



MHRA PUBLIC ASSESSMENT REPORT

Non-steroidal anti-inflammatory drugs and cardiovascular risks in the general population

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PLAIN-LANGUAGE SUMMARY

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK, and inform healthcare professionals and the public of the latest updates. In our public assessment reports, we discuss the evidence on a safety issue associated with a particular drug or drug class. The following public assessment report discusses the issue of cardiovascular^a risks associated with non-steroidal anti-inflammatory drugs (NSAIDs), and the results of two published studies which explore this safety issue in the general population.

NSAIDs are important medicines that are widely used to treat diseases such as arthritis (characterised by swollen joints with restricted movement) and bring relief for many other painful conditions^b. Cardiovascular events in association with NSAID use is not a newly identified risk; in 2006, the European Union [Committee for Medicinal Products for Human Use](#) (CHMP^c) concluded in a [Europe-wide review](#) that NSAIDs increased the risk of cardiovascular events but that the balance of benefits to risks remained favourable. Since 2006, two important studies have been published which examine the risk of thrombotic^d cardiovascular events, such as myocardial infarction (MI)^e in association with NSAIDs. One study used the UK [THIN](#) (The Health Improvement Network) database and the other study used data from Danish national registries.

Results

Both studies found a very small increase in the risk of cardiovascular events:

- that may apply to all users of NSAIDs, not only those with baseline cardiovascular risk factors
- after relatively short-term NSAID use (that may increase with increasing duration of use)
- in association with the following specific NSAIDs:
 - celecoxib (any dose)
 - high dose diclofenac (>150mg/day)
 - high dose ibuprofen (>1200mg/day)

No detectable effect on cardiovascular risk was demonstrated for another specific NSAID, naproxen, at any dose.

These findings are in line with the conclusions of the 2006 CHMP review.

^a Related to the heart and blood circulation system

^b NSAIDs currently licensed for use in the UK: aceclofenac (brand name Preservex); acemetacin (Emflex); aspirin (Alka-Seltzer, Anadin, Angettes, Beechams Powders, Micropirin, MigraMax, Nu-seals); celecoxib (Celebrex); dexibuprofen (Seractil); dexketoprofen (Keral); diclofenac sodium (Arthrotec, Dicloflex, Diclomax, Dyloject, Econac, Fenactol, Mobigel, Motifene, Rheumatac, Rheumalgan, Solaraze, Volsaid, Voltarol); etodolac (Eccoxolac, Eccoxolac SR, Lodine SR); etoricoxib (Arcoxia); fenbufen (Lederfen); flurbiprofen (Froben, Froben SR, Ocufer, Strefen); ibuprofen (Anadin Ultra, Brufen, Calprofen, Cuprofen, Dexcel, Feminax, Hedex, Ibuderm, Nurofen, Pedeas, Solpadeine); indometacin (Indolar, Pardelprin); ketoprofen (Axorid, Orudis, Oruvail, Ketocid, Ketovail,); ketorolac (Acular, Toradol); meloxicam (Mobic); nabumetone (Relifex); naproxen (Naprosyn, Synflex, Napratac); piroxicam (Feldene); tenoxicam (Mobiflex); tiaprofenic acid (Surgram); tolfenamic acid (Clotam Rapid).

^c Responsible for preparing opinions from the European Medicines Agency on all questions concerning medicines for human use

^d Related to blood clots

^e Heart attack

Conclusions

The results from these two epidemiological studies lend support to the view that all non-steroidal anti-inflammatory drug (NSAID) users may be at an increased cardiovascular risk, irrespective of their baseline risk for cardiovascular illness or the duration of NSAID use.

Advice to healthcare professionals

Information and advice to healthcare professionals remains that patients should use the lowest effective dose and the shortest duration of NSAID treatment necessary to control symptoms, and that the need for long-term treatment should be reviewed periodically.

1. INTRODUCTION

(See glossary for explanation of terms used in this document)

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK, and inform healthcare professionals and the public of the latest updates. In our public assessment reports, we discuss the evidence on a safety issue associated with a particular drug or drug class. Regarding the issue of cardiovascular risks associated with the use of non-steroidal anti-inflammatories (NSAIDs), a comprehensive Europe-wide review of clinical-trial and epidemiological data in October 2006^[1], led to advice from the CHMP^a that NSAIDS may be associated with a small increased risk of thrombotic events such as myocardial infarction (MI) or stroke, especially when used at high doses and for long-term treatment. The following public assessment report discusses the issue of cardiovascular risks associated with NSAIDS, and the results of two epidemiological studies published after 2006, which explored this safety issue.

^a The Committee for Medicinal Products for Human Use: responsible for preparing opinions from the [European Medicines Agency](#) on all questions concerning medicinal products for human use

2. BACKGROUND

NSAIDs are medicines that are widely used to treat diseases such as arthritis and many other painful conditions. The NSAIDs which are currently licensed for use in the UK are: **aceclofenac** (brand name Preservex); **acemetacin** (Emflex); **aspirin** (Alka-Seltzer, Anadin, Angettes, Beechams Powders, Micropirin, MigraMax, Nu-seals); **celecoxib** (Celebrex); **dexibuprofen** (Seractil); **dexketoprofen** (Keral); **diclofenac sodium** (Arthrotec, Dicloflex, Diclomax, Dyloject, Econac, Fenactol, Mobigel, Motifene, Rheumatac, Rheumalgan, Solaraze, Volsaid, Voltarol); **etodolac** (Eccoxolac, Eccoxolac SR, Lodine SR); **etoricoxib** (Arcoxia); **fenbufen** (Lederfen); **flurbiprofen** (Froben, Froben SR, Ocuflen, Strefen); **ibuprofen** (Anadin Ultra, Brufen, Calprofen, Cuprofen, Dexcel, Feminax, Hedex, Ibuderm, Nurofen, Pedeas, Solpadeine); **indometacin** (Indolar, Pardelprin); **ketoprofen** (Axorid, Orudis, Oruvail, Ketocid, Ketovail,); ketorolac (Acular, Toradol); **meloxicam** (Mobic); **nabumetone** (Relifex); **naproxen** (Naprosyn, Synflex, Napratac); **piroxicam** (Feldene); **tenoxicam** (Mobiflex); **tiaprofenic acid** (Surgram); tolfenamic acid (Clotam Rapid).

2.1 COX-isoenzyme selectivity of NSAIDs

NSAIDs act by blocking cyclo-oxygenase (COX), an inflammation-promoting enzyme that catalyses the rate-limiting step in the formation of prostanoids from arachidonic acid and exists in two main isoforms: COX-1 and COX-2. NSAIDs vary in their selectivity for COX-1 and COX-2, and are generally categorised as either non-selective COX inhibitors or selective COX-2 inhibitors (coxibs), according to their relative selectivity. COX-1 and COX-2 are thought to participate differentially in physiological situations and disease processes.

Non-selective NSAIDs interact competitively with both isoforms of the COX enzyme. The coxibs have a higher selectivity for the COX-2 isoform; however, COX-2 selectivity of NSAIDs is a continuous variable and varies in vivo according to the dose of NSAID that is given. Relative COX selectivity is assigned on the basis of in vitro assays, and can differ according to the assay used; however the basic principle of all methods is to measure the generation of prostanoids from endogenous sources of arachidonic acid. COX-1 selectivity is usually based on the production of thromboxane (TXB₂) by platelets during blood clotting, and COX-2 selectivity is usually based on the production of prostaglandin E₂ (PGE₂) by monocytes. The ratio of the amount of a given NSAID to inhibit COX-1 activity and COX-2 activity by 50% gives its relative COX selectivity.

2.2 Adverse effects resulting from COX inhibition

Prostanoids that are derived largely, but not exclusively, via COX-1, give cytoprotection of gastric mucosa and contribute to normal platelet function via the production of thromboxane (TXA₂). Inhibition of the COX-1 isoform is therefore associated with adverse gastrointestinal effects and impaired normal platelet function.

COX-2 is induced predominantly in the presence of inflammation or cell injury, when it catalyses the production of prostacyclin (PGI₂). During endothelial injury, PGI₂ is thought to counteract the consequences of platelet activation and additionally to act as a vasodilator. Originally, inhibition of the COX-2 isoform was thought to be responsible for the anti-inflammatory, anti-pyretic and analgesic properties of NSAIDs. However, it is also possible that blockade of COX-2 can impair endothelial health, cause a prothrombotic state and promote cardiovascular disease.

In addition, aspirin is the only NSAID that irreversibly inhibits COX by acetylation, and may therefore have potential to interact with other NSAIDs.

