloxicam vs diclofenac, respectively. 254 patients receiving meloxicam (5.48%) vs 373 (7.96%) on diclofenac (p < 0.001) withdrew from the study due to AEs – GI AEs: 3.02% vs 6.14%; p < 0.001, respectively.	• Attrition was greater in the meloxicam group due to lack of efficacy. • Comparative doses considered to be 7.5 mg vs 100 mg (meloxicam vs diclofenac) contrary to WHO DDD – see above
Dequeker et al (1998) [iv] (SELECT TRIAL)	Multi-centred, double blind, double-dummy, randomized, parallel gp trial, over 28 days. Intention to treat analysis.	Meloxicam 7.5 mg (n=4320) vs piroxicam 20 mg (n=4336) in osteoarthritic patients.	**Efficacy:** Comparable efficacy assessed on 100 mm VAS: - mean treatment difference (meloxicam vs. piroxicam) at the end of trial was 1.97 mm (95% CI 1.01 to 2.94), NS **Safety:** Adverse events lower in the meloxicam vs. piroxicam group (22.5% vs. 27.9%; p < 0.001), Piroxicam vs meloxicam: - GIT adverse events: 15.4% vs 10.3%; p < 0.001 - nausea/vomiting: 3.4% vs 2.5%: p < 0.05 - abdominal pain: 3.6% vs 2.1%; p <	• 79% of patients in both treatment groups were pre-treated with NSAIDs. • 1.7% in meloxicam vs. 1.6% in piroxicam group withdrew due to lack of efficacy. • Comparative doses considered to be 7.5 mg vs 20 mg (meloxicam vs piroxicam) contrary to WHO DDD – see above.

			0.001 - 16 vs 7 perforations, ulcerations or bleeding (PUBs) (RR: 1.4). - 4 vs 0 complicated PUBs (RR:1.9).	
Hosie (1996)[xi]	Multi-centred, double blind, double-dummy, randomized trial, over 6 months. Intent to treat analysis.	Meloxicam 7.5 mg (n=169) vs diclofenac 100 mg slow release (n=167) in osteoarthritic patients	**Efficacy:** Meloxicam showed a greater reduction of overall pain (mm on VAS -28.1 ± 29.4 vs -30.9 ± 29.1), pain on movement (mm on VAS -29.5 ± 31.1 vs 32.8 ± 28.5), greater global efficacy (mm on VAS 35.9±29.1 vs 32.1±27.4) and less duration of stiffness following inactivity (minutes --43± 167 vs -33±62), all NS. NS QoL scores were comparable to diclofenac (-2.3±3.7 vs -2.2±4.2) **Safety:** -Adverse effects reported in 101/169 (59.8%) vs 101/167 (60.5%) of meloxicam vs diclofenac groups, respectively. - More SAEsin diclofenac vs melociam group (22% vs 15.8%) -More patients withdrew due to adverse effects in the diclofenac (22%) vs meloxicam (12.4%) groups.	• 66 patients withdrew due to AEs (n=21, meloxicam; n=31; diclofenac) or lack of efficacy (7 in each group). • Comparative doses considered to be 7.5 mg vs 100 mg (meloxicam vs diclofenac) contrary to WHO DDD – see above. • Median dose of concomitant paracetmol was lower in meloxicam vs diclofenac group (185vs 245 mg/day, p-0.0123).
Hosie (1997)[xii] ACCESSED ABSTRACT ONLY	Randomised, double-blind, parallel-group trial, over 6 months.	Meloxicam 15 mg (n=306) vs piroxicam 20 mg (n=149) for proven osteoarthritis of the knee or hip (details of diagnosis not reported in the abstract).	**Efficacy:** - Comparable effectiveness between meloxicam and piroxicam for overall pain, pain on movement, joint stiffness, global efficacy and quality of life (effect sizes not provided in the abstract). **Safety:** -Incidence and type of AEs reported were similar in both study groups -More GIT AEs reported in 24.2% of meloxicam-treated patients vs.30.2% of piroxicam-treated patients.	Details of patients withdrawing from the study not provided for in the publication abstract.
Valat (2001)[xiii]	Multi-centred, double blind, double-dummy, randomized, parallel gp trial, over 14 days. Intention to treat analysis.	Meloxicam 7.5 mg (n=169) vs diclofenac 100 mg slow release (n=167) for osteoarthritis in the lumbar spine.	**Efficacy:** Statistically significant reduction in pain on motion of lumbar spine (assessed on 100 mm VAS) with meloxicam vs. diclofenac after 3 days (mean(SD)): 15 (18) mm vs 17 (21 mm); p <0.05. **Safety:** - GIT adverse events greater with diclofenac vs meloxicam (17.8% vs 12.8%), NS. -Global tolerability was significantly better than diclofenac, assessed by patients (p=0.049) and investigators (p=0.0072).	• 5 patients withdrew due to AEs in meloxicam group vs. 10 in diclofenac group. No withdrawals due to lack of efficacy. • Comparative doses considered to be 7.5 mg vs 100 mg (meloxicam vs diclofenac) contrary to WHO DDD – see above.
Linden (1996)[xiv]	Multi-centred, randomised, double-blind, parallel group trial, over 42 days. Intention to treat analysis.	Meloxicam 30 mg (n=29) evaluated separately and evaluated descriptively but not reported in the publication; and meloxicam 15 mg (n=129) vs piroxicam 20 mg (n=127) in an ITT, for osteoarthritis of the hip.	**Efficacy:** - No significant difference in pain at movement between meloxicam vs piroxicam at 42 days. **Safety:** - More GIT AEs reported with piroxicam vs meloxicam (22.8% vs 20.9%). -Global tolerance (100 mm VAS) was similar in both treatment groups.	• 12 patients withdrew due to AEs in meloxicam group vs. 10 in piroxicam group. Withdrawl due to lack of efficacy was not reported.
Goei(1997)[xv]	Multi-centred, randomised, double-blind trial, over 6 weeks. Intention to treat analysis.	Meloxicam 15 mg (n=128) vs diclofenac 100 mg slow release (n=130) for	**Efficacy:** - Trend seen for efficaciousness, favouring meloxicam (pain on movement, global efficacy and paracetamol consumption), NS.	• 21 patients withdrew due to AEs in meloxicam group vs. 24 in diclofenac group.

