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EMA/348171/2015
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Ibuprofen and dexibuprofen containing medicinal products (systemic formulations)

Procedure number: EMEA/H/A-31/1401

Note

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Background information on the procedure

The cardiovascular (CV) risk of non-steroidal anti-inflammatory drugs (NSAIDs) has been kept under close review over the past years.

A previous review conducted in 2006 concluded that NSAIDs as a class were associated with an increased risk of arterial thrombotic events, although the risk was considered to be higher for selective cyclooxygenase-2 (COX-2) inhibitors (also known as coxibs). Clinical trial data at that time suggested that ibuprofen at a high dose (2400 mg daily) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies did not suggest that ibuprofen at low doses (≤1200 mg daily) is associated with an increased risk of myocardial infarction[1]. The Product Information (PI) of all NSAIDs and coxibs was updated to include extensive information about cardiovascular risks. Additional contraindications and stronger warnings were recommended for coxibs compared to non-selective NSAIDs, reflecting the difference in the strength of the evidence for an increased risk associated with their use.

Further epidemiological studies were needed to obtain additional data on pertinent safety aspects of NSAIDs and therefore the Agency recommended that the European Commission (EC) fund an independent study to further explore the gastrointestinal and cardiovascular risk of NSAIDs. The results of the 'safety of non-steroidal anti-inflammatory drugs' (SOS) research project funded by the EC under the Seventh Framework Programme, were considered in a review of cardiovascular risks of NSAIDs conducted by the Committee for Medicinal Products for Human Use (CHMP) in 2012, together with a number of new studies which had since become available. The CHMP considered that the findings in relation to the cardiovascular risks for ibuprofen are in line with the previous evidence, i.e. that ibuprofen at a high dose may be associated with an increased risk of thrombotic events, and the data do not consistently suggest that ibuprofen at low doses is associated with an increased risk of cardiovascular events[2]. The CHMP noted that the existing prescribing information reflected the known level of cardiovascular and other risks for these medicines.

Regarding the possible interaction between acetylsalicylic acid and ibuprofen the most recent EU-wide review was completed by the CHMP Pharmacovigilance Working Party (PhVWP) in 2008. At that time, studies of ex-vivo platelet aggregation and thromboxane B2 (TXB2) suggested the potential for ibuprofen to reduce the anti-platelet effects of acetylsalicylic acid (Catella-Lawson *et al*, 2001; Cryer *et al*, 2005); however, evidence of a clinically important effect had not been convincingly demonstrated in either pharmacoepidemiological studies or clinical trials. As a result of this review, PhVWP recommended that the product information for acetylsalicylic acid and ibuprofen be updated to include a warning reflecting the data available at the time.

Since then, further new data on cardiovascular effects of NSAIDs have become available. The Coxib and traditional NSAID Triallists' (CNT) collaborative group published results from a large meta-analysis of more than 600 randomised clinical trials[3]. The results suggest that the cardiovascular risk with high dose diclofenac is similar to selective COX-2 inhibitors, but also indicate that the risk with high dose ibuprofen (2400mg) may also be similar to COX-2 inhibitors. In addition, there is accumulating

[1] Information on the review conducted in 2006 can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500054344.pdf
[2] Information on the review conducted in 2012 can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/11/WC500134717.pdf
[3] Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Coxib and traditional NSAID Trialists' (CNT) Collaboration. The Lancet - 30 May 2013

evidence[4,5] that ibuprofen inhibits the antiplatelet action of low-dose acetylsalicylic acid for cardiovascular prophylaxis.

In light of the above, and given the widespread use of ibuprofen, UK considered that it is in the interest of the Union to refer ibuprofen and dexibuprofen containing products for systemic use to the PRAC and request, that it gives its recommendation under Article 31 of Directive 2001/83/EC, on whether the new evidence on the risk of thrombotic events when used at high doses, doses at or above 2400mg per day, in adults and new evidence on interaction with low-dose acetylsalicylic acid require any updates to the advice to healthcare professionals and patients including warnings or contraindications as expressed in the current ibuprofen product information, or whether any other regulatory measure would be needed.

The procedure described in Article 32 of Directive 2001/83/EC was applicable.

1. Scientific discussion

1.1. Introduction

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used for the reduction of inflammation, pain and fever. It is commonly used and is widely available without prescription, typically at doses ≤1200mg daily, to treat a range of conditions including pain, fever, rheumatic conditions and minor ailments. Ibuprofen is also prescribed for the chronic management of rheumatic conditions such as osteoarthritis (typically doses higher than 1200mg daily).

Ibuprofen has been found to be more selective towards COX-1 than COX-2. It is well established that only the S(+)-enantiomer of (racemic) ibuprofen is capable of inhibiting COX-1 and COX-2 at clinically relevant concentrations, with the R(-) enantiomer being virtually inactive (Adams et al, 1976; Geisslinger et al, 1989; Evans et al, 1991; Boneberg et al, 1996).