2.3 The CHMP 2006 European review

A comprehensive Europe-wide review of clinical trial and epidemiological data was completed by the CHMP in October 2006¹. The committee recommended the following general prescribing advice for healthcare professionals and patients:

- NSAIDs should be used at the lowest effective dose for the shortest possible time
- NSAIDs should be prescribed on the basis of their overall safety profile and the patient's individual risk factors
- NSAIDs should not be switched without careful consideration of their overall safety profiles, the patient's risk factors and their preferences.

With respect to the cardiovascular risk of these products, CHMP concluded that a small increase in the absolute risk of thrombotic events cannot be excluded for non-selective NSAIDs, especially when used at high doses for long-term therapy. More specifically:

2.3.2 Non-selective COX-inhibitors

Ibuprofen

Available data for the cardiovascular safety of ibuprofen are inconsistent; however in general, epidemiological studies do not suggest an increased risk of MI in association with use of low dose ibuprofen (≤ 1200 mg per day). At high doses (2400 mg per day), a thrombotic risk (eg, MI or stroke) similar to that of COX-2 inhibitors has been observed, together with an adverse pattern of cardiorenal events.

Diclofenac

The available data suggest that diclofenac has a thrombotic cardiovascular safety profile with closer similarity to those of COX-2 inhibitors than naproxen. This is most likely due to its moderate COX-2 selectivity, although its effect on blood pressure may also be important. However, the data are insufficient to conclude that the magnitude of this increased risk is in the same range as that for COX-2 inhibitors.

Overall, diclofenac, particularly at a high dose (150 mg per day), may be associated with an increased risk of arterial thrombotic events (eg, MI or stroke).

Naproxen

The data suggest that naproxen (1000 mg per day) may be associated with a lower risk for arterial thrombotic events than COX-2 inhibitors. The data do not suggest an increased risk of MI; however, a small risk cannot be excluded.

2.3.2 COX2 inhibitors

New epidemiological evidence and updated clinical trial data (the Adenoma Prevention with Celecoxib study [APC], the Prevention of Colorectal Sporadic Adenomatous Polyps study [PreSAP], the Adenomatous Polyp Prevention On Vioxx study [APPROVe] and meta-analyses) continue to suggest an increased thrombotic risk with COX-2 inhibitors compared with non-use (in epidemiological studies), and compared with placebo (in clinical studies). This possibly accounts for about three extra events per 1000 patient-years. The increased risk relates mainly to MI, and includes cerebrovascular and peripheral vascular events in some studies. For the majority of patients, the potential increase in thrombotic risk is small. However, in patients with pre-existing risk factors for, or a history of, cardiovascular disease, the risk may be higher.

Warnings in product information were updated in line with these new data (see section 2.4).

2.4 Current product information for NSAIDs related to cardiovascular risk

As a consequence of the 2006 CHMP review of NSAIDs, updated warnings about cardiovascular safety were incorporated into their Summaries of Product Characteristics^a (SPCs):

All NSAIDs:

Section 4.2^b for all NSAIDs includes a recommendation to use the lowest effective dose for the shortest possible duration because of the potential increase in cardiovascular risk with increasing dose and duration.

Section 4.3: All NSAIDs are contraindicated in severe heart failure.

Section 4.8: Product information for all NSAIDs refers to a variety of cardiorenal and cardiovascular events.

Cox-2 inhibitors:

Section 4.3: The COX-2 inhibitors are additionally contraindicated in patients with congestive heart failure, established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

Section 4.4: Product information for the COX-2 inhibitors carries extensive warnings about the risk of cardiovascular disease such as MI and stroke, particularly at high doses and for a long duration of exposure, providing detailed information on the need to exercise caution when prescribing in patients with significant risk factors. Extensive warnings are also provided about the increased cardiorenal risk.

Non-selective NSAIDs:

Section 4.4: A similar warning to COX-2 inhibitors about an increase in cardiovascular risk, particularly with high doses and longer durations, is provided together with a risk: benefit statement on prescribing in patients with risk factors for cardiorenal and cardiovascular events.

For ibuprofen, diclofenac and naproxen, specific information about the perceived level of risk is provided based on the outcome of the CHMP review. Thus:

Ibuprofen:

Trial data suggest that use of ibuprofen, particularly at a high dose (2400 mg per day) and in long term treatment, may be associated with a small increased risk of arterial thrombotic events (for example MI or stroke). Epidemiological studies do not suggest that low dose ibuprofen (eg ≤1200 mg per day) is associated with an increased risk of myocardial infarction.

Diclofenac:

Data suggest that use of diclofenac, particularly at a high dose (150 mg per day) and in long term treatment, may be associated with a small increased risk of arterial thrombotic events.

Naproxen:

^a Product information

^b Section 4.2 of an SPC gives the posology and method of administration of a drug; section 4.3 highlights the contraindications, section 4.4 gives special warnings and precautions for use and section 4.8 indicates the undesirable effects of a drug, observed during clinical trials and after licensing

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example MI or stroke). Although data suggest that the use of naproxen (1000 mg per day) may be associated with a lower risk, some risk cannot be excluded.

3. DATA ON NSAID USE IN THE GENERAL POPULATION

The following section reviews two published epidemiological studies that investigated the cardiovascular risk of NSAIDs in the general population.

3.1. UK 'THE HEALTH IMPROVEMENT NETWORK' (THIN) DATABASE STUDY^[2]

3.1.1 Purpose of study

The primary purpose of this study was to evaluate the association between the use of NSAIDs, according to their dose, frequency of use and duration of use, and risk of non-fatal MI in the general population.

Evidence suggests that for COX-1 inhibition by non-selective NSAIDs to be clinically relevant; ie, to prevent thrombus formation, the isoenzyme needs to be inhibited by $\geq 95\%$. NSAIDs without this degree of COX-1 selectivity exhibit functional COX-2 selectivity, namely inhibition of the COX-2 isoenzyme without inhibition of platelet function. The investigators therefore measured the degree of functional COX selectivity using average circulating concentrations of NSAIDs (taken from blood of study participants) with the aim of determining whether the degree of inhibition of COX-2 in vitro at these concentrations predicts the relative risk of MI for individual NSAIDs.

3.1.2 Methods

A retrospective, population-based cohort study with nested case-control analysis was performed using the THIN database in the UK. The study cohort included patients without cancer aged 50–84 years between January 2000–October 2005, who were enrolled for at least 2 years with a general practitioner (GP). Patients were followed to the earliest occurrence of: MI, cancer, 85th birthday, death, or end of study period.

Cases were identified as those with a recorded diagnosis of MI during the study period ($n=12\,499$), and only patient details of incident cases ($n=10\,653$) were retained after review of their computerised profiles. All fatal cases, defined as death within 1 month of MI, were excluded to leave a total of 8 852 cases of incident, non-fatal MI. The validity of case ascertainment was tested in a random sample of approximately 500 patients by sending questionnaires to their GPs; a 95% confirmation rate was achieved. A group of 20 000 controls was randomly selected from the list of eligible patients and matched with cases by sex, age within 1 year and calendar year using incidence density sampling. The likelihood of being selected as a control using this method is proportional to person-time at risk.

NSAID exposure was classified as: 'current' use, when the supply of the most recent NSAID prescription lasted until at least 7 days before the index date (record of MI); 'recent' use, when the NSAID supply ended 8–90 days before the index date; 'past' use, when the most recent supply ended 91–365 days before the index date; 'new' use, defined as those with no record of NSAIDs use in the year before the study start date (ie, prior to the year 2000 or reaching age 50 years); and 'non-use', when there was no NSAID use recorded in the year before the index date. 'Current' use of NSAIDs was further categorised as 'single' use, referring to only one NSAID used in the month before index date; 'multiple' use, referring to two or more NSAIDs used in the month before index date; and 'switcher', referring to one NSAID used in the week before index date and at least one different NSAID used 8–30 days before index date. A sensitivity analysis to best define 'current' use was done using a 0–30 day window of use before index date.

The effect of duration of NSAID use, dose and its plasma half-life/formulation was evaluated in users classed as 'current', 'single' and 'new'. Doses were categorised as

either 'low-medium' or 'high', where the cut-off values corresponding to low-medium doses of the key NSAIDs were: celecoxib ≤ 200 mg, diclofenac ≤ 100 mg; etodolac ≤ 400 mg; etoricoxib ≤ 90 mg; ibuprofen ≤ 1200 mg; indomethacin ≤ 75 mg; meloxicam ≤ 7.5 mg; naproxen ≤ 750 mg, piroxicam ≤ 10 mg; and rofecoxib ≤ 25 mg.

COX selectivity was evaluated in vitro in whole blood assays using therapeutic concentrations of NSAIDs derived from patient blood. Odds ratios (OR) and 95% confidence intervals (CI) for the risk of MI were estimated. Results were adjusted for a number of variables and those that changed them by more than 10% were included in the multivariable model. Specific stratified analyses were performed by age, sex and history of coronary artery disease (CAD). Linear regression was used to measure the correlation between risk of MI obtained from the THIN study and the indexes of COX inhibition of individual NSAIDs.