		osteoarthritis of the knee. Intention to treat analysis.	**Safety:** - More AEs reported in diclofenac vs. meloxicam groups - 44 (34.4%) vs 47 (36.2%). - Most frequent AEs were GIT: 34(26.2%) vs 21 (16.4%) in the diclofenac vs meloxicam groups, respectively. - 1 patient in the diclofenac group was hospitalized due to a gastric ulcer, at 22 days. - Both drugs were well tolerated when assessed by the patients on a visual analog scale (VAS).	Withdrawl due to lack of efficacy was not reported. - 5/128 patients in meloxicam group vs 3/130 in diclofenac group withdrew, due to lack of efficacy. - Cardiovascular disorders reported were 3% in the meloxicam group vs 1% in the diclofenac group.

The MELISSA trial showed no difference between meloxicam 15 mg and diclofenac 100 mg for pain on active movement (actual difference between treatments mean 2.29, 95% CI 1.38 to 3.20) and pain at rest (1.54, 95% CI0.59 to 2.49)[vi], as assessed with 100 mm visual analogue scale (VAS). There was greater attrition in the meloxicam group due to lack of efficacy – dropout rate was 80/4635 vs. 49/4688; $p < 0.01$ for meloxicam *vs*. diclofenac, respectively (actual difference 0.68%; odds ratio 1.66, 1.16 to 2.38, $p < 0.01$).

3. Piroxicam

A RCT[xvi] showed no difference between diclofenac 100 mg/day (n=32) and sustained-release etodolac 400 mg/day (n=32) for treating osteoarthritis of the knee determined by 100 mm visual analogue scale; whilst another 8-week, multi-centered, double-blind RCT[xvii] showed comparable efficacy between piroxicam and standard formulation etodolac for treating osteoarthritis of the knee and hip with no statistically significant differences in any efficacy assessment at any observation. More adverse events were reported with etodolac vs. piroxicam (30% vs. 46%; $p < 0.01$); whilst the difference in gastrointestinal adverse events (20% vs. 29%) was not significant. Decrease in haemoglobin occurred in 22% of patients, but with no significant difference between the 2 groups.

A meta-analysis[xviii] of RCTs comparing piroxicam to other NSAIDs showed a trend of comparable global efficacy to other NSAIDs (OR 1.06; 95% CI 0.96 to 1.18). Similar results were shown when short-term trials (≤ 4 weeks) and long-term trials were analysed; OR 1.18; 95% CI 0.96 to 1.34 and OR 1.07; 95% CI 0.97 to 1.19, respectively. However, for mobility or stiffness, piroxicam was reported to be significantly more efficacious than indomethacin ($p = 0.04$, but no effect size provided) whilst comparable to other NSAIDs (effect size 0.02; 95% CI -0.14 to 0.18, p=0.82). Piroxicam was also shown to be significantly better in terms of articular swelling vs. other NSAIDs (effect size 0.26; 95% CI 0.07 to 0.44; p=0.008). However, a number of limitations of this meta-analysis cautions of the reliability of the results. Search terms were not provided; details of the RCTs were not described; RCTs with all indications for NSAIDs were included; results of quality assessment of RCTs using Jadad score were not provided and the pooled results of global efficacy and safety was from clinically heterogeneous RCTs (differs in population and outcomes).

Safety considerations

1. Naproxen

Cardiovascular effects

Trelle *et al* found no association between naproxen and myocardial infarction compared with placebo (rate ratio 0.82, 95% CI 0.37 to 1.67)[xix]. However, in their secondary outcomes of stroke, cardiovascular death, and death from any cause, naproxen was associated with increased incidence of stroke (1.76, 95% CI 0.91 to 3.33). Cardiovascular death (0.98, 95% CI 0.41 to 2.37) and death from any cause (1.23, 95% CI 0.71 to 2.12) was not associated with naproxen use.

In the Lancet meta-analysis, naproxen was not associated with significant risk of major vascular events (rate ratio 0.93, 95% CI 0.69 to 1.27; p=0.66)[ii]. There was no increase in major coronary events (0.84, 95% CI 0.52 to 1.35, p=0.48). There was no evidence for increased risk of stroke (0.97, 95% CI 0.59 to 1.60, p=0.90). There was increased risk of hospitalization due to heart failure with naproxen (1.87, 95% CI 1.10 to 3.16, p=0.0197). There was no risk of vascular death associated with naproxen (1.08, 95% CI 0.48 to 2.47, p=0.80).

A systematic review of population-based controlled observational studies by McGettigan *et al* showed a relative risk of 1.09, 95% CI 1.02 to 1.16 for pooled cardiovascular risk[viii]. Different doses of naproxen do not appear to affect its safety on cardiovascular outcomes.

Gastrointestinal effects

The Lancet meta-analysis showed increased risk of upper gastrointestinal bleed associated with naproxen compared to placebo (4.22, 95% CI 2.71 to 6.56, p<0.0001)[ii]. [There was an association with increased incidence of upper gastric bleeds within the first 6 months with naproxen (6.31, 95% CI 3.81 to 10.44).

2. Meloxicam

Cardiovascular effects

The pooled cardiovascular effects of meloxicam by McGettigan *et al* showed a pooled RR 1.20, 95% CI 1.07 to 1.33; p=0.7, I^2=0 against meloxicam's favour[vii]. The data on meloxicam is, however, relatively sparse. The meta-analysis of observational studies showed that of the NSAIDs, meloxicam was associated with the 3rd highest risk, after diclofenac and indomethacin, but was comparable to ibuprofen (RR 1.18, 95% CI 1.11 to 1.25, p<0.0001, I^2=81.90).

Pooled analysis of data from 28 trials[xx] showed a similar risk of thromboembolic events for meloxicam, at either dose (0.2%), compared to piroxicam (0.1%) and naproxen (0.0%), but a lower risk to that observed with diclofenac (0.8%). Limitations in this analysis include the short duration of included RCTs (< 60 days) and the pooling of source data eliminating the effect of randomisation.

