Medicines Adverse Reactions Committee

Meeting date	**14 March 2019**		Agenda item		3.2.2
Title	**NSAIDs and cardiovascular risk: an update**				
Submitted by	Medsafe Pharmacovigilance Team		Paper type		For advice
Active constituent	**Medicine**	**Form**	**Strength**	**Class**	**Sponsor**
Celecoxib	**Celecoxib Pfizer**	**capsule**	**100 mg** **200 mg**	**Rx** **Rx**	Pfizer
	Celostea	capsule	100 mg 200 mg	Rx Rx	Mylan
Diclofenac potassium	Voltaren Rapid	capsule or tablet	12.5 mg	P	GSK
	Voltaren Rapid	capsule or tablet	25 mg	R	GSK
	Diclofenac (Dr Reddy's)	tablet	25 mg	R	Dr Reddy's
Diclofenac sodium	**Voltaren**	**injection**	**75mg/3ml**	**Rx**	Novartis
	Voltaren	**suppository**	**12.5 mg** **25 mg** **50 mg** **100 mg**	**Rx** **Rx** **Rx** **Rx**	Novartis
	Voltaren D	**tablet D**	**50 mg**	**Rx**	Novartis
	Diclofenac Sandoz	**tablet EC**	**25 mg** **50 mg**	**Rx** **Rx**	Novartis
	Voltaren	tablet EC	50 mg	Rx	Novartis
	Apo-Diclo SR	**tablet MR**	**75 mg** **100 mg**	**Rx** **Rx**	Apotex
	Voltaren SR	tablet MR	75 mg 100 mg	Rx Rx	Novartis
Etoricoxib	Arcoxia	tablet	30 mg 60 mg 90 mg 120 mg	Rx Rx Rx Rx	Merck Sharp & Dohme
Ibuprofen	**Fenpaed**	**oral suspension**	**100 mg/5ml**	**P, Rx***	AFT
	Multiple products	oral liquid	100 mg/5ml	P	
	Fenpaed Double Strength	oral liquid	200 mg/5ml	P	AFT
	Ibuprofen Relieve	**tablet**	**200 mg**	**Rx**	Mylan
	Ibugesic	tablet	200 mg	Rx	REX Medical
	Multiple products	capsule or tablet	200 mg	G, P*	
	Brufen	tablet	400 mg 600 mg	Rx Rx	Mylan
	Brufen SR	**tablet MR**	**800 mg**	**Rx**	Mylan

	Multiple combination products containing ibuprofen plus paracetamol and/or phenylephrine also available (General Sale or Pharmacy Only medicines)				
Ketoprofen	**Oruvail**	**capsule MR**	**200 mg**	**Rx**	Sanofi-Aventis
Mefenamic acid	Ponstan	capsule	§ 250 mg	P, Rx*	Pfizer
Meloxicam	Arrow-Meloxicam	tablet	7.5 mg	Rx	Teva Pharma
	Melorex	tablet	7.5 mg 15 mg	Rx Rx	REX Medical
	Mobic	tablet	7.5 mg	Rx	Boeringer Ingelheim
Naproxen	**Noflam**	**tablet**	**250 mg** **500 mg**	**Rx** **Rx**	Mylan
	Naprosyn SR	**tablet MR**	**750 mg** **1000 mg**	**Rx** **Rx**	Clinect
Naproxen sodium	Naprogesic	tablet	275 mg	P	Bayer
	Sonaflam	tablet	275 mg	P	Multichem
Sulindac	**Aclin**	**tablet**	**100 mg** **200 mg**	**Rx** **Rx**	Mylan
Tenoxicam	**Tilcotil**	**tablet**	**20 mg**	**Rx**	Mylan
*D dispersible; EC enteric coated; G General Sale; MR modified release; P Pharmacy Only; R Restricted Medicine; Rx Prescription Medicine; * classification depends on pack size; § part subsidy*					

Funding	Funded medicines are highlighted in bold above.
Previous MARC meetings	NSAID cardiovascular risk has been discussed previously at the following meetings: – 173rd Meeting – 8 March 2018 [Celecoxib and cardiovascular risk] – 161st Meeting – 12 March 2015 [Ibuprofen and cardiovascular disorders] – 154th Meeting – 13 June 2013 [Diclofenac and cardiovascular risk] – 132nd Meeting – 13th December 2007 [Non-specific NSAIDs and cardiovascular adverse effects, including congestive heart failure – scheduled 12 monthly review]
Prescriber Update	– NSAIDs and Heart Disease (December 2017) – Ibuprofen and Cardiovascular Risk (September 2015) – NSAIDs and Risk of Cardiovascular Events (September 2013) – Non-selective NSAIDs – Cardiovascular, Skin and Gastrointestinal Risks (June 2008)
Usage data	See section 2.2

Advice sought	**The Committee is asked to advise whether:** – The contraindications and warnings in the New Zealand data sheets for NSAIDs adequately reflect the current evidence on their cardiovascular risk. – If not, what changes to the data sheets does the committee recommend? – Further communication (other than MARC's Remarks) on the cardiovascular risks of NSAIDs is needed.

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1.0 PURPOSE

At the 173rd MARC meeting on 8 March 2018, Medsafe sought advice about a Changed Medicine Notification (CMN) from Pfizer regarding the datasheet for Celecoxib Pfizer (celecoxib) 100 mg and 200 mg capsules. The CMN proposed to relocate the contraindication for patients with significant established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease to the precaution section of the datasheet. Pfizer had submitted the results of the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (PRECISION) Study [1] in support of the proposed change. Medsafe asked the Committee to consider whether the proposed change is appropriate and, if approved, should similar changes be made to the data sheets for all non-aspirin NSAIDs.

The Committee was not satisfied that the PRECISION study data supported the proposed down-grading of the contraindication to a precaution in patients with significant cardiovascular disease. The Committee also expressed concern that there is a high risk of worsening heart failure with NSAIDs.

The Committee requested a review of the risk of adverse cardiovascular events with NSAIDs following the recent publication of a number of studies on this topic. Medsafe has previously presented papers to the MARC on the cardiovascular risk associated with specific NSAIDs in June 2013 (diclofenac) and March 2015 (ibuprofen). These papers are provided as Annex 1 and Annex 2, respectively.

The purpose of this paper is to examine the medical literature on the cardiovascular risk of NSAIDs that has been published since the previous MARC reviews.

2.0 BACKGROUND

2.1 Selective vs. non-selective NSAIDS

NSAIDs exhibit their anti-inflammatory effect through inhibition of cyclo-oxygenase (COX), the rate-limiting enzyme in prostaglandin synthesis. There are at least two major isoforms of the COX enzyme: COX-1 and COX-2. Both isoforms catalyse the conversion of arachidonic acid to intermediate prostaglandins (prostaglandin G_2, then prostaglandin H_2). Tissue-specific isomerases convert prostaglandin H_2 to various prostanoids, including prostaglandins I_2 (prostacyclin), D_2, E_2, $F_{2\alpha}$ and thromboxane A_2. (Figure 1)

COX-1 is expressed constitutively in most tissues, e.g. myocardium, platelets, parietal cells, and kidney cells, and regulates normal cellular processes such as gastric cytoprotection, platelet aggregation, vascular homeostasis, and kidney function. COX-2 is a highly regulated enzyme that is normally undetectable in most tissues, but is expressed in response to inflammation. By blocking COX enzymes, NSAIDs inhibit to varying degrees the synthesis, and therefore the effects, of prostaglandins, prostacyclin, and thromboxane A_2 (Figure 1).

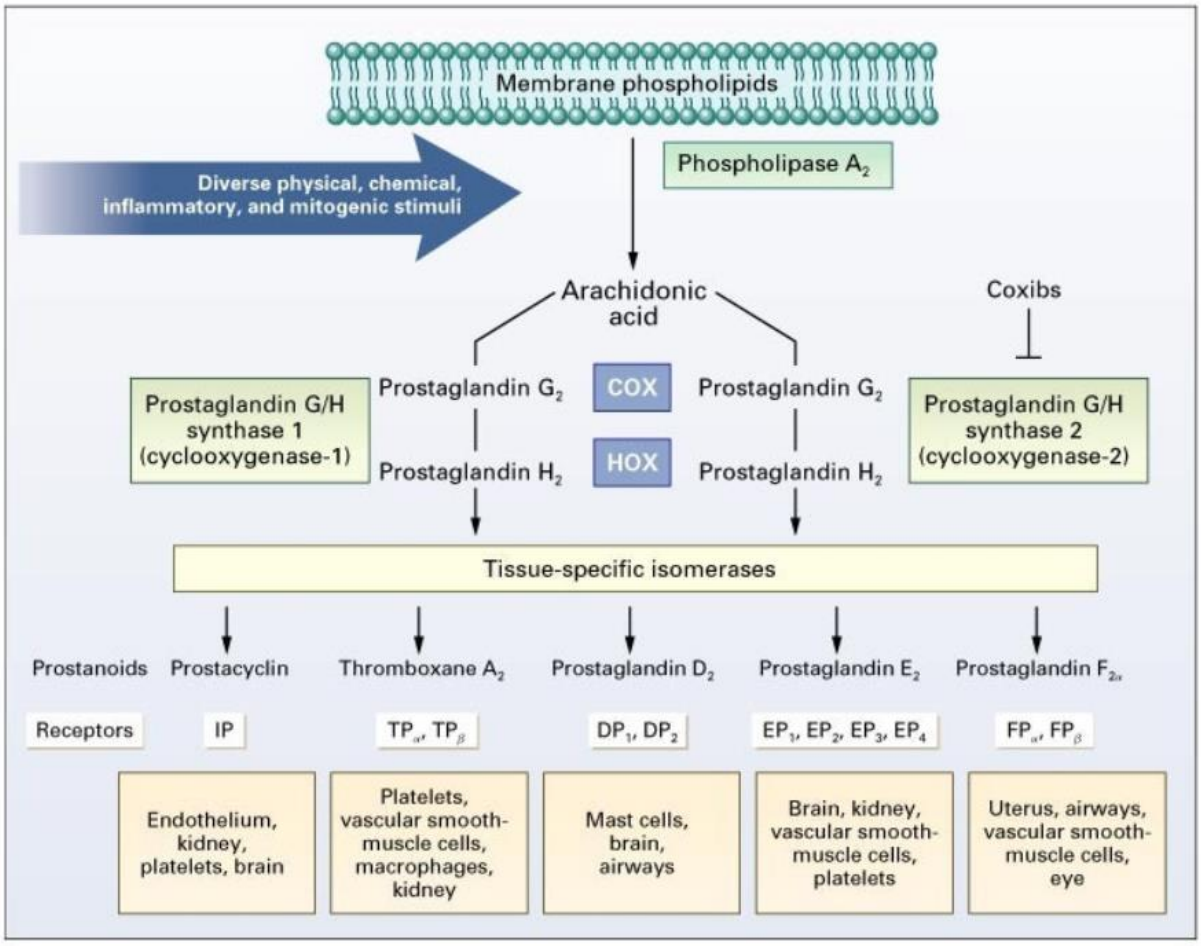


Figure 1. Production and actions of prostaglandins and thromboxane [2]
Arachidonic acid, a 20-carbon fatty acid containing four double bonds, is liberated from the sn2 position in membrane phospholipids by phospholipase A_2, which is activated by diverse stimuli. Arachidonic acid is converted by cytosolic prostaglandin G/H synthases, which have both cyclooxygenase (COX) and hydroperoxidase (HOX) activity, to the unstable intermediate prostaglandin H_2. The synthases are colloquially termed cyclooxygenases and exist in two forms, cyclooxygenase-1 and cyclooxygenase-2. Coxibs selectively inhibit cyclooxygenase-2. Prostaglandin H_2 is converted by tissue-specific isomerases to multiple prostanoids. These bioactive lipids activate specific cell-membrane receptors of the superfamily of G-protein–coupled receptors. Some of the tissues in which individual prostanoids exert prominent effects are indicated. IP denotes prostacyclin receptor, TP thromboxane receptor, DP prostaglandin D_2 receptor, EP prostaglandin E_2 receptor, and FP prostaglandin $F_{2\alpha}$ receptor.

The clinical effects of NSAIDs depend largely on their selectivity for COX-1 and COX-2, which is relative rather than absolute. COX selectivity can be represented on a continuum (Figure 2). Among the COX-2 inhibitors, lumaricoxib has the highest COX-2 selectivity, followed in order by rofecoxib, etoricoxib, valdecoxib, parecoxib, and celecoxib. COX selectivity also varies among the traditional NSAIDs: for example, indomethacin and naproxen are relatively COX-1 selective, while diclofenac and meloxicam are relatively COX-2 selective. Of note, the COX-2 inhibitor celecoxib and the traditional NSAID diclofenac have a similar degree of COX-2 selectivity (Figure 2).

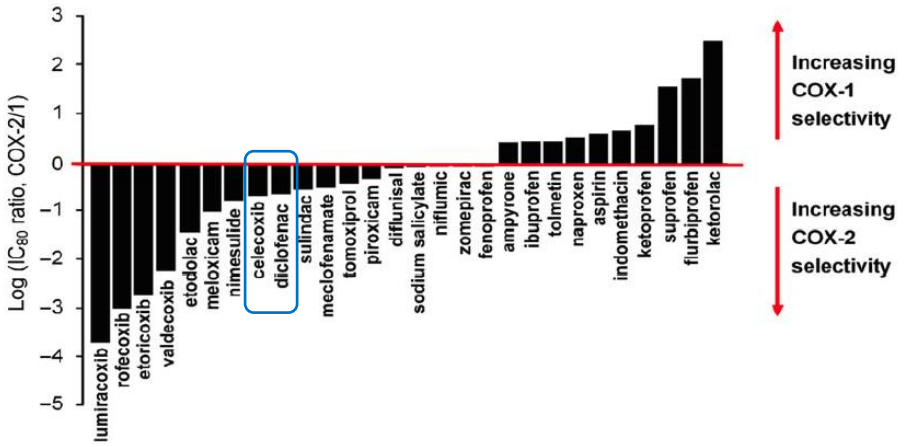


Figure 2. Relative COX selectivity of NSAIDs displayed by the concentration of the drugs (IC80)[1] required to inhibit COX-1 and COX-2 activity by 80% [3]

The degree of COX-2 vs. COX-1 selectivity depends on the potency and plasma half-life of the NSAID. For example, diclofenac has a short half-life of 1–2 hours and is prescribed at relatively high doses to produce a drug concentration high enough to ensure effective analgesia throughout the dose interval. Consequently, early in the dosing interval the plasma concentration of diclofenac greatly exceeds the level necessary to inhibit COX-2. At this level, it is also high enough to inhibit COX-1. As the plasma concentration falls, diclofenac continues to inhibit COX-2 completely, but its inhibition of COX-1 gradually subsides. The discordant offset rates of COX-1 vs. COX-2 inhibition creates a 'window' of COX-2 selectivity. In comparison, neither ibuprofen nor naproxen exhibit this window, because their inhibition of COX-1 exceeds that of COX-2 at all times during the dosing interval. (Figure 3)

[1] IC_{80} is the drug concentration corresponding to 80% of maximum inhibition

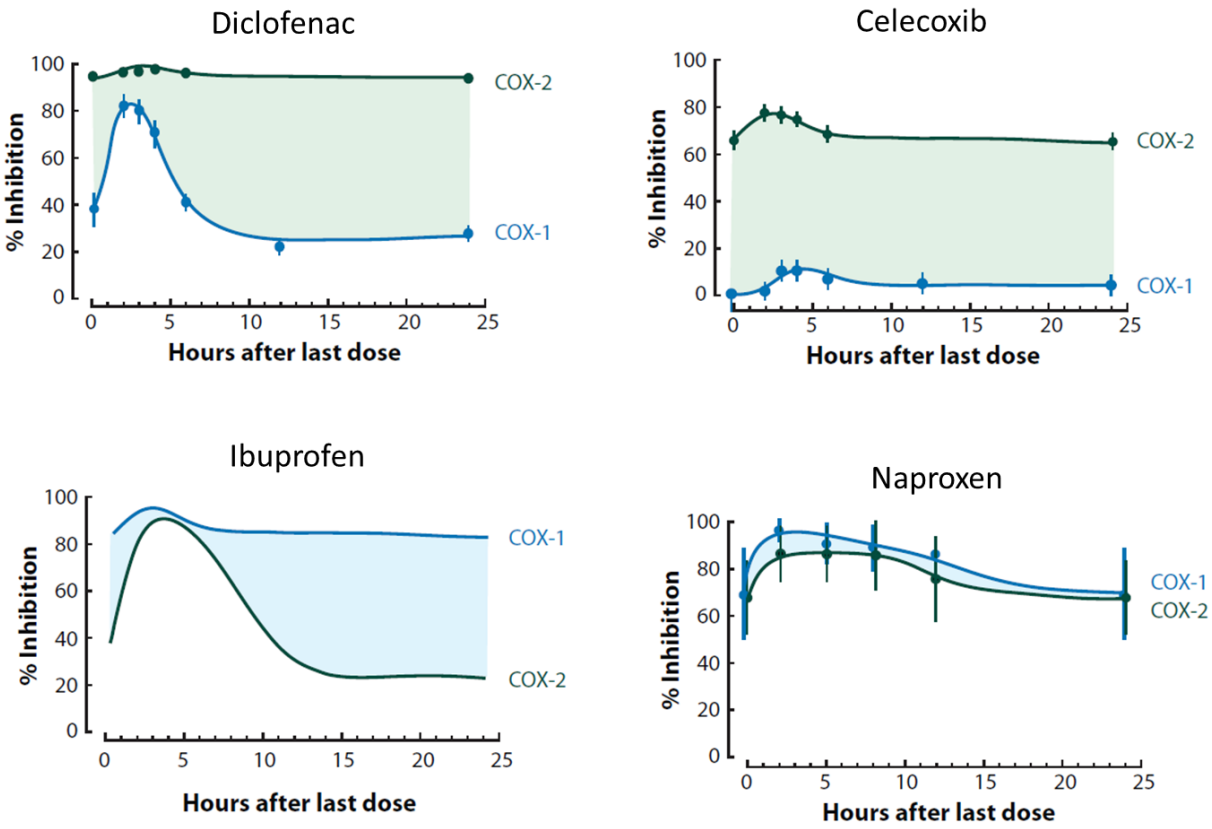


Figure 3. Dynamic relationship of COX-1 and COX-2 inhibition during dose interval. (Adapted from Grosser et al, 2010 [4])

COX-2 inhibitors were developed with the expectation that their relative COX-2 selectivity would provide anti-inflammatory activity, without increasing the risk of gastrointestinal complications associated with traditional NSAIDs (attributed to their inhibition of COX-1-mediated prostaglandin production in the gastric mucosa). However, even before the first 'coxib' entered the market in 1999, it was anticipated that their selective COX-2 inhibition would shift the prothrombotic/antithrombotic balance on the endothelial surface in favour of thrombosis. COX-2 mediates the production of vascular prostacyclin (PGI_2), which inhibits thrombosis. Inhibition of COX-2 therefore prevents the production of PGI_2, leaving the prothrombotic effects of COX-1-mediated thromboxane A2 unopposed [2].

Other factors contributing to the cardiovascular toxicity of COX-2 inhibitors include acceleration of atherogenesis, blood pressure elevation, and risk of heart failure decompensation. Prostacyclin also acts as an endogenous antiarrhythmic agent through its inhibition of epicardial sympathetic nerve activity. COX-2 inhibition could therefore render patients more susceptible to arrhythmias such as atrial fibrillation. Adverse renal effects associated with NSAIDs (e.g. fluid retention, electrolyte disturbances, and blood pressure destabilization), further contribute to the increased risk of cardiovascular adverse effects [5]. (Figure 4. Cardiovascular processes affected by COX-1 and COX-2 activity [4].

The inhibition of COX-2 up-regulation may be particularly harmful during myocardial ischaemia where thromboxane A2 and prostacyclin are released from the acutely ischaemic myocardium and their balance is related to the arrhythmia risk and infarct size [5].

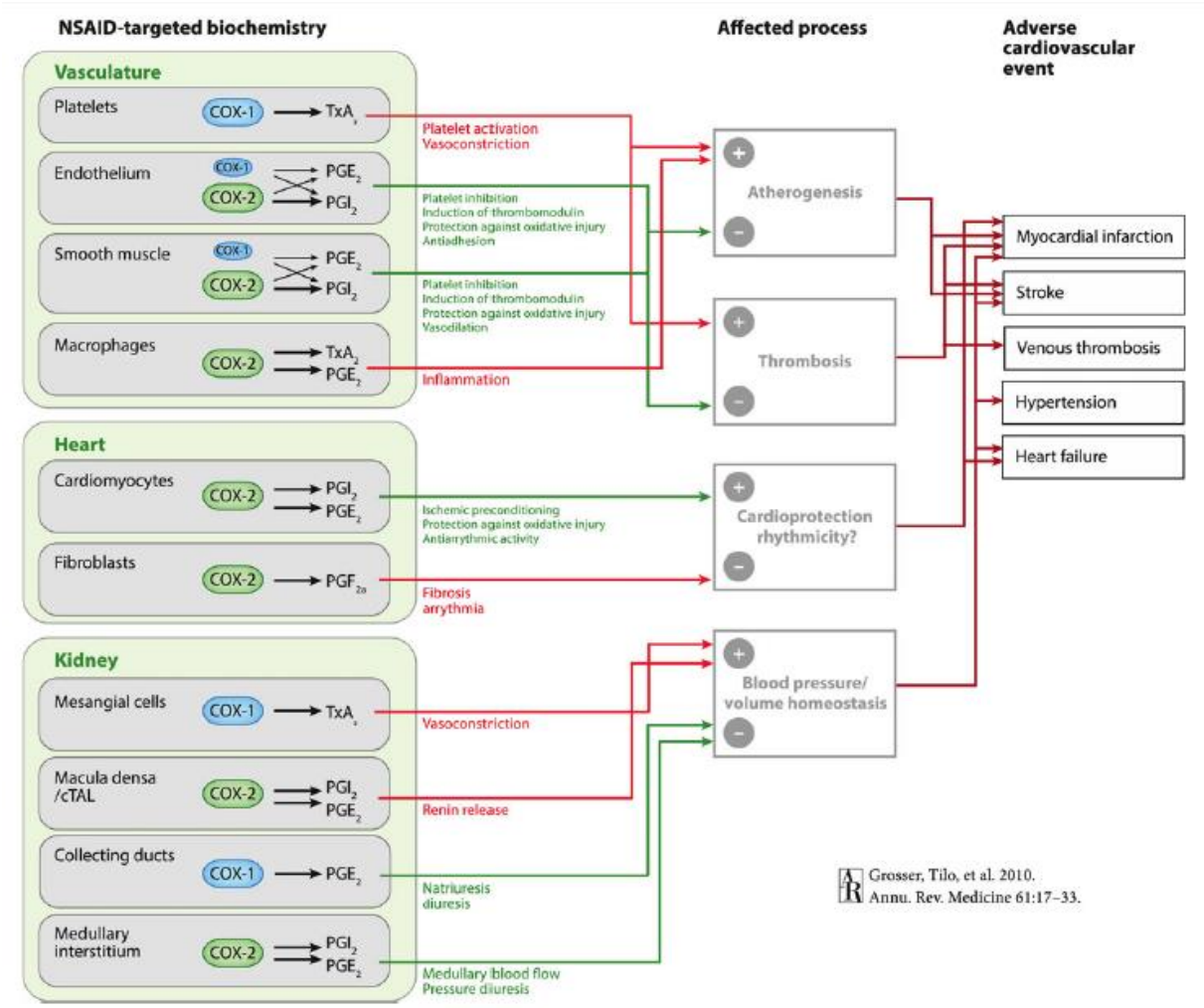


Figure 4. Cardiovascular processes affected by COX-1 and COX-2 activity [4].

2.1.1 NSAIDs and cardiovascular risk – the story so far

2.1.1.1 Clinical studies

During the early 2000s, data began to emerge from large randomized controlled clinical trials demonstrating cardiovascular thromboembolic risk with rofecoxib [6-9]. The Vioxx Gastrointestinal Outcomes Research (VIGOR) study, a randomised controlled trial comparing rofecoxib with naproxen in patients with rheumatoid arthritis, showed rofecoxib users had a 2.4-fold increased risk for the combined outcome of thrombotic cardiovascular events [6].

Concerns were raised as to whether there may be an increased cardiovascular risk with all selective COX-2 inhibitors, but the emerging evidence for a class effect was inconsistent. In 2000, the Celecoxib Long-term Arthritis Safety Study (CLASS), which compared the gastrointestinal toxicity of celecoxib with that of ibuprofen and diclofenac, had found no difference in the incidence of cardiovascular events [10]. However, a pooled analysis of data from VIGOR, CLASS and two smaller trials found that celecoxib and rofecoxib carried an increased cardiovascular risk [11].

In September 2004, Merck Pharmaceuticals voluntarily withdrew rofecoxib when a clinical trial of familial adenomatous polyposis (Adenomatous Polyp Prevention on Vioxx [APPROVe]) identified an elevated risk of serious cardiovascular events (including myocardial infarction and stroke) associated with long-term (>18 months) use of rofecoxib [12].

Around this time, two studies of parecoxib/valdecoxib vs. placebo for analgesia in patients undergoing coronary artery bypass grafting (CABG) reported an increased risk of cardiovascular events in those receiving parecoxib/valdecoxib compared to placebo [13, 14].

In 2005, the Adenoma Prevention with Celecoxib (APC) study was discontinued early due to a dose-related increase in the composite endpoint of death from cardiovascular causes, myocardial infarction, stroke or heart failure associated with celecoxib use compared to placebo [15]. Celecoxib at the unapproved dose of 400 mg twice daily was shown to have a higher risk of the composite endpoint of death from cardiovascular causes, myocardial infarction, stroke or heart failure (HR 3.4, 95% CI 1.4 – 7.8) compared to placebo. At the approved dose of 200 mg twice daily, the hazard ratio was increased compared to placebo but the difference was not statistically significant (HR 2.3, 95% CI 0.9 – 5.5).

In 2006, the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study compared etoricoxib with diclofenac and found no difference in rates of thrombotic cardiovascular events [16]. The same year the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) showed that naproxen carried an increased risk of cardiovascular and cerebrovascular disease in elderly patients with dementia [17].