One limitation of this general practice database study is that over-the-counter (OTC) use of ibuprofen in the UK was not captured. This could potentially influence the findings for this NSAID, as those who receive ibuprofen on prescription may have a higher baseline cardiovascular risk.

3.1.3 Results

Incidence of MI

The final cohort consisted of 716 395 patients followed for an average of 4.1 years and 8852 non-fatal incident MIs (an incidence of 4.1 per 1 000 person-years). As expected, the incidence of MI was higher in those with a history of CAD (13.9 per 1000 person-years) compared to those with no history (3.0 per 1000 person-years).

Effect of NSAID use, treatment duration and dose on risk of MI

Table 1 shows the risk of MI in NSAIDs users estimated according to recency of exposure, duration of use and dose administered.

Table 1. Relative risk of MI according to use, duration and dose of NSAIDs²

NSAID Exposure	Cases (n=8852)	Controls (n=20 000)	Relative risk*	95% CI
Recency of use				
Non-use	6434	15 513	Reference	
Current use	940	1570	1.34	1.23–1.47
Single	901	1510	1.35	1.23–1.48
Multiple	20	33	1.27	0.71–2.27
Switcher	19	27	1.14	0.61–2.13
Recent use	598	1061	1.27	1.14–1.42
Past use	880	1856	1.02	0.94–1.12
Duration of use				
≤ 30 days	152	318	1.13	0.92–1.39
31–365 days	295	506	1.34	1.15–1.56
1–3 years	214	339	1.39	1.16–1.67
>3 years	240	347	1.53	1.28–1.82

Daily dose [†]				
Low–medium dose	521	963	1.23	1.09–1.38
High dose	380	547	1.57	1.36–1.81

*Relative risk adjusted for age; sex; calendar year; body mass index (BMI); GP visits; referrals; smoking; Townsend score^a; ischaemic heart disease; diabetes mellitus; rheumatoid arthritis; chronic obstructive pulmonary disease; use of anticoagulants, antihypertensives, oral steroids, and aspirin.

[†]Specific cutoff values for dose were as follows: aceclofenac >200 mg; acemetacin >120 mg; azapropazone >600 mg; celecoxib >200 mg; diclofenac >100 mg; diflunisal >1500 mg; etodolac >400 mg; etoricoxib >90 mg; fenbufen >900 mg; fenoprofen >1200 mg; flurbiprofen >150 mg; ibuprofen >1200 mg; indomethacin >75 mg; ketoprofen >150 mg; ketorolac >30 mg; mefenamic acid >1000 mg; meloxicam >7.5 mg; nabumetone >1000 mg; naproxen >750 mg, piroxicam >10 mg; rofecoxib >25 mg; sulindac >200 mg; tenoxicam >10 mg; tiaprofenic >600 mg; and valdecoxib >20 mg. Doses ≤cut-off value were classed as 'low–medium dose' and doses >cut-off value were classed as 'high dose'.

CI=confidence interval

A similar small increase in risk of MI was observed in 'current' users (RR 1.34 [95% CI: 1.23–1.47]) and 'recent' users (RR 1.27 [1.14–1.42]). No increase in risk was apparent in 'past users' (RR 1.02 [0.94–1.12]). 'Current single' NSAIDs users, comprised 96% of all current users, therefore the numbers of multiple NSAIDs users and 'switchers' were insufficient to give reliable estimates of risk.

The risk of MI in current users of NSAIDs was not significantly raised with up to 1 month of use, although a small increase in risk could not be excluded (1.13 [0.92–1.39]). This is important as it would include most OTC users, who are likely to use NSAIDs sporadically for short periods of time. In the UK about 40% of all NSAIDs prescriptions are for less than 1 month (MHRA data). However, use of NSAIDs between 1–12 months significantly increased risk of MI (1.34 [1.15–1.56]), and longer duration of use appeared to also increase the risk, with a maximum increase of 1.53-fold (1.28–1.82) for more than 3 years' use.

The risk of MI appeared to be higher in users of high-dose NSAIDs compared with low–medium dose NSAIDs (1.57 [1.36–1.81] vs 1.23 [1.09–1.38] respectively), although the difference is not statistically significant.

Effect of NSAIDs by formulation and dose

Table 2 shows the relative risk of MI in association with NSAIDs estimated according to their plasma half-lives and formulation.

Table 2. Effect of NSAID formulation (stratified by dose) on relative risk of MI²

NSAID Exposure	Cases (n = 8852)	Controls (n = 20 000)	Relative risk*	95% CI
Overall				
Non-use	6434	15 513	Reference	
Short/no slow release [†]	498	867	1.33	1.18–1.50
Long/no slow release [‡]	250	425	1.27	1.07–1.50
Slow release§	153	218	1.59	1.28–1.98

^a Common method used to estimate social deprivation in public health studies

Low-medium dose				
Non-use	6434	15 513	Reference	
Short/no slow release [†]	300	599	1.16	1.00–1.35
Long/no slow release [‡]	154	270	1.22	0.99–1.51
Slow release [§]	67	94	1.65	1.19–2.29
High dose				
Non-use	6434	15 513	Reference	
Short/no slow release [†]	198	268	1.71	1.41–2.08
Long/no slow release [‡]	96	155	1.35	1.03–1.76
Slow release [§]	86	124	1.55	1.16–2.07

*Relative risk adjusted for age; sex; calendar year; BMI; GP visits; referrals; smoking; Townsend score; ischaemic heart disease; diabetes mellitus; rheumatoid arthritis; chronic obstructive pulmonary disease; use of anticoagulants, antihypertensives, oral steroids, and aspirin.

[†]Short half-life group: aceclofenac; acemetacin; celecoxib; diclofenac; etodolac; fenbufen; fenoprofen; flurbiprofen; ibuprofen; indomethacin; ketoprofen; mefenamic acid; tiaprofenic acid; valdecoxib.

[‡]Long-half-life group: apazone; meloxicam; nabumetone; maprofen; piroxicam; sulindac; tenoxicam; rofecoxib; etoricoxib

[§]Slow-release group: ibuprofen; indomethacin; etodolac; diclofenac; ketoprofen.

CI=confidence interval

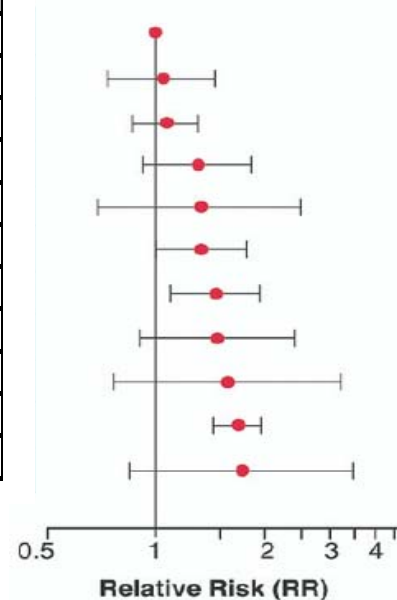
Although the risk of MI was marginally higher in users of slow-release preparations than in users of regular formulations, the 95% CIs for the direct comparison included 1 and no obvious pattern was apparent when the analyses were stratified by dose. Few conclusions can be drawn from these data.

Relative risk of MI for individual NSAIDs

Figure 1 shows the risk estimates for key NSAIDs (reproduced with permission from [Rodriguez et al, 2008](#) [figure 1A])

NSAID	Cases (n=8852)	Controls (n=20 000)	Relative risk	95% CI
Non-use	6434	15 513	1.00	
Naproxen	54	119	1.04	(0.74–1.45)
Ibuprofen	143	314	1.06	(0.86–1.30)
Meloxicam	59	99	1.30	(0.92–1.82)
Etodolac	16	29	1.32	(0.69–2.50)
Celecoxib	81	144	1.33	(1.00–1.77)
Rofecoxib	98	139	1.46	(1.10–1.92)
Indomethacin	29	45	1.47	(0.90–2.41)
Etoricoxib	14	18	1.57	(0.76–3.25)
Diclofenac	353	483	1.67	(1.44–1.94)
Piroxicam	14	21	1.72	(0.84–3.50)