Gastrointestinal effects

MELISSA[v] showed an increased incidence of gastrointestinal disorders with diclofenac (18.71%) compared to meloxicam (13.31%), p<0.001; difference of 5.4% favouring meloxicam. There was no difference between groups regarding incidence of perforations, ulcerations, or bleeding (PUBs). Yocum *et al*[xxi] showed increased gastrointestinal adverse event rates for diclofenac (30%) compared with meloxicam (3.75mg and 7.5mg, 21%; 15mg 18%), at 12 weeks treatment; absolute risk reduction of 9% when comparing meloxicam 7,5 mg to diclofenac 100 mg;

increasing to 12% for meloxicam 15 mg compared to diclofenac 100 mg. Attrition rate was similar between all groups.

SELECT[iv] showed a decreased incidence of gastrointestinal adverse events with meloxicam 7.5mg daily compared with piroxicam 20mg daily (10.3% vs 15.4%, $p < 0.001$; actual difference of 5.1% favouring meloxicam).

Pooled analysis of data from 28 meloxicam trials[xx] showed a 0.03% risk of upper gastrointestinal events for meloxicam 7.5 mg compared to diclofenac 100-150 mg, naproxen 1 g and piroxicam 20 mg, $p<0.02$. The risk increased to 0.2% for meloxicam 15 mg compared to piroxicam 20 mg, $p < 0.03$. The study suggests that the risk of serious gastrointestinal complications was generally lower than other NSAIDs but is dose dependant. However, limitations of this analysis included the short duration of included studies (< 60 days) and the poorly defined definition of gastrointestinal events that was heterogenous across studies.

3. Piroxicam

Cardiovascular effects

McGettigan *et al's* meta-analysis of observational studies[vii] for cardiovascular risk showed that piroxicam was not associated with increased risk (RR 1.08, 95% CI 0.91, 1.30, p=0.3, I^2=18.9%), and was comparable to cardiovascular risk associated with naproxen (RR 1.09, 95% CI 1.02 to 1.16, $p <0.0001$, I2 = 70.7%). However, cardiovascular risk rate for piroxicam was not statistically significant and studies were heterogenous.

Gastrointestinal effect

Pooled analysis of data from 28 meloxicam trials[xx] showed that piroxicam compared to placebo, was associated with an increased risk of gastrointestinal complications (RR 1.66; 95% CI 1.14, p=2.44), similar to that of naproxen (RR 1.83; 95% CI 1.25, p=2.68), whilst meloxicam (RR 1.24; 95% CI 0.98, p=1.56) and ibuprofen had a lower risk (RR 1.19; 95% CI 0.93, p=1.54). Limitations of this analysis have been described above. However, study of case-controls[xxii] showed that piroxicam had a higher risk for hospitalization of upper gastrointestinal bleed when compared to non-NSAID use than naproxen (RR 13, 95% CI 7.8 to -20 vs RR 7.3, 95%CI 4.7 to 11; risk difference of 6.65%).

Dermatological effect

The US FDA spontaneous adverse events reporting system found an association of Stevens-Johnson syndrome and toxic epidermal necrolysis with NSAIDs (particularly piroxicam and tenoxicam – relative risk of 34). However, the estimated incidence is low - 1 per 100 000 patients during the 1st 8 weeks of therapy[xxiii, xxiv].

Evidence quality:

Studies of meloxicam in arthritis are relatively scarce. In the trials available, there is a heavy pharmaceutical industry presence. There are two very large meta-analyses for the safety of naproxen. It is expected that towards the end of 2015 the results from the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen) trial will be available, with the aim of comparing cardiovascular safety of celecoxib with naproxen or ibuprofen. [9]

Furthermore, studies for naproxen and piroxicam (older NSAIDs) are limited, of poor methodological quality and mostly observational.

Summary:
The available evidence suggests that ibuprofen, meloxicam, naproxen and piroxicam shows comparable efficacy in terms of analgesia.

The FDA has recently included a black box warning for all NSAIDs with regards to cardiovascular side effects and heart failure. Although naproxen appears to be the safest NSAID in this regard, the community appears to be awaiting the results of the PRECISION trial before making a recommendation for the use of naproxen in susceptible patient populations[xxv]. Piroxicam shows a trend towards lower cardiovascular risk, similar to naproxen; whilst limited data suggests a moderate cardiovascular risk associated with meloxicam comparable to ibuprofen.

Meloxicam appears to have few gastrointestinal effects, while being effective for pain relief at both 7.5 mg and 15 mg, with the caveat that these results are heavily influenced by industry. The safety of meloxicam did not appear to be affected by patient demographics (e.g. age, gender)[iv].

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National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Pain

Adverse effects of NSAIDS

Observational data[1],[2] has pointed to differences in the incidence of cardiovascular adverse events associated with various non-steroidal anti-inflammatory agents (NSAIDs). In particular, there are concerns about the risks associated with diclophenac relative to ibuprofen and naproxen. In a pair-wise comparison, the relative risk ratio for naproxen was lower than for ibuprofen (RRR = 0.92, 99% CI 0.87 to 0.99). Diclophenac versus ibuprofen: 1.13 (99% CI 1.03 to 1.24.)

Table 4. Selected pair-wise comparisons of individual drugs.

Drug Tested	Reference Drug in the Comparison				
	Rofecoxib	Diclofenac	Ibuprofen	Naproxen	Celecoxib
Etoricoxib	1.29 (0.86, 1.93), $n=3$ studies	1.36 (0.89, 2.09), $n=3$ studies	**1.68** (1.14, 2.49), $n=3$ studies	**1.75** (1.16, 2.64), $n=3$ studies	
Etodolac		0.95 (0.78, 1.16), $n=5$ studies	1.04 (0.88, 1.24), $n=7$ studies	1.10 (0.96, 1.26), $n=7$ studies	
Diclofenac	1.0 (0.89, 1.12), $n=18$ studies		**1.13** (1.03, 1.24), $n=27$ studies	**1.22** (1.11, 1.35), $n=25$ studies	**1.15** (1.02, 1.30), $n=19$ studies
Naproxen			**0.92** (0.87, 0.99), $n=32$ studies	—	0.96 (0.81, 1.13), $n=23$ studies
Meloxicam				**1.11** (1.0, 1.23), $n=6$ studies	
Indomethacin				**1.23** (1.10, 1.39), $n=15$ studies	

Values are pooled RRRs and 99% CIs. Bold indicates significant difference at $p<0.0033$ (the Bonferroni-adjusted threshold p-value; $n=15$ comparisons; alpha = 0.05).
doi:10.1371/journal.pmed.1001098.t004

Table 5. Results of sensitivity analyses on selected pair-wise comparisons.