Results from these major randomized trials of various selective COX-2 inhibitors compared to either traditional NSAIDs or placebo were inconsistent. Patient populations varied between the studies in terms of age and underlying disease, making meta-analyses difficult.

In 2006, a large meta-analysis of 138 randomised controlled trials, (comprising a total of 145 373 participants) concluded that selective COX-2 inhibitors are associated with a moderate increase in the risk of vascular events, as are high dose regimens of ibuprofen and diclofenac, but not high dose naproxen [18].

Similarly, a network meta-analysis of large-scale randomised controlled trials comparing any NSAID with other NSIADs or placebo, (comprising 116 429 patients across 31 trials with a total of 115 000 patient years of follow-up) concluded that all of the NSAIDs included in the study carried some cardiovascular risk. Among the seven NSAIDs analysed (naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib, lumiracoxib), naproxen was found to have the lowest cardiovascular risk. [19]

In 2011, a Danish register population-based cohort study investigated whether the duration of NSAID treatment increased the risk of death or re-infarction in patients with a history myocardial infarction. The study showed that, in patients with prior MI, cardiovascular risk was independent of duration of NSAID use. The increased risk of death and recurrent MI became apparent immediately (diclofenac) or early (rofecoxib, ibuprofen) after treatment initiation, challenging the view that NSAIDs are not harmful during short-term (<1 week) use [20].

Also in 2011, a meta-analysis of 30 case-control studies and 21 cohort studies found the highest overall risks were with rofecoxib and diclofenac, and the lowest risks were with ibuprofen and naproxen. The study found that the risk was elevated with low doses of rofecoxib, celecoxib, and diclofenac, and rose with higher doses, Ibuprofen risk was only evident with higher doses. Naproxen did not cause any additional risks at any dose. Additionally, the study showed that the relative risk estimates were constant with different background risks for cardiovascular disease, and increased early in the course of treatment [21].

The Coxib and traditional NSAID Trialists (CNT) Collaboration undertook a meta-analyses of 280 trials of NSAIDs vs. placebo (124 513 participants, 68 342 person-years of follow-up), and 474 trials of one NSAID vs. another NSAID (229 296 participants, 165456 person-years of follow-up) [22]. The main cardiovascular outcomes were major vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death), major coronary events (non-fatal myocardial infarction or coronary death), stroke, mortality, and heart failure.

The study showed an increased risk of major vascular events for coxibs (RR=1·37, 95% CI 1·14–1·66; p=0·0009) and diclofenac (1·41, 1·12–1·78; p=0·0036) compared to placebo. This increase was mainly driven by an increase in major coronary events (coxibs 1·76, 1·31–2·37; p=0·0001; diclofenac 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) compared to placebo, but not major vascular events (1·44, 0·89–2·33). Naproxen did not significantly increase major vascular events (0·93, 0·69–1·27) compared to placebo. The proportional effects on major vascular events were found to be independent of baseline characteristics, including vascular risk. Heart failure risk was found to be roughly doubled by all NSAIDs.

The study concluded that the vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs.

2.1.1.2 Action taken by the US FDA

The emerging evidence of an increased cardiovascular risk associated with certain selective COX-2 inhibitors in the early 2000s raised concerns about a possible class effect. To address these concerns, the U.S. Food and Drug Administration (FDA) undertook a review the cardiovascular safety of all NSAIDs, including COX-2 selective and traditional NSAIDs [23].

In February 2005, the FDA's Arthritis Advisory Committee and Drug Safety & Risk Management Advisory Committee met to discuss the risk of cardiovascular thromboembolic events associated with NSAIDs. The committees agreed there appeared to be a class effect for cardiovascular risk with the (then) approved COX-2 selective NSAIDs (ie, rofecoxib, celecoxib, and parecoxib/valdecoxib[2]). There was less agreement regarding the non-selective NSAIDs, but the general recommendation was that these drugs should carry similar warnings.

Specifically, the FDA concluded:

- The three (then) approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib, and valdecoxib) are associated with an increased risk of serious adverse CV events compared to placebo. The available data did not permit a rank ordering of these drugs with regard to CV risk.
- Data from large long-term controlled clinical trials that had included a comparison of COX-2 selective and non-selective NSAIDs did not clearly demonstrate that COX-2 selective agents confer a greater risk of serious adverse CV events than non-selective NSAIDs.
- Long-term placebo-controlled clinical trial data were not available to adequately assess the potential for non-selective NSAIDs to increase the risk of serious adverse CV events.
- The available data were best interpreted as consistent with a class effect, ie, the increased risk of serious adverse CV events applies to all COX-2 selective and non-selective NSAIDs.
- Short-term use of NSAIDs to relieve acute pain, particularly at low doses, did not appear to confer an increased risk of serious adverse CV events (with the exception of valdecoxib in hospitalized patients immediately after coronary artery bypass (CABG) surgery).

Based on these conclusions, the FDA took the following action[3]:

[2] Parecoxib (Dynastat, Pfizer) is an intravenously administered prodrug of valdexocib (Bextra, Pfizer). The New Zealand approval for Bextra lapsed in 2003. Dynastat and a generic parecoxib product both have current approval.

[3] Unrelated to the cardiovascular adverse effects, the FDA review identified an increased rate of serious and potentially life-threatening skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) associated with valdecoxib, compared to other COX-2 selective agents. The overall benefit-risk profile for valdecoxib was found to be unfavourable and the FDA asked Pfizer to voluntarily withdraw Bextra (valdecoxib) from the U.S. market.

- A boxed warning highlighting the increased risk of serious adverse CV events was included in the labelling for all prescription NSAIDs.
- Use of all prescription NSAIDs in patients immediately post-operative from CABG surgery was contraindicated.
- A Medication Guide for NSAIDs was developed to inform patients of the risk of serious adverse CV events and serious GI bleeding.
- The agency requested that all sponsors of non-selective NSAIDs conduct and submit for FDA review a comprehensive review and analysis of available controlled clinical trial databases to further evaluate the potential for increased CV risk.

In 2006, in response to the FDA's request for additional data describing the CV risk associated with NSAIDs, Pfizer initiated the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (PRECISION) study, which aimed to evaluate the relative safety of celecoxib, naproxen and ibuprofen. The results of this study were published in 2016 (see section 3.1.2.1) [24].

In February 2014, the Arthritis Advisory Committee and Drug Safety & Risk Management Advisory Committee met again to discuss new information on the cardiovascular risks of NSAIDs published since the 2005 label change. In particular, the committees reviewed the results of the CNT meta-analysis [22]. This study reinforced the FDA's earlier conclusion that the risk of CV events is present for both non-selective and COX-2 selective NSAIDs, but it raised the possibility that the risk may be lower for naproxen. Based on this review, in September 2015 the FDA strengthened the existing label warning that all non-aspirin NSAIDs increase the risk of myocardial infarction or stroke [25]. The FDA labels were revised to reflect the following information:

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.
- The available information is not sufficient to enable ranking of NSAIDs according to their caridovascular risk.
- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.
- In general, patients with heart disease or risk factors for heart disease have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors because they have a higher risk at baseline.
- Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.
- There is an increased risk of heart failure with NSAID use.

2.1.1.3 Action taken by the EMA

In 2005, following the voluntary withdrawal of rofecoxib and post-marketing reports of serious thrombotic events associated with celecoxib, the Committee for Medicinal Products for Human Use (CHMP) undertook a class review of the cardiovascular safety of all selective COX-2 inhibitors. The CHMP concluded that selective COX-2 inhibitors, as a class, are associated with an increased risk of thrombotic events that is dose and duration dependent. The product information for selective COX-2 inhibitors was therefore updated to include:

- Contraindications against use in patients with established ischemic heart disease and/or cerebrovascular disease (stroke), and in patients with peripheral arterial disease.
- Reinforced warnings to healthcare professionals to exercise caution when prescribing COX-2 selective NSAIDs to patients with risk factors for heart disease, such as hypertension, hyperlipidaemia, diabetes, and smoking.
- Advice to doctors that the medicine should be used at the lowest effective dose for the shortest possible duration of treatment.

In 2006, the CHMP undertook a formal review of the cardiovascular safety of non-selective NSAIDs [26]. The Committee concluded that the overall benefit-risk balance remained positive, but a small increase in the absolute risk for thrombotic events could not be excluded for non-selective NSAIDs, especially when used at high doses for long-term treatment [27].

The CHMP highlighted a lack of information on the cardiovascular effects of traditional (non-selective) NSAIDs. The EMA therefore asked the European Commission (EC) to fund research into the gastrointestinal and cardiovascular toxicity associated with NSAIDs, which lead to the **S**afety **O**f non-**S**teroidal anti-inflammatory drugs (SOS) project [28].

The SOS project comprised a systematic review of CVD and GI risk information from clinical trials and published observational studies, followed by a multi-country study in existing health care databases in the UK, Netherlands, Germany and France designed to assess and compare the risk of cardiovascular and gastrointestinal events in NSAID users (see section 3.1.2.4, SCOT study).

The CHMP undertook a further review of the cardiovascular safety of NSAIDs in October 2011, which included the results of the SOS project and other studies on the cardiovascular safety of NSAIDs that had been published since the previous review. The CHMP concluded that the cardiovascular risks for naproxen and ibuprofen were in line with the previous evidence.

Overall, the data suggested:

- Naproxen may be associated with a lower risk of arterial thrombotic events than COX-2 inhibitors and other NSAIDs, but a small risk could not be excluded.
- Ibuprofen at high dose may be associated with an increased risk of thrombotic events, but the data for low dose ibuprofen was inconsistent.
- Diclofenac has a less favourable cardiovascular risk profile compared to naproxen and ibuprofen, with risks similar to those of COX-2 inhibitors.
- For other traditional NSAIDs the data were considered insufficient to conclude on thrombotic risk.

The CHMP therefore reiterated their previous conclusion that increased cardiovascular risk for NSAIDs, as a class effect, cannot be excluded [29].

In June 2013, the EMA determined that the cardiovascular risk with systemic diclofenac was similar to that of selective COX-2 inhibitors, and that risk minimisation measures in place for COX-2 inhibitors should also apply to diclofenac. Use of diclofenac was therefore contraindicated in patients with established congestive heart failure (NYHA class II-IV), ischaemic heart disease, peripheral arterial disease or cerebrovascular disease. Furthermore, patients with significant risk factors for cardiovascular events (eg, hypertension, hyperlipidaemia, diabetes mellitus, or smoking) should only be treated with diclofenac after careful consideration. The SmPC was also updated with advice that diclofenac should be used for the shortest duration possible and at the lowest effective daily dose.

In June 2015 the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) completed a review on the cardiovascular safety of ibuprofen, and concluded that high dose ibuprofen (at or above 2400 mg per day) is associated with an increased risk of cardiovascular adverse events, similar to that seen for COX-2 inhibitors and diclofenac. The PRAC confirmed that there was no increased cardiovascular risk with ibuprofen doses up to 1200 mg per day. The PRAC recommended that updated advice on the cardiovascular risk of high-dose ibuprofen be included in the product information for ibuprofen.

2.1.2 Previous MARC agenda items concerning NSAIDs and cardiovascular risk

2.1.2.1 Diclofenac and cardiovascular risk

The cardiovascular risk associated with diclofenac was discussed at the 154th MARC meeting on 3 June 2013. The paper is attached as Annex 1.

The Committee concluded that there was a small increase in the risk of cardiovascular events with the use of diclofenac, particularly with increasing dose and duration of use. They considered that if some of the confounders were adjusted for, the estimates of the risk may move closer to one and a null association. However, with the widespread use of diclofenac, the Committee agreed that even a small increased risk of cardiovascular adverse effects may translate to a large number of patients potentially being affected.

The Committee was unable to determine from the new data a clear difference in risk between different NSAIDs. The Committee noted that other NSAID adverse reactions are also important, including the risk of gastrointestinal events, renal injury and severe skin reactions. The Committee noted that other types of pain relievers also have undesirable effects, which should be considered before prescribing.

The Committee considered that the information contained in the New Zealand diclofenac data sheets could be more specific and recommended changes to the data sheet. Specifically:

Indications section

- Diclofenac should only be prescribed when the benefits are considered to outweigh the potential risks (see Warnings and Precautions)

Warning and Precautions section:

- Patients who have had a recent myocardial infarction (within the last 6 to 12 months) should not use diclofenac.
- Patients on long-term treatment should be regularly reviewed with regards to efficacy, adverse effects, the development of cardiovascular risk factors, and the ongoing need for therapy. Consideration should be given to monitoring blood pressure, haemoglobin levels, and renal function.
- Prescribers should inform the individual patient of the possible increased risk when prescribing diclofenac for patients at high risk of cardiovascular events. This includes risk factors such as diabetes, ischaemic heart disease, cardiac failure, hyperlipidaemia, hypertension or smoking.
- Physicians and patients should remain alert for such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of cardiovascular toxicity and the steps to take should they occur.

2.1.2.2 Ibuprofen and cardiovascular risk

The cardiovascular risk associated with ibuprofen was discussed at the 161st MARC meeting on 12 March 2015. The paper is attached as Annex 2.

The Committee noted that the information on cardiovascular risks was is not consistent between the various ibuprofen data sheets.

The Committee agreed that the ibuprofen data sheets should be harmonised so that information on cardiovascular risks is clear and consistent across all data sheets. In addition, information on there being no consistent evidence that concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with non-steroidal anti-inflammatory drugs (NSAIDs) should be included in all data sheets.

The Committee recommended that Medsafe request the sponsors of ibuprofen to update the information on cardiovascular risks in data sheets so that it is consistent across all data sheets.

2.2 Usage data

New Zealand usage data is provided from PharmHouse beta, which includes PHARMAC funded medicines dispensed from community pharmacies. Several NSAID products are available without prescription (eg, ibuprofen and diclofenac), and the use of self-purchased medicines is not included in the PharmHouse beta data (ie the usage data for this medicines will be an underestimate).

The data presented in Table 1 shows the number of people who received a dispensing of the medicine at least once during the year, for each year from 2013 to 2017. This data is presented graphically in Figure 5.

Note that celecoxib was first funded in 2017.

Table 1. PHARMAC funded NSAIDs dispensed from community pharmacies for period 2013 -2017 (data shown for all DHBs combined). Source PharmHouse beta

Number of people	Year					
Active ingredient	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
Ibuprofen	1212795	1315828	1456245	1477995	1561585	7024448
Diclofenac sodium	686842	641616	639275	647862	601053	3216648
Naproxen	262532	283379	285461	300936	289841	1422149
Celecoxib					164524	164524
Tenoxicam	33616	31746	27959	25103	19556	137980
Mefenamic acid	12124	12252	12649	12983	12902	62910
Ketoprofen	2338	1807	1758	1826	1469	9198
Sulindac	876	869	882	899	815	4341
Meloxicam	152	172	167	182	167	840
Tiaprofenic acid	568	9				577
Total	**2211843**	**2287678**	**2424396**	**2467786**	**2651912**	**12043615**

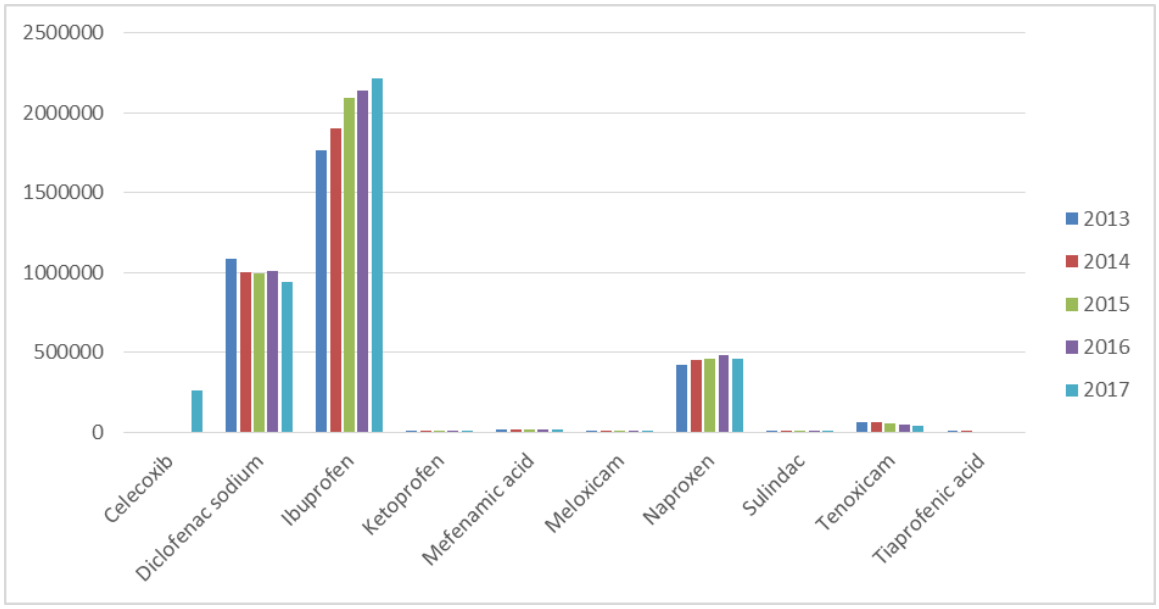


Figure 5. PHARMAC funded NSAIDs dispensed from community pharmacies for period 2013 -2017 (data shown for all DHBs combined). Source PharmHouse beta

2.3 Data sheets

2.3.1 New Zealand

2.3.1.1 Traditional NSAIDs (ibuprofen, diclofenac, naproxen)

The approved New Zealand data sheets for funded brands of the commonly used traditional NSAIDs (ibuprofen, diclofenac, and naproxen), contain essentially the same information concerning *Contraindications* and *Special warnings and precautions*.

Contraindications

Severe heart failure (NYHA grade IV)

Special warnings and precautions

Cardiovascular thrombotic events

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration.

Physicians and patients should remain alert for such CV events even in the absence of previous CV symptoms. Patients should be informed about signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Clinical trial and epidemiological data suggest that the use of coxibs and some NSAIDs (particularly at high doses or long-term treatment) may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke).

Hypertension

NSAIDS may lead to the onset of new hypertension or worsening of pre-existing hypertension, and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart failure

Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore, caution is advised in patients with fluid retention or heart failure.

2.3.1.2 Selective COX-2 inhibitor (celecoxib)

The approved NZ data sheet for celecoxib carries stronger contraindications to the traditional NSAIDs. The information provided in the warnings and precautions section carries essentially the same message as for the traditional NSAIDs.

Contraindications

Patients with unstable ischaemic heart disease of thrombus aetiology, documented myocardial infarction or stroke within 3 months.

Patients with congestive heart failure (NYHA grades II-IV)

Special warnings and precautions

Cardiovascular Effects

COX-2 inhibitors, including celecoxib, have been associated with an increased risk of serious CV thrombotic adverse events, myocardial infarction and stroke, which can be fatal (see section 5.1, Clinical Efficacy and Safety, Cardiovascular Safety).

All NSAIDs, both COX-2 selective and non-selective may cause an increased risk of serious CV thrombotic events. This risk may increase with dose and duration of use. The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline.

Two large, controlled clinical trials of a different COX-2 selective inhibitor for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. In the absence of comparable data with celecoxib, it may be assumed that patients at high risk of CV disease (including patients with diabetes, ischaemic heart disease, cardiac failure, hyperlipidaemia, hypertension, or smokers) who are undergoing any major surgery may face an increased risk of developing a CV event. Patients with significant established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease as well as patients at high risk for CV disease including those with significant and multiple risk factors for CV events should only be treated with celecoxib after careful consideration of the patient's overall risk and the potential risks and benefits of alternative analgesic therapies. See section 4.3 Contraindications.

To minimise the potential risk for an adverse CV event in patients treated with celecoxib, the lowest effective dose should be used for the shortest duration possible (see section 4.2 Dose and Method of Administration).

Prescribers should inform the individual patient of the possible increased risks when prescribing celecoxib for patients at high risk of CV adverse events. Physicians and patients should remain alert for such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and symptoms of serious CV toxicity and the steps to take if they occur. Celecoxib is not a

substitute for CV prophylaxis because of its lack of effect on platelets; therefore, concurrent anti-platelet therapies should not be discontinued. There is no evidence that concurrent use of aspirin decreases the risk of CV adverse events associated with COX-2 inhibitors, including celecoxib.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Systematic Reviews and Meta-analyses

3.1.1.1 Gunter et al, 2017 (J Clin Pharm & Ther)

Non-steroidal anti-inflammatory drug-induced cardiovascular adverse events: a meta-analysis [30]

This study aimed to determine whether COX-2 selectivity leads to an increased CV risk. The paper is provided as Annex 3.

Methods

Medline, Embase and Cochrane databases were searched for randomised controlled trials and prospective cohort studies involving at least one of eight pre-selected NSAIDs (ibuprofen, diclofenac, naproxen, meloxicam, etoricoxib, celecoxib, lumiracoxib and rofecoxib). Studies were included if they reported CV events (defined as MI, stroke or death from a CV event) for one of the included NSAIDs. Studies were excluded if non-English language, non-human, duration of treatment less than 1 month (because chronic use not assessed), or lack of CV data.

Primary endpoints included any MI, any stroke, and CV death. A composite CV outcome was defined as the total number of events of MI, stroke and CV death.

Odds ratios (ORs) were used with 95% confidence intervals (CI). Statistical significance was set at $P < 0.05$. Precision funnel plots were developed to determine heterogeneity, and heterogeneity was further assessed using Egger's test.

For each NSAID, the NSAID of interest was compared with placebo, all NSAIDs, non-selective NSAIDs (ibuprofen, diclofenac, naproxen), coxibs (rofecoxib, celecoxib, etoricoxib and lumiracoxib), and coxibs excluding rofecoxib. Comparisons were made for each outcome (MI, stroke, CV death and composite CV). Three studies included in the analysis (CADEUS, Reicin 2002 and PROBE) defined a groups of NSAIDs as non-selective NSAIDs, and these were treated in the analysis in a similar way to ibuprofen, diclofenac and naproxen. Individual NSAIDs other than the eight pre-selected NSAIDs were not included in the comparisons. In studies that compared different regimens of the same NSAID, data from both regimens were combined for the analysis.

Results

Study retrieval occurred from May-August 2014 and was performed by two of the authors. The initial search retrieved 4985 articles, of which 26 studies involving 24 RCTs and two prospective cohort studies were included in the analysis.

The studies included in the meta-analyses are shown in Table 2. The study involving meloxicam did not meet inclusion criteria; therefore, meloxicam was not included in the statistical analysis. Of all 26 studies, 228 391 patients were represented, with celecoxib representing the most at 28.6% (n = 65 341) and ibuprofen the least at 2.79% (n = 6382).

The number of events reported by study treatment are shown in Table 3.

Table 2. General study characteristics – Gunter 2017

Study	Treatment	First author	Populations	Study type[a]	Mean age	Number of patients	Total follow-up (months)	Low dose aspirin allowed
ADAPT[39]	Celecoxib 200 mg BID vs. naproxen 220 mg BID vs. placebo	ADAPT Research Group	Alzheimer's Disease	RCT	74	2528	36	Y
ADVANTAGE[40]	Rofecoxib 25 mg QD vs. naproxen 500 mg BID	Lisse JR	Osteoarthritis	RCT	63	5557	4	Y
APC[41]	Celecoxib 200 mg BID vs. celecoxib 400 mg BID vs. placebo	Solomon SD	Colorectal adenomatous polyps	RCT	59	2035	34	Y
APPROVe[15]	Rofecoxib 25 mg QD vs. placebo	Baron J	Colorectal Adenoma	RCT	59	2587	48	Y
Bingham 2007 – 1[42]	Etoricoxib 30 mg QD vs. celecoxib 200 mg QD	Bingham CO	Osteoarthritis	RCT	62	599	7	Y
Bingham 2007 – 2[42]	Etoricoxib 30 mg QD vs. celecoxib 200 mg QD	Bingham CO	Osteoarthritis	RCT	62	608	7	Y
Bogaty 2004[43]	Rofecoxib 25 mg QD vs. placebo	Bogarty P	Ischaemic heart disease	RCT	59	35	9	N
CADEUS[44]	Celecoxib vs. rofecoxib vs. tNSAIDs	Laharie D	French cohort	Cohort	63	46 454	2·5	Y
CLASS[30,31]	Celecoxib 400 mg BID vs. ibuprofen 800 mg TID vs. diclofenac 75 mg BID	Silverstein FE	Rheumatoid arthritis and osteoarthritis	RCT	60	7968	12	Y
EDGE[45]	Diclofenac 50 mg TID vs. etoricoxib 90 mg QD	Baraf HS	Osteoarthritis	RCT	63	7111	9	Y
EDGE II[46]	Diclofenac 75 mg BID vs. etoricoxib 90 mg QD	Krueger K	Rheumatoid arthritis	RCT	60	4086	19	Y
Fleischmann 2008[47]	Lumiracoxib 100 mg QD vs. lumiracoxib 100 mg BID vs. celecoxib 200 mg QD	Fleischmann R	Osteoarthritis	RCT	62	3032	12	Y
Ghosh 2007[48]	Diclofenac 75 mg QD vs. etoricoxib 90 mg QD vs. placebo	Ghosh S	Osteoarthritis	RCT		427	1	N
Harrison-Woolrych 2005[49]	Rofecoxib 12·5, 25, 50 mg QD vs. celecoxib 100, 200, 400 mg QD	Harrison-Woolrych M	New Zealand cohort	Cohort	59	58 849	48	Y
MEDAL[22]	Etoricoxib 60 mg QD vs. etoricoxib 90 mg QD vs. diclofenac 75 mg BID	Combe B	Osteoarthritis	RCT	64	23 504	20	N
Papadimitrakopoulou 2008[50]	Celecoxib 100 mg BID vs. celecoxib 200 mg BID vs. placebo	Papadimitrakopoulou VA	Premalignant oral lesions	RCT	62	50	7	N
PreSAP[29]	Celecoxib 400 mg QD vs. placebo	Arber N	Colorectal adenomatous polyps	RCT	61	1738	36	Y
PROBE[51]	Celecoxib vs. nsNSAIDs	Cryer B	Osteoarthritis	RCT	63	8067	6	N
Reicin 2002[52]	Rofecoxib 12·5, 25, 50 mg vs. nsNSAIDs	Reicin AS	Osteoarthritis	RCT	65	5435	4	N
SUCCESS-I[53]	Celecoxib 100 mg BID vs. celecoxib 200 mg BID vs. naproxen 500 mg BID vs. diclofenac 50 mg BID	Singh G	Osteoarthritis	RCT	62	13 274	3	Y
TARGET[b,54]	Ibuprofen 800 mg TID vs. lumiracoxib 400 mg QD and lumiracoxib 400 mg QD vs. naproxen 500 mg BID	Farkouh ME	Osteoarthritis	RCT	64	18 325	14	Y
Van Adelsberg 2007[55]	Rofecoxib 25 mg QD vs. placebo	Van Adelsberg J	Men with prostate cancer risk	RCT	63	4741	73	Y
VICTOR[56]	Rofecoxib 25 mg QD vs. placebo	Kerr DJ	Colorectal cancer	RCT	65	2327	9	Y
VIGOR[57]	Naproxen 500 mg BID × rofecoxib 50 mg QD	Bombardier C	Rheumatoid arthritis	RCT	58	8076	14	N
Weaver 2006[58]	Rofecoxib 12·5 mg QD vs. nabumetone 500 mg BID vs. placebo	Weaver AL	Osteoarthritis	RCT	63	978	1·5	Y

NSAIDs, non-steroidal anti-inflammatory drugs; nsNSAIDs, non-selective NSAIDs; tNSAIDs, traditional NSAIDs; BID, twice a day; QD, once a day; TID, three times a day.
[a]Randomized controlled trial (RCT).
[b]TARGET is composed of two arms (lumiracoxib vs. ibuprofen and lumiracoxib vs. naproxen), although presented as one study here, data were analysed as two studies (TARGET I/L and TARGET N/L).