CI=confidence interval

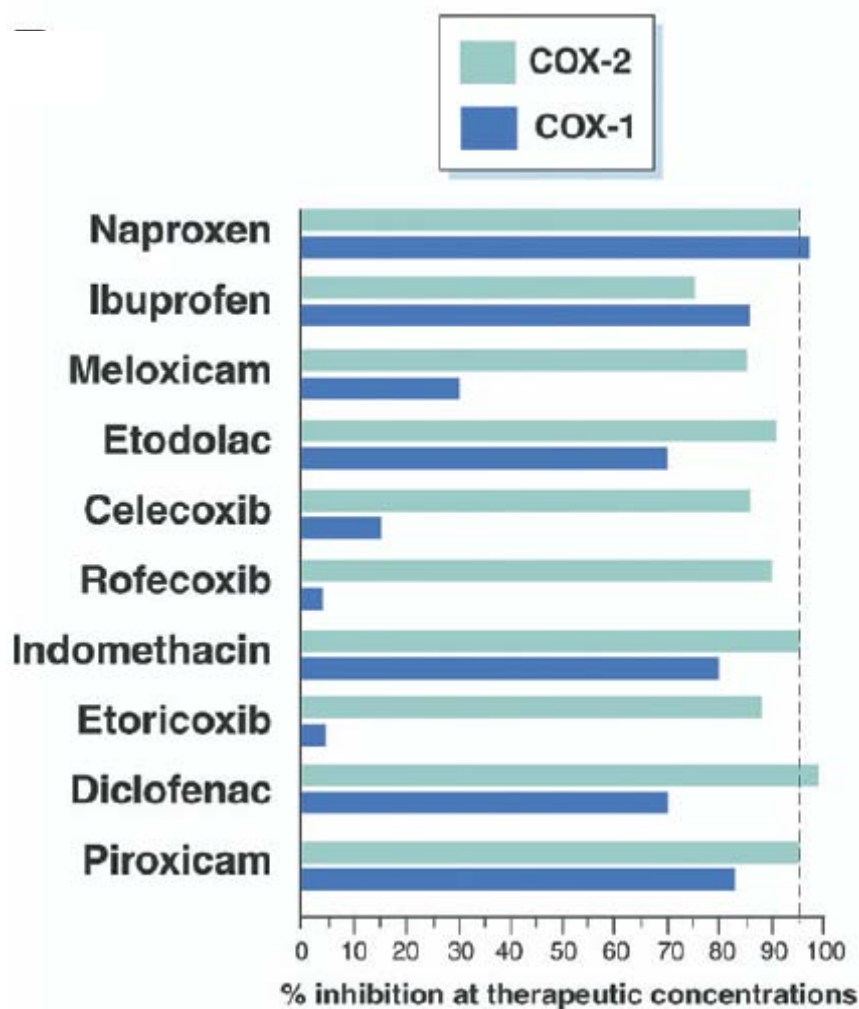


A small increase in risk of MI was observed for all NSAIDs other than naproxen and ibuprofen. However, as the numbers of users of etodolac, indometacin, etoricoxib and piroxicam were small (<100), the estimates obtained are unreliable; only rofecoxib and diclofenac were clearly associated with a greater risk of MI compared with non-use.

In vitro COX selectivity of NSAIDs at therapeutic concentrations

COX-2 selectivity was measured in vitro using average circulating blood concentrations of the NSAIDs, taken mostly from the population of the THIN database (figure 2).

Figure 2. Effects of therapeutic concentrations of NSAIDs on whole blood COX-1 and COX-2 *in vitro* (Reproduced with permission from [Rodriguez et al, 2008](#) [figure 1B])

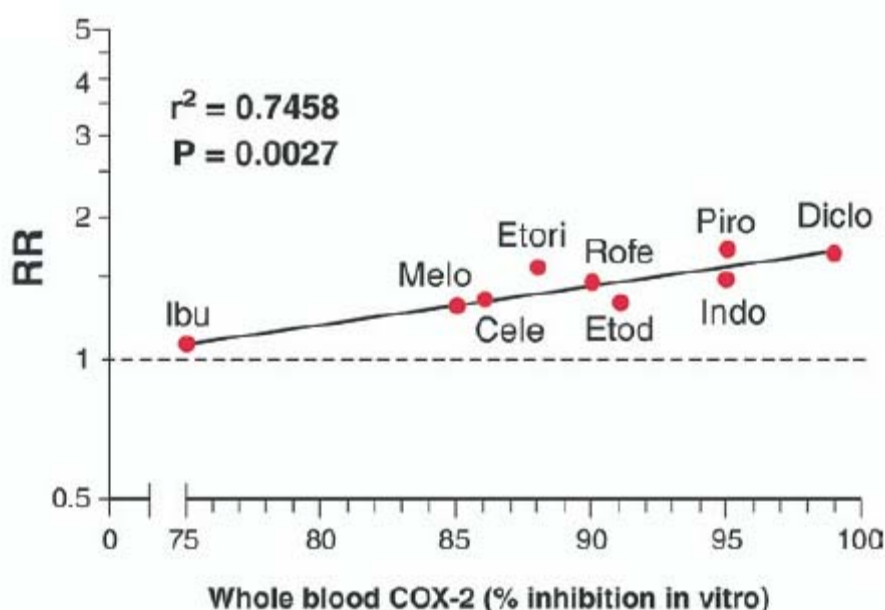


With the exception of naproxen and ibuprofen, all NSAIDs showed greater selectivity for COX-2 than COX-1 in this assay. At average therapeutic doses naproxen was the only NSAID that caused $\geq 95\%$ inhibition of the COX-1 isoform, a level that is necessary to prevent platelet function in vivo.

Relationship between COX-2 inhibition and risk of MI

A statistically significant correlation was observed between the measured degree of COX-2 inhibition and the estimated risk of MI compared with non-use in current users of NSAIDs ($p=0.0027$, figure 3). Naproxen was not included in this analysis as it functionally inhibits COX-1 at therapeutic levels.

Figure 3. Relationship between COX-2 inhibition and risk of MI (reproduced with permission from [Rodríguez et al, 2008](#) [Figure 1C])



The linear regression analysis yielded a significant correlation (r^2) between the two variables. Cele=celecoxib; Diclo=diclofenac; Etod=etodolac; Etori=etoricoxib; Ibu=ibuprofen; Indo=indomethacin; Melo=meloxicam; Piro=piroxicam; Rofe=rofecoxib; RR=relative risk

The investigators used an arbitrary cut-off value for COX-2 selectivity of 90% to divide the NSAIDs into those with <90% selectivity (ibuprofen, meloxicam, celecoxib and etoricoxib) and those with $\geq 90\%$ selectivity (rofecoxib, etodolac, indometacin, piroxicam and diclofenac). The risk of MI for NSAIDs with <90% COX-2 selectivity (1.18 [1.02–1.38]) was significantly lower than the risk for those with $\geq 90\%$ COX-2 selectivity (1.60 [1.41–1.81], $p<0.01$).

These in vitro findings suggest that for NSAIDs that are not sufficiently COX-1 selective to inhibit platelet function, cardiovascular risk is related to the level of COX-2 inhibition.

Effect of NSAID dose

Table 3 shows the relative risk of MI estimated for low-medium doses and high doses of individual NSAIDs.

Table 3. Relative risk of MI according to daily dose of individual NSAID²

NSAIDs	Cases (n = 8852)	Controls (n = 20 000)	Relative risk*	95% CI
Non-use	6434	15 513	1	
Celecoxib				

Low-medium dose	76	134	1.35	1.00–1.82
High dose	5	10	1.05	0.33–3.35
Diclofenac				
Low-medium dose	141	216	1.51	1.20–1.89
High dose	212	267	1.80	1.49–2.18
Ibuprofen				
Low-medium dose	120	279	1.00	0.80–1.25
High dose	23	35	1.56	0.90–2.71
Indomethacin				
Low-medium dose	16	22	1.58	0.80–3.10
High dose	13	23	1.36	0.67–2.79
Meloxicam				
Low-medium dose	30	46	1.40	0.87–2.27
High dose	29	53	1.21	0.75–1.94
Naproxen				
Low-medium dose	17	46	0.90	0.50–1.60
High dose	37	73	1.12	0.74–1.69
Rofecoxib				
Low-medium dose	94	138	1.41	1.07–1.87
High dose	4	1	6.50	0.70–60.33

*Relative risk adjusted for age; sex; calendar year; BMI; GP visits; referrals; smoking; Townsend score; ischaemic heart disease; diabetes mellitus; rheumatoid arthritis; chronic obstructive pulmonary disease; use of anticoagulants, antihypertensives, oral steroids, and aspirin. CI=confidence interval

The number of users within each dose sub-category is limited for many NSAIDs and so few conclusions can be made. However, the increased risk of MI in users of diclofenac was greatest with high doses (>100 mg). No increase in risk of MI was observed in users of low-dose ibuprofen (≤ 1200 mg); however, the risk estimate was slightly raised in association with higher doses. There were too few naproxen users to draw any conclusions about dose effect with this drug.

The risk of MI associated with diclofenac was further stratified by dose and formulation because of the large number of diclofenac users (table 4).