Comparison	RRR	RR_{CD}	P_{C1}	P_{C0}	RRR_{adj}	Percent Bias
Etoricoxib versus naproxen	1.75	11.00	0.25	0.10	1.00	75.00
Etoricoxib versus ibuprofen	1.68	9.40	0.25	0.10	1.00	68.48
Indomethacin versus naproxen	1.23	2.80	0.25	0.10	1.00	22.88
Diclofenac versus naproxen	1.22	2.70	0.25	0.10	1.00	21.79
Diclofenac versus celecoxib	1.15	2.10	0.25	0.10	1.00	14.86
Diclofenac versus ibuprofen	1.13	1.95	0.25	0.10	1.00	13.01
Naproxen versus ibuprofen	0.92	0.50	0.25	0.10	1.00	−7.89

RR_{CD} is the association between confounder and disease outcome. P_{C1} is the prevalence of confounder in the exposed. P_{C0} is the prevalence of confounder in the unexposed. RRR_{adj} is the "true", or fully adjusted, RRR. Percent bias is the percentage change to the RRR that would be introduced by a hypothetical confounding variable under the assumptions in the table.
doi:10.1371/journal.pmed.1001098.t005

While these effects are clearly discernible, the problems of biases associated with studies of this nature are well known and always difficult to quantify.

[1] McGettigan P, Henry D (2011) Cardiovascular Risk with Non-Steroidal Anti-Inflammatory Drugs: Systematic Review of Population-Based Controlled Observational Studies. PLoS Med 8(9): e1001098. doi:10.1371/journal.pmed.1001098

[2] McGettigan P, Henry D (2013) Use of nonsteroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. PLoS Med 10: e1001388. doi:10.1371/journal.pmed.1001388

An individual patient meta-analysis[3] assists with this by pooling larger numbers of patients from RCTs, but still suffers from the external validity issues related to careful patient selection. The results of this are best seen in this figure from the report:

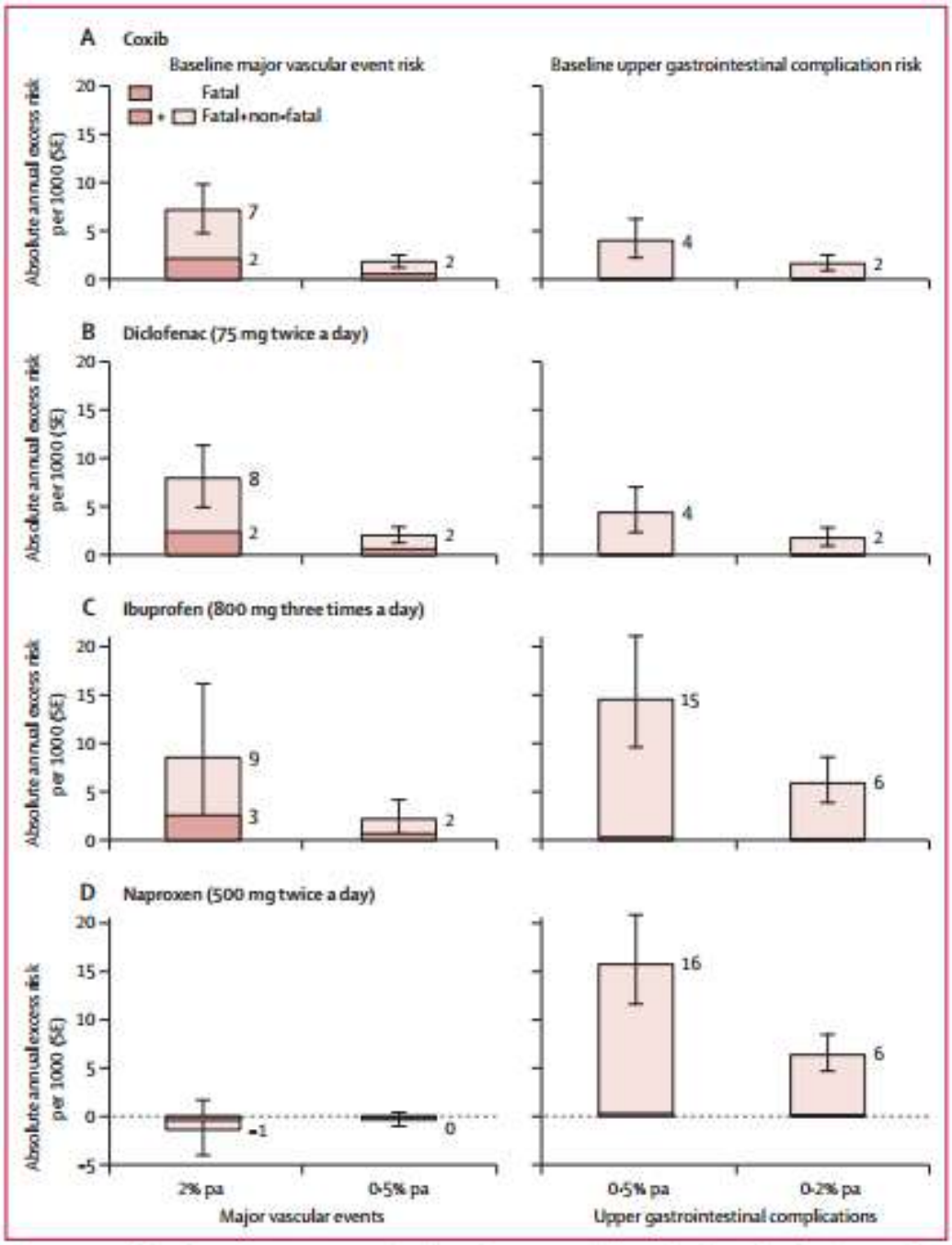

Figure 5: **Annual absolute effects per 1000 of coxibs and tNSAIDs at different baseline risks of major vascular events and upper gastrointestinal complications**

For each category of drug (coxib, diclofenac, ibuprofen, and naproxen), the predicted annual absolute risks of major vascular events (±1 SE) are shown (left) for patients with predicted risk of 2·0% or 0·5% per annum of a major vascular event. For comparison, predicted annual absolute risks of upper gastrointestinal complications (±1 SE) are shown for patients with predicted risks of 0·5% or 0·2% per annum (right). Absolute annual risks for

[3] Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-infl ammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet2013; 382: 769–79.