Table 3. Number of events by study and treatment – Gunter 2017

Study[a]	Drug	Number of patients	Myocardial infarction	Stroke	CV death
ADAPT	Celecoxib	726	8	7	4
ADAPT	Naproxen	719	13	10	3
ADAPT	Placebo	1083	13	7	3
ADVANTAGE	Naproxen	2772	1	6	–
ADVANTAGE	Rofecoxib	2785	5	0	–
APC	Celecoxib	1356	–	–	9
APC	Placebo	679	–	–	1
APPROVe	Placebo	1300	18	9	13
APPROVe	Rofecoxib	1287	34	19	16
Bingham 2007-1	Celecoxib	241	0	1	–
Bingham 2007-1	Etoricoxib	231	0	0	–
Bingham 2007-2	Celecoxib	247	1	0	–
Bingham 2007-2	Etoricoxib	244	0	1	–
Bogaty 2004	Placebo	17	1	0	–
Bogaty 2004	Rofecoxib	18	0	0	–
CADEUS	Celecoxib	11 780	0	1	–
CADEUS	nsNSAIDs[b]	22 919	2	4	–
CADEUS	Rofecoxib	11 755	3	1	–
CLASS	Celecoxib	3987	19	4	10
CLASS	Diclofenac	1996	4	6	6
CLASS	Ibuprofen	1985	9	6	3
EDGE	Diclofenac	3518	14	10	5
EDGE	Etoricoxib	3593	19	7	4
EDGE II	Diclofenac	2054	25	12	7
EDGE II	Etoricoxib	2032	14	8	7
Fleischmann 2008	Celecoxib	758	–	–	1
Fleischmann 2008	Lumiracoxib	2274	–	–	7
Ghosh 2007	Diclofenac	142	0	1	–
Ghosh 2007	Etoricoxib	162	0	0	–
Ghosh 2007	Placebo	123	0	0	–
Harrison-Woolrych 2005	Celecoxib	32 446	42	16	–
Harrison-Woolrych 2005	Rofecoxib	26 403	60	26	–
MEDAL	Diclofenac	11 787	68	–	–
MEDAL	Etoricoxib	11 717	69	–	–
Papadimitrakopoulou 2008	Celecoxib	32	0	1	0
Papadimitrakopoulou 2008	Placebo	18	0	0	0
PreSAP	Celecoxib	933	–	–	23
PreSAP	Placebo	628	–	–	12
PROBE – Cryer B	Celecoxib	4035	2	3	3
PROBE – Cryer B	nsNSAIDs	4032	3	3	0
Reicin 2002	nsNSAIDs	1564	5	3	–
Reicin 2002	Placebo	711	2	1	–
Reicin 2002	Rofecoxib	5610	12	15	–
SUCCESS-I	Celecoxib	8800	11	–	–
SUCCESS-I	Diclofenac	4394	1	–	–
SUCCESS-I	Naproxen	905	1	–	–
TARGET (I/L)	Ibuprofen	4397	7	9	10
TARGET (I/L)	Lumiracoxib	4376	5	8	8
TARGET (N/L)	Naproxen	4730	10	12	8
TARGET (N/L)	Lumiracoxib	4741	18	16	11
Van Adelsberg 2007	Placebo	2372	4	5	–
Van Adelsberg 2007	Rofecoxib	2369	5	2	–
VICTOR	Placebo	1160	1	2	–
VICTOR	Rofecoxib	1167	3	5	–
VIGOR	Naproxen	4029	4	8	8
VIGOR[c]	Rofecoxib	4047	20	8	8
Weaver 2006	Placebo	196	0	–	–
Weaver 2006	Rofecoxib	390	3	–	–

NSAIDs, non-steroidal anti-inflammatory drugs; nsNSAIDs, non-selective NSAIDs; CV, cardiovascular.
[a]Different dosage strengths of the same NSAID were combined in Fleischmann 2008, APC, Papadimitrakopoulou 2008 and Reicin 2002.
[b]nsNSAIDs: In CADEUS, these were unspecified. In PROBE, this represents meloxicam, naproxen, nabumetone, diclofenac, ibuprofen and etodolac. In Reicin 2002, this represents ibuprofen, diclofenac and nabumetone.
[c]Updated data presented by Curfman *et al.* were used.[59]

Forest plots showing the odds ratios for comparisons between NSAIDs for each outcome are shown in Figure 6 - Figure 10.

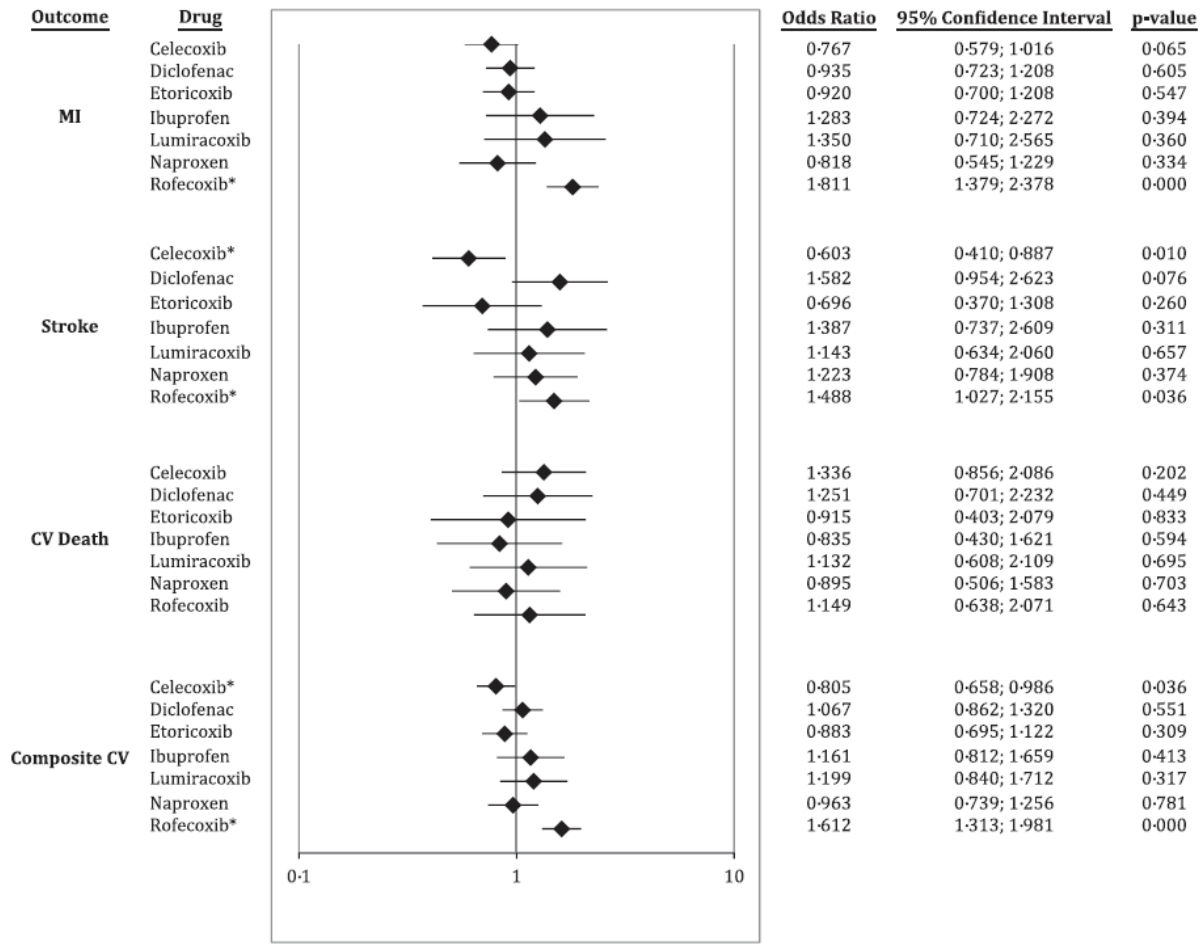


Figure 6. Comparison with all NSAIDs – Gunter 2017

Each NSAID was compared against all other NSAIDs for each outcome. (*) indicates statistical significance.

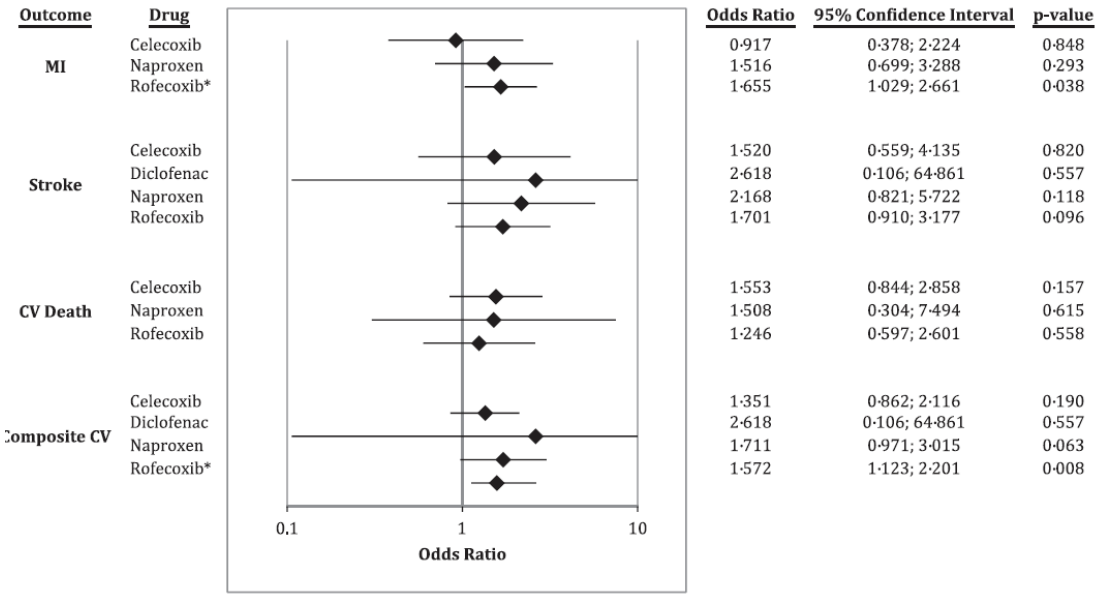


Figure 7. Comparison with placebo – Gunter 2017

NSAIDS with direct comparisons to placebo are shown here. (*) denotes statistical significance.

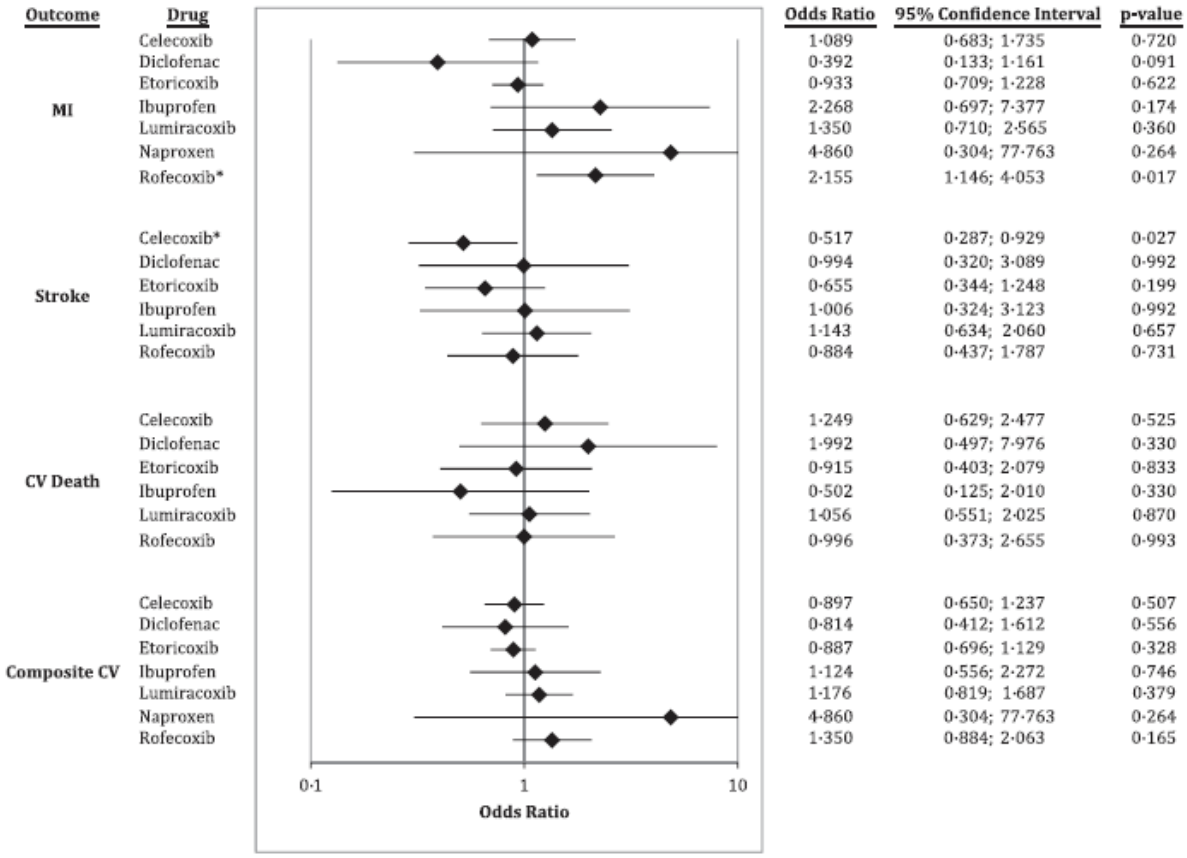
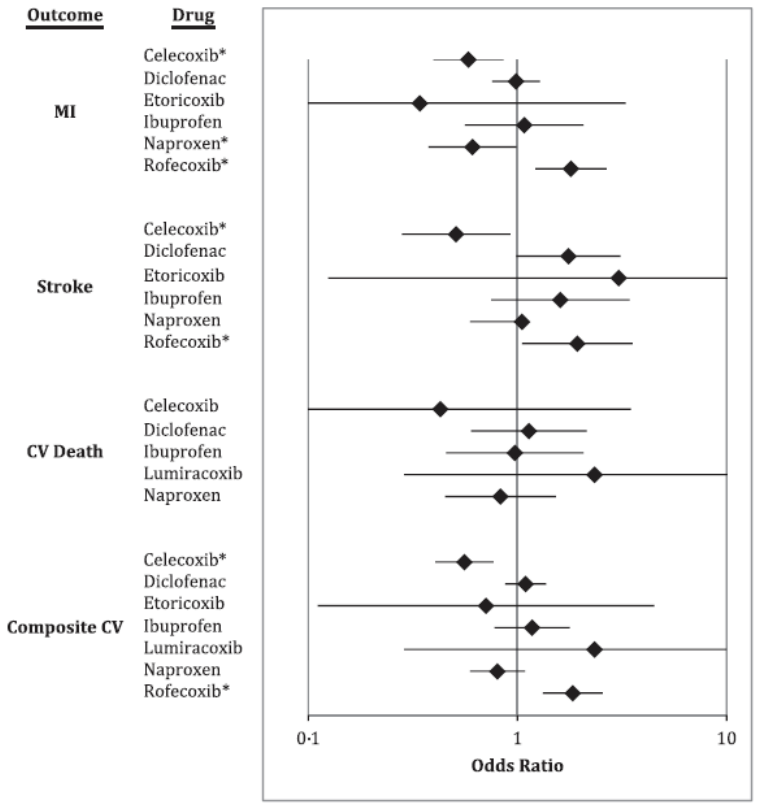


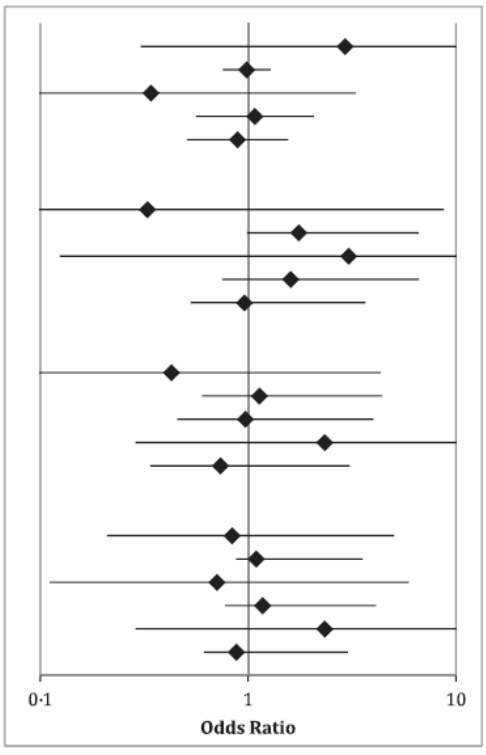
Figure 8. Comparisons with the traditional NSAID – Gunter 2017.
Each NSAID was compared to three traditional NSAIDs (ibuprofen, naproxen and diclofenac). (*) denotes statistical significance.



Outcome	Drug	Odds Ratio	95% Confidence Interval	p-value
MI	Celecoxib*	0·583	0·396; 0·857	0·006
	Diclofenac	0·984	0·756; 1·281	0·903
	Etoricoxib	0·341	0·035; 3·291	0·352
	Ibuprofen	1·077	0·560; 2·070	0·825
	Naproxen*	0·609	0·375; 0·989	0·045
	Rofecoxib*	1·800	1·217; 2·662	0·003
Stroke	Celecoxib*	0·509	0·280; 0·925	0·027
	Diclofenac	1·754	0·988; 3·114	0·055
	Etoricoxib	3·049	0·124; 75·219	0·495
	Ibuprofen	1·603	0·749; 3·433	0·225
	Naproxen	1·051	0·637; 1·733	0·846
	Rofecoxib*	1·933	1·052; 3·549	0·034
CV Death	Celecoxib	0·428	0·053; 3·483	0·427
	Diclofenac	1·134	0·599; 2·145	0·700
	Ibuprofen	0·971	0·456; 2·066	0·939
	Lumiracoxib	2·337	0·287; 19·029	0·427
	Naproxen	0·830	0·451; 1·528	0·549
Composite CV	Celecoxib*	0·557	0·404; 0·767	0·000
	Diclofenac	1·094	0·874; 1·369	0·435
	Etoricoxib	0·708	0·111; 4·506	0·715
	Ibuprofen	1,174	0·776; 1·777	0·448
	Lumiracoxib	2·337	0·287; 19·029	0·427
	Naproxen	0·802	0·593; 1·085	0·153
	Rofecoxib*	1·838	1·323; 2·554	0·000

Figure 9. Comparison with the coxibs – Gunter 2017

Each NSAID was compared to the four coxibs (celecoxib, rofecoxib, etoricoxib and lumaricoxib). (*) indicates statistical significance.



Outcome	Drug	Odds Ratio	95% Confidence Interval	p-value
MI	Celecoxib	2·931	0·304; 28·280	0·352
	Diclofenac	0·984	0·756; 1·281	0·903
	Etoricoxib	0·341	0·035; 3·291	0·352
	Ibuprofen	1·077	0·560; 2·070	0·825
	Naproxen	0·890	0·508;1·559	0·684
Stroke	Celecoxib	0·328	0·013; 8·090	0·495
	Diclofenac	1·754	0·988; 3·114	0·055
	Etoricoxib	3·049	0·124; 75·219	0·495
	Ibuprofen	1·603	0·749; 3·433	0·225
	Naproxen	0·960	0·530; 1·737	0·892
CV Death	Celecoxib	0·428	0·053; 3·483	0·427
	Diclofenac	1·134	0·599; 2·145	0·700
	Ibuprofen	0·971	0·456; 2·066	0·939
	Lumiracoxib	2·337	0·287; 19·029	0·427
	Naproxen	0·736	0·338; 1·604	0·440
Composite CV	Celecoxib	0·837	0·209; 3·353	0·802
	Diclofenac	1·094	0·874; 1·369	0·435
	Etoricoxib	0·708	0·111; 4·506	0·715
	Ibuprofen	1·174	0·776; 1·777	0·448
	Lumiracoxib	2·337	0·287; 19·029	0·427
	Naproxen	0·879	0·612; 1·261	0·482

Figure 10. Comparison with coxibs without rofecoxib – Gunter 2017

NSAIDs that were not compared with rofecoxib show the same results as comparisons with all coxibs.

Myocardial infarction:

- Rofecoxib showed an increase in MI when compared to all NSAIDs (OR: 1.811, 95% CI: 1.379–2.378, P < 0.001; Figure 6), placebo (OR: 1.655, 95% CI: 1.029–2.661, P = 0.038; Figure 7), traditional NSAIDs (OR: 2.155, 95% CI: 1.146– 4.053, P = 0.017;Figure 8) and coxibs (OR: 1.800, 95% CI: 1.217–2.662, P = 0.003; Figure 9).
- Celecoxib and naproxen both showed a decrease in MI when compared to other coxibs (OR: 0.583, 95% CI: 0.396–0.857, P = 0.006) and (OR: 0.609, 95% CI: 0.375–0.989, P = 0.045), respectively] (Figure 9); but this difference did not persist when rofecoxib was removed from the comparison (Figure 10).
- All other NSAIDs - no statistical difference.

Stroke:

- Celecoxib showed a decrease in stroke when compared with all NSAIDs (OR: 0.603, 95% CI: 0.410–0.887, P = 0.010; Figure 6), traditional NSAIDs (OR: 0.517, 95% CI: 0.287–0.929, P = 0.027; Figure 8), and coxibs (OR: 0.509, 95% CI: 0.280–0.925, P = 0.027; Figure 9).
  But there was no difference when compared to placebo (Figure 7) or when rofecoxib was removed from the coxibs (Figure 10).
- Rofecoxib exhibited a higher incidence in stroke when compared with all NSAIDs (OR: 1.488, 95% CI: 1.027–2.155, P = 0.036; Figure 6) and other coxibs (OR: 1.933, 95% CI: 1.052–3.549, P = 0.034; Figure 9)

CV death:

- No NSAID exhibited significant difference in CV death in any outcome.

Composite CV:

- Celecoxib exhibited an overall lower incidence of the composite CV outcome when compared with all NSAIDs (OR: 0.805, 95% CI: 0.658–0.986, P = 0.036; Figure 6) and the other coxibs (OR: 0.557, 95% CI: 0.404–0.767, P < 0.001; Figure 9). This positive effect did not occur when rofecoxib was excluded from the coxibs (Figure 10).
- Rofecoxib demonstrated an increase in overall events when compared against all NSAIDs (OR: 1.612, 95% CI: 1.313–1.981, P < 0.001;Figure 6), placebo (OR: 1.572, 95% CI: 1.123–2.201, P = 0.008; Figure 7) and other coxibs (OR: 1.838, 95% CI: 1.323–2.554, P < 0.001; Figure 9).

Heterogeneity was assessed for each medication and outcome. Two analyses showed heterogeneity: ibuprofen in the CV death outcome and rofecoxib in the stroke outcome.

Discussion and Conclusions

Rofecoxib was the only NSAID to show an increase in CV adverse effects, while other coxibs and traditional NSAIDs demonstrated no difference.

The authors noted several weaknesses of the meta-analysis. None of the studies that met the inclusion criteria included the traditional NSAID meloxicam. As meloxicam is a relatively strong COX-2 inhibitor (Figure 2), comparison of this drug with other NSAIDs may have helped to distinguish the role of COX-2 selectivity in CV risk.

Several of the comparisons suffered from a lack of data and studies resulting in wide confidence intervals, particularly for individual NSAIDs compared to placebo and for the CV death outcome.

The meta-analysis did not address drug dose, duration, concurrent aspirin use, or baseline CV risk.

The authors noted the strengths of this meta-analysis were that it comprised a large patient population spanning multiple disease states and multiple NSAIDS, and for each drug comparisons were made with all NSAIDs, the class of drug (traditional NSAID and coxib) and placebo. The data were analysed both with and without rofecoxib to understand the extent of the role it plays in the CV adverse events attributed to the coxibs.

The authors conclude that the findings of this meta-analysis suggest that CV adverse effects of NSAIDs may not be based on the COX-2 selectivity of NSAIDs.

Comment

The meta-analysis includes 24 RCTs and two large observational studies. The RCTs date from 2000 to 2013, with all but one published prior to 2010 (eg, ADAPT, APC, APPROVe, CLASS, PreSAP, VICTOR and VIGOR). The most recent study (Cryer, 2013) was a 'prospective, randomised, open label, blinded endpoint (PROBE) study that aimed to assess if celecoxib is associated with a lower incidence of GI events than traditional NSAIDs (ie, the study was not designed to assess cardiovascular endpoints).