Table 4 Dose-dependency of MI relative risk in users of diclofenac²

Dose (mg)	Relative risk (95%CI)
50	1.12 (0.57–2.19)
75	1.31 (0.80–2.16)
100	1.65 (1.26–2.18)
150	1.80 (1.49–2.18)

CI=confidence interval

A clear and statistically significant dose-response was observed ($p < 0.0001$) where the relative risk of MI gradually increased with dose to a maximum of 1.80 (1.49–2.18) in

users of 150 mg diclofenac (table 4). There are currently few robust data on the risk of thrombotic cardiovascular events in association with diclofenac at 100 mg per day and this study provides some evidence that it may be raised. At doses of 50 mg and 75 mg no clear increase was observed, although the numbers of patients in each substratum are not provided and may have been too small.

The risk of MI was marginally higher in association with slow-release diclofenac (1.85 [1.42–2.39]), although the 95% CIs for this estimate and for the normal release formulation (1.59 [1.34–1.90]) showed extensive overlap.

Effect of concomitant NSAID and aspirin use on risk of MI

This study also evaluated whether the cardioprotective effect of aspirin on MI was affected by concomitant use of NSAIDs. It has been suggested that competition for the platelet COX-1 isoenzyme by NSAIDs may reduce the ability of aspirin to bind irreversibly, thereby reducing its effectiveness.

Although concomitant aspirin use with naproxen and ibuprofen suggested a minor antagonism, none of the terms for interaction was statistically significant (table 5).

Table 5. Effect of concomitant NSAIDs and aspirin on relative risk of MI*²

NSAID	Aspirin alone	NSAID alone[†]	Aspirin + NSAID[†]	
Relative risk	(95% CI)	Relative risk	Relative risk	p
		(95% CI)	(95% CI)	
All NSAIDs	1.04 (0.96–1.12)	1.39 (1.25–1.55)	1.33 (1.11–1.60)	0.36
Celecoxib	1.04 (0.96–1.12)	1.44 (1.04–2.01)	1.13 (0.63–2.03)	0.86
Diclofenac	1.03 (0.95–1.12)	1.79 (1.52–2.12)	1.41 (1.03–1.93)	0.61
Ibuprofen	1.04 (0.96–1.12)	1.02 (0.80–1.32)	1.22 (0.83–1.78)	0.14
Meloxicam	1.03 (0.95–1.12)	1.61 (1.09–2.40)	0.78 (0.41–1.51)	0.17
Naproxen	1.04 (0.96–1.12)	1.00 (0.68–1.47)	1.26 (0.60–2.62)	0.33
Rofecoxib	1.04 (0.96–1.12)	1.47 (1.06–2.05)	1.51 (0.92–2.47)	0.49

*Relative risk adjusted for age; sex; calendar year; BMI; GP visits; referrals; smoking; Townsend score; ischaemic heart disease; diabetes mellitus; rheumatoid arthritis; chronic obstructive pulmonary disease; use of anticoagulants, antihypertensives and oral steroids.

[†]Specific NSAID exposure indicated in the left column

Reference group for estimates of relative risk is the same for all comparisons: nonusers of aspirin and NSAIDs

Sub-analyses and stratification by age, sex and history of CAD

The results were little affected when analyses were restricted to new users (ie, those with no record of NSAID use in the year prior to their first prescription in the study), and were not affected when the definition of a 'current' user was broadened to include those whose supply of NSAIDs had finished 1 month before the index date.

Stratification of the results showed that NSAID-associated risk of MI reduced with older age. Thus, RR fell from 1.61 (1.27–2.04) in patients aged 50–59 years, to 1.34 (1.18–1.53) in those aged 60–74 years and 1.22 (1.03–1.45) in those aged 75–84 years. The stratum-specific CIs within each covariate are overlapping; however, if the observed fall in RR with increasing age is real, it could be attributable to the phenomenon of 'depletion

of susceptibles', whereby a younger population includes those who are predisposed to suffer an MI but haven't yet been exposed to sufficient 'triggers' whilst older populations are freer from such 'at risk' people.

The risk of MI was slightly higher in those with a history of CAD (RR 1.41 [1.27–1.47]) than in those without (1.18 [0.98–1.42]). Patient sex did not affect the risk estimates.

3.1.4 Discussion of study

In general this study appears to have been carefully designed and completed. One limitation of using the THIN database is that OTC sales of ibuprofen are not captured. However, since patients who receive ibuprofen on prescription are likely to have a higher cardiovascular risk than those who buy it OTC this would be expected to result in an over-estimation of the risk in association with this drug. Another limitation is that the amount of data in many of the sub-group analyses is too small to provide reliable risk estimates. Furthermore, while attempts have been made to take all potential confounding factors into consideration, the RRs estimated in this observational study are mostly relatively small (<1.5) and must therefore be interpreted with some caution, as some uncontrolled confounding or bias is likely to remain. Nevertheless, the results of this study are fully in line with the conclusions of the 2006 CHMP review.

This study identified a 34% increase in the relative risk of MI in current NSAIDs users. Risk increased in those who used NSAIDs for more than 1 month and appeared to increase slightly more with long-term use (to 53% after >3 years). There was some suggestion that risk of MI was higher in association with slow-release formulations, although the data were not clear.

No increase in risk of MI was found for naproxen users. However, a clear dose-response was observed for ibuprofen and diclofenac (the only NSAIDs with sufficient exposure to provide reliable estimates), with significant increases in risk observed with high-dose ibuprofen (>1200 mg per day) and daily doses of diclofenac of ≥ 100 mg. It is important to bear in mind that there may be important differences in the underlying diseases or in the prescribing pattern for diclofenac compared with either naproxen or ibuprofen in interpreting these findings.

A history of CAD increased the risk of the adverse cardiovascular effect of NSAIDs slightly, as did being younger (age 50–59 years). Little evidence was found for a major effect of concomitant NSAIDs on the cardioprotective action of aspirin, although there may have been some suggestion for a slight interaction with ibuprofen and naproxen. This study aimed to investigate how NSAIDs increase the risk of MI. The investigators used plasma from NSAIDs users to evaluate the pharmacodynamic properties of the individual drugs, with respect to their COX-selectivity. Their results suggest that of the NSAIDs evaluated, only naproxen and ibuprofen were more selective for whole blood COX-1 isoenzyme than COX-2. As a result the investigators propose that only naproxen and high-dose ibuprofen are sufficiently COX-1 selective (ie, >95%) to functionally inhibit platelet activity in vivo. They further hypothesise that the longer half-life of naproxen (>12 h) compared with ibuprofen (about 2 h) means that complete suppression of platelet activity may be achieved in some naproxen users (possibly resulting in cardioprotection), but this will not occur in users of low-dose ibuprofen and will be rare among users of high-dose ibuprofen.

For functional COX-2 selective inhibitors, the degree to which whole blood COX-2 was inhibited at therapeutic concentrations showed significant correlation with the level of MI risk. No correlation was observed with the level of COX-1 inhibition, which the investigators interpreted as support for the hypothesis that the cardiovascular hazard associated with NSAIDs involves the inhibition of COX-2-dependent prostacyclin. They

concluded that the assessment of whole blood COX-2 inhibition may represent a surrogate end point to predict the cardiovascular risk of NSAIDs, and that the separation of NSAIDs into selective COX-2 and non-selective COX-2 inhibitors adds little to this prediction.

Summary

This study confirms that:

- All NSAIDs (non-selective and coxibs) may be associated with a small increased risk of MI, particularly when used at high doses, for long-term treatment and in those with a history of CAD
- Diclofenac has a thrombotic profile that shows greater similarity to the coxibs than to naproxen and ibuprofen, particularly at high doses. Subgroup analyses provide some evidence that 100 mg per day diclofenac may be associated with an increase in MI risk.
- Ibuprofen does not increase the risk of MI at low doses but at high doses a risk similar to that of coxibs has been observed
- Naproxen is associated with a lower risk of MI than ibuprofen and diclofenac and at low doses is not associated with any discernable increase in risk

This study also raises the possibility that risk does not increase in association with use of NSAIDs for <30 days and that risk falls to baseline values within 3 months of stopping. However, these findings relate to all NSAIDs and it is conceivable that individual products have different effects in this respect.

3.2 DANISH COHORT STUDY^[3]

3.2.1 Purpose of study

This study was conducted to determine whether the increased risk of cardiovascular events associated with NSAID use observed in clinical studies applies to healthy people. In this study, a 'healthy' individual was defined as having had no previous hospital admissions in the previous 5–10 years and no prescriptions for certain concomitant medications.