Although this figure illustrates the balance between CVS and vascular events, it is still not clear what the actual patient impact of a vascular event versus a GIT complication would be; short of translating this into QALYs, this remains difficult to balance.

A further issue concerns duration of therapy; although not formally addressed, it is likely that the CVS effects of short term use are much lower than pertaining to long duration use in high risk patients (e.g. those with rheumatoid arthritis or osteoarthritis.)

Conclusion: It is clear that there are measurable differences in side-effect profiles of NSIADs; whether these are sufficiently large to justify formulary changes is less certain.

National Essential Medicine List Medication Review Process
Adult Hospital level
Component: Musculoskeletal disorders

Date: 26 November 2015

Medication: Naproxen, meloxicam and piroxicam in arthritis

Introduction:
Inflammatory arthritis results in structural damage to joints, which results in persistent pain in these patients. The management of pain is an important aspect of the management of arthritis. Comorbidities are highly prevalent in this group of patients, so considering the safety of various analgesics with this in mind is important.

Search strategy and article selection:

A search of the Cochrane database identified 1 relevant review (updated 2012). The review assessed the efficacy and safety of pharmacological pain treatment in inflammatory arthritis with gastrointestinal or liver comorbidities, or both. [i]

Meloxicam in arthritis:

1. PubMed: ("Arthritis"[Mesh] AND "meloxicam"[Supplementary Concept]) AND "Treatment Outcome"[Mesh] AND ((Clinical Trial[ptyp] OR Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp]) AND "humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms])
   Results: 17. Two studies rejected: 1 did not match the drug under review, 1 did not match the disease state under review.

2. Google scholar: the following terms were used: ‘meloxicam’, ‘cardiovascular safety’, ‘gastrointestinal safety’ and ‘meta analysis’.

3. Bandolier website: the following term was used “meloxicam”.
   Results: 1 – “Nabumetone & meloxicam gastrointestinal safety”; that summarized the meta-analysis by Schoenfeld et al (1999).

Naproxen in arthritis:

1. PubMed: "Arthritis"[Mesh] AND "Naproxen"[Mesh] AND ("safety"[MeSH Terms] OR "safety"[All Fields]) AND ((Controlled Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Multicenter Study[ptyp] OR Observational Study[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms])
   Results: 85. Studies were excluded because: they did not match the drug under review; they compared treatment combinations not under review. Studies that were only available in abstract form were excluded.

2. An article identified from a report on the PRECISION trial identified one further meta-analysis from Lancet that was considered eligible for inclusion in this review[ii]. The

primary vascular outcome was major vascular events (non-fatal myocardial infarctions, non-fatal stroke, or death from a vascular cause). Other vascular outcomes included major coronary events (non-fatal myocardial infarction or death from coronary disease), stroke, and hospitalization for heart failure. The primary gastrointestinal outcome was upper gastrointestinal complications (upper gastrointestinal perforation, obstruction or bleed).

3. Bandolier website: the following term was used "naproxen".
   Results: 2 – "The Oxford League table of analgesic efficacy"; "NSAIDs and adverse effects" and" Myocardial infarction: aspirin, NSAIDs, and COXIBs".

Piroxicam in arthritis:

1. PubMed: ("Arthritis"[Mesh] AND "piroxicam"[Supplementary Concept]) AND "Treatment Outcome"[Mesh] AND ((Clinical Trial[ptyp] OR Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp]) AND "humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms])
   Results: 18. Studies were excluded as they did not match the medicine or the formulation under review; the comparator medicine was not standard of care; study determined non-pharmacological outcomes or studies compared duration therapy.

2. Google scholar: the following terms were used: 'piroxicam', 'meta-analysis' and 'safety'.

3. Bandolier website: the following term was used "piroxicam".
   Results: 2 – "The Oxford League table of analgesic efficacy"; "NSAIDs and adverse effects".

Comparable doses

Comparative doses were derived from the WHO defined daily doses index[iii]:

Medicine	**WHO ATC DDD**
Meloxicam	15 mg
Naproxen	500 mg
Piroxicam	20 mg
Ibuprofen	1200 mg
Diclofenac	100 mg

Evidence synthesis:

The SELECT[iv] and MELISSA[v] trials, and the study by Yocum *et al*[vi] , were sponsored by Boehringer Ingelheim GmbH, manufacturers of Mobic® (meloxicam). There was no mention of the method of randomization in these trials. These trials indicated adverse events using the Adverse Reaction Terminology List/Coding Thesaurus Of the World Health Organization, although they are presented in different formats in each study. The MELISSA trial had an increased attrition rate with the meloxicam group due to lack of efficacy. The McGettigan study is a systematic review only[vii]. The manufacturer-funded meta-analyses [viii,ix] suggesting a lower risk of gastro-intestinal complications with meloxicam, were of low-quality; as details of the quality and individual results of the included RCTs were not reported.

Effectiveness

1. Naproxen

Compared with oral acetaminophen naproxen had significantly better effect sizes for pain at 3 months (0.20, 95% CI 0.03 to 0.37), in the treatment for osteoarthritis of the knee. However when compared to celecoxib, there was no difference in effect size (0.05, 95% CI -0.08 to 0.17) The Oxford League table of analgesic efficacy[x] shows a NNT of 2.5 for ibuprofen 400 mg compared to a NNT of 2.7 for naproxen 400-550 mg and a NNT of 3.4 for naproxen 200/220 mg.