The two observational studies included in the analysis were a Prescription Event Monitoring study from the former NZ Intensive Medicines Monitoring Programme (Harrison-Woolrych, 2005), and a French population-based cohort study (CADEUS) that was designed to assess hospital admission rates for GI and CV events in real-life use of NSAIDs (Laharie, 2010). The nature of the data varies significantly between the two observational studies, and between the observational studies and the RCTs. The results of the meta-analysis should therefore be interpreted with caution.

The study aimed to determine whether COX-2 selectivity leads to increased cardiovascular risk. Each NSAID was compared with all NSAIDs combined, placebo, 'non-selective' NSAIDS, and with 'coxibs' (both with and without rofecoxib) for the defined cardiovascular outcomes (myocardial infarction, stroke, CV death, and all CV outcomes combined).

Although the discussion mentions that some non-selective NSAIDs (eg, diclofenac and meloxicam) are relatively COX-2 selective, this selectivity is not taken into account in the comparison with the group of so-called 'non-selective' NSAIDs, which includes diclofenac.

The grouping of drugs in this study as 'coxibs' and tNSAIDs does not accurately reflect the COX-2 selectivity of the individual NSAIDs. The authors' conclusion that CV adverse effects may not be related to COX-2 selectivity is, therefore, not justified by the results. It would be interesting to see whether re-analysis of the data with diclofenac grouped more appropriately with the selective COX-2 inhibitors would produce a different result, and whether the conclusion would be different.

3.1.1.2 Ungprasert et al, 2015 (Eur J Intern Med)

Non-steroidal anti-inflammatory drugs and risk of heart failure exacerbation: A systematic review and meta-analysis [31]

This meta-analysis of observational studies compared the risk of heart failure exacerbation in patients with pre-existing heart failure (HF) who took NSAIDs compared to patients with heart failure who did not take NSAIDs. The study aimed to better characterise the association between NSAIDs and HF, and to quantify the magnitude of the risk.

Methods

Medline and Embase databases were searched to May 2015 for potentially relevant articles using pre-define terms for HF and NSAIDs, including the names of individual NSAIDs. Inclusion criteria were:

1. Observational study (case-control or cohort)
2. Relative risk (RR), odds ratio (OR) hazard ratio (HR) or standardised incidence ratio (SIR) with 95% confidence intervals (CI) or exacerbation of heart failure for conventional NSAIDs and/or COX-2 inhibitors were provided
3. Patients with pre-existing HF were used as a reference group (cohort study) or patients with pre-existing HF but without exacerbation were used as control (case-control study).

Newcastle-Ottawa quality assessment scale was used to evaluate the quality of the included studies.

Data was extracted using a standardised data collection form. Statistical analyses were performed using Review Manager 5.3 software from the Cochrane Collaboration. Adjusted point estimates were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird which assigned weight of each study based on its standard error. A random-effect model was used given the high likelihood of between study variance due to the different study designs and populations. Point estimates from case-control and cohort studies were combined to increase the power (ie, OR of case-control study used as an estimate of the RR to pool with RR or HR of cohort study). Separate analyses were conducted for conventional NSAIDs, celecoxib and rofecoxib.

Statistical heterogeneity was assessed by Cochran's Q test, and complemented with the I^2 statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance (I^2 heterogeneity: 0-25% insignificant, >25-50% low, >50-27% moderate, >75% high).

Results

The search yielded 8356 potentially relevant articles of which 84 articles met the inclusion criteria for review based on title and abstract. A further 78 articles were subsequently excluded following full length review (72 not observational studies, 4 reported risk of incident not recurrent HF, 1 reported combination incident and recurrent HF, and 1 used patients without pre-existing HF as control). A total of 6 articles were included in the meta-analysis.

All of the included studies reported risk of exacerbation of HF among conventional NSAID users. Elevated risk was consistently observed in every study with the RRs ranging from 1.20 to 2.20. The pooled RR of all studies was 1.39 (95% CI 1.20 – 1.62) with I^2 of 15%. (Figure 11)

A subgroup analysis was performed to investigate if there was a difference in risk between study designs. The elevated risk was consistently observed across each study design (case-control, retrospective cohort and prospective cohort).

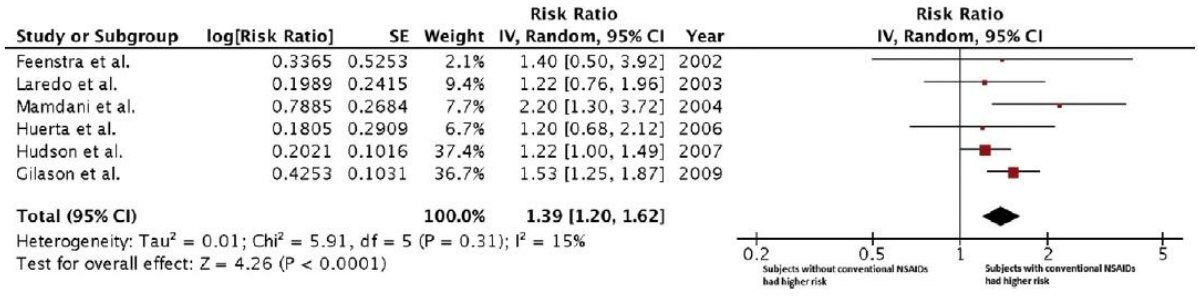


Figure 11. Forest plot of conventional NSAID studies – Ungprasert 2015

Risks of exacerbation of HF among celecoxib and rofecoxib uses were reported in four studies. The pooled RR of celecoxib studies was 1.34 (95% CI 0.98 – 1.85), which was not statistically different from conventional NSAIDs (p = 0.87). (Figure 12)

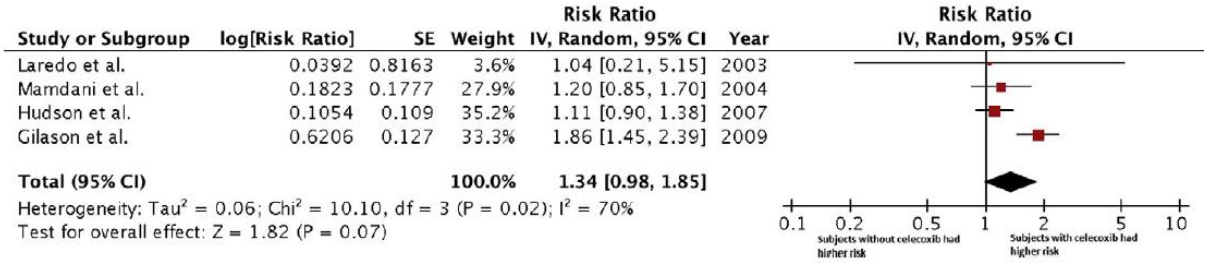


Figure 12. Forest plot of celecoxib studies – Ungprasert 2015

In contrast, the pooled RR of rofecoxib was 2.04 (95% CI, 1.68–2.48), which was significantly higher than conventional NSAIDs (p = 0.02). (Figure 13)

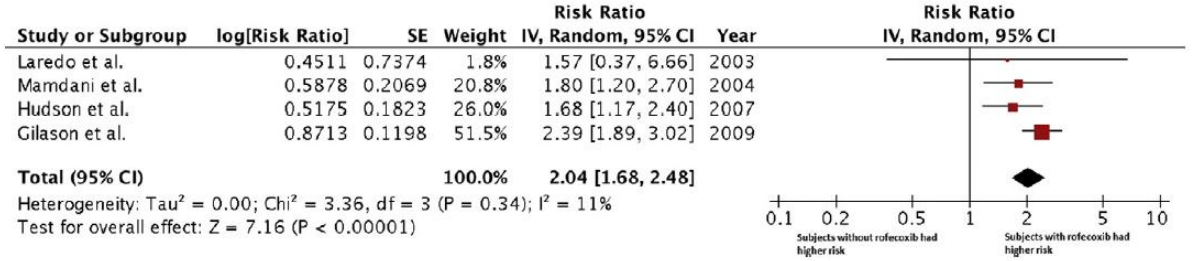


Figure 13. Forest plot of rofecoxib studies – Ungprasert 2015

Sensitivity analyses were performed by excluding one study at a time from the pooled analyses of conventional NSAID and rofecoxib analyses. The sensitivity analyses confirmed robustness of the results as the new pooled RRs remained significantly elevated.

Discussion and conclusions

The studies included in this meta-analysis were assessed as being of high quality. The authors note the following limitations:

- Most of the included studies were medical registry-based, with inherent limitation of coding inaccuracy and incompleteness.
- Most of the studies identified NSAID exposure based on prescription information from pharmaceutical databases, which does not guarantee actual consumption of the medicine, and does not capture OTC NSAID use.
- One study (Laredo 2003) used structured interview to capture drug exposure, which is limited by recall bias.
- Information on the severity of HF exacerbation was not available. Most of the studies identified cases of HF exacerbation from hospital admission databases; milder cases are not captured in this data.
- Most of the included studies were conducted in older populations (mean age > 70 years), so results may not be generalizable to younger patients with HF.
- Observational studies have an inherent risk of bias, such as selection and detection biases.

The authors concluded that patients with pre-existing HF who took NSAIDs had a significantly higher risk of HF exacerbation compared to patients with pre-existing HF who did not take NSAIDs. The excess risk was approximately 40% for conventional NSAIDs and celecoxib. The highest risk was observed among rofecoxib users, which was approximately double that for non-users.

Comment

Only six studies met the inclusion criteria for the meta-analysis, of which only four included coxibs.

The meta-analysis showed that use of NSAIDs significantly increased the risk of HF exacerbation in patients with pre-existing HF, compared to non-use of NSAIDs. The risk was similar for tNSAIDs and celecoxib.

3.1.2 Randomised Controlled Trials

3.1.2.1 Nissen et al, 2016 (NEJM)

Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis (PRECISION) [24]

The PRECISION trial was mandated by the US FDA following the outcome of the APC study in 2005[15], which identified a dose-related higher cardiovascular risk for celecoxib compared to placebo. PRECISION aimed to assess the non-inferiority of celecoxib compared to ibuprofen and naproxen in relation to cardiovascular outcomes. The study was sponsored by Pfizer. The published paper is provided as Annex 4.

Methods

PRECISION was a randomised, multicentre, double-blind, non-inferiority trial involving patients who were at increased cardiovascular risk (eg, coronary artery disease, occlusive disease of non-coronary arteries, diabetes mellitus, or high risk of atherosclerotic vascular disease) and had rheumatoid arthritis (RA) or osteoarthritis (OA). Randomisation was stratified according to the primary diagnosis (RA or OA), aspirin use, and geographic region. Other inclusion criteria were age ≥ 18 years, and requiring daily treatment with NSAIDs for arthritis pain.

Patients were randomly assigned in a 1:1:1 ratio to receive celecoxib 100 mg twice daily, ibuprofen 600 mg three times a day, or naproxen 375 mg twice daily. For patients with RA, investigators could increase the dose of celecoxib to 200 mg bd, ibuprofen to 800 mg tds or naproxen to 500 mg bd for symptomatic relief. For patients with OA, increases in ibuprofen or naproxen dose was permitted, but regulatory dose restrictions meant the dose escalation of celecoxib was not possible for these patients. Esomeprazole 20-40 mg was provided to all patients for gastric protection. Patients who were taking low-dose aspirin (≤ 325 mg daily) were permitted to continue this therapy.

The primary composite outcome, in a time-to-event analysis, was the first occurrence of an adverse event that met Antiplatelet Trialists Collaboration (APTC) criteria (ie, death from cardiovascular causes, including haemorrhagic death, non-fatal myocardial infarction, or nonfatal stroke). A secondary composite outcome, major adverse cardiovascular events, included the component of the primary outcome plus coronary revascularization or hospitalization for unstable angina or transient ischemic attack.

Naproxen was designated the primary comparator for assessment of non-inferiority for celecoxib. Non-inferiority was also assessed for celecoxib vs ibuprofen and ibuprofen vs naproxen. Non-inferiority required a hazard ratio (HR) of 1.12 or lower, as well as an upper 97.5% confidence limit of 1.33 or lower in both the intention-to-treat (ITT) population and the on-treatment population (OT; 'on-treatment' defined as during treatment and up to 30 days after discontinuation).

The trial was event-driven, requiring 762 events to provide 90% power to determine non-inferiority. Under the assumption of an annual event rate of 2% and a treatment discontinuation rate of 40%, the required sample size was estimated to be 20,000 patients. However, the observed event rate was lower, the discontinuation rate higher, and the enrolment rate slower than anticipated. The protocol was therefore amended to have the study provide 80% power, and the upper 97.5% confidence limit for non-inferiority in the OT population was modified to 1.40, which required 580 events in the intention-to-treat population and 420 events in the on-treatment population.

The protocol pre-specified a minimum follow-up time of 18 months, with censoring of data from event-free patients after 30 months in the ITT and after 43 months in the OT population.

A Cox proportional-hazards model with adjustment for stratification factors was used to calculate the hazard ratios and confidence intervals. A one-sided non-inferiority p value of less than 0.025 was considered to indicate statistical significance for the primary endpoint, with no adjustment for multiple comparisons.

Results

Enrolment took place between Oct 2006 and June 2014 at 926 centres across 13 countries. A total of 24,081 patients were randomly assigned to the celecoxib group (mean [±SD] daily dose, 209 ± 37 mg), the naproxen group (852 ± 103 mg), or the ibuprofen group (2045 ± 246 mg) for a mean treatment duration of 20.3 ± 16.0 months and a mean follow-up period of 34.1 ± 13.4 months. A comparison of the baseline characteristics of patients in each of the treatment groups is provided in Table 4.

During the trial, 68.8% of the patients stopped taking the study drug, and 27.4% of the patients discontinued follow-up.

Table 4. Baseline characteristics of patient in the ITT population – Nissen 2016

Baseline Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Celecoxib Group (N=8072)	Naproxen Group (N=7969)	Ibuprofen Group (N=8040)
Age — yr	63.0±9.5	63.3±9.4	63.2±9.4
Female sex — no. (%)	5175 (64.1)	5096 (63.9)	5174 (64.4)
Race — no. (%)†			
White	6058 (75.0)	5926 (74.4)	5991 (74.5)
Black	1090 (13.5)	1134 (14.2)	1108 (13.8)
Asian	164 (2.0)	172 (2.2)	173 (2.2)
Unspecified or other	760 (9.4)	737 (9.2)	768 (9.6)
Body-mass index‡	32.7±7.3	32.6±7.3	32.5±7.4
Primary arthritis diagnosis — no. (%)			
Osteoarthritis	7259 (89.9)	7178 (90.1)	7208 (89.7)
Rheumatoid arthritis	813 (10.1)	791 (9.9)	832 (10.3)
Current aspirin use — no. (%)	3701 (45.8)	3652 (45.8)	3712 (46.2)
Cardiovascular risk category — no. (%)			
Primary prevention	6209 (76.9)	6186 (77.6)	6206 (77.2)
Secondary prevention	1863 (23.1)	1783 (22.4)	1834 (22.8)
History of diabetes — no. (%)	2843 (35.2)	2768 (34.7)	2885 (35.9)
History of hypertension — no. (%)	6296 (78.0)	6145 (77.1)	6303 (78.4)
History of dyslipidemia — no. (%)	5080 (62.9)	4966 (62.3)	5002 (62.2)
Current smoker — no. (%)	1689 (20.9)	1631 (20.5)	1680 (20.9)
Current statin use — no. (%)	4367 (54.1)	4304 (54.0)	4307 (53.6)
Current DMARD use — no. (%)	572 (7.1)	602 (7.6)	584 (7.3)
Systolic blood pressure — mm Hg§	125.3±10.5	125.0±10.6	125.4±10.4
Diastolic blood pressure — mm Hg	75.5±8.0	75.4±8.0	75.5±7.9
Creatinine level — mg/dl	0.9±0.23	0.9±0.22	0.9±0.22
HAQ disability index¶	1.1±0.61	1.1±0.61	1.1±0.61
VAS score — mm‖	54.0±23.5	54.1±24.0	54.1±23.6

* Plus–minus values are means ±SD. Percentages may not total to 100 because of rounding. DMARD denotes disease-modifying antirheumatic drug.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ P=0.044 for the comparison among the three treatment groups.
¶ The Health Assessment Questionnaire (HAQ) disability index is based on 20 questions in eight categories regarding daily functioning; overall scores range from 0 to 3, with 0 indicating no disability and 3 indicating complete disability.
‖ Visual Analogue Scale of Pain (VAS) scores range from 0 to 100 mm, with higher scores indicating worse pain; differences greater than 13.7 mm are considered to be clinically significant.

In the ITT analyses, a primary outcome event occurred in 188 patients in the celecoxib group (2.3%), 201 patients in the naproxen group (2.5%), and 218 patients in the ibuprofen group (2.7%)

- HR for celecoxib vs. naproxen, 0.93; 95% CI, 0.76 to 1.13;
- HR for celecoxib vs. ibuprofen, 0.85; 95% CI, 0.70 to 1.04;
- P<0.001 for non-inferiority in both comparisons.

(Table 5 and Figure 14A)

In the OT analysis, a primary outcome event occurred in 134 patients in the celecoxib group (1.7%), 144 patients in the naproxen group (1.8%), and 155 patients in the ibuprofen group (1.9%)

- HR for celecoxib vs. naproxen, 0.90; 95% CI, 0.71 to 1.15;
- HR for celecoxib vs. ibuprofen, 0.81; 95% CI, 0.65 to 1.02;
- P<0.001 for non-inferiority in both comparisons.

(Table 6 and Figure 14B)

Table 5. Adjudicated outcomes in the ITT population – Nissen 2016

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

* Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with adjustment for stratification factors.
† The primary composite outcome in the time-to-event analysis was the first occurrence of an adverse event that met Antiplatelet Trialists Collaboration (APTC) criteria (death from cardiovascular causes, including hemorrhagic death; nonfatal myocardial infarction; or nonfatal stroke). The P value for the noninferiority of celecoxib as compared with either naproxen or ibuprofen with regard to this outcome was <0.001.
‡ The composite outcome of major adverse cardiovascular events included the components of the primary APTC outcome plus coronary revascularization or hospitalization for unstable angina or transient ischemic attack (TIA).
§ Definitions are provided in the Supplementary Appendix.

Table 6. Adjudicated outcomes in the OT population – Nissen 2016

Adjudicated Outcomes in the On-Treatment Population.

Outcome	Celecoxib (N=8030)	Naproxen (N=7933)	Ibuprofen (N=7990)	Celecoxib vs. Naproxen Adjusted Hazard Ratio (95% CI)*	Celecoxib vs. Ibuprofen Adjusted Hazard Ratio (95% CI)*
	number of patients (percent)				
Primary APTC outcome†	134 (1.7)	144 (1.8)	155 (1.9)	0.90 (0.71–1.15)	0.81 (0.65–1.02)
Major adverse cardiovascular events‡	247 (3.1)	253 (3.2)	284 (3.6)	0.95 (0.80–1.13)	0.82 (0.69–0.97)
Composite of serious gastrointestinal events	54 (0.7)	115 (1.4)	115 (1.4)	0.45 (0.33–0.63)	0.44 (0.32–0.61)
Clinically significant gastrointestinal events§	27 (0.3)	52 (0.7)	59 (0.7)	0.51 (0.32–0.81)	0.43 (0.27–0.68)
Iron-deficiency anemia of gastrointestinal origin§	27 (0.3)	66 (0.8)	58 (0.7)	0.40 (0.25–0.62)	0.43 (0.27–0.68)
Renal events	42 (0.5)	62 (0.8)	73 (0.9)	0.66 (0.44–0.97)	0.54 (0.37–0.80)
Hospitalization for congestive heart failure	28 (0.3)	35 (0.4)	38 (0.5)	0.78 (0.47–1.27)	0.70 (0.43–1.13)
Hospitalization for hypertension	25 (0.3)	32 (0.4)	37 (0.5)	0.76 (0.45–1.28)	0.64 (0.39–1.07)
Death from any cause	53 (0.7)	79 (1.0)	73 (0.9)	0.65 (0.46–0.92)	0.68 (0.48–0.97)
Components of composite outcomes					
Death from cardiovascular causes	35 (0.4)	49 (0.6)	51 (0.6)	0.69 (0.45–1.07)	0.64 (0.42–0.99)
Nonfatal myocardial infarction	58 (0.7)	53 (0.7)	76 (1.0)	1.06 (0.73–1.54)	0.72 (0.51–1.01)
Nonfatal stroke	43 (0.5)	45 (0.6)	32 (0.4)	0.93 (0.61–1.42)	1.26 (0.80–1.99)
Hospitalization for unstable angina	46 (0.6)	44 (0.6)	49 (0.6)	1.02 (0.68–1.54)	0.89 (0.59–1.33)
Revascularization	132 (1.6)	122 (1.5)	158 (2.0)	1.06 (0.83–1.35)	0.79 (0.62–0.99)
Hospitalization for TIA	12 (0.1)	16 (0.2)	21 (0.3)	0.73 (0.35–1.55)	0.54 (0.27–1.10)

* Hazard ratios were estimated with the use of a Cox proportional-hazards model with adjustment for stratification factors.
† The primary composite outcome in the time-to-event analysis was the first occurrence of an adverse event that met APTC criteria (death from cardiovascular causes, including hemorrhagic death; nonfatal myocardial infarction; or nonfatal stroke). The P value for the noninferiority of celecoxib as compared with either naproxen or ibuprofen with regard to this outcome was <0.001.
‡ The composite outcome of major adverse cardiovascular events included the components of the primary APTC outcome plus coronary revascularization or hospitalization for unstable angina or TIA.
§ Definitions are provided in the Supplementary Appendix.

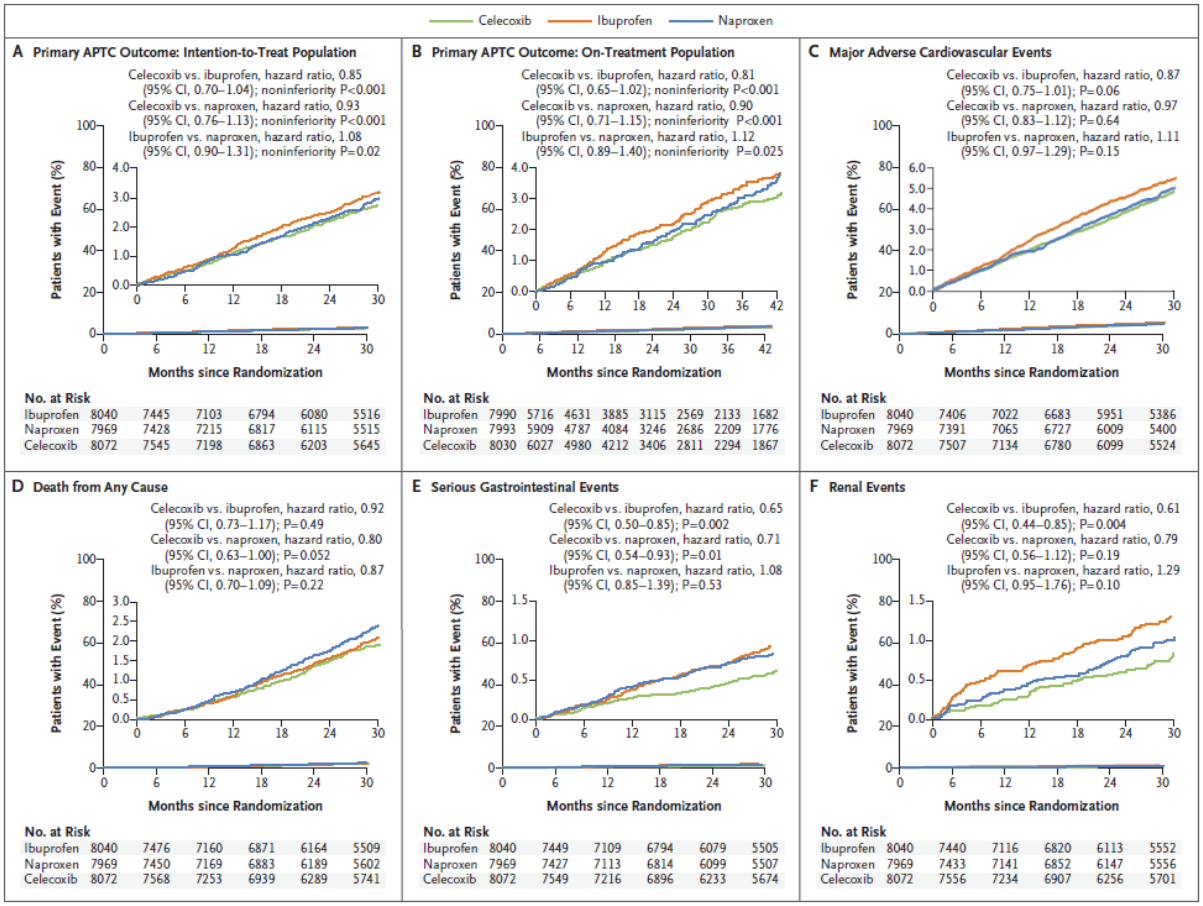


Figure 14. Summary of primary and secondary outcome measures in the PRECISION trial – Nissen 2016

Discussion and conclusions

Non-inferiority was demonstrated for celecoxib compared to ibuprofen and naproxen in both the ITT and OT populations.

To establish non-inferiority, the trial design required that pre-specified criteria be met in both the ITT population and the OT population. Each of these analyses provides complementary insights into drug safety. The ITT analysis preserves the integrity of randomization, but tends to dilute safety signals when patients do not adhere to the study treatment. The OT analysis considers events that occur only while patients are actually taking the study drug, which can strengthen safety signals.

The OT analyses are included to provide a complete accounting of outcomes, but the results in this population may have been influenced by between-group differences in rates of treatment discontinuation; therefore, these results are reported without P values and should be considered exploratory.

The authors noted the following limitations:

- Lower than expected adherence and retention.
- The regulatory dose restriction on celecoxib may have provided a safety advantage for celecoxib.
- The trial was not designed to assess the effects of aspirin in the relative safety of NSAIDs.