3.2.2 Methods

Study Populations

Two study populations were selected from all Danish residents aged 10 years or older. Study population A comprised individuals who had had no hospital admissions in the 5 years before the index date (first claimed prescription of an NSAID, or 1st June 2001 for non-users, or 1st January 1997 for non-users who died before then) and no claimed prescription for concomitant cardiovascular medications^a after 1995 and before the date of their first claimed prescription for NSAID. Population B was a sub-population of A and comprised individuals who had had no hospital admissions in the 10 years before the index date and no claimed prescription for selected concomitant medications after 1995 and before the date of their first claimed prescription for NSAID (see fig 1 in Fosbøl et al, 2009³). Follow-up of all individuals was for 9 years, from 1997 to 2005.

Information on the individual use of NSAIDs according to claimed prescriptions during the study period was obtained through the Danish Registry of Medicinal Product

^a β -blockers, digoxin, angina medication, diuretics, calcium-channel blockers, angiotensin-converting enzyme inhibitors and angiotensin-2 receptor blockers, antithrombotic agents, chronic obstructive pulmonary disease agents, glucose-lowering medication, corticosteroids, analgesics (including morphines), chemotherapy, immunosuppressive agents, disease-modifying antirheumatic agents, and anaesthetics.

Statistics^a, and information on previous hospital admissions and admissions due to MI was obtained from the Danish National Patient Registry. Survival status was obtained from the National Person Registry.

Dose and duration of treatment

Duration of treatment was calculated from the number of pills dispensed and the estimated daily dose. Dose was categorised as low or high according to the upper recommended limit for the minimum dose. High doses corresponded to:

Ibuprofen >1200 mg	(recommended dose range in UK: 600–2400 mg per day)
Diclofenac ≥100 mg	(recommended dose range in UK: 75–150 mg per day)
Naproxen >500 mg	(recommended dose range in UK: 500–1250 mg per day)
Rofecoxib >25 mg	(recommended dose range in UK: 12.5–50 mg per day)
Celecoxib >200 mg	(recommended dose range in UK: 200–400 mg per day)

Naproxen, diclofenac and especially ibuprofen are used to treat less serious conditions compared with some of the other NSAIDs. It should therefore be borne in mind that patients prescribed the COX-2 inhibitors may have a different risk profile to those who are prescribed the less selective NSAIDs.

Outcome measures

The primary outcome in this study was a composite of death and myocardial infarction, while the secondary outcome was death alone

Statistical methods

The risk of death and MI in association with NSAIDs was calculated using two methods: Cox proportional-hazard regression analysis (with NSAID exposure entered into the model as a time-dependent variable) and a case-crossover design (with the individual acting as their own control in a different period). A potential limitation of Cox proportional hazard regression analysis is that it does not take unidentified confounding factors into consideration. However, case crossover analyses have the advantage of eliminating all biases that remain constant in a study (including chronic illness confounders), by using data from each individual participant at the start of the study as their own 'control' values. Cox regression analyses were adjusted for age, sex and calendar year, and sensitivity analyses were performed for those with cancer diagnosed between the index date and event. This analysis was repeated considering only the first NSAID treatment period as exposure.

In the case-crossover analyses the case period was defined as 0–30 days before MI or death, and two control periods were defined as 60–90 and 90–120 days before the event. Conditional logistic regression was used in both the Cox regression analyses and case-crossover analyses.

3.2.3 Results

Study population

In 1997, 4 614 807 Danish citizens were aged 10 years or older. Of these, 3 112 052 were excluded from the study because they had been admitted to hospital in the 5 years

^a In Denmark all residents possess a unique identification number which allows linkage of data on an individual level between national registries. Pharmacies are required to register all dispensed prescriptions in a national prescription registry (Danish Registry of Medicinal Product Statistics) and records have been completed with respect to date on dispensing, quantity dispensed, and dose since 1995. Information on hospital admissions is recorded in the Danish National Patient Registry and deaths are recorded in the National Person Registry (updated at least fortnightly).

before either their first claimed NSAID prescription or June 1st 2001, or had been prescribed one of a number of specified concomitant medications. Population A therefore consisted of 1 028 437 people (22% of the entire population) of whom 459 912 (45%) had claimed a prescription for an NSAID during the study period, and population B (no hospital admissions in the previous 10 years and no concomitant medicines) consisted of 153 465 people (about 3% of entire population) of whom 44 250 (about 29%) had claimed an NSAID prescription during the study period. Population A included substantially more women (42%) than population B (28%) and was on average slightly younger: median age (interquartile range [IQR]) 39 (25–51) years vs 43 (26–56) years. The most commonly prescribed class of medicine in population A in the 6 months before index date was antibiotics (11%) followed by antidepressants (2%) and gastric protective agents (1 %). Cholesterol-lowering agents were used by less than 1% of the population.

Dose and duration of treatment

The most commonly prescribed non-selective NSAID was ibuprofen (around 24%), followed by diclofenac (around 14%) and naproxen (about 3%). Prescribing levels for rofecoxib and celecoxib were substantially lower and almost identical (both around 1%). Generally, users of non-selective NSAIDs tended to be younger than users of the COX-2 inhibitors (approximately 40 years vs 50 years). These results suggest that this population, although healthier than in some studies, may still have had some co-morbidities.

In all cases the median dose of treatment was equivalent to the upper recommended minimum dose (table 6). Median treatment duration varied from 13 days for rofecoxib to 24 days for naproxen; here, 'median treatment duration' is thought to refer to the median duration per NSAID prescription and not the median person-time exposed to NSAIDs (as calculated from information provided on the person-years of exposure and number of individuals).

Table 6. Median dose and duration of NSAID treatment in healthy Danish individuals (population A)³

NSAID	Median dose (mg [IQR])	Median treatment duration (days [IQR])
Ibuprofen	1200 (800–1200)	14 (14–24)
Diclofenac	100 (800–1200)	14 (9–19)
Naproxen	500 (472–500)	24 (24–31)
Rofecoxib	25 (12.5–25)	13 (12–27)
Celecoxib	200 (200–200)	19 (9–33)

IQR=interquartile range

No information is provided on the number of prescriptions issued in the different age-groups or whether there was a relationship between the number of prescriptions (ie cumulative exposure) and risk of death and MI.

Outcome measures

Death rates

The authors calculated death rates (unadjusted for age, sex or year) that occurred during treatment with each of the NSAIDs within populations A and B (table 7).

Surprisingly, for all NSAIDs the rate of NSAID-associated death was significantly higher in population B (the so-called healthier population) compared with population A. In both populations, higher death rates (deaths per 1000 person-years) occurred in association

with the use of the COX-2 inhibitors (population A, mean: 51, range: 45–57) compared with non-selective NSAIDs (population A, mean: 13, range: 12–14). This may reflect the higher cardiovascular risk of COX-2 inhibitors and their use in older and less healthy individuals.

Numbers needed to harm ranged from 1329 in naproxen users in population A to –165 in naproxen users in population B (ie, a protective effect) and 14 in rofecoxib users in population B.

Table 7. Death rates in healthy Danish individuals during treatment with NSAIDs, with estimated numbers needed to harm³

NSAID	Deaths (n)	Time, person-years	Death rate per 1000 person-years	NNH (95%CI) per 1000 person-years
Ibuprofen				
Pop A	1052*	98 893 [†]	11 (10–11)	446 (346–625)
Pop B	99*	6242 [†]	16 (13–19)	432 (184–1251)
Diclofenac				
Pop A	588*	33 077 [†]	18 (17–19)	104 (90–122)
Pop B	81*	2632 [†]	31 (25–38)	77 (51–158)
Naproxen				
Pop A	136*	14 963 [†]	9 (8–11)	1329 (436–2450)
Pop B	11*	908 [†]	12 (5–19)	–165 (–76–[–941]) [‡]
Rofecoxib				
Pop A	246*	4920 [†]	50 (44–56)	24 (21–28)
Pop B	33*	378 [†]	87 (59–116)	14 (10–25)
Celecoxib				
Pop A	248*	4885 [†]	51 (45–57)	24 (21–28)
Pop B	23*	336 [†]	68 (41–95)	20 (13–43)
Non-users				
Pop A	41 487	4 936 836	8 (8–8)	NA
Pop B	16 582	912 477	18 (18–18)	
Total Population				
Pop A	56 305	9 028 028	6 (6–6)	NA
Pop B	18 579	1 303 821	14 (14–14)	

*Deaths during treatment with the specified NSAID; [†]Person-years of treatment with the specified NSAID; [‡]A negative NNH represents an NSAID that has a lower death rate compared to individuals with no NSAID use
 NNH=number needed to harm; CI=confidence interval; pop=population; NA=not applicable

Relative risk of death or death and MI

Compared with no NSAID use, hazard ratios (HRs) for death that were estimated using Cox regression analysis (adjusted for age, sex and calendar year) in population A show the same ranking order as the unadjusted death rates, namely: rofecoxib>celecoxib>diclofenac>no use>ibuprofen >naproxen (table 8).