2. Meloxicam

To date, no RCTs of meloxicam have been included in Cochrane reviews. The double-blinded RCTs that were identified comparing melxicam to other NSAIDs were generally comparable in terms of efficacy, except in 2 RCTs [v, vi] (where attrition was greater in the meloxicam group due to lack of efficacy).

RCT	Study design	Study comparators	Effect	Comments
Hawkey et al (1998) [v] (MELISSA TRIAL)	Double-blnd, randomised, RCT; n=9323, over 28 days.	Meloxicam 7.5mg (n=4635) vs diclofenac 100mg slow release (n=4688) in osteoarthritic patients.	**Efficacy:** - Diclofenac more efficacious than meloxicam (assessed by VAS scale) statistically significant but not clinically significant (differences were small & did not reach pre-determined levels of clinical significance) -Significantly more patients discontinued meloxicam because of lack of efficacy (80/4635 vs 49/4688; p < 0.01). **Safety:** -Fewer GI adverse events with meloxicam(13%) vs. diclofenac (19%; p < 0.001).; with less dyspepsia (p < 0.001), nausea & vomiting (p < 0.05), abdominal pain (p < 0.001) & diarrhoea (p < 0.001). -Patient days of hospitalization was 5 vs 121 for meloxicam vs diclofenac, respectively. 254 patients receiving meloxicam (5.48%) vs 373 (7.96%) on diclofenac (p < 0.001) withdrew from the study due to AEs – GI AEs: 3.02% vs 6.14%; p < 0.001, respectively.	• Attrition was greater in the meloxicam group due to lack of efficacy. • Comparative doses considered to be 7.5 mg vs 100 mg (meloxicam vs diclofenac) contrary to WHO DDD – see above
Dequeker et al (1998) [iv] (SELECT TRIAL)	Multi-centred, double blind, double-dummy, randomized, parallel gp trial, over 28 days. Intention to treat analysis.	Meloxicam 7.5 mg (n=4320) vs piroxicam 20 mg (n=4336) in osteoarthritic patients.	**Efficacy:** Comparable efficacy assessed on 100 mm VAS: - mean treatment difference (meloxicam vs. piroxicam) at the end of trial was 1.97 mm (95% CI 1.01 to 2.94), NS **Safety:** Adverse events lower in the meloxicam vs. piroxicam group (22.5% vs. 27.9%; p < 0.001), Piroxicam vs meloxicam: - GIT adverse events: 15.4% vs 10.3%; p < 0.001 - nausea/vomiting: 3.4% vs 2.5%: p < 0.05 - abdominal pain: 3.6% vs 2.1%; p <	• 79% of patients in both treatment groups were pre-treated with NSAIDs. • 1.7% in meloxicam vs. 1.6% in piroxicam group withdrew due to lack of efficacy. • Comparative doses considered to be 7.5 mg vs 20 mg (meloxicam vs piroxicam) contrary to WHO DDD – see above.

			0.001 - 16 vs 7 perforations, ulcerations or bleeding (PUBs) (RR: 1.4). - 4 vs 0 complicated PUBs (RR:1.9).	
Hosie (1996)[xi]	Multi-centred, double blind, double-dummy, randomized trial, over 6 months. Intent to treat analysis.	Meloxicam 7.5 mg (n=169) vs diclofenac 100 mg slow release (n=167) in osteoarthritic patients	**Efficacy:** Meloxicam showed a greater reduction of overall pain (mm on VAS -28.1 ± 29.4 vs -30.9 ± 29.1), pain on movement (mm on VAS -29.5 ± 31.1 vs 32.8 ± 28.5), greater global efficacy (mm on VAS 35.9±29.1 vs 32.1±27.4) and less duration of stiffness following inactivity (minutes --43± 167 vs -33±62), all NS. NS QoL scores were comparable to diclofenac (-2.3±3.7 vs -2.2±4.2) **Safety:** -Adverse effects reported in 101/169 (59.8%) vs 101/167 (60.5%) of meloxicam vs diclofenac groups, respectively. - More SAEsin diclofenac vs melociam group (22% vs 15.8%) -More patients withdrew due to adverse effects in the diclofenac (22%) vs meloxicam (12.4%) groups.	• 66 patients withdrew due to AEs (n=21, meloxicam; n=31; diclofenac) or lack of efficacy (7 in each group). • Comparative doses considered to be 7.5 mg vs 100 mg (meloxicam vs diclofenac) contrary to WHO DDD – see above. • Median dose of concomitant paracetmol was lower in meloxicam vs diclofenac group (185vs 245 mg/day, p-0.0123).
Hosie (1997)[xii] ACCESSED ABSTRACT ONLY	Randomised, double-blind, parallel-group trial, over 6 months.	Meloxicam 15 mg (n=306) vs piroxicam 20 mg (n=149) for proven osteoarthritis of the knee or hip (details of diagnosis not reported in the abstract).	**Efficacy:** - Comparable effectiveness between meloxicam and piroxicam for overall pain, pain on movement, joint stiffness, global efficacy and quality of life (effect sizes not provided in the abstract). **Safety:** -Incidence and type of AEs reported were similar in both study groups -More GIT AEs reported in 24.2% of meloxicam-treated patients vs.30.2% of piroxicam-treated patients.	Details of patients withdrawing from the study not provided for in the publication abstract.
Valat (2001)[xiii]	Multi-centred, double blind, double-dummy, randomized, parallel gp trial, over 14 days. Intention to treat analysis.	Meloxicam 7.5 mg (n=169) vs diclofenac 100 mg slow release (n=167) for osteoarthritis in the lumbar spine.	**Efficacy:** Statistically significant reduction in pain on motion of lumbar spine (assessed on 100 mm VAS) with meloxicam vs. diclofenac after 3 days (mean(SD)): 15 (18) mm vs 17 (21 mm); p <0.05. **Safety:** - GIT adverse events greater with diclofenac vs meloxicam (17.8% vs 12.8%), NS. -Global tolerability was significantly better than diclofenac, assessed by patients (p=0.049) and investigators (p=0.0072).	• 5 patients withdrew due to AEs in meloxicam group vs. 10 in diclofenac group. No withdrawals due to lack of efficacy. • Comparative doses considered to be 7.5 mg vs 100 mg (meloxicam vs diclofenac) contrary to WHO DDD – see above.
Linden (1996)[xiv]	Multi-centred, randomised, double-blind, parallel group trial, over 42 days. Intention to treat analysis.	Meloxicam 30 mg (n=29) evaluated separately and evaluated descriptively but not reported in the publication; and meloxicam 15 mg (n=129) vs piroxicam 20 mg (n=127) in an ITT, for osteoarthritis of the hip.	**Efficacy:** - No significant difference in pain at movement between meloxicam vs piroxicam at 42 days. **Safety:** - More GIT AEs reported with piroxicam vs meloxicam (22.8% vs 20.9%). -Global tolerance (100 mm VAS) was similar in both treatment groups.	• 12 patients withdrew due to AEs in meloxicam group vs. 10 in piroxicam group. Withdrawl due to lack of efficacy was not reported.
Goei(1997)[xv]	Multi-centred, randomised, double-blind trial, over 6 weeks. Intention to treat analysis.	Meloxicam 15 mg (n=128) vs diclofenac 100 mg slow release (n=130) for	**Efficacy:** - Trend seen for efficaciousness, favouring meloxicam (pain on movement, global efficacy and paracetamol consumption), NS.	• 21 patients withdrew due to AEs in meloxicam group vs. 24 in diclofenac group.