No inferences can be made regarding effects of NSAIDs compared to placebo or regarding the safety of intermittent treatment with low dose OTC preparations

The authors concluded that, at moderate doses, celecoxib was found to be non-inferior to ibuprofen or naproxen with regard to cardiovascular safety.

Comment

The study demonstrated non-inferiority for celecoxib compared to both ibuprofen and naproxen.

However, the study has some significant limitations that affect the interpretation of these results.

More than a quarter of patients were lost to follow-up and 70% discontinued their randomly assigned treatment during the study. By 6 months after randomisation, a quarter of patients had already discontinued treatment [32].

The mean doses of study medicine compared in this study are not comparable. The mean daily dose for celecoxib was 209 ± 37 mg, which is at the lower end of the recommended dose range. In comparison, the mean daily dose for ibuprofen was 2045 ± 246 mg, which is above the recommended 1200 mg maximum daily dose[4]. High dose ibuprofen (2400 mg per day) has previously been shown to be associated with a higher cardiovascular risk compared to doses of 1200 mg or below. (Annex 2).

Demonstration of non-inferiority compared to this higher dose of ibuprofen therefore does not infer a favourable cardiovascular safety profile.

Similarly, the mean daily dose of naproxen reported in this study was 852 ± 103 mg, which is higher than the recommended maintenance dose of 500 mg per day.

3.1.2.2 Solomon et al, 2017 (Am J Med)

The Risk of Major NSAID Toxicity with Celecoxib, Ibuprofen, or Naproxen: A Secondary Analysis of the PRECISION Trial [33]

This study is a post-hoc analysis of the PRECISION trial data to compare the risk of major NSAID toxicity for celecoxib, naproxen and ibuprofen. The analysis also examines whether various patient subgroups had differential risk of any major NSAID toxicity based on treatment assignment.

Methods

The PRECISION study methods are described in section 3.1.2.1.

This analysis focused on a composite safety outcome. A 'modified ITT' population (defined as the OT population) was used for the analysis.

Superiority hypotheses were tested, and no adjustments were made for multiple comparisons. Statistical significance, $P < .05$ for comparisons between treatment groups or $P < .10$ for treatment subgroup interaction, was based on nominal *P* values. Cumulative event curves were constructed for each of the three treatment arms for the primary and secondary outcomes.

HRs and corresponding 95% CIs comparing treatment groups for the primary and secondary outcomes of interest were calculated using Cox proportional hazards regression models, adjusting for stratification factors (geographic region), arthritis diagnosis (OA or RA), and low-dose aspirin use. Interactions between treatment group and potential risk factors were tested in the Cox regression

[4] The New Zealand data sheet for Brufen (ibuprofen 200 mg), dated 9 Oct 2017, gives a maximum daily dose of 6 tablets (1200 mg) in 24 hours. https://medsafe.govt.nz/profs/Datasheet/b/brufen200mgtab.pdf

models for each drug-to-drug comparison by adding the interaction term to the model. The protocol specified the censoring of analyses after 43 months.

Results

The frequency of any major NSAID toxicity differed across the 3 treatment arms: 4.1% of celecoxib users experienced a major NSAID toxicity, compared with 4.8% of naproxen users (*P* = .02) and 5.3% of ibuprofen users (*P* < .001), (Table 7).

Examination of the time until any major NSAID toxicity shows that events began early and increased at consistent rates across the follow-up.

For all three treatment arms, the adjusted HRs for the primary outcome show significantly higher risks for both naproxen users compared with the celecoxib users (HR, 1.20; 95% CI, 1.04-1.39, *P* = .02) and for ibuprofen users (HR, 1.38; 95% CI, 1.19-1.59, *P* < .001), (Figure 15A). Trends for the secondary outcome were similar, (Figure 15B).

These HRs translate into numbers needed to harm for the primary major NSAID toxicity as follows: naproxen compared with celecoxib 135 (95% CI, 72-971) and ibuprofen compared with celecoxib 82 (95% CI, 53-173).

Naproxen users experienced a reduced risk of major NSAID toxicities compared with ibuprofen users for the primary outcome (HR, 0.84; 95% CI, 0.73-0.98; *P* = .048) and for the extended secondary outcome (HR, 0.87; 95% CI, 0.76-0.98; *P* = .048).

Table 7. Frequency of major NSAID toxicity in the PRECISION trial modified ITT (ie, OT) population – Solomon 2017

	Total N = 23,953	Celecoxib N = 8030	Naproxen n = 7933	Ibuprofen N = 7990
Major NSAID toxicity*	1136 (4.7)	328 (4.1)	383 (4.8)	425 (5.3)
Major adverse CV events	784 (3.3)	247 (3.1)	253 (3.2)	284 (3.6)
Renal events	177 (0.7)	42 (0.5)	62 (0.8)	73 (0.9)
Serious gastrointestinal events	138 (0.6)	27 (0.3)	52 (0.7)	59 (0.7)
All-cause mortality	205 (0.9)	53 (0.7)	79 (1.0)	73 (0.9)
Expanded major NSAID toxicity†	1496 (6.2)	418 (5.2)	516 (6.5)	562 (7.0)
Heart failure exacerbations	234 (1.0)	63 (0.8)	79 (1.0)	92 (1.2)
Hypertension admissions	94 (0.4)	25 (0.3)	32 (0.4)	37 (0.5)
Iron-deficiency anemia	151 (0.6)	27 (0.3)	66 (0.8)	58 (0.7)

CV = cardiovascular; NSAID = nonsteroidal anti-inflammatory drug.

The totals are based on patients who took at least 1 dosage of study drug and thus are included in the modified intention-to-treat population. The cells in the table represent n (%). Major adverse cardiovascular events are defined as the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, revascularization, or hospital for transient ischemic attack.

*Major toxicity includes major adverse cardiovascular events, serious gastrointestinal events (gastroduodenal hemorrhage, gastric outlet obstruction, gastroduodenal small or large bowel perforation, large or small bowel hemorrhage, acute gastrointestinal hemorrhage, symptomatic gastric or duodenal ulcer or anemia defined as a decrease in hemoglobin ≥2 g/dL or hematocrit ≥10% with no clinical evidence of acute gastrointestinal bleed), renal events (development of renal insufficiency or renal failure, defined on the basis of development of any of the following: serum creatinine ≥2.0 mg/dL and increase of ≥0.7 mg/dL from baseline; hospitalization for acute renal failure with a doubling of the baseline serum creatinine or hyperkalemia with ≥50% elevation in serum creatinine; or initiation of dialysis), and all-cause mortality.

†Expanded major toxicity includes major toxicity; plus heart failure exacerbations, such as incident heart failure or heart failure hospitalizations; hypertension hospitalizations; or iron-deficiency anemia of gastrointestinal origin.

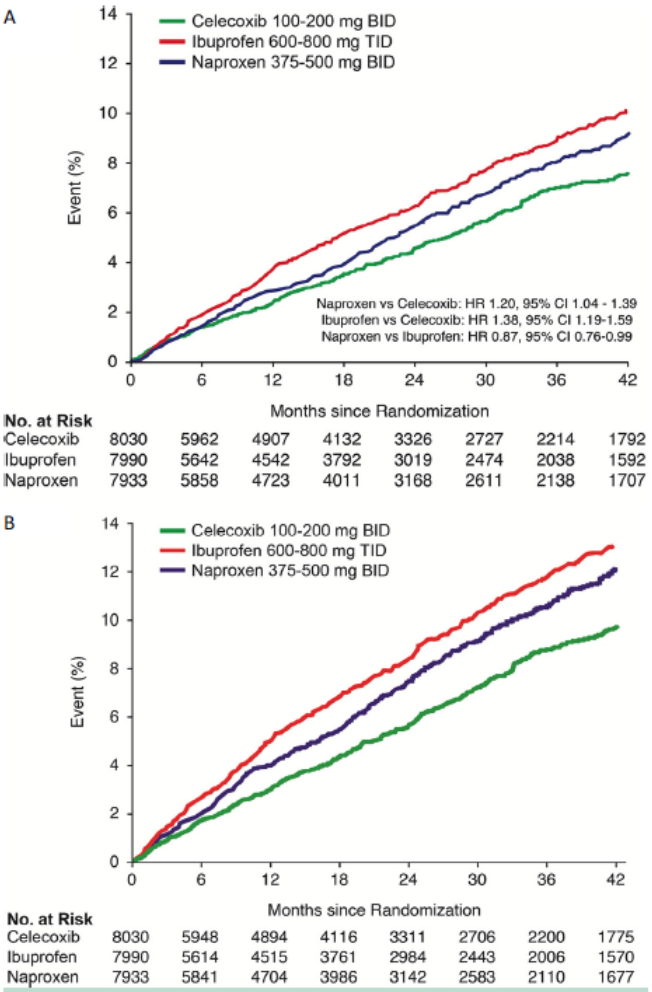


Figure 2 Cumulative incidence of major toxicity in PRECISION trial. The HRs are estimated in Cox proportional hazards regression models that include aspirin use and type of arthritis. **A**, The primary outcome of major NSAID toxicity. **B**, The expanded major NSAID toxicity outcome. CI = confidence interval; BID = 2 times per day; TID = 3 times per day.

Figure 15. Cumulative incidence of major toxicity in PRECISION trial – Solomon 2017

Discussion and conclusions

Limitations of the study were the same as were noted for the PRECISION trial. In particular, the authors note that dose up-titration differs across the treatment arms, and is greater for naproxen and ibuprofen than for celecoxib. This disparity was expected due to the regulatory restriction on celecoxib dose in the United States. The authors also acknowledge that the PRECISION trial was not designed specifically to answer the question posed in the post-hoc analysis, ie, whether celecoxib has a lower risk of NSAID toxicity compared to ibuprofen and naproxen.

Comment

This post-hoc analysis of the PRECISION study data compared the frequency and cumulative incidence of major NSAID toxicity as a combined outcome (including MACE, renal events, serious GI events and all-cause mortality). Hazard ratios were not provided for the individual components of the major toxicity outcome measure, such as MACE.

The analysis has the same limitations as the original study regarding dose comparability. As noted previously (section 3.1.2.1), the mean ibuprofen daily dose was well above the currently recommended 1200 mg daily maximum, and at a level that is now known to be associated with an increased cardiovascular risk. Comparison of ibuprofen at this level with the 'normal' doses of celecoxib creates a dose bias in favour of celecoxib. Similarly, the mean naproxen daily dose was disproportionate to the celecoxib dose.

The study also looked at risk factors for major NSAID toxicity, but did not look separately at risk factors for specific toxicities such as MACE.

3.1.2.3 Ruschitzka et al, 2017 (Eur Heart J)

Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) Trial. [34]

PRECISION-ABPM was a pre-specified sub-study of the PRECISION study.

Methods

Ambulatory blood pressure (ABP) measurements were obtained from all participants. ABP was measured every 20 min during daytime (06: 00–21: 59 h), and every 30min during night-time (22: 00–05: 59 h).

The primary ABPM sub-study endpoint was the change from baseline in 24-h mean systolic BP (SBP) at Month 4. Secondary endpoints were:

- the change from baseline in 24h mean SBP at Month 2,
- change from baseline in 24h average diastolic BP (DBP) at Months 2 and 4,
- 24-h pulse pressure (PP = SBP-DBP) change from baseline at Months 2 and 4,
- the mean awake (06: 00–21: 59 h) and sleep (22: 00–05: 59 h) SBP and DBP and
- mean arterial pressure change from baseline at Months 2 and 4.

Assuming a standard deviation of approximately 7.5 mmHg and using a Bonferroni adjustment for multiple treatment comparisons a sample size of 117 evaluable patients per arm allowed detection of a 3 mmHg difference between any two treatment groups, with 80% power and at the 0.0167 (=0.05/3) level of significance. Assuming a 35% drop-out rate, the study required randomization of 180 patients per arm (for a total of 540) to obtain 117 evaluable patients.

The ABPM analyses were based on the sub-study modified intention-to-treat (MITT) population, consisting of all randomized patients who had valid ambulatory BP data for analyses, thus excluding subjects with missing ABPM recording at baseline or subjects with a baseline ABPM but with no follow-up ABPM recordings.

The primary analysis used an analysis of covariance (ANCOVA) model with treatment and region as factors, and the baseline 24h average SBP and BMI as covariates. The least squares (LS) mean for each of the three treatment groups, the difference between each pair of the LS means, and the P-values for these differences were presented. Each of the three comparisons was considered statistically significant if the P-value was less than 0.0167. 95% confidence intervals (CIs) were presented for the primary analysis to allow for comparisons to other studies utilizing unadjusted intervals.

Results

Five hundred eighty-nine patients were screened and 545 enrolled from 60 centres in the USA between 18 September 2008 and 25 March 2013; 101 patients were excluded from analysis leaving 444 analysable participants with successful baseline, 2 or 4 months post-randomization ABPM assessments. There were 146 patients assigned to celecoxib (mean daily dose 208 ± 34mg), 147 to naproxen (852 ± 98mg), and 151 to ibuprofen (2031 ± 237mg). The groups had similar baseline characteristics, including BP, serum creatinine, plasma glucose, and glycosylated haemoglobin concentrations.

Sixty-two percent of the patients were treated with ACE inhibitors or ARBs, 35% with a diuretic and 22% with a calcium channel blocker, while 53% received multiple antihypertensive therapies.

A total of 374 (84%) of 444 patients completed 4 months of the sub-study, which included the primary outcome and ABP assessment. The remaining 70 patients (20 celecoxib, 33 ibuprofen, and 17 naproxen) did not have a valid Month 4 ambulatory BP assessment; 15 of these 70 patients were withdrawn from the study or treatment due to an adverse event prior to Month 4: 4 (2.7%) of the patients had been randomized to celecoxib, 7 (4.6%) to ibuprofen, and 4 (2.7%) to naproxen.

The hourly ambulatory SBP curves over 24 h at baseline and at Month 4 for the 3 treatment groups are shown in Figure 16. A consistent increase from baseline in SBP was observed in the ibuprofen group (P-value for change in 24-h SBP< 0.001). The change from baseline to Month 4 in 24-h SBP was not statistically significant for celecoxib and naproxen (P= 0.801 and 0.117, respectively); Figure 16B.

The change in mean 24h SBP in celecoxib, ibuprofen, and naproxen-treated patients was -0.3 mmHg (95% CI, -2.25, 1.74), 3.7 mmHg (95% CI, 1.72, 5.58), and 1.6 mmHg (95% CI, -0.40, 3.57), respectively (Figure 17).

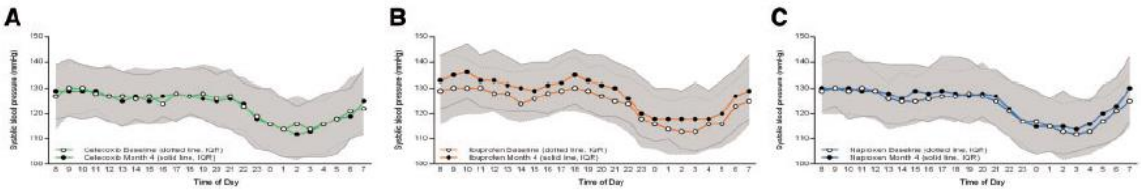


Figure 16. Hourly ambulatory SBP curves over 24 h for (A) celecoxib, (B) ibuprofen and (C) naproxen – Ruschitzka 2017

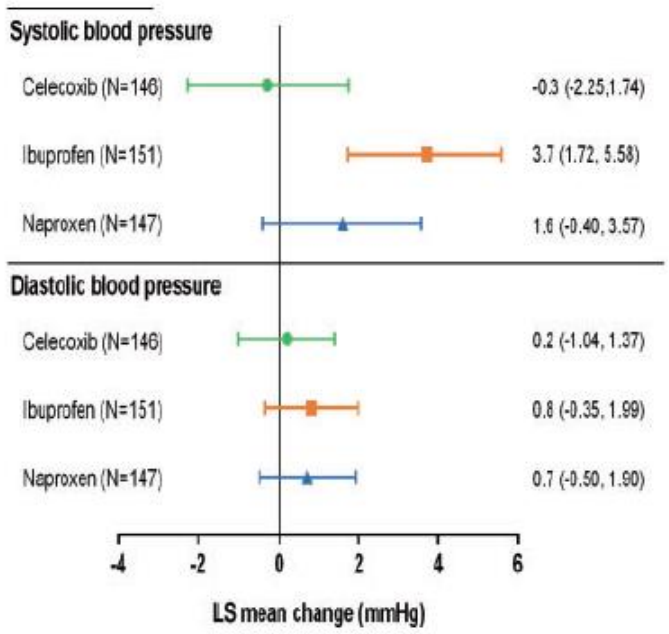


Figure 17. Change in ambulatory 24 h sBP and DBP from baseline at 4 months – Ruschitzka 2017

These changes resulted in a statistically significant difference of -3.9 mmHg (95% CI, -6.19, -1.61; P≤ 0.001) between celecoxib and ibuprofen (highlighted in Table 8). Differences of -1.8mmHg (95% CI, -4.15, 0.47; P= 0.12) between celecoxib and naproxen, and of -2.1 mmHg (95% CI, -4.36, 0.23; P=0.08) between naproxen and ibuprofen were not statistically significant. (Table 8)

Table 8. Effects of celecoxib, ibuprofen, and naproxen on 24 h ambulatory blood pressure – Ruschitzka 2017

Parameter	Celecoxib 100–200 mg BID *n* = 146	*P*-value	Ibuprofen 600–800 mg TID *n* = 151	Naproxen 375–500 mg BID *n* = 147	*P*-value
Systolic blood pressure					
Baseline	124.18 ± 12.351		125.24 ± 11.775	123.55 ± 11.00	
After 4 months	124.00 ± 13.213		128.65 ± 13.542	125.46 ± 12.487	
Change from Baseline	-0.18 ± 9.400		3.42 ± 12.259	1.91 ± 9.796	
Change from BL vs. Ibuprofen (Difference in LS Mean (CI))	-3.9 (-6.19, -1.61)	0.0009		-2.06 (-4.36, 0.23)	0.08
Change from BL vs. Naproxen (Difference in LS mean (CI))	-1.84 (-4.15, 0.47)	0.12			
Diastolic blood pressure					
Baseline	70.88 ± 8.00		70.53 ± 8.457	70.12 ± 7.399	
After 4 months	70.87 ± 8.770		71.26 ± 9.002	70.85 ± 7.922	
Change from baseline	-0.01 ± 5.933		0.74 ± 6.878	0.74 ± 6.294	
Change from BL vs. Ibuprofen (difference in LS Mean (CI))	-0.65 (-2.04, 0.74)	0.36		-0.12 (-1.51, 1.27)	0.87
Change from BL vs. Naproxen (Difference in LS mean (CI))	-0.53 (-1.94, 0.87)	0.46			
Mean blood pressure					
Baseline	89.65 ± 8.454		89.86 ± 8.806	88.87 ± 7.475	
After 4 months	89.69 ± 9.481		91.56 ± 9.295	90.26 ± 8.470	
Change from Baseline	0.04 ± 6.972		1.71 ± 8.742	1.39 ± 7.357	
Change from BL vs. Ibuprofen (Difference in LS Mean (CI))	-1.75 (-3.4, -0.10)	0.04		-0.69 (-2.34, 0.96)	0.41
Change from BL vs. Naproxen (Difference in LS mean (CI))	-1.06 (-2.72, 0.61)	0.21			
Pulse pressure					
Baseline	53.31 ± 9.920		54.71 ± 10.087	53.43 ± 9.833	
After 4 months	53.13 ± 9.871		57.39 ± 11.804	54.60 ± 10.334	
Change from baseline	-0.17 ± 4.884		2.68 ± 7.018	1.17 ± 5.348	
Change from BL vs. Ibuprofen (Difference in LS Mean (CI))	-2.99 (-4.3, -1.68)	<0.0001		-1.71 (-3.02, -0.40)	0.01
Change from BL vs. Naproxen (Difference in LS mean (CI))	-1.28 (-2.60, 0.04)	0.06			

Discussion and conclusions

The authors concluded that the PRECISION-ABPM trial reveals differential BP effects of treatment with celecoxib vs. the non-selective NSAID ibuprofen.

Comment

The study showed a statistically significant increase in ambulatory 24h SBP for ibuprofen. This increase resulted in a statistically significant difference between celecoxib and ibuprofen in the change from baseline at 4 months for SBP.

However, this sub-study of the PRECISION trial has the same limitations of dose comparability as were noted in the parent study. Not surprisingly, the high mean daily doses of ibuprofen studied in this trial resulted in elevated SBP (a known adverse effect of high dose NSAIDs), but was not observed with the relatively low mean daily dose of celecoxib.

3.1.2.4 Macdonald et al, 2017 (Eur Heart J)

Randomized trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib: the Standard care vs. Celecoxib Outcome Trial (SCOT) [35]

The SCOT trial used a Prospective Randomised Open label Blinded Endpoint evaluation (PROBE) design to compare the CV and GI safety of continuing prescribed 'non-selective' NSAID (nsNSAID) therapy vs. switching to prescribed celecoxib in individuals with OA or RA. The study aimed to mimic normal clinical practice and patient behaviour. Accordingly, there were no study visits after randomisation, study treatments were dispensed in community pharmacies, and follow-up used electronic medical records of hospitalisations and deaths. The trial, which was mandated by the EMA, was funded by Pfizer through an Investigator Initiated Research Grant. The University of Dundee was the study sponsor. The published paper is provided as Annex 5.

Methods

The study was conducted in the UK, Denmark and the Netherlands in patients aged 60 years or over without significant CV disease (a history of coronary or cerebrovascular disease or New York Heart Association class III or IV heart failure).

Study participants were identified in primary care. Those who responded to an invitation letter and satisfied inclusion and exclusion criteria were randomised to switch to prescribed celecoxib or continue their usual prescribed nsNSAID. Subjects could optionally provide a blood sample for later analyses of lipids and uric acid levels.

Prescribed nsNSAIDs with an estimated frequency of usage of >12% (ibuprofen and diclofenac) were assigned to unique strata and other NSAIDs were pooled in a single stratum for the purpose of randomisation. Randomisation was also stratified by OA or RA status. The trial treatments were prescribed at approved doses and adjusted as clinically indicated.

The primary endpoint was the composite of hospitalisation for non-fatal MI or other biomarker positive acute coronary syndrome, non-fatal stroke or CV death.

Secondary outcomes were:

- hospitalisation or death for upper GI ulcer complications (bleeding, perforation, or obstruction
- hospitalisation for upper GI ulcer complications or primary outcome
- hospitalisation for heart failure

- hospitalisation for heart failure or primary outcome
- death from any cause
- new or worsening renal failure
- hospitalisation for critical limb ischaemia
- hospitalisation for pulmonary embolism.

Follow-up was by record-linkage. Treatment-related adverse events and all serious adverse events reported by study sites were also recorded and reconciled with the record-linkage data. For potential endpoints, support documentation was retrieved from hospital records, de-identified and reviewed by CV or GI endpoint committees.

Baseline characteristics were compared using two-sample t-tests (or Mann–Whitney tests) and v2 (or Fisher's exact) tests, as appropriate. Cox proportional hazards models were used to analyse time-to-first event data. Where the number of events was <30, the Cox model was replaced by an exact Poisson regression model. Statistical significance was based on the Wald statistic, and two-sided 95% confidence intervals (CIs) for the estimated hazard ratio (HR) (or rate ratio for the Poisson model).

The main non-inferiority analysis for the primary and secondary outcomes used OT comparisons. The non-inferiority limit was HR of 1.4 for the primary CV endpoint requiring 277 first primary endpoints for 80% power. OT analyses censored subjects after the first of: discontinuation from the randomized treatment group (for the nsNSAID group this involved withdrawal from any nsNSAID), death, withdrawal of consent, or end-of-study date. These analyses were supported by a modified ITT analysis censoring on the first of death, withdrawal of consent for follow-up, or end-of-study date.

Treatment-by-subgroup interactions were tested in Cox models (or by exact Poisson regression analysis) incorporating subgroup-by-treatment interactions. Time-to-event curves were estimated by the Kaplan–Meier method.

Results

Enrolment took place between January 2008 and March 2013. In total, 7297 patients from 9 trial centres and 706 primary care practices were randomised. The median ITT follow-up for the primary outcome was 3.0 years (maximum 6.3 years, 22 600 person-years). The two groups (celecoxib and nsNSAID) were well balanced, except that the celecoxib group had a slightly higher proportion of males than the nsNSAID group (41.9 % vs. 39.2 %, respectively).

In the prescribed celecoxib group, 50.9% withdrew from the randomized therapy compared with 30.2% not continuing with any prescribed nsNSAID therapy (P<0.0001). The most common reason for withdrawal from the celecoxib group was lack of efficacy (23.3% vs. 9.7 % for the nsNSAID group). Adverse event was the reason for withdrawal in 17.3% celecoxib group withdrawals vs. 14.1 % of nsNSAID group withdrawals.

The mean doses of NSAIDs taken per day in Scotland, where full data were available, were 169.8 (SD 80.6) mg for celecoxib, 79.4 (38.3) mg for diclofenac, 675.9 (345.9) mg for ibuprofen, and 581.0 (263.4) mg for naproxen.

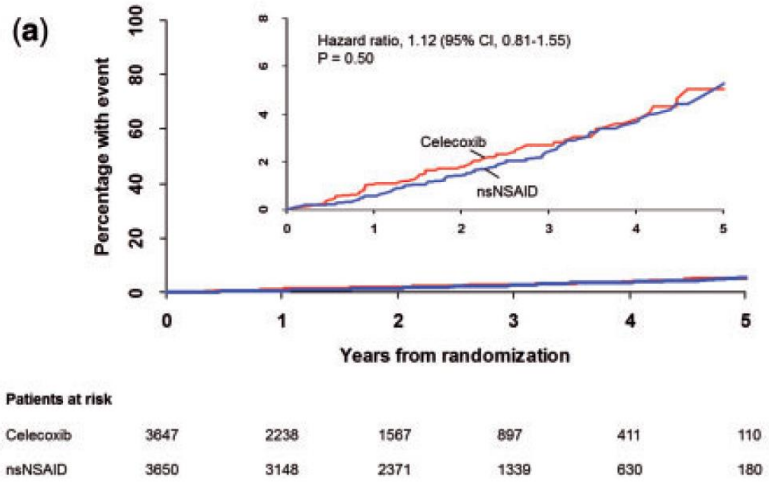
A total of 278 primary endpoints occurred in 249 (1.12 per 100 patient-years) participants in the ITT analysis, 146 (0.90 per 100 patient-years) of these during the OT period (Table 9 and Figure 18).