Table 8. Cox regression hazard ratios for death and the composite endpoint of death and MI – population A ³

NSAID	Death		Death and MI	
	n*	(HR, 95% CI)	n*	(HR, 95%CI)
No use		1.00		1.00
Ibuprofen	1052	0.89 (0.83–0.94) [†]	1303	1.01 (0.96–1.07)
Diclofenac	588	1.47 (1.35–1.59) [†]	715	1.63 (1.52–1.76) [†]
Naproxen	136	0.80 (0.67–0.94) [‡]	178	0.97 (0.83–1.12)
Rofecoxib	246	2.12 (1.87–2.40) [†]	266	2.13 (1.89–2.41) [†]
Celecoxib	248	2.05 (1.81–2.32) [†]	262	2.01 (1.78–2.27) [†]

*Number of deaths or composite end-point events (MI and death) during treatment with the specific NSAID. The analyses are adjusted for age, sex and calendar year.

[†]p<0.01; [‡]p<0.05

HR=hazard ratio; CI=confidence interval

Rofecoxib, celecoxib and diclofenac increased the risk of death by 112%, 105% and 47%, respectively. In contrast, ibuprofen and naproxen significantly lowered the risk by 11% and 20%, respectively. HRs for rofecoxib and celecoxib for the outcome of death and MI (the primary composite outcome) remained largely unchanged relative to those for death alone and were substantially increased relative to no NSAID use (113% and 101% respectively). Similarly, the risk of death and MI in diclofenac users was increased (63%) compared to the risk of death alone. Ibuprofen and naproxen no longer had a protective effect and instead had no effect compared with non-use. In the case-crossover analysis, a broadly similar pattern of risk was observed, with slightly higher point estimates. No information for the cause of death is provided, and therefore MI case-fatality rates for individual NSAIDs cannot be calculated.

Effect of age

Age was found to be an important factor associated with the risk of death and MI in NSAID users (table 9).

Table 9. Cox regression hazard ratios for the composite endpoint of death and MI in individuals aged 30–50 years (about 60% of population A)³

NSAID	Death and MI (HR, 95%CI)
No use	1.00
Ibuprofen	1.76 (1.54–2.01)
Diclofenac	2.80 (2.35–3.34)
Naproxen	1.83 (1.30–2.63)
Rofecoxib	7.69 (5.67–10.43)
Celecoxib	5.51 (3.93–7.74)

HR=hazard ratio; CI=confidence interval

HRs in the 30–50 year group are substantially higher than those presented for the population as a whole and are consistent with the findings for an age-effect in the THIN study². This again may be due to the phenomenon of ‘depletion of susceptibles’.

Effect of dose

In both the Cox regression and case-crossover analyses a clear increase in risk of death, and death and MI was observed with higher doses of rofecoxib, celecoxib and

diclofenac, compared with lower doses (table 10). For ibuprofen a dose-dependent effect was only identified in the Cox regression analysis. No clear evidence of dose-dependency was observed for naproxen.

Table 10. Effect of NSAID dose on Cox regression hazard ratios for death and the composite endpoint of death and MI – population A³

NSAID	Death (Hazard ratios, 95%CI)	Death and MI (Hazard ratios, 95%CI)
Ibuprofen		
Low dose: ≤1200mg	0.78 (0.73–0.84)*	0.92 (0.86–0.97)*
High dose: >1200mg	1.77 (1.55–2.02)*	1.84 (1.62–2.08)*
Diclofenac		
Low dose: <100mg	0.87 (0.73–1.03)	1.05 (0.90–1.21)
High dose: ≥100mg	1.83 (1.67–2.01)*	1.99 (1.83–2.17)*
Naproxen		
Low dose: ≤500mg	0.70 (0.58–0.86)*	0.90 (0.76–1.06)
High dose: >500mg	1.25 (0.90–1.72)	1.28 (0.95–1.74)
Rofecoxib		
Low dose: ≤25mg	1.97 (1.72–2.25)*	2.00 (1.76–2.27)*
High dose: >25mg	6.02 (4.10–8.85)*	5.59 (3.81–8.21)*
Celecoxib		
Low dose: ≤200mg	1.65 (1.42–1.92)*	1.64 (1.42–1.90)*
High dose: >200mg	4.38 (3.50–5.47)*	4.16 (3.34–5.19)*

The analyses are adjusted for age, sex and calendar year. *p<0.01
HR=hazard ratio; CI=confidence interval

The results showed: no increase in risk with low dose diclofenac and a significant increase with high doses; an increased risk with ibuprofen which was only observed at high doses and only in the Cox proportional hazard analysis (which also identified a cardioprotective effect at low doses); no effect on risk with naproxen; that celecoxib and rofecoxib were associated with a higher cardiovascular risk than the non-selective NSAIDs. However, the results from the case-crossover analysis suggest that there is some uncontrolled confounding in the Cox regression analyses. The authors comment that the results are similar for population A and population B (data for population B not shown in this report), and for the two different analyses. This suggests that the results are robust and indicate a dose-dependent relationship in 'healthy' users.

Initial treatment period

A sub-analysis restricted to those with no record of prior medication or co-morbidity showed results for the endpoint of death and MI that were similar to those for the main study population, and provided evidence for dose-dependency.

This restricted sub-analysis is likely to be subject to less confounding than the Cox regression analyses. Although the authors state that risk estimates for this period are similar to those for the rest of the treatment interval they are, in fact, slightly higher. Table 11 shows the HRs (95% CIs) for the composite end point by Cox proportion analysis.

Table 11. Cox regression hazard ratios for the composite endpoint of death and MI during the initial treatment period – population A³

NSAID	Death and MI (HR, 95%CI)
No use	1.00
Ibuprofen	1.31 (1.15–1.49)*
Diclofenac	2.50 (2.18–2.88)*
Naproxen	1.45 (1.08–1.94) [†]
Rofecoxib	3.50 (2.88–4.26)*
Celecoxib	3.05 (2.53–3.68)*

*p<0.0001; [†]p=0.01

HR=hazard ratio; CI=confidence interval

HRs for death and MI at less than 10 days and more than 10 days of treatment suggested no significant difference in risk associated with the first days of treatment compared to the rest of the treatment interval. However, most events occurred after more than 10 days of treatment.

Additional analyses

Results were unchanged for analyses of: patients without a cancer diagnosis between the index date and outcome; exclusion of individuals who had been hospitalised up to 30 days before their death; and stratification by sex.

A sensitivity analysis concluded that the availability of ibuprofen OTC did not influence the results.

3.2.4 Discussion of study

The investigators concluded that the use of all NSAIDs studied, particularly rofecoxib, celecoxib and diclofenac, and particularly at high doses, increases the risk of MI and death in healthy individuals, even in the short-term. Use of NSAIDs should therefore be minimised, caution should be exercised in all individuals and, in particular, high doses should be avoided if possible.

Relative risks remained fairly consistent in two different populations, upon analysis by two different methods, and when restricted to the first NSAID prescription. There is therefore little doubt about the internal robustness of these findings. However, there is a lack of detailed information about the study design, particularly the health status of the population and the pattern of NSAIDs use which hampers interpretation of the results.

By excluding a large proportion of the population (from study entry) due to previous hospital admission or use of co-medication the authors attempted to restrict their analyses to a population of healthy users. However, it is unclear whether this definition of healthy is appropriate and whether this approach has significant advantages over the standard approach of adjusting results afterwards using statistical methods. A number of points support the suggestion that, whilst this population was arguably more healthy than many that have previously been studied to investigate this risk, it is highly likely that some unquantifiable level of baseline risk may have persisted.

Considering the range of indications for NSAIDs there is likely to be a division of users: those who use them sporadically for acute pain relief and those who use them regularly for the management of chronic conditions. This study aimed to capture the former population only; however, in view of the narrower indications of the COX-2 inhibitors it is highly likely that the COX-2 users in this study had a chronic condition. This is supported by their older age in this study. It is also possible that individuals with no previous

medical history (who were therefore eligible for inclusion in the study) may have been prescribed NSAIDs at the start of a long-term medical condition such as osteoarthritis or rheumatoid arthritis. In addition, doses of most of the drugs in the 'high dose' category are likely to be reserved for patients who have not responded to lower doses of NSAIDs. The lack of information on the pattern of NSAID use does not allow further characterisation of the user population.

Overall, it is likely that the population in this study, like other epidemiological studies, included a mix of people who had different risk factors, albeit possibly to a lesser extent. In spite of these limitations, the results of this study lend support to the idea that NSAIDs can increase the risk of thrombotic cardiovascular events in all users, not just those who have an increased baseline risk or who are chronic NSAIDs users.