		osteoarthritis of the knee. Intention to treat analysis.	**Safety:** - More AEs reported in diclofenac vs. meloxicam groups - 44 (34.4%) vs 47 (36.2%). - Most frequent AEs were GIT: 34(26.2%) vs 21 (16.4%) in the diclofenac vs meloxicam groups, respectively. - 1 patient in the diclofenac group was hospitalized due to a gastric ulcer, at 22 days. - Both drugs were well tolerated when assessed by the patients on a visual analog scale (VAS).	Withdrawl due to lack of efficacy was not reported. - 5/128 patients in meloxicam group vs 3/130 in diclofenac group withdrew, due to lack of efficacy. - Cardiovascular disorders reported were 3% in the meloxicam group vs 1% in the diclofenac group.

The MELISSA trial showed no difference between meloxicam 15 mg and diclofenac 100 mg for pain on active movement (actual difference between treatments mean 2.29, 95% CI 1.38 to 3.20) and pain at rest (1.54, 95% CI0.59 to 2.49)[vi], as assessed with 100 mm visual analogue scale (VAS). There was greater attrition in the meloxicam group due to lack of efficacy – dropout rate was 80/4635 vs. 49/4688; $p < 0.01$ for meloxicam *vs*. diclofenac, respectively (actual difference 0.68%; odds ratio 1.66, 1.16 to 2.38, $p < 0.01$).

3. Piroxicam

A RCT[xvi] showed no difference between diclofenac 100 mg/day (n=32) and sustained-release etodolac 400 mg/day (n=32) for treating osteoarthritis of the knee determined by 100 mm visual analogue scale; whilst another 8-week, multi-centered, double-blind RCT[xvii] showed comparable efficacy between piroxicam and standard formulation etodolac for treating osteoarthritis of the knee and hip with no statistically significant differences in any efficacy assessment at any observation. More adverse events were reported with etodolac vs. piroxicam (30% vs. 46%; $p < 0.01$); whilst the difference in gastrointestinal adverse events (20% vs. 29%) was not significant. Decrease in haemoglobin occurred in 22% of patients, but with no significant difference between the 2 groups.

A meta-analysis[xviii] of RCTs comparing piroxicam to other NSAIDs showed a trend of comparable global efficacy to other NSAIDs (OR 1.06; 95% CI 0.96 to 1.18). Similar results were shown when short-term trials (≤ 4 weeks) and long-term trials were analysed; OR 1.18; 95% CI 0.96 to 1.34 and OR 1.07; 95% CI 0.97 to 1.19, respectively. However, for mobility or stiffness, piroxicam was reported to be significantly more efficacious than indomethacin ($p = 0.04$, but no effect size provided) whilst comparable to other NSAIDs (effect size 0.02; 95% CI -0.14 to 0.18, p=0.82). Piroxicam was also shown to be significantly better in terms of articular swelling vs. other NSAIDs (effect size 0.26; 95% CI 0.07 to 0.44; p=0.008). However, a number of limitations of this meta-analysis cautions of the reliability of the results. Search terms were not provided; details of the RCTs were not described; RCTs with all indications for NSAIDs were included; results of quality assessment of RCTs using Jadad score were not provided and the pooled results of global efficacy and safety was from clinically heterogeneous RCTs (differs in population and outcomes).

Safety considerations

1. Naproxen

Cardiovascular effects

Trelle *et al* found no association between naproxen and myocardial infarction compared with placebo (rate ratio 0.82, 95% CI 0.37 to 1.67)[xix]. However, in their secondary outcomes of stroke, cardiovascular death, and death from any cause, naproxen was associated with increased incidence of stroke (1.76, 95% CI 0.91 to 3.33). Cardiovascular death (0.98, 95% CI 0.41 to 2.37) and death from any cause (1.23, 95% CI 0.71 to 2.12) was not associated with naproxen use.

In the Lancet meta-analysis, naproxen was not associated with significant risk of major vascular events (rate ratio 0.93, 95% CI 0.69 to 1.27; p=0.66)[ii]. There was no increase in major coronary events (0.84, 95% CI 0.52 to 1.35, p=0.48). There was no evidence for increased risk of stroke (0.97, 95% CI 0.59 to 1.60, p=0.90). There was increased risk of hospitalization due to heart failure with naproxen (1.87, 95% CI 1.10 to 3.16, p=0.0197). There was no risk of vascular death associated with naproxen (1.08, 95% CI 0.48 to 2.47, p=0.80).