In the ITT analysis, 125 participants (1.14 per 100 patient-years) in the prescribed celecoxib group had a primary outcome compared with 124 (1.10 per 100 patient-years) in the prescribed nsNSAID group (HR 1.04; 95% CI, 0.81–1.33; P= 0.75). Statistically significant non-inferiority was demonstrated in the ITT analysis. (Figure 18B)

In the OT analysis, 65 participants (0.95 per 100 patient-years) in the celecoxib group had a primary outcome compared with 81 (0.86 per 100 patient-years) in the nsNSAID group (HR 1.12; 95% CI, 0.81–1.55; P=0.50). (Figure 18A)

Table 9. Treatment comparisons (celecoxib vs. nsNSAIDs) for primary outcome and secondary endpoints - MacDonald 2017

	On-treatment analysis			Intention-to-treat analysis		
	Celecoxib	nsNSAID		Celecoxib	nsNSAID	
Numbers of subjects	3647	3650		3647	3650	
Follow-up, years (primary outcome)	6842	9460		10 993	11 318	
	n (*n*/100PY)	*n* (*n*/100PY)	HR (95% CI); *P*	*n* (*n*/100PY)	*n* (*n*/100PY)	HR (95% CI); *P*
Primary endpoint	65 (0.95)	81 (0.86)	1.12 (0.81, 1.55); 0.50	125 (1.14)	124 (1.10)	1.04 (0.81, 1.33); 0.75
Hospitalization for non-fatal MI	38 (0.56)	40 (0.42)	1.34 (0.86, 2.09); 0.20	70 (0.63)	56 (0.49)	1.29 (0.91, 1.84); 0.15
Non-fatal stroke	16 (0.23)	25 (0.26)	0.89 (0.47, 1.67); 0.71	31 (0.28)	36 (0.32)	0.89 (0.55, 1.44); 0.63
CV death	15 (0.22)	17 (0.18)	1.22 (0.61, 2.46); 0.57	32 (0.29)	39 (0.34)	0.85 (0.53, 1.35); 0.49
Biomarker positive ACS	0 (0)	1 (0.01)	—	0 (0)	1 (0.01)	—
Secondary endpoints						
(a) Hospitalization or death for upper GI ulcer complications	7 (0.10)	5 (0.05)	1.96 (0.54, 7.84); 0.38	10 (0.09)	5 (0.04)	2.08 (0.65, 7.74); 0.27
(b) Secondary endpoint (a) or Primary endpoint	72 (1.05)	86 (0.91)	1.16 (0.85, 1.59); 0.34	132 (1.20)	129 (1.14)	1.06 (0.83, 1.35); 0.65
(c) Hospitalization for heart failure	7 (0.10)	10 (0.11)	0.96 (0.31, 2.78); 1.00	11 (0.10)	15 (0.13)	0.76 (0.31, 1.76); 0.61
(d) Secondary endpoint (c) or Primary endpoint	70 (1.02)	86 (0.91)	1.14 (0.83, 1.56); 0.43	130 (1.18)	132 (1.17)	1.02 (0.80, 1.29); 0.90
(e) All-cause mortality	35 (0.51)	41 (0.43)	1.20 (0.76, 1.88); 0.43	99 (0.89)	111 (0.97)	0.92 (0.70, 1.21); 0.56
(f) Hospitalization for new or worsening renal failure	4 (0.06)	3 (0.03)	1.83 (0.31, 12.49); 0.67	7 (0.06)	8 (0.07)	0.90 (0.28, 2.83); 1.00



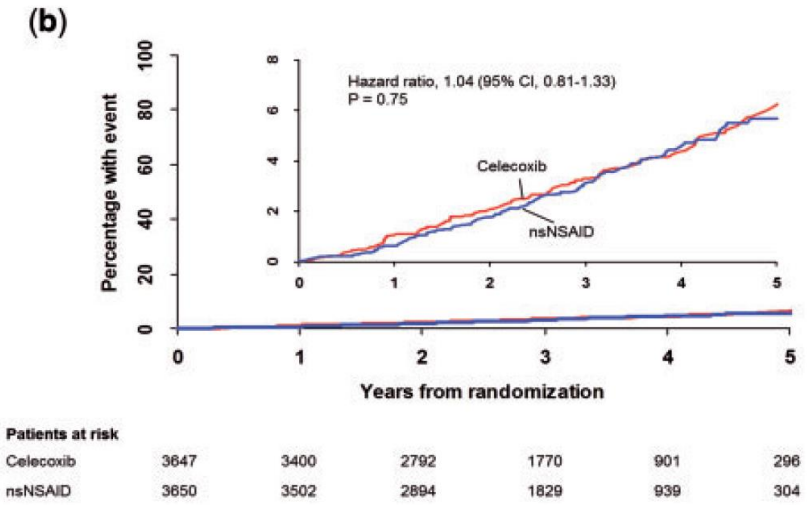


Figure 18. Primary composite endpoint: (a) on-treatment and (b) intention-to-treat – MacDonald 2017

Results for the primary outcome for the initial nsNSAID strata are shown in Figure 19.

There were no statistically significant subgroup interactions. Absolute differences in the rates (celecoxib – nsNSAID group) of the primary endpoint were 0.8, 95% CI (-0.5, 2.0) events per 1000 patient-years for the on-treatment analysis and 0.4, 95% CI (-1.1, 1.8) events per 1000 patient-years for the ITT analysis.

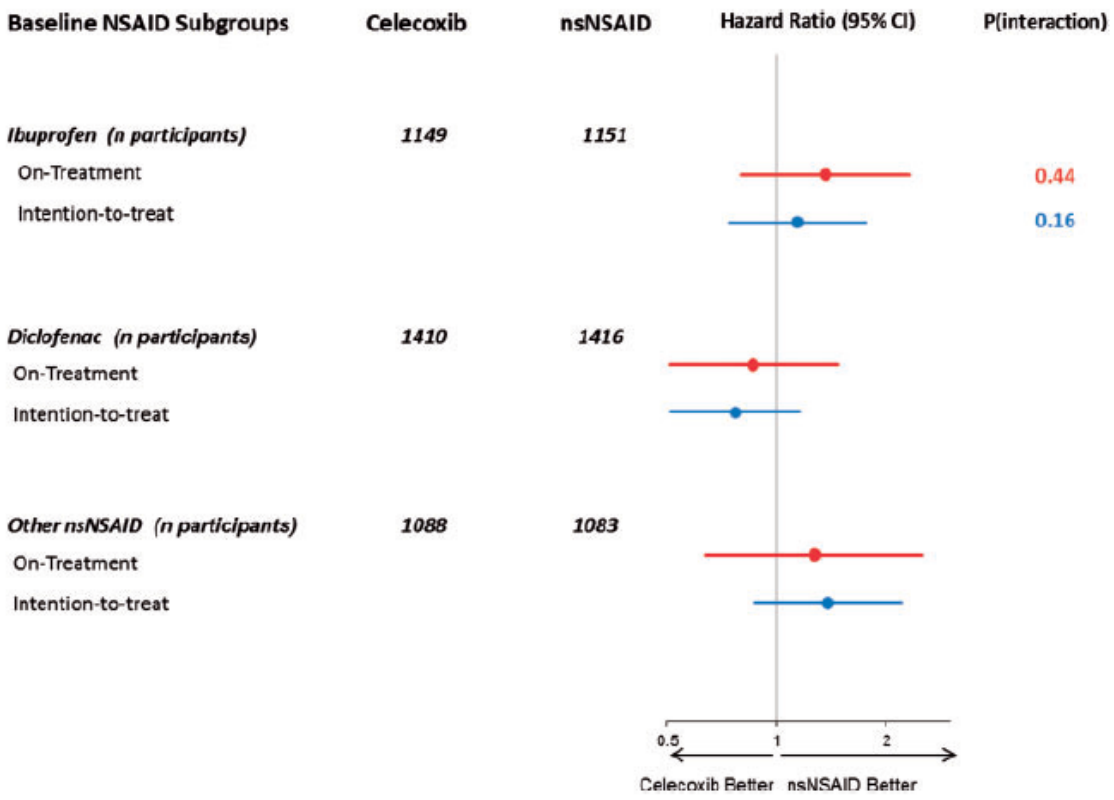


Figure 19. Forest plot for primary endpoint by subgroups of baseline NSAID use for OT and ITT analyses – MacDonald 2017

Discussion and conclusions

During the trial there was significant public debate about COX-2 inhibitor safety which may have dissuaded primary care physicians from up-titrating celecoxib and influenced overall withdrawal rates. In addition, EMA warnings about the CV risks of diclofenac resulted in primary care physicians being unhappy to continue to prescribe diclofenac, resulting in a protocol amendment that allowed patients in the nsNSAID group to switch to other prescribed nsNSAIDs.

The low CV event rate resulted in reduced power to establish non-inferiority in the OT analysis. Increasing the size of the trial once the low event rate had become apparent was not feasible. The differential discontinuation rate (48.2 % for celecoxib vs. 31.5 % for nsNSAIDs) further affected the OT analyses. The reasons for this differential withdrawal were considered complex and likely to be associated with both patient and prescriber preference, on a background of adverse publicity about NSAIDs in general at the time the study was being conducted.

The authors concluded that in patients 60 years and over, free from CV disease and taking prescribed chronic nsNSAIDs, CV events were infrequent and similar on celecoxib and nsNSAIDs. There was no advantage of a strategy of switching prescribed nsNSAIDs to prescribed celecoxib. This study excluded an increased risk of the primary endpoint of more than two events per 1000 patient-years associated with switching to prescribed celecoxib.

Comment

In contrast to the PRECISION study, the mean doses for each of the NSAIDs (based on the information available from Scotland) were fairly comparable: celecoxib 169.8 (SD 80.6) mg, diclofenac 79.4 (38.3) mg, ibuprofen 675.9 (345.9) mg, and naproxen 581.0 (263.4) mg.

This study showed that there was no statistically significant difference in the primary composite endpoint or any of its components between the celecoxib and nsNSAID groups in either the OT or ITT analyses.

Non-inferiority was demonstrated in the ITT analysis; however, the study predetermined that non-inferiority would be assessed on the OT comparison.

The pre-specified HR non-inferiority limit was set at 1.4 for the primary CV endpoint. Ie, in the comparison of the primary composite endpoint between celecoxib and nsNSAID, the upper bound of the 95% CI for the HR should not exceed 1.4.

In the OT analysis, the hazard ratio for the primary composite endpoint for celecoxib vs. nsNSAID was 1.12 (95% CI 0.81 to 1.55); ie, the upper bound of the 95% CI exceeded the pre-specified margin of 1.4, so non-inferiority was not achieved.

A low CV event rate was considered to have reduced the power to establish non-inferiority in the OT analysis.

3.1.3 Observational studies

3.1.3.1 Schmidt et al, 2018 (BMJ)

Diclofenac use and cardiovascular risks: series of nationwide cohort studies [36]

Diclofenac is a traditional NSAID with COX-2 selectivity similar to COX-2 inhibitors. Its cardiovascular risk compared to other traditional NSAIDs has not been examined in a randomised controlled trial. Such a trial would now be considered unethical due to concerns about its cardiovascular risk.

This Danish study comprised a series of nationwide cohort studies, each mimicking the strict design criteria of a clinical trial (emulated trial design), to compare rates of major adverse cardiovascular events among diclofenac initiators with rates among non-initiators or initiators of active comparator drugs.

In Denmark, individual level linkage of all Danish registries is possible by use of a unique personal identification number. Information for this study was obtained from the following sources:

- Danish National Patient Registry, which covers all Danish hospitals, was used to identify the study population, their comorbidities and non-fatal endpoints.
- Danish National Health Insurance Service Registry for data on general practice visits.
- Danish National Prescription Registry was used to identify drug use.
- Danish Civil Registration System – records all changes in vital status and migration for the entire Danish population
- Danish Register of Causes of Death

Apart from low-dose ibuprofen (200 mg) and diclofenac (from 16 July 2007 t o14 December 2008), all non-aspirin NSAIDs require a prescription in Denmark, and prescription medicines are subsidised.

Methods

The population based registries were used to emulate the eligibility criteria, washout period, treatment groups and follow-up period of a clinical controlled trial.

Eligible individuals were aged ≥ 18 years with at least one year of continuous prescription records before date of study entry, and who did not redeem NSAID prescriptions in the 12 month washout period before enrolment.

Exclusion criteria were previous cardiovascular disease (angina pectoris, MI, coronary intervention, heart failure, stroke, peripheral vascular disease, VTE, atrial fibrillation of flutter, or use of digoxin, nitrates, antiplatelet drugs or anticoagulant drugs within one year), chronic kidney disease, chronic liver disease, other alcoholism related diseases, ulcer disease, malignancy, schizophrenia (or use of antipsychotic drugs) or dementia.

All initiators of diclofenac and naproxen were identified during the month of January 1996. Each person was followed up to a non-fatal endpoint, death, loss to follow-up, or 30 days of follow-up. Enrolment was repeated in the months of February and March, and subsequently for every month up to December 2016, (Figure 20).The series of 252 emulated trials were then statistically pooled into one model, generating a sample size of 1 370 832 diclofenac initiators and 291 490 naproxen initiators. A similar approach was used to identify ibuprofen initiators (n=3 878 454) and propensity score matched initiators of paracetamol (n=764 781) and NSAID non-initiators (n=1 303 209).

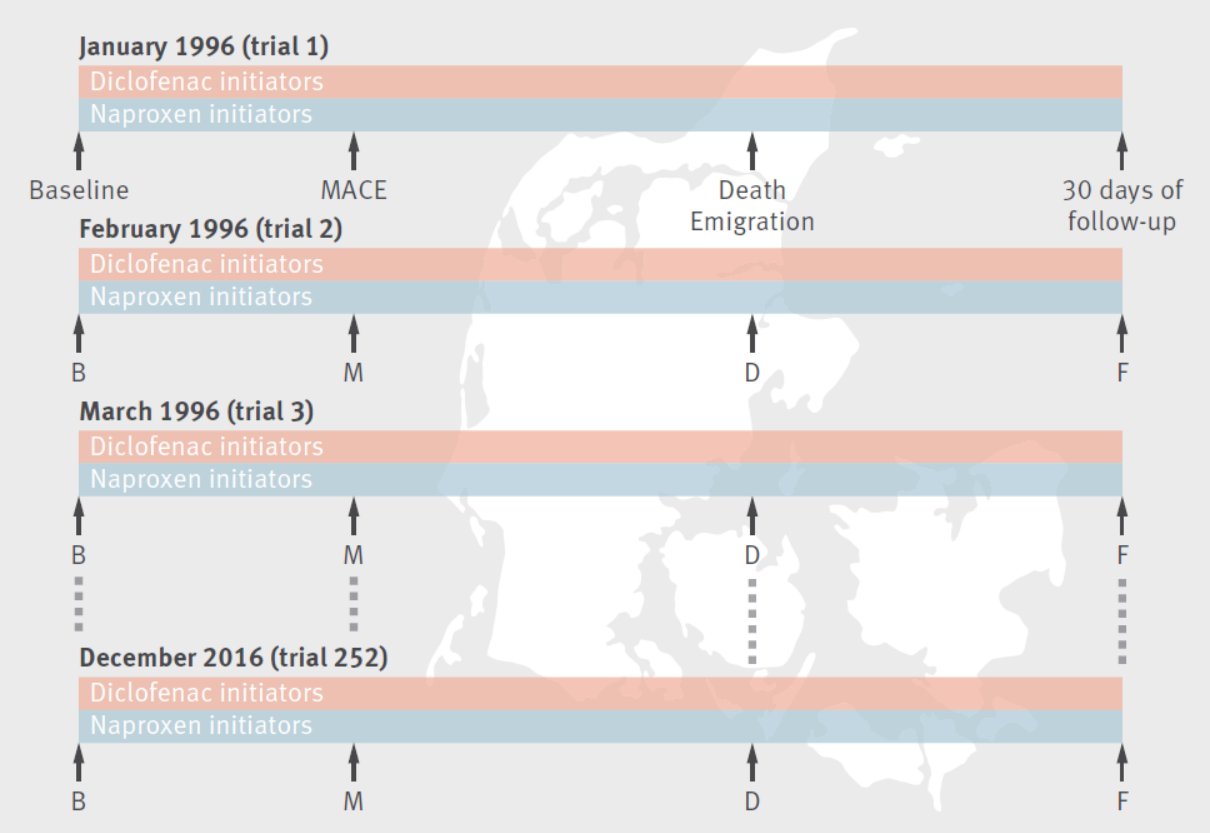


Figure 20. Emulated trial design, to compare rates of major adverse cardiovascular events among diclofenac initiators with rates among non-initiators or initiators of active comparator drugs in Denmark – Schmidt 2018

B=baseline; MACE =major adverse cardiovascular events; D=death or emigration; F=30 days of follow-up.

Cox proportional hazards regression was used to compute the intention to treat hazard ratio (as a measure of the incidence rate ratio) of major adverse cardiovascular events within 30 days of initiation.

Individuals could participate in more than one of the trials.

The active NSAID comparator models adjusted for baseline covariates including sex, age, year, comorbidity and drug treatment use. In addition to the primary low risk population (defined by eligibility criteria), sampling was repeated for patients with diabetes mellitus (ie, moderate risk) and for patients with previous myocardial infarction or heart failure (ie, high risk). In the latter, cardiovascular drugs use within one year was omitted as an exclusion criterion. The study population was also stratified by age (< 65 years, 65-79 years, or ≥ 80 years), sex, calendar period (1996-2002, 2003-2009, and 2010-2016), and diclofenac dose (< 100mg vs. 100mg tablets).

Results

The MACE rate among diclofenac initiators increased by 50% compared with non-initiators (incidence rate ratio 1.5, 95% confidence interval 1.4 to 1.7), 20% compared with paracetamol or ibuprofen initiators (both 1.2, 1.1 to 1.3), and 30% compared with naproxen initiators (1.3, 1.1 to 1.5), (Figure 21).

The event rate for diclofenac initiators compared to no NSAID was increased for each component of the combined endpoint: atrial fibrillation/flutter 1.2 (1.1 to 1.4), ischaemic stroke 1.6 (1.3 to 2.0),

heart failure 1.7 (1.4 to 2.0), myocardial infarction 1.9 (1.6 to 2.2), and cardiac death 1.7 (1.4 to 2.1), (Figure 21).

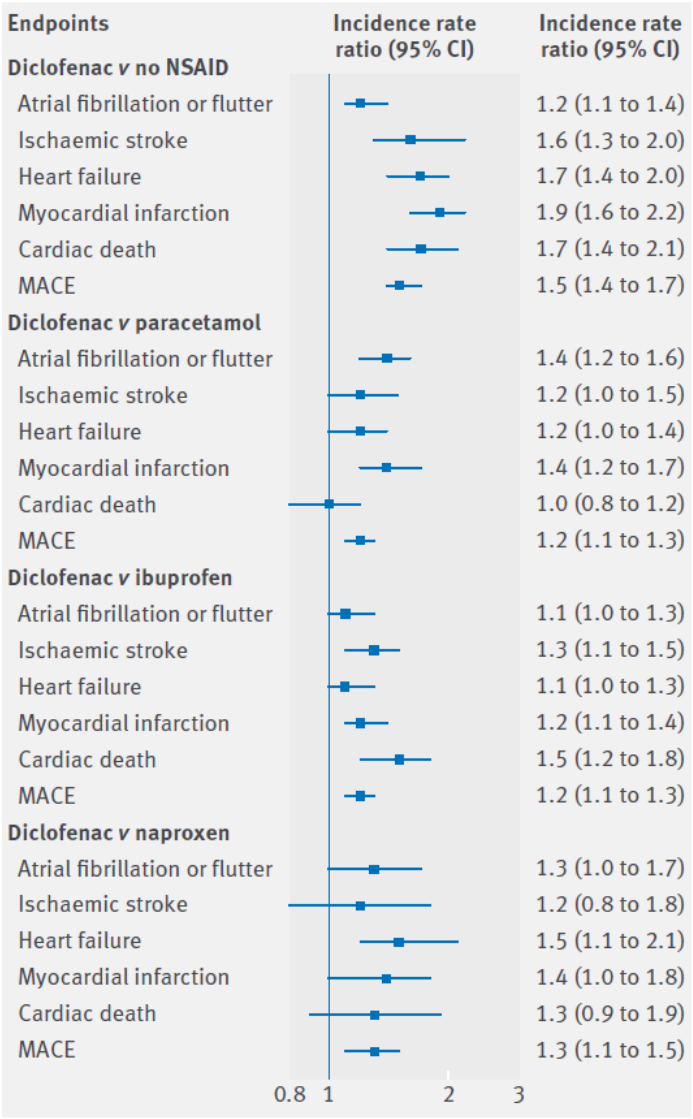


Figure 21. Cardiovascular risks at 30 days associated with diclofenac initiation compared with no NSAID initiation and initiation of paracetamol, ibuprofen, or naproxen – Schmidt 2018.

The risk of MACE was found to be elevated for men and women, and for each of the defined age groups, (Figure 22).

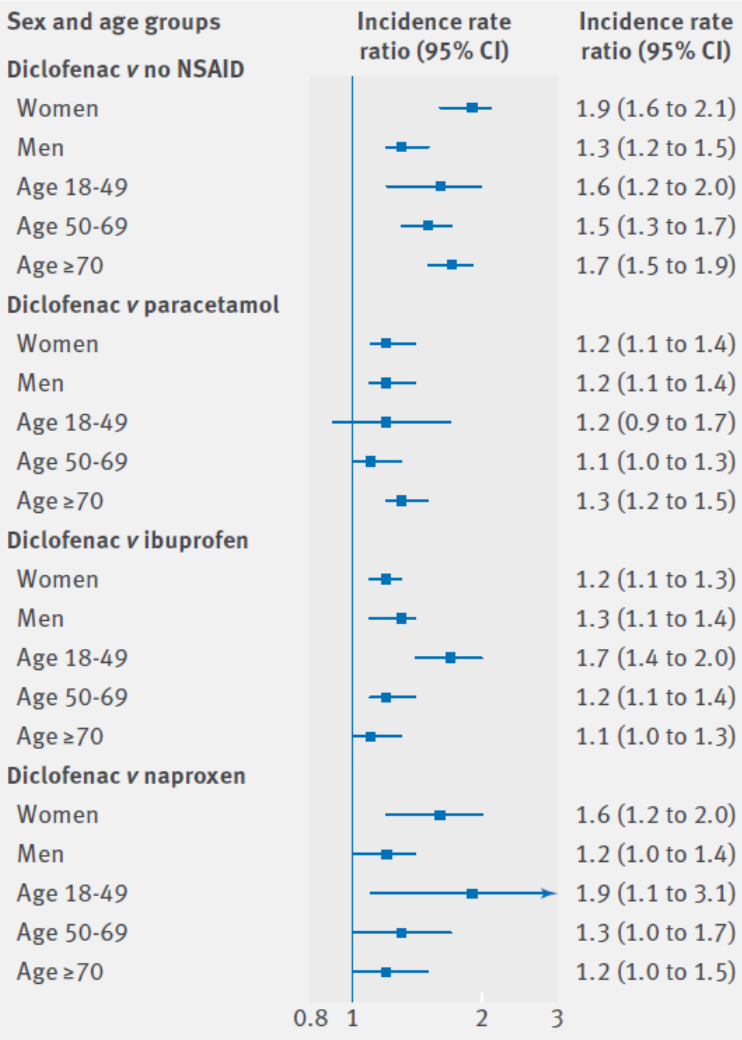


Figure 22. Risk for major adverse cardiovascular events (MACE) after diclofenac initiation according to sex and age – Schmidt 2018.

The risk of MACE was elevated for both low and high dose diclofenac in comparisons with no NSAID, paracetamol, ibuprofen, and naproxen. The relative risk of MACE was highest in individuals with low or moderate baseline risk, although the absolute risk was highest in individuals with high baseline risk. (Figure 23).

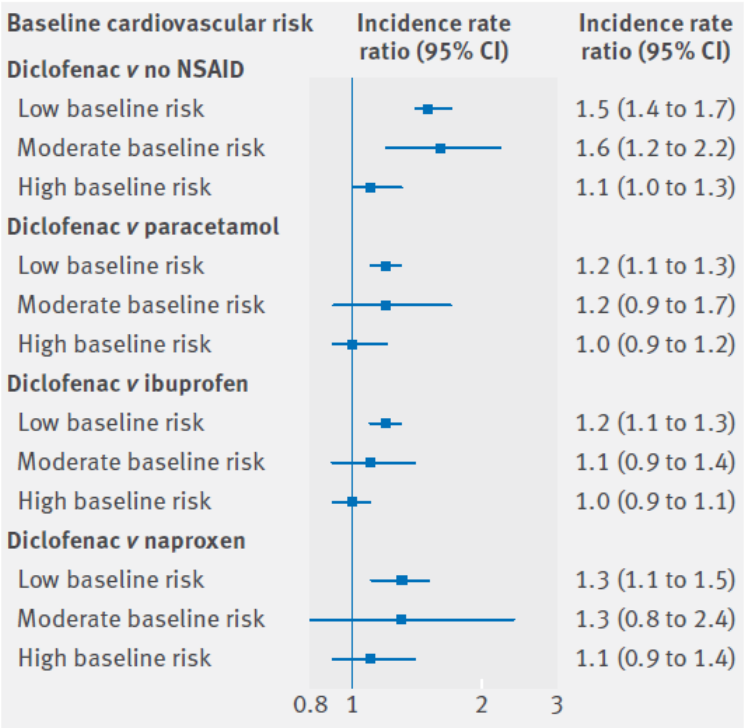


Figure 23. Risk of MACE after diclofenac initiation according to baseline CV risk – Schmidt 2018

Discussion and conclusions

The population based design in the setting of a tax supported, universal healthcare system largely removed selection biases. The study had no missing data on exposure, confounders, or events. The prescription registry permitted a near complete identification of diclofenac use. However, the authors noted that the emulated trial design lacked baseline randomisation and unmeasured confounding cannot be excluded.