4. CONCLUSIONS

The conclusions of the two studies discussed in this report are consistent with each other, with those of the most recent European review and with product information. They provide further confirmation of a dose-dependent increase in cardiovascular risk in association with use of celecoxib, high-dose diclofenac and high-dose ibuprofen (>1200 mg per day) and no detectable effect of naproxen. Any increase in risk was noted after relatively short-term use (and may increase with increasing duration of use), in people with no or few risk factors for cardiovascular disease and occurred in association with low doses of some NSAIDs.

4.1 Information and advice for healthcare professionals

- The findings from these two studies lend support to the view that some increased cardiovascular risk may apply to all NSAIDs users, irrespective of their baseline risk and duration of use, and not only to chronic users or those with risk factors. However, the greatest concern relates to chronic use of high doses (especially for coxibs and diclofenac) in patients at risk
- Patients should use the lowest effective dose and the shortest duration of treatment necessary to control symptoms, and the need for long-term treatment should be reviewed periodically
- Overall evidence continues to indicate that naproxen is associated with a lower thrombotic risk than coxibs, and no significant risk has been identified for ibuprofen doses of up to 1200 mg daily
- The findings from these studies do not change previous advice to support safer NSAID use that was issued by the CHMP in 2006.

5. REFERENCES

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6. GLOSSARY

Acetylation

A chemical reaction with a substance called acetyl acid that attaches an group of acetyl atoms to another compound

Anticoagulant

An agent that prevents the clotting of blood

Antihypertensive

A drug that reduces high blood pressure (hypertension)

Anti-inflammatory

A drug that reduces inflammation

Antipyretic

A substance that reduces fever or suppresses it

Arachidonic acid

An essential fatty acid that is necessary for growth

Arthritis

A disease involving inflammation of the joints, characterised by swelling, pain and restricted movement

ASA

Abbreviation on a medication indicating it contains acetylsalicylic acid (aspirin)

Assay

An analysis that determines the presence and amount of a substance, or how powerful a drug is

Baseline

The time at the start of the study

Bias

A factor in a study (ie. a patient's underlying medical condition) that may cause the final results to vary from the true results

Body mass index (BMI)

The weight of a person (kg) divided by the height of that person (m^2). Used as an indicator of whether a person is underweight or overweight

Cardiorenal

Related to the heart and the kidney

Cardiovascular

Related to the circulatory system comprising the heart and blood vessels

Case-control

A study design where cases and controls (individuals with and without a certain condition, respectively) are grouped and compared

Catalyses

Where a substance (an **enzyme** in the body) alters the rate of a chemical reaction but is itself unchanged at the end

Cerebrovascular

Related to the blood vessels of the brain

Chronic

Marked by a long duration, and by frequent recurrence over a long time

Chronic obstructive pulmonary disease

An adult disease characterised by airflow obstruction in the lungs

Clinical trial

A research study which tests the effectiveness and safety of medicines on humans

Cohort

A group of people who share a common characteristic or experience within a defined time

Co-morbidity

One or more medical conditions or diseases co-existing with another

Concomitant

When two or more medicines are given or taken approximately at the same time (eg, one after the other on the same day)

Confounding factors

Risk factors that can affect each other and the development of a medical condition.

They can ultimately affect the results of a study, especially if one risk factor is related to another

Congestive heart failure

A medical condition where the heart pumps ineffectively, causing fluid to collect in the lungs

Contraindication

Any medical condition, or a symptom of a medical condition, that makes a particular treatment improper or undesirable

Correlation

A statistical relationship between two variables or characteristics, and the extent to which one characteristic may affect the other

Cox proportional-hazard regression analysis

A mathematical model used for measuring survival data from a study

Cyclo-oxygenase

An **enzyme** that helps to form substances in the body called **prostanoids**

Diabetes mellitus

A medical condition where the body is not capable of effectively breaking down sugars to provide energy, due to a lack of the hormone insulin

Dysmenorrhoea

Painful menstruation

Endogenous

Arising within, or derived from, the body

Endothelial

A layer of cells that lines the inside of blood vessels

Enzyme

A protein produced by living cells which helps specific bodily reactions to occur

Epidemiology (Epidemiological)

A branch of medical science that assesses the incidence, distribution, and control of medical conditions or diseases in a population

Gastrointestinal

Related to the stomach and intestines

Half-life

The time required for the concentration or amount of drug in the body to be reduced by half

Hazard ratio

A measure of risk of an event occurring. Hazard ratios greater than 1 suggest increased risk, those that equal 1 suggest equal risk, and those that are less than 1 suggest decreased risk. They are usually accompanied by a 95% confidence interval (CI)—this indicates there is a 95% chance that the real difference between the two groups lies within this interval. If the 95% CI does not cross 1, then the hazard ratio is statistically significant.

Incidence density sampling

A method of selecting the controls in a **case-control** study, which involves matching each individual who has a particular condition with an individual who does not have the condition but is at risk of developing it.

Inflammation

The body's response to injury, which involves pain, heat, redness and swelling

In vitro

Biological occurrences taking place outside the body (traditionally in a test tube)

In vivo

Biological occurrences observed within the body

Isoform

Different structures of a protein

Ischaemic heart disease

Inadequate flow of blood to the heart, caused by constriction or blockage of the blood vessels supplying it

Magnitude

The size of an object or occurrence

Mean

An average, calculated by the sum of all values by the total number of values

Median

An average: the middle value in a range of values in a sample

Monocyte

A type of white blood cell that consumes bacteria and tissue debris

Myocardial infarction

Injury to heart muscle as a result of reduced oxygen supply, leading to a heart attack

Nested case-control study

A type of study design where new **cases** and **controls** are put into **cohorts** that were defined before the study begins

Number needed to harm

A measure of treatment harm: the average number of people from a defined population who need to be treated (with a specific medicine) for a given time to cause one additional adverse event

Odds ratio

A measure of risk for one group compared with another. Odds ratios greater than 1 suggest increased risk, those that equal 1 suggest equal risk, and those that are less than 1 suggest decreased risk. They are usually accompanied by a 95% confidence interval (CI), which indicates there is a 95% chance that the real difference between the two groups lies within this interval. If the 95% CI does not cross 1, then the odds ratio is statistically significant.

Peripheral

In the circulatory system: blood vessels supplying the arms and legs

Person-years

The total sum of the number of years that each member of a study population has been under observation, e.g. years of treatment with a certain drug

Pharmacodynamics

The effects of drugs in the body

Physiology

The study of how living organisms and their separate parts function

Platelets

Cells found in the blood stream which are important for clotting

Placebo

A dummy treatment which is given to the **control** group in a medical research study to compare their results with those from the group receiving a medicine.

Posology

The science of the dosage of medicines

Primary endpoint

The main question that a study aims to answer

Prothrombotic

A risk of blood clot formation

Prostanoid

A class of hormone-like substances derived from a chemical called **arachidonic acid** that participate in a wide range of body functions, including **inflammation** (**prostacyclin** belongs to the prostanoid family)

Prostacyclin (see *prostanoid*)

Proxy

A substitute (medicine, etc)

p-value

A measure of the statistical probability of an event occurring by chance. Usually, $p < 0.05$ suggests the event is statistically significant and did not occur by chance; $p \geq 0.05$ suggests the event is not statistically significant and occurred by random chance

Regression analysis

A statistical tool for investigating relationships between variables, especially the effect of one variable upon another

Relative risk

A measure of risk for one group compared with another. Relative risks greater than 1 suggest increased risk, those that equal 1 suggest equal risk, and those that are less than 1 suggest decreased risk. They are usually accompanied by a 95% confidence interval (CI), which indicates there is a 95% chance that the real difference between the two groups lies within this interval. If the 95% CI does not cross 1, then the relative risk is statistically significant.

Renal

Of the kidneys

Retrospective (cohort) study

A research study in which the medical records of groups of individuals who are alike except for one certain characteristic are compared for a particular outcome

Rheumatoid arthritis

A common form of **arthritis**, causing painful, swollen and stiff joints of fingers, wrists, feet and ankles

Risk factor

A substance or activity that leads an individual to have a greater likelihood of developing an illness or medical condition

Stratified/stratification

A method of separating patients in a study into groups based on different characteristics

Sub-group analysis

Investigation of a particular sub-group of study participants

Summaries of Product Characteristics

Detailed information that accompanies any licensed medicine, which lists its composition and characteristics

Therapeutic (concentrations)

The amount of medicine needed to treat a disease or condition

Thrombotic

Leading, or related to, a blood clot

Thromboxane

A substance in the body formed from the breakdown of **arachidonic acid**, which can induce clot formation

Townsend score

A common method used to estimate social deprivation in public health studies

Toxicity

The degree to which a substance is poisonous

Vascular

Relating to, or supplied with, blood vessels

Vasodilator

A drug that causes widening of the blood vessels and therefore an increase in blood flow