A systematic review of population-based controlled observational studies by McGettigan *et al* showed a relative risk of 1.09, 95% CI 1.02 to 1.16 for pooled cardiovascular risk[viii]. Different doses of naproxen do not appear to affect its safety on cardiovascular outcomes.

Gastrointestinal effects

The Lancet meta-analysis showed increased risk of upper gastrointestinal bleed associated with naproxen compared to placebo (4.22, 95% CI 2.71 to 6.56, p<0.0001)[ii]. [There was an association with increased incidence of upper gastric bleeds within the first 6 months with naproxen (6.31, 95% CI 3.81 to 10.44).

2. Meloxicam

Cardiovascular effects

The pooled cardiovascular effects of meloxicam by McGettigan *et al* showed a pooled RR 1.20, 95% CI 1.07 to 1.33; p=0.7, I^2=0 against meloxicam's favour[vii]. The data on meloxicam is, however, relatively sparse. The meta-analysis of observational studies showed that of the NSAIDs, meloxicam was associated with the 3rd highest risk, after diclofenac and indomethacin, but was comparable to ibuprofen (RR 1.18, 95% CI 1.11 to 1.25, p<0.0001, I^2=81.90).

Pooled analysis of data from 28 trials[xx] showed a similar risk of thromboembolic events for meloxicam, at either dose (0.2%), compared to piroxicam (0.1%) and naproxen (0.0%), but a lower risk to that observed with diclofenac (0.8%). Limitations in this analysis include the short duration of included RCTs (< 60 days) and the pooling of source data eliminating the effect of randomisation.

Gastrointestinal effects

MELISSA[v] showed an increased incidence of gastrointestinal disorders with diclofenac (18.71%) compared to meloxicam (13.31%), p<0.001; difference of 5.4% favouring meloxicam. There was no difference between groups regarding incidence of perforations, ulcerations, or bleeding (PUBs). Yocum *et al*[xxi] showed increased gastrointestinal adverse event rates for diclofenac (30%) compared with meloxicam (3.75mg and 7.5mg, 21%; 15mg 18%), at 12 weeks treatment; absolute risk reduction of 9% when comparing meloxicam 7,5 mg to diclofenac 100 mg;

increasing to 12% for meloxicam 15 mg compared to diclofenac 100 mg. Attrition rate was similar between all groups.

SELECT[iv] showed a decreased incidence of gastrointestinal adverse events with meloxicam 7.5mg daily compared with piroxicam 20mg daily (10.3% vs 15.4%, $p < 0.001$; actual difference of 5.1% favouring meloxicam).

Pooled analysis of data from 28 meloxicam trials[xx] showed a 0.03% risk of upper gastrointestinal events for meloxicam 7.5 mg compared to diclofenac 100-150 mg, naproxen 1 g and piroxicam 20 mg, $p<0.02$. The risk increased to 0.2% for meloxicam 15 mg compared to piroxicam 20 mg, $p < 0.03$. The study suggests that the risk of serious gastrointestinal complications was generally lower than other NSAIDs but is dose dependant. However, limitations of this analysis included the short duration of included studies (< 60 days) and the poorly defined definition of gastrointestinal events that was heterogenous across studies.

3. Piroxicam

Cardiovascular effects

McGettigan *et al's* meta-analysis of observational studies[vii] for cardiovascular risk showed that piroxicam was not associated with increased risk (RR 1.08, 95% CI 0.91, 1.30, p=0.3, I^2=18.9%), and was comparable to cardiovascular risk associated with naproxen (RR 1.09, 95% CI 1.02 to 1.16, $p <0.0001$, I2 = 70.7%). However, cardiovascular risk rate for piroxicam was not statistically significant and studies were heterogenous.

Gastrointestinal effect

Pooled analysis of data from 28 meloxicam trials[xx] showed that piroxicam compared to placebo, was associated with an increased risk of gastrointestinal complications (RR 1.66; 95% CI 1.14, p=2.44), similar to that of naproxen (RR 1.83; 95% CI 1.25, p=2.68), whilst meloxicam (RR 1.24; 95% CI 0.98, p=1.56) and ibuprofen had a lower risk (RR 1.19; 95% CI 0.93, p=1.54). Limitations of this analysis have been described above. However, study of case-controls[xxii] showed that piroxicam had a higher risk for hospitalization of upper gastrointestinal bleed when compared to non-NSAID use than naproxen (RR 13, 95% CI 7.8 to -20 vs RR 7.3, 95%CI 4.7 to 11; risk difference of 6.65%).

Dermatological effect

The US FDA spontaneous adverse events reporting system found an association of Stevens-Johnson syndrome and toxic epidermal necrolysis with NSAIDs (particularly piroxicam and tenoxicam – relative risk of 34). However, the estimated incidence is low - 1 per 100 000 patients during the 1st 8 weeks of therapy[xxiii, xxiv].

Evidence quality:

Studies of meloxicam in arthritis are relatively scarce. In the trials available, there is a heavy pharmaceutical industry presence. There are two very large meta-analyses for the safety of naproxen. It is expected that towards the end of 2015 the results from the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen) trial will be available, with the aim of comparing cardiovascular safety of celecoxib with naproxen or ibuprofen. [9]

Furthermore, studies for naproxen and piroxicam (older NSAIDs) are limited, of poor methodological quality and mostly observational.

Summary:
The available evidence suggests that ibuprofen, meloxicam, naproxen and piroxicam shows comparable efficacy in terms of analgesia.

The FDA has recently included a black box warning for all NSAIDs with regards to cardiovascular side effects and heart failure. Although naproxen appears to be the safest NSAID in this regard, the community appears to be awaiting the results of the PRECISION trial before making a recommendation for the use of naproxen in susceptible patient populations[xxv]. Piroxicam shows a trend towards lower cardiovascular risk, similar to naproxen; whilst limited data suggests a moderate cardiovascular risk associated with meloxicam comparable to ibuprofen.

Meloxicam appears to have few gastrointestinal effects, while being effective for pain relief at both 7.5 mg and 15 mg, with the caveat that these results are heavily influenced by industry. The safety of meloxicam did not appear to be affected by patient demographics (e.g. age, gender)[iv].

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