These findings are consistent with the known COX-2 selectivity of diclofenac compared to ibuprofen and naproxen.

The authors conclude that diclofenac poses a cardiovascular health risk compared with non-use, paracetamol use, and use of other traditional NSAIDs. The authors consider there is little justification to initiate diclofenac treatment before other traditional NSAIDs, and that it should not be available over the counter.

This study also highlights that the use of diclofenac as the reference group is a potential flaw in safety trials of other NSAIDs. Future trials should instead use low dose (≤ 1200 mg/day) ibuprofen or naproxen (≤ 500mg/day) as comparators.

Comment

This registry-based 'emulated clinical trial' involving over 6 million linked patient records clearly indicates that diclofenac has an increased cardiovascular risk even at low dose and within the first 30 days of initiation in patients with a low baseline risk compared to no NSAID, paracetamol, ibuprofen and naproxen.

This study also shows that there is no difference between diclofenac and ibuprofen or naproxen in the risk of MACE among patients with diabetes mellitus (moderate CV risk) or previous MI or heart

failure (high CV risk) at baseline (Figure 23). This finding supports the contraindication of all traditional NSAIDs in patients with underlying cardiovascular disease.

The use of 'non-initiators' as a comparator group should not be considered a proxy for 'placebo'. Patients who seek treatment for a particular condition are likely to be different from those who do not seek treatment. The non-treatment group in this study is therefore likely to be different from those who sought treatment and were prescribed and NSAID. The paracetamol group is a better comparator than the non-treatment group because the indications for paracetamol (pain, fever) are similar to NSAIDs.

Unfortunately, this study did not include a comparison with celecoxib.

3.1.3.2 Sondergaard et al, 2017 (Eur Heart J)

Non-steroidal anti-inflammatory drug use is associated with increased risk of out-of-hospital cardiac arrest: a nationwide case-time-control study. [37]

This Danish registry study aimed to assess the association between NSAID use and the risk of out-of-hospital cardiac arrest. The published study report is provided as Annex 7.

Methods

Altogether, 28 947 out-of-hospital cardiac arrest patients (OHCA) were identified from the Danish Cardiac Arrest Registry during 2001 - 2010. The Danish Cardiac Arrest Registry contains all out-of-hospital cardiac arrests in Denmark, where a resuscitation attempt has been initiated. Cases with obvious late signs of death are not included in the registry.

Exposure to NSAIDs were identified from the Danish Prescription Registry, classified as follows: non-selective NSAIDs (diclofenac, naproxen, ibuprofen), and the selective cyclooxygenase-2 (COX-2) inhibitors (rofecoxib, celecoxib), and others.

The association between NSAIDs and risk of cardiac arrest was analysed in case-time-control models. Exposure to NSAIDs up to 30 days before cardiac arrest was compared with exposure to NSAIDs in a previous control period from 60 to 90 days before cardiac arrest in the same cardiac arrest patient. Thereby patients were used as their own controls in another time period, which eliminated confounding from characteristics that remain stable over time (e.g. chronic comorbidity).

Additionally, a control group from the background population (matched with patients 1:4 for age and sex) was used to adjust for possible time-variant biases related to exposure.

Results

Within the 30-day case period, 3376 (11.7 %) persons were treated with an NSAID. Ibuprofen was the most commonly prescribed NSAID followed by diclofenac comprising 51.0 and 21.8 % of total NSAIDs, respectively. Compared with non-users, NSAID users were more often women, had generally less cardiovascular diseases, such as ischaemic heart disease, myocardial infarction and heart failure, but were more likely to have cancer and rheumatic diseases ($P<0.05$).

Use of non-selective NSAIDs was associated with a significantly increased risk of cardiac arrest, odds ratio (OR) 1.32 [95% confidence interval (95% CI) 1.18–1.48], whereas no significant risk was associated with use of the COX-2 selective inhibitors, OR 1.19 (95% CI 0.89–1.59), (Figure 24).

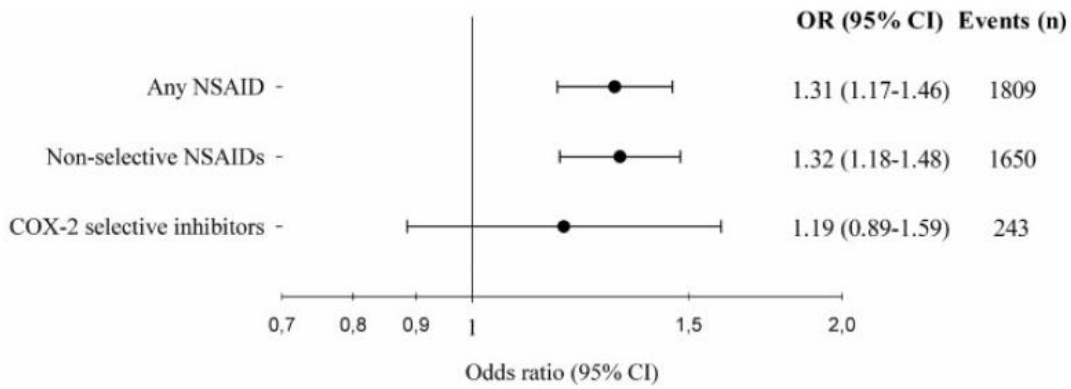


Figure 24. Risk of OHCA following treatment with NSAID – Sondergaard 2017
ORs derive from conditional logistic regression analyses on case-time-control models. Events comprises only persons with discordant exposure history, thus contributing to the analyses

The increased risk associated with use of nonselective NSAIDs was driven by an increased risk of OHCA associated with use of diclofenac, OR 1.50 (95% CI 1.23–1.82) and ibuprofen, OR 1.31 (95% CI 1.14–1.51), (Figure 25). Naproxen use was not significantly associated with cardiac arrest, and the authors did not find any significant associations between cardiac arrest and use of the COX-2 selective inhibitors, rofecoxib, and celecoxib.

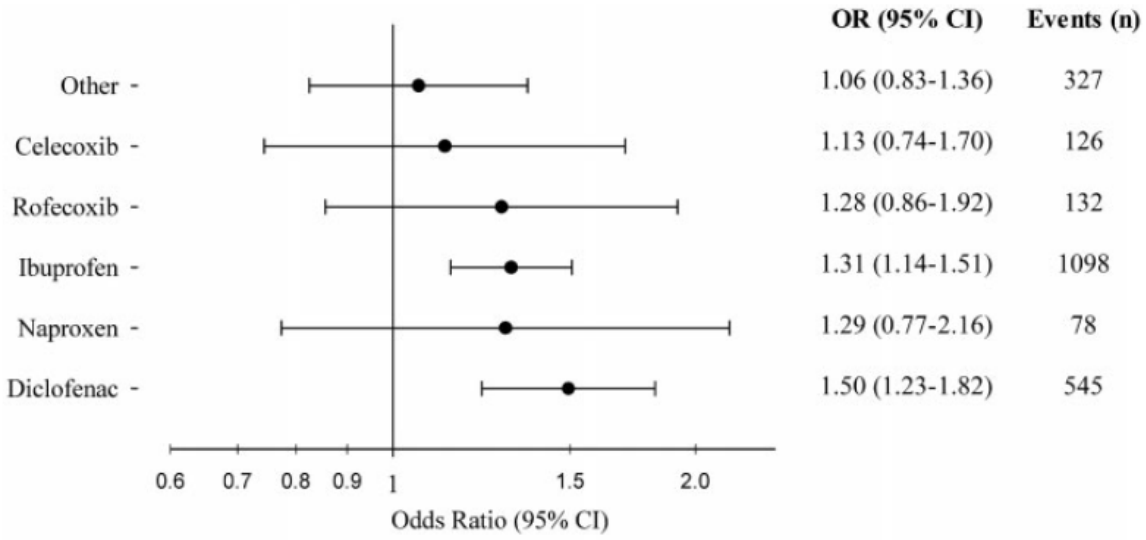


Figure 25. Risk of OHCA following treatment with the most common types of NSAIDs – Sondergaard 2017.
ORs derive from conditional logistic regression analyses on case-time-control models. Events comprises only persons with discordant exposure history, thus contributing to the analyses

The results were verified in several sensitivity analyses, such as excluding patients admitted within 60 days before cardiac arrest, excluding patients with cancer, and including only cardiac arrests of presumed cardiac causes.

Discussion and conclusions

In this nationwide case-time control study use of non-selective NSAIDs was found to be associated with an increased risk of out-of-hospital cardiac arrest. The result was primarily driven by an increased risk of cardiac arrest in ibuprofen and diclofenac users. No significant association was found between cardiac arrest and use of the COX-2 selective inhibitors, rofecoxib and celecoxib, nor

with the non-selective NSAID naproxen; however, these results were marked by low statistical power due to low use rofecoxib, celecoxib, and naproxen in Denmark.

Comment

For a self-controlled cohort study, subsequent exposures should not appreciably be affected by previous events [38]. The choice of a self-controlled study design for out-of-hospital cardiac arrest (which carries a high probability of death) introduces the possibility of selection bias. Among individuals who have experienced a prior cardiac arrest, only those who survived are available to be exposed to the treatment under investigation. Therefore, the NSAID exposure is limited to a population that has either never experienced or has experienced and survived an OHCA.

The OR for OHCA was elevated for all of the NSAIDs included in the analysis, but statistical significance was demonstrated only for ibuprofen and diclofenac. Low numbers in the celecoxib, rofecoxib and naproxen exposure groups resulted in wide confidence intervals.

The effect of dose and duration of NSAID treatment were not examined in this study.

Figure 24 shows the ORs for 'COX-2 selective' and 'non-selective' NSAIDs based on the traditional categorisations rather than the actual extent of COX-2 selectivity. It would be interesting to see the effect on the ORs if diclofenac was accounted for in the COX-2 selective inhibitors instead of the non-selective inhibitors.

3.1.3.3 Bally et al, 2017 (BMJ)

Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data [39]

This study aimed to characterise the determinants, time course, and risks of acute myocardial infarction (MI) associated with the use of oral NSAIDs by pooling population based observational studies that reflect 'real world' use. The authors performed an individual patient data (IPD) meta-analysis of studies from Canadian and European healthcare databases to determine the time course for risk of acute MI and the effects of dose and duration of continuous use for the main NSAIDs.

The published study report is provided as Annex 8.

Methods

Studies were eligible if they were sourced from computerised drug prescription or medical databases, were conducted in the general or an elderly population, documented acute myocardial infarction as specific outcome, studied selective cyclo-oxygenase-2 inhibitors (including rofecoxib) and traditional NSAIDs, compared risk of acute myocardial infarction in NSAID users with non-users, allowed for time dependent analyses, and minimised effects of confounding and misclassification bias.

Drug exposure was modelled as an indicator variable incorporating the specific NSAID, its recency, duration of use, and dose. The outcome measures were the summary adjusted odds ratios of first acute MI after study entry for each category of NSAID use at index date (date of acute MI for cases, matched date for controls) vs. non-use in the preceding year and the posterior probability of acute MI.

The full text of 82 studies was screened for eligibility, of which 67 were excluded based on eligibility criteria. Of the remaining 15 studies, seven were excluded because the definition of exposed time

precluded valid pooling of patient level data, and four studies were excluded because permission to access IPD was not granted. The remaining four studies were included in the analysis.

A nested case-control dataset was created to serve as a reference for harmonising the IPD. The reference dataset (RAMQ) comprised data from the universal, computerised public insurance database of Quebec (Régie de l'assurance maladie Québec, RAMQ). The other datasets available for IPD meta-analysis were a population based case-control study from Finland and two nested case-control studies from the UK (General Practice Research Database, GPRD) and Canada (Saskatchewan).

Results

A cohort of 446 763 individuals including 61 460 with acute MI was constructed from the four studies.

Table 10 reports the adjusted ORs for acute MI for past use, recent use, and the five dose duration categories of current NSAID use compared with non-use of any NSAID in the year before the index date (only pooled results shown). (Table 10)

Taking any dose of NSAID for one week, one month, or more than a month was associated with an increased risk of MI.

The ORs (95% credible intervals) for each drug (any dose, 1-7 days use) compared to non-use of NSAID for myocardial infarction were:

- celecoxib 1.24 (0.91 to 1.82)
- ibuprofen 1.48 (1.00 to 2.26)
- diclofenac 1.50 (1.06 to 2.04) *
- naproxen 1.53 (1.07 to 2.33) *
- rofecoxib 1.58 (1.07 to 2.17) *

Greater risk of myocardial infarction was documented for higher dose of NSAIDs.

With use for longer than one month, risks did not appear to exceed those associated with shorter durations.

Table 10. Risk of acute MI with various NSAID multidimensional indicator categories of use defined by recency of use, daily dose, and duration in pooled studies. – Bally 2017

Variables*†	Pooled studies (n=446 763) (61 460 cases) Adjusted odds ratio (95% CrI)
Non-use	
No NSAIDs in year PTID	1 (reference)
Celecoxib	
Past:	
Ended 31-365 days PTID	1.03 (0.90 to 1.13)
Recent:	
Ended 1-30 days PTID	1.15 (0.86 to 1.40)
Current:	
Any dose for 1-7 days	1.24 (0.91 to 1.82)
≤200 mg/day for 8-30 days	1.23 (1.00 to 1.62)
>200 mg/day for 8-30 days	1.23 (0.78 to 1.80)
≤200 mg/day for >30 days	1.20 (1.01 to 1.47)
>200 mg/day for >30 days	1.25 (0.94 to 1.66)
Diclofenac	
Past:	
Ended 31-365 days PTID	1.11 (1.01 to 1.27)
Recent:	
Ended 1-30 days PTID	1.08 (0.78 to 1.43)
Current:	
Any dose for 1-7 days	1.50 (1.06 to 2.04)
≤100 mg/day for 8-30 days	1.19 (0.94 to 1.48)
>100 mg/day for 8-30 days	1.22 (0.92 to 1.62)
≤100 mg/day for >30 days	1.42 (1.18 to 1.68)
>100 mg/day for >30 days	1.48 (1.08 to 1.95)
Ibuprofen	
Past:	
Ended 31-365 days PTID	1.06 (0.93 to 1.19)
Recent:	
Ended 1-30 days PTID	1.15 (0.93 to 1.48)
Current:	
Any dose for 1-7 days	1.48 (1.00 to 2.26)
≤1200 mg/day for 8-30 days	1.04 (0.72 to 1.35)
>1200 mg/day for 8-30 days	1.75 (1.00 to 2.93)
≤1200 mg/day for >30 days	1.32 (1.02 to 1.74)
>1200 mg/day for >30 days	1.47 (1.04 to 2.04)
Naproxen	
Past:	
Ended 31-365 days PTID	1.07 (0.93 to 1.23)
Recent:	
Ended 1-30 days PTID	1.30 (1.04 to 1.63)
Current:	
Any dose for 1-7 days	1.53 (1.07 to 2.33)
≤750 mg/day for 8-30 days	1.23 (0.90 to 1.61)
>750 mg/day for 8-30 days	1.76 (1.14 to 2.65)
≤750 mg/day for >30 days	1.21 (0.95 to 1.52)
>750 mg/day for >30 days	1.21 (0.91 to 1.57)
Rofecoxib	
Past:	
Ended 31-365 days PTID	1.00 (0.87 to 1.12)
Recent:	
Ended 1-30 days PTID	1.18 (0.95 to 1.50)
Current:	
Any dose for 1-7 days	1.58 (1.07 to 2.17)
≤25 mg/day for 8-30 days	1.27 (0.83 to 1.69)
>25 mg/day for 8-30 days	2.65 (1.46 to 4.67)
≤25 mg/day for >30 days	1.35 (1.17 to 1.62)
>25 mg/day for >30 days	1.56 (1.09 to 2.18)

CrI = credible interval, PTID = prior to index date. Pooled results only shown – see published paper (Annex 8) for full table showing results from individual studies. Statistically significant results (lower bound of CrI > 1) are circled in red.

Discussion and conclusions

All NSAIDs, including naproxen, were found to be associated with an increased risk of acute myocardial infarction. Risk of myocardial infarction with celecoxib was comparable to that of traditional NSAIDs, but lower than for rofecoxib. Risk was generally greatest during the first month of NSAID use and with higher doses.

The meta-analysis of patient-level data suggests that use of common NSAIDs increases a person's relative risk of acute MI by about 20 to 50% overall and possibly by 75% with high-dose ibuprofen or naproxen used for one to four weeks.

Comment

This study was a meta-analysis of individual patient data from four large healthcare databases.

The study found that diclofenac, naproxen and rofecoxib (at any dose for 1-7 days) were each associated with an increased risk of MI. Celecoxib has a similar risk of MI to that of traditional NSAIDs. High-dose naproxen (> 750 mg/day) for 7-30 days could be associated with a 75% increase in MI risk. The authors conclude that all traditional NSAIDs, including naproxen, appear to be associated with an increased risk of acute myocardial infarction.

The results of this study differ from that of the CNT Collaboration study findings on which the 2015 US FDA label updates were largely based. The CNT Collaboration study found that major vascular events were increased by about one-third by a coxib or diclofenac, and suggested that naproxen may be associated with a lower risk that for other traditional NSAIDs [22].

In a commentary on this study, Stehlik et al suggest that some possible reasons for the divergent results may have been: selection bias as a result of the strict inclusion criteria and small number of studies, restriction of the outcomes to acute MI (instead of the broader cardiovascular outcome measures used in many of the other studies), the focus on the first 7 days of treatment among current NSAID users, and the use of IDP meta-analysis on observational data (rather than RCT data) [40].

3.1.3.4 Arfè et al, 2016 (BMJ)

Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries; nested case-control study [41]

This nested case-control study based on electronic healthcare databases from four European countries formed part of the Safety of Non-steroidal Anti-Inflammatory (SOS) Project, a multinational project funded by the European Commission under the seventh Framework Programme. The published study is provided as Annex 9.

Methods

This study was based on five electronic health databases from four European countries: the Netherlands, Italy, Germany, and the UK. Overall, these databases covered over 37 million people with different time windows of data availability between 1999 and 2010, (Table 11). Data harmonisation was performed to ensure a common data model was used in the analyses.

Table 11. Databases used in the nested case-control study – Arfè 2016

Country	Database*	Type of database	Size of covered population	Covered period	Diagnoses coding	Drugs coding
Netherlands	PHARMO (PHARMO Institute for Drug Outcomes Research)	Record linkage	2.2 million	1999-2008	ICD-9-CM	Anatomical Therapeutic Chemical classification system
Italy	SISR (Sistema Informativo Sanitario Regionale)†	Healthcare use	7.5 million	2003-08	ICD-9-CM	Anatomical Therapeutic Chemical classification system
	OSSIFF (Osservatorio Interaziendale per la Farmacoepidemiologia e la Farmacoeconomia)	Healthcare use	2.9 million	2000-08	ICD-9-CM	Anatomical Therapeutic Chemical classification system
Germany	GePaRD (German Pharmacoepidemiological Research Database)	Claims	13.7 million	2004-09	ICD-10-GM	Anatomical Therapeutic Chemical classification system
UK	THIN (The Health Improvement Network)	General practice	11.1 million	1999-2010	READ version 2	BNF/Multilex codes

ICD-9-CM=International Classification of Diseases, 9th revision, clinical modification; ICD-10-GM=International Classification of Diseases, 10th revision, German modification; READ=READ clinical classification system; BNF=British National Formulary; Multilex=Multifunctional Standardised Lexicon for European Community Languages drug terminology.
*Other databases participated in the SOS Project but did not contribute data to this study.[16]
†Because OSSIFF covers a subset of patients also covered by SISR, this database excluded the common subset of patients to avoid overlap.

A cohort of individuals starting NSAID treatment was selected from all databases. In detail, adults (age ≥ 18 years) who received at least one NSAID prescription or dispensation (ATC code M01A; excluding topical NSAIDs) during 2000-10 were considered eligible to enter the cohort. The date of first recorded prescription or dispensation was defined as the date of cohort entry.

Person-years of follow-up were recorded from the date of cohort entry to the earliest date of outcome onset (first hospital admission with a primary diagnosis of heart failure), censoring (end of registration in the database due to death or emigration, diagnosis of malignancy (except non-melanoma skin cancer) or end of database specific data availability.

A case-control study was nested into the cohort of new users of NSAIDs. The endpoint of interest was the first hospital admission for HF identified during follow-up, the date of which was defined as the index date. Each case was matched to up to 100 controls. NSAID exposure during follow-up was determined for each cohort member based on dispensing records. A total of 27 NSAIDs were identified (including 23 traditional NSAIDs and four selective COX-2 inhibitors). NSAID use was classified as current (up to 14 days preceding the index date), recent (15-183 days before index date) and past (> 183 days before index date).

Associations were assessed by multivariable conditional logistic regression models. The dose-response relation between NSAID use and heart failure risk was also assessed.

Results

Among nearly 10 million new users of NSAIDs identified across all databases, 7 680 181 met the inclusion criteria for the study cohort. Cohort members accumulated 24 555 063 person-years of follow-up and generated 92 163 cases of heart failure admitted to hospital (incident rate, 37.5 heart failure events per 10 000 person years). Cases were matched to 8 246 403 controls.

Mean age was 77 (SD 11) years and 76 (10) years among cases and controls, respectively. About 45% of both cases and controls were men. Compared with controls, cases had more comorbidities (mainly cardiovascular disease, such as acute myocardial infarction, other ischaemic heart diseases, atrial fibrillation and flutter, and valvular disease and endocarditis) and received concomitant drug treatments more often (eg, anticoagulants, cardiac glycosides, nitrates, and cytochrome P450 2C9 inhibitors).

In the year before start of NSAID treatment (cohort entry), 9.1 % of cases and 2.5 % of controls had a history of heart failure diagnosis, recorded as either an outpatient diagnosis or a secondary hospital diagnosis.

A total of 16 081 (17.4%) cases and 1 193 537 (14.4%) matched controls were current users of NSAIDs.

The distribution of current use of individual NSAIDs among all cases and controls is shown in Figure 26. Among controls, the most frequently used traditional NSAIDs were diclofenac (2.9%), nimesulide

(2.4%), and ibuprofen (1.7%); the most frequently used COX 2 inhibitors were celecoxib (1.4%), rofecoxib (1.0%), and etoricoxib (0.6%).

Current use of any NSAID (use in preceding 14 days) was found to be associated with a 19% increase in risk of hospital admission for heart failure (adjusted OR 1.19; 95% CI 1.17 to 1.22), compared with past use of any NSAIDs (use >183 days in the past). (Figure 26)

Conversely, there was no evidence that recent use of any NSAID was associated with differences in heart failure risk with respect to past use (1.00; 0.99 to 1.02).

A statistically significantly higher risk of heart failure was observed in association with current use of nine individual NSAIDs (ketorolac, etoricoxib, indomethacin, rofecoxib, piroxicam, diclofenac, ibuprofen, nimesulide, and naproxen) compared to past use of any NSAIDs. Other less frequently used NSAIDs (eg, sulindac, acemethacin, and dexibuprofen) were also found to be associated with an increased risk of heart failure, although the 95% confidence intervals included the null value. Odds ratios ranged from 0.83 (95% confidence interval 0.57 to 1.20) for oxaprozin to 1.84 (1.67 to 2.04) for ketorolac. (Figure 26)

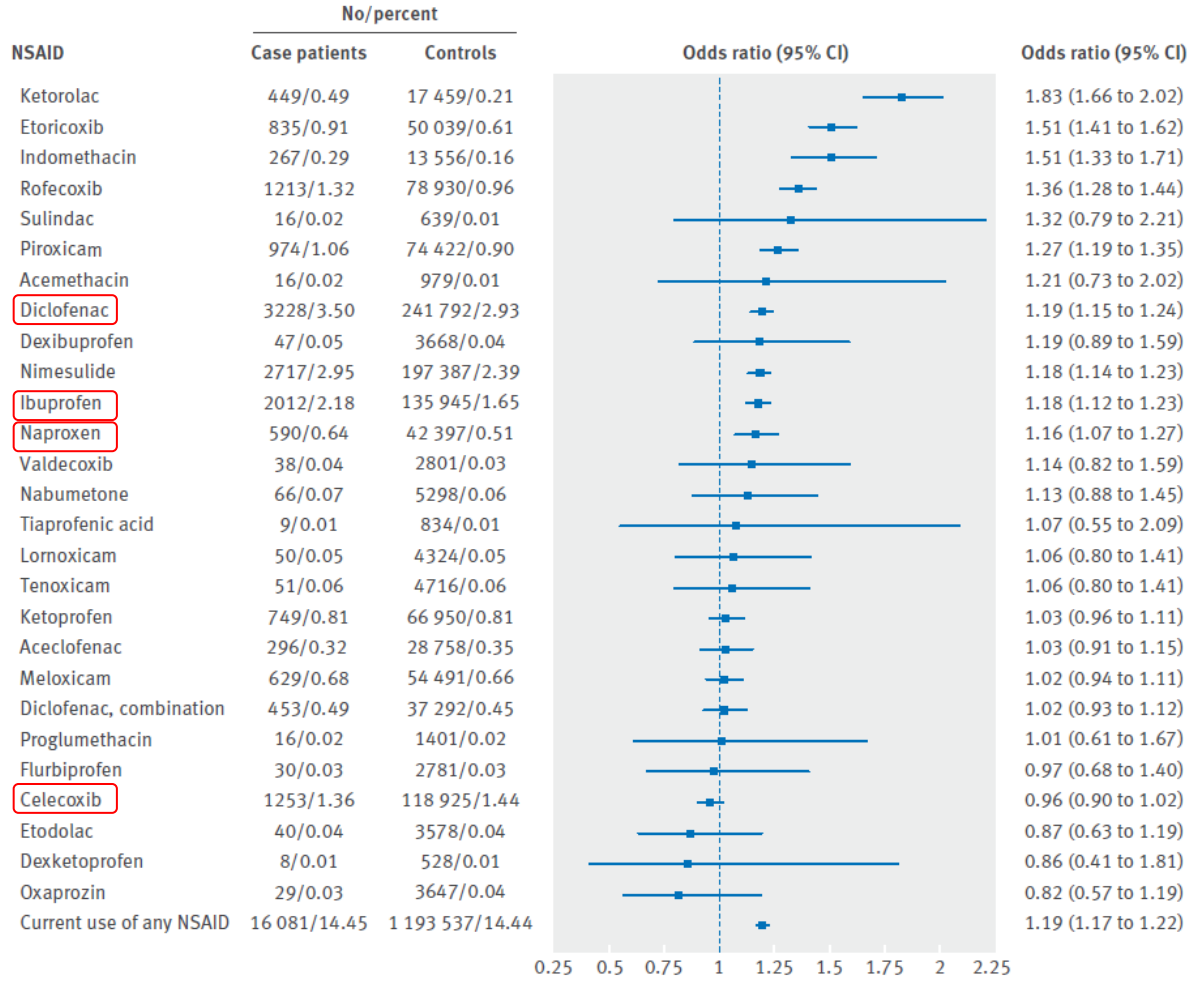


Figure 26. Distribution of current use of individual NSAIDs among cases and controls and pooled associations between current use of individual NSAIDs and risk of hospital admission for heart failure, with past use of any NSAID as reference – Arfè 2016.

Estimates obtained by pooling individual data from all available databases. Pooled odds ratios and 95% confidence intervals estimated by fitting a conditional logistic regression model after correcting for available covariates

For the nine individual NSAIDs significantly associated with heart failure risk, their association was confirmed regardless of whether there was recorded evidence of a prior heart failure diagnosis and regardless of sex.

A meta-analysis of database specific ORs indicated that current users of any NSAID had a 24% higher risk of heart failure than past users (odds ratio 1.24; 95% confidence interval 1.12 to 1.36). Although between database heterogeneity was relevant (I^2 > 70 %), meta-analytic estimates of odds ratios were generally consistent with corresponding values obtained from the analysis of pooled individual level data.

Defined daily doses (DDD) were available for 25 179 cases and 2 083 706 controls from the PHARMO and THIN databases, and were used for the daily dose analysis.

Current users of very high doses of diclofenac, etoricoxib, indomethacin, piroxicam, and rofecoxib had more than a two-fold higher risk of heart failure than past users. The odds ratio associated with current high dose use of ibuprofen was also compatible with an increased risk of heart failure, despite the wide confidence interval. Finally, there was no evidence that celecoxib increased the risk of hospital admission heart failure at commonly used doses compared with past use of any NSAIDs. However, we cannot exclude an increase in risk when celecoxib is used at very high doses, given the wide confidence intervals obtained for this dose class.

Risk of heart failure doubled for diclofenac, etoricoxib, indomethacin, piroxicam, and rofecoxib used at very high doses (≥ 2 DDD equivalents), although some CIs were wide. Even medium doses (0.9-1.2 DDD equivalents) of indomethacin and etoricoxib were associated with increased risk. There was no evidence that celecoxib increased the risk of admission for heart failure at commonly used doses.

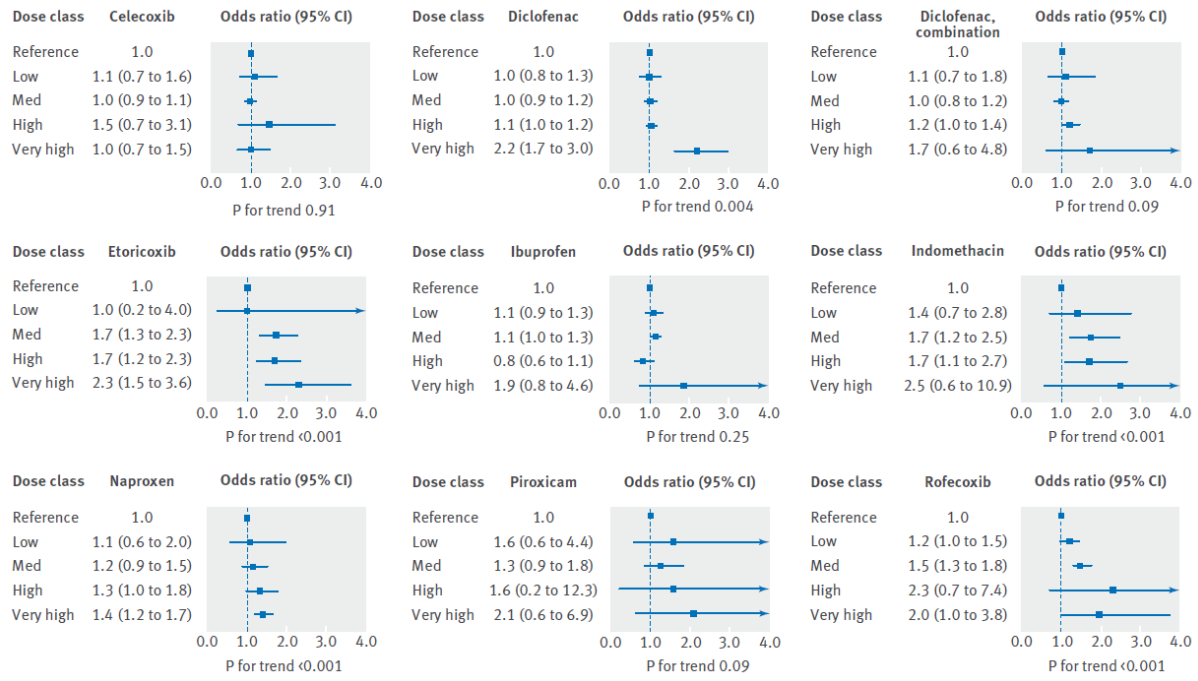


Figure 27. Dose-response relationship between currently prescribed doses of specific NSAIDs and risk of HF, compared with past use of any NSAID - Arfè 2016.

Pooled data obtained from PHARMO and THIN databases for this analysis. Currently prescribed doses of each NSAID categorised as low (0.8 defined daily dose equivalents), medium (0.9-1.2), high (1.3-1.9), and very high (≥ 2). Odds ratios and 95% confidence intervals estimated by fitting a conditional logistic regression model after correcting for available covariates.

Discussion and conclusions

The following study limitations were noted:

- The study did not capture OTC NSAID use, so patients classified as non-current users of NSAIDs might actually have been current users of OCT NSAIDs. Such misclassification would tend to bias estimates toward the null, potentially underestimating the actual association between use of individual NSAIDs and HF risk.
- Validity of outcomes could not be assessed. HF is often associated with other CV disease (eg, MI), which could affect how hospital discharge codes are recorded. Outcome misclassification is likely to be non-differential (ie, independent of current NSAID use) leading to a bias moving estimated associations toward the null.
- The dose-response analysis may have been underpowered for some NSAID dose classes.
- Differences in patient characteristics at baseline could account for some of the observed variations in relative risk estimates associated with different individual NSAIDs.
- Potential confounding from conditions that modify the risk of both HF and NSAID use eg, gout.

The authors conclude that the most frequently used traditional NSAIDs and selective COX-2 inhibitors are associated with an increased risk of hospital admission for heart failure. The risk appears to vary between individual NSAIDs, and this effect is dose dependent.

Comment

This case-control study was nested in a cohort comprising 7 680 181 new NSAID users derived from 5 large European healthcare databases. A total of 16 081 cases were current users of NSAIDs, and were matched with 1 193 573 controls.

Cases of hospital admission for HF were more likely to be current users of NSAIDs compared to controls. The ORs for specific NSAID use were: diclofenac 1.19 (1.15 to 1.24), ibuprofen 1.18 (1.12 to 1.23), naproxen 1.16 (1.07 to 1.27), and celecoxib 0.96 (0.90 to 1.02). Additionally, the OR for hospital admission for HF was 1.19 (1.17 to 1.22) for current use of any NSAID compared to past use.

The observed increase in risk of hospital admission for HF with increasing NSAID dose, such as diclofenac, ibuprofen, and naproxen, is consistent with the known effects of traditional NSAIDs on blood pressure and kidney function. COX-2 derived prostacyclin acts as an endogenous anti-arrhythmic agent by inhibiting epicardial sympathetic nerve activity. COX-2 inhibition may therefore increase the possibility of an arrhythmia such as atrial fibrillation/flutter tipping the patient into HF.

This study indicates an increased risk of hospital admission for HF with all NSAIDs. The increase risk may vary by NSAID and by dose, but the evidence provided in this paper is not sufficient to support specific dose related guidance on the level of risk for specific NSAIDs.

3.2 CARM data

From April 1965 to 30 September 2018, the Centre for Adverse Reactions Monitoring (CARM) has received a total of 4515 reports involving one or more NSAIDs. Of these, 433 reports include at least one cardiovascular reaction term. The 433 reports contain a total of 528 cardiovascular ADRs for 445

NSAIDs. Of the 528 cardiovascular ADRs, 484 ADRs were assessed as causally related (possible, probable or certain).

NSAIDs most frequently reported in relation to cardiovascular ADRs were diclofenac (126 ADRs), indomethacin (58), celecoxib (46), naproxen (42), ibuprofen (35), rofecoxib (23), and piroxicam, etoricoxib and meloxicam (20 each).

Dizziness (115 ADRs), Hypotension (48), Syncope (31), flushing (21) account for 215 of these ADRs.

The CARM data summary is provided in Annex 10.

4.0 DISCUSSION AND CONCLUSIONS

Since the MARC previously discussed the cardiovascular safety of diclofenac in 2013, and ibuprofen in 2015, several new studies on the cardiovascular safety of NSAIDs have been published. These studies include two key clinical trials (PRECISION [24] and SCOT [35]), and two large observational studies using healthcare databases (Schmidt 2018 [36] and Bally 2017 [39]). In addition, there have been two meta-analyses of older studies (Gunter 2017 [30] and Ungprasert 2015 [31]), a Danish healthcare registry study examining the risk of Out of Hospital Cardiac Arrest with NSAIDs (Sondergaard 2017 [37]), and a case-control study nested in a cohort derived from European electronic healthcare databases that examines the risk of hospital admission for heart failure exacerbation in new users of NSAIDs (Arfè 2016 [41]).

Of particular note are the PRECISION and SCOT trials, which were mandated by the FDA and EMA, respectively, due to concerns that increased cardiovascular risk may be a possible class effect for all NSAIDs.

The PRECISION study was a large, multicentre, double-blind, non-inferiority trial involving patients with risk factors for cardiovascular events who had either RA or OA. Although patients were randomised to receive celecoxib 100 mg bd, ibuprofen 600 mg tds or naproxen 375 mg bd, dose escalation was allowed to achieve symptom control, in line with the approved dose recommendations at the time of the study. Accordingly, for patients with RA (approximately 10% of the study population), investigators could increase the dose of celecoxib to 200 mg bd, ibuprofen to 800 mg tds or naproxen to 500 mg bd for symptomatic relief. For patients with OA (approximately 90% of the study population), increases in ibuprofen or naproxen dose was permitted, but regulatory dose restrictions for the OA indication meant that dose escalation of celecoxib was not possible for these patients. As a result, the mean daily doses of ibuprofen (2045 ± 246 mg) and naproxen (852 ± 103 mg) were near the high end of the approved dose range at that time, while the mean daily dose of celecoxib (209 ± 37 mg) remained close to the low end of the then approved dose range.

Studies have since indicated that there is an increased cardiovascular risk when ibuprofen is taken at doses above 1200 mg per day (Annex 2). All NSAIDs are now recommended to be taken at the lowest effective dose for the shortest possible duration.

Consequently, demonstration of non-inferiority of low dose celecoxib compared to high dose ibuprofen in the PRECISION trial does not infer that celecoxib has an acceptable cardiovascular safety profile. (Instead, it could be interpreted as showing that the cardiovascular risk of low dose celecoxib is no worse than for high dose ibuprofen).

Two further analyses have been published based on the PRECISION trial data. Solomon *et al* 2017 [33] undertook a *post-hoc* analysis to compare the risk of major NSAID toxicity as a combined outcome measure (including cardiovascular, gastrointestinal, renal and all-cause mortality events) for celecoxib, naproxen or ibuprofen. The cardiovascular composite safety endpoint MACE was a component of the major NSAID toxicity endpoint, but was not reported on separately.

Ruschitzka *et al* 2017 [34] reported on the PRECISION-ABPM, which was a pre-specified sub-study of the PRECISION study that focused on ambulatory blood pressure monitoring in the modified ITT group. Although an increase in SBP at 4 months compared to baseline was reported for ibuprofen, which resulted in a statistically significant difference compared to celecoxib, the non-comparability of the mean daily doses that limited the interpretation of the PRECISION study also applied to this study.

The SCOT study was a primary care based PROBE design study to compare CV (and GI) safety of continuing prescribed nsNSAID vs. switching to prescribed celecoxib in patients with OA or RA. Endpoints were detected through record-linkage. The primary endpoint was a composite of hospitalisation for non-fatal MI or other biomarker positive acute coronary syndrome, non-fatal stroke or CV death. The mean NSAID daily doses used in this study were comparable. The study was not able to demonstrate non-inferiority between the celecoxib and nsNSAID groups, which was attributed to a low CV event rate that had resulted in reduced power to establish non-inferiority.

Schmidt *et al* 2018 undertook a large observational study with an emulated trial design to compare rates of MACE among diclofenac initiators, non-initiators, and initiators of active comparator drugs (naproxen, ibuprofen, and paracetamol). The study showed that diclofenac has an increased cardiovascular risk even at low dose and within the first 30 days of initiation in patients with a low baseline risk compared to no NSAID, paracetamol, ibuprofen and naproxen. This finding is consistent with the known cardiovascular safety profile of diclofenac. The study did not include celecoxib.

Bally *et al* 2017 undertook a Bayesian meta-analysis of individual patient data from four database observational studies to assess the risk of acute MI with NSAIDs in 'real world' use. The study compared use of each NSAID with non-use. All NSAIDs, including naproxen, were found to be associated with an increased risk of acute MI compared to non-use. Risk of MI with celecoxib was comparable to traditional NSAIDs. Risk was generally highest during the first month of NSAID use and with higher doses.

Gunter *et al* 2017 undertook a large meta-analysis of 24 clinical trials and two cohort studies to compare eight selected NSAIDs (ibuprofen, diclofenac, naproxen, meloxicam, etoricoxib, celecoxib, lumiracoxib and rofecoxib) for the endpoints MI, stroke, CV death and a composite endpoint of all three endpoints. Rofecoxib was the only NSAID to show an increase in CV adverse effects. No difference was detected for any of the other coxibs or traditional NSAIDs when compared to placebo, all NSAIDs, traditional NSAIDs or coxibs (excluding rofecoxib). The authors concluded that CV adverse effects may not be related to COX-2 selectivity, based on their grouping of NSAIDs as either 'coxibs' or traditional NSAIDs. However, this conventional grouping does not take into account the known COX-2 selectivity of some traditional NSAIDs (eg, diclofenac).

Ungprasert *et al* 2015 undertook a meta-analysis of six clinical trials to compare traditional NSAIDs vs. celecoxib and rofecoxib for the endpoint heart failure exacerbation. In patients with pre-existing HF, those who took NSAIDs had significantly higher risk of HF exacerbation compared to those who did not take NSAIDs. The risk was similar for tNSAIDs and celecoxib.

Sondergaard *et al* 2017 undertook a Danish registry study that aimed to assess the association between NSAID use and the risk of out-of-hospital cardiac arrest (OHCA). The OR for OHCA was elevated for all of the NSAIDs included in the analysis, but statistical significance was demonstrated only for ibuprofen and diclofenac. Low numbers in the celecoxib, rofecoxib and naproxen groups resulted in wide confidence intervals.

Arfè *et al* 2016 undertook a nested case-control study in a large cohort derived from five large European healthcare databases. The study looked at hospital admissions for heart failure among new users of NSAIDs. The study found that cases of hospital admission for HF were more likely to be current users of NSAIDs compared to controls. The authors conclude that the most frequently used

traditional NSAIDs and selective COX-2 inhibitors are associated with an increased risk of hospital admission for heart failure. The risk appears to vary between individual NSAIDs, and the effect is dose dependent.

These studies are further summarised in Table 12.

In conclusion, the studies published on the cardiovascular safety of NSAIDs since the MARC last reviewed this issue in 2013 (diclofenac) and 2015 (ibuprofen) do not provide sufficient evidence to enable differentiation between NSAIDs according to their individual cardiovascular risk profiles. Accordingly, there is insufficient evidence to support down-grading of the contraindications or warnings in relation to cardiovascular risk for specific NSAIDs.

Table 12. Summary of recent studies on cardiovascular risk of NSAIDs

Study	*Type*	*Drugs*	*Outcomes*	*Comment*
Nissen 2016 (PRECISION)	*RCT*	*celecoxib ibuprofen naproxen*	*composite (death from cardiovascular causes, including haemorrhagic death, non-fatal myocardial infarction, or nonfatal stroke)*	*Non-comparable doses limit the interpretability of this study*
MacDonald 2017 (SCOT)	*RCT*	*celecoxib nsNSAID*	*composite (hospitalisation for non-fatal MI or other biomarker positive acute coronary syndrome, non-fatal stroke or CV death)*	*Non-inferiority was not demonstrated for celecoxib compared to prescribed NSAIDs*
Schmidt 2018	*Individual level data linkage study (emulated trial design)*	*ibuprofen naproxen diclofenac paracetamol no NSAID*	*MACE*	*Diclofenac found to have increased cardiovascular risk even at low dose compared to no NSAID, paracetamol, ibuprofen and naproxen*
Bally 2017	*Bayesian meta-analysis (IPD)*	*ibuprofen naproxen diclofenac celecoxib rofecoxib*	*Acute MI*	*Diclofenac, naproxen, and rofecoxib found to have increased cardiovascular risk. Celexocib has similar risk of MI to traditional NSAIDs.*
Sondergaard 2017	*self-controlled cohort study*	*ibuprofen naproxen diclofenac celecoxib rofecoxib*	*OHCA*	*Diclofenac and ibuprofen associated with increased risk of OHCA.* *Naproxen, celecoxib and rofecoxib not significantly associated with OHCA.*
Arfè 2016	*nested case control study*	*all NSAIDs*	*hospital admission for HF exacerbation*	*Current use of any NSAID associated with increased risk of hospital admission for HF*
Gunter 2017	*meta-analysis (aggregated data)*	*ibuprofen diclofenac naproxen meloxicam celecoxib rofecoxib*	*MI, stroke, CV death, composite (MI/stroke/CV death)*	*Rofecoxib was only NSAID to show increase in CV adverse effects. No difference for other coxibs and traditional NSAIDs compared to placebo, all NSAIDs, traditional NSAIDs or coxibs (excluding rofecoxib).*

		etoricoxib *lumiracoxib*		
Ungprasert 2015	*meta-analysis (aggregated data)*	*tNSAIDs* *celecoxib* *rofecoxib*	*HF exacerbation*	*No statistically significant difference in risk of HF exacerbation between celecoxib and traditional NSAIDs*

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The contraindications and warnings in the New Zealand data sheets for NSAIDs adequately reflect the current evidence on their cardiovascular risk.
- If not, what changes to the data sheets does the committee recommend?
- Further communication (other than MARC's Remarks) on the cardiovascular risks of NSAIDs is needed.

6.0 ANNEXES

1. Diclofenac and cardiovascular risk – 154th MARC meeting, 13 June 2013
2. Ibuprofen and cardiovascular risk – 161st MARC meeting, 12 March 2015
3. Gunter 2017
4. Nissen 2016
5. Macdonald 2017
6. Schmidt 2018
7. Sondergaard 2017
8. Bally 2017
9. Arfè 2016
10. CARM data

7.0 REFERENCES

1. U.S. National Library of Medicine. *Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen (PRECISION) Study*. ClinicalTrials.gov 19 June 2017 [cited 2019 Feb 07]; Available from: https://clinicaltrials.gov/ct2/show/study/NCT00346216.
2. FitzGerald, G.A. and C. Patrono, *The Coxibs, Selective Inhibitors of Cyclooxygenase-2.* New England Journal of Medicine, 2001. **345**(6): p. 433-442.
3. Antman, E.M., D. DeMets, and J. Loscalzo, *Cyclooxygenase Inhibition and Cardiovascular Risk.* Circulation, 2005. **112**(5): p. 759-770.
4. Grosser, T., Y. Yu, and G.A. Fitzgerald, *Emotion recollected in tranquility: lessons learned from the COX-2 saga.* Annu Rev Med, 2010. **61**: p. 17-33.
5. Schmidt, M., et al., *Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology.* Eur Heart J Cardiovasc Pharmacother, 2016. **2**(2): p. 108-18.
6. Bombardier, C., et al., *Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group.* N Engl J Med, 2000. **343**(21): p. 1520-8, 2 p following 1528.
7. Bresalier, R.S., et al., *Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial.* N Engl J Med, 2005. **352**(11): p. 1092-102.

8. Lisse, J.R., et al., *Gastrointestinal tolerability and effectiveness of rofecoxib versus naproxen in the treatment of osteoarthritis: a randomized, controlled trial.* Ann Intern Med, 2003. **139**(7): p. 539-46.

9. Baron, J.A., et al., *A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas.* Gastroenterology, 2006. **131**(6): p. 1674-82.

10. Silverstein, F.E., et al., *Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study.* JAMA, 2000. **284**(10): p. 1247-55.

11. Mukherjee, D., S.E. Nissen, and E.J. Topol, *Risk of Cardiovascular Events Associated With Selective COX-2 Inhibitors.* JAMA, 2001. **286**(8): p. 954-959.

12. Baron, J.A., et al., *Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial.* The Lancet, 2008. **372**(9651): p. 1756-1764.

13. Nussmeier, N.A., et al., *Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery.* N Engl J Med, 2005. **352**(11): p. 1081-91.

14. Ott, E., et al., *Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery.* The Journal of Thoracic and Cardiovascular Surgery, 2003. **125**(6): p. 1481-1492.

15. Solomon, S.D., et al., *Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention.* N Engl J Med, 2005. **352**(11): p. 1071-80.

16. Cannon, C.P., et al., *Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison.* Lancet, 2006. **368**(9549): p. 1771-81.

17. ADAPT Research Group, *Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT).* PLoS Clin Trials, 2006. **1**(7): p. e33.

18. Kearney, P.M., et al., *Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials.* BMJ, 2006. **332**(7553): p. 1302-8.

19. Trelle, S., et al., *Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis.* BMJ, 2011. **342**: p. c7086.

20. Schjerning Olsen, A.M., et al., *Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study.* Circulation, 2011. **123**(20): p. 2226-35.

21. McGettigan, P. and D. Henry, *Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies.* PLoS Med, 2011. **8**(9): p. e1001098.

22. Coxib and traditional NSAID Trialists' (CNT) Collaboration, et al., *Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials.* Lancet, 2013. **382**(9894): p. 769-79.

23. U.S. Food and Drug Administration and Centre for Drug Evaluation and Research *Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, February 10-11, 2014 Nonsteroidal anti-inflammatory drugs and cardiovascular thrombotic risk. (Briefing Materials)* 2014.

24. Nissen, S.E., et al., *Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis.* N Engl J Med, 2016. **375**(26): p. 2519-29.

25. U.S. Food and Drug Administration. *FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks of strokes*. 2015 26 Feb 2018 [cited 2019 14 Feb]; Available from: https://www.fda.gov/Drugs/DrugSafety/ucm451800.htm.

26. European Medicines Agency, *Public CHMP Assessment Report for Medicinal Products Containing Non-Selective Non Steroidal Anti-Inflammatory Drugs (NSAIDs)*. 2006: London

27. European Medicines Agency, *Opinion of the Committee for Medicinal Products for Human Use Pursuant to Article 5(3) of Regulation (EC) No 726/2004, for Non selective Non Steroidal Anti-Inflammatory Drugs (NSAIDs)*. 2006.

28. CORDIS. *Safety Of non-Steroidal anti-inflammatory drugs (SOS)*. Seventh Framework Programme [cited 2019 18 Feb]; Available from: https://cordis.europa.eu/project/rcn/89349/factsheet/en.

29. European Medicines Agency *Assessment report for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and cardiovascular risk.* . 2012.

30. Gunter, B.R., et al., *Non-steroidal anti-inflammatory drug-induced cardiovascular adverse events: a meta-analysis.* J Clin Pharm Ther, 2017. **42**(1): p. 27-38.

31. Ungprasert, P., N. Srivali, and W. Kittanamongkolchai, *Non-steroidal anti-inflammatory drugs and risk of heart failure exacerbation: A systematic review and meta-analysis.* Eur J Intern Med, 2015. **26**(9): p. 685-90.

32. Pepine, C.J. and P.A. Gurbel, *Cardiovascular safety of NSAIDs: Additional insights after PRECISION and point of view.* Clin Cardiol, 2017. **40**(12): p. 1352-1356.

33. Solomon, D.H., et al., *The Risk of Major NSAID Toxicity with Celecoxib, Ibuprofen, or Naproxen: A Secondary Analysis of the PRECISION Trial.* Am J Med, 2017. **130**(12): p. 1415-1422 e4.

34. Ruschitzka, F., et al., *Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) Trial.* Eur Heart J, 2017. **38**(44): p. 3282-3292.

35. MacDonald, T.M., et al., *Randomized trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib: the Standard care vs. Celecoxib Outcome Trial (SCOT).* Eur Heart J, 2017. **38**(23): p. 1843-1850.

36. Schmidt, M., H.T. Sorensen, and L. Pedersen, *Diclofenac use and cardiovascular risks: series of nationwide cohort studies.* BMJ, 2018. **362**: p. k3426.

37. Sondergaard, K.B., et al., *Non-steroidal anti-inflammatory drug use is associated with increased risk of out-of-hospital cardiac arrest: a nationwide case-time-control study.* Eur Heart J Cardiovasc Pharmacother, 2017. **3**(2): p. 100-107.

38. Petersen, I., I. Douglas, and H. Whitaker, *Self controlled case series methods: an alternative to standard epidemiological study designs.* BMJ, 2016. **354**: p. i4515.

39. Bally, M., et al., *Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data.* BMJ, 2017. **357**: p. j1909.

40. Stehlik, P., L. Rosella, and D. Henry, *Commentary: Renewed controversy over cardiovascular risk with non-steroidal anti-inflammatory drugs.* Int J Epidemiol, 2018. **47**(2): p. 362-367.

41. Arfe, A., et al., *Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study.* BMJ, 2016. **354**: p. i4857.