Ibuprofen contains equal quantities of R(-)-ibuprofen and S(+)-ibuprofen. As it is the S(+)-enantiomer which confers the anti-inflammatory and analgesic activity and not the R(-)-enantiomer, dexibuprofen which contains only S(+)-ibuprofen is also available as a medicinal product. The approved indications for dexibuprofen are similar to those for ibuprofen.

The recommended daily dose of dexibuprofen is 600mg – 900mg, divided in up to three single doses. The recommended maximum daily dose is 1200mg (i.e. half of the maximum recommended daily dose for ibuprofen in most EU counties).

The scope of the procedure includes medicinal products containing (racemic) ibuprofen and dexibuprofen (S(+)-ibuprofen). Although there is very little data available regarding the arterial thrombotic risks of dexibuprofen or regarding a possible interaction between dexibuprofen and low-dose acetylsalicylic acid, it is reasonable to assume that dexibuprofen shares similar risks with (racemic) ibuprofen, hence its inclusion in the scope of this referral procedure.

The scope of the referral procedure includes only systemic formulations (e.g. oral formulations, rectal preparations) but does not include products authorised for use solely in children or topical preparations intended for local effects with low systemic absorption (e.g. creams, gels, sprays, vaginal and ophthalmic preparations).

[4] Hohlfeld T (2013); Thrombosis and Haemostasis; 109: 825–833
[5] MacDonald TM, Wei L. Lancet 2003;361:573-4

The present review focuses on the cardiovascular risk of ibuprofen/dexibuprofen as well as on the interaction between ibuprofen/dexibuprofen and acetylsalicylic acid. Several data sources informed the recommendation of the PRAC, including available data from previous reviews, clinical studies including results from a large meta-analysis of more than 600 randomised clinical trials published by the CNT collaborative group, published literature as well as data submitted by marketing authorisation holders (MAHs) of medicinal products containing ibuprofen/dexibuprofen.

An overview of the relevant information for the discussion is presented hereinafter. Of note, as most data were reviewed previously by the CHMP, the PRAC having acknowledged those conclusions focused the current review mostly on any newly available evidence on thrombotic risks with ibuprofen/dexibuprofen as well as on the interaction between ibuprofen/dexibuprofen and acetylsalicylic acid.

1.2. Cardiovascular (arterial thrombotic) risk

1.2.1. Summary of evidence from previous reviews

The cardiovascular risks of dexibuprofen have not been assessed in previous EU-wide reviews, thus the data described in this section relate to (racemic) ibuprofen.

Previously considered data included clinical trial data from three meta-analyses (Kearney et al (2006), Chen and Ashcroft (2007) and Trelle et al (2011)), observational data from four studies (Hernandez-Diaz et al (2006), Varas-Lorenzo et al (2011) and McGettigan and Henry (2006a; 2011)), case-control and cohort studies as well as data from the SOS Project.

The **Kearney et al (2006)** meta-analysis included 138 trials (total of 145,373 patients) involving a comparison of a selective COX-2 inhibitor versus placebo or versus traditional NSAID (or both). The pre-specified outcomes were serious vascular event, as defined by the Antiplatelet Trialists' Collaboration (non-fatal myocardial infarction (MI), non-fatal stroke, or vascular death); fatal or non-fatal MI; fatal or non-fatal stroke; and vascular death (including death from MI or stroke). No statistically significant difference between ibuprofen and coxibs was observed for any of the study endpoints. An important limitation of this study, however, is that it did not stratify results by duration of the trials or doses administered. The dose effect is of particular importance as the dose of non-selective NSAIDs used in the studies was in most cases the maximum authorised daily dose (2400mg ibuprofen; 150mg diclofenac; 1000mg naproxen) compared to more varied coxib doses. The meta-analysis included trials which ranged in duration from 4 to 208 weeks and the authors did not comment on whether the heterogeneity in duration, doses or treatment indications could have impacted the results.

The **Chen and Ashcroft (2007)** meta-analysis did not report a statistical difference between ibuprofen and coxibs for the risk of MI (OR 1.29, 95% CI 0.65-2.59) but this study is of limited value (especially with respect to ibuprofen) as it contains a small number of ibuprofen trials compared to the meta-analysis by Kearney et al (2006) (6 trials compared to 24 in Kearney et al), which might have resulted in the slightly higher risk for ibuprofen reported in this study vs Kearney et al (however in both studies this was not statistically significantly different to the combined coxib group). Both the Kearney et al 2006 and Chen and Ashcroft (2007) meta-analyses pooled the events observed in the coxibs treatment arms which, whilst increasing statistical power also assumes that the effects of the coxibs are similar, which may not be the case.

In the network meta-analysis by **Trelle et al (2011)**, ibuprofen was associated with a marginally statistically significant increased risk for stroke as shown below (table 1); the lower limit of the 95% CI was 1. For the composite Antiplatelet Trialists' Collaboration (APTC) endpoint, ibuprofen was associated

with the highest risk of all NSAIDs in this study, a result which was inconsistent with the understanding at the time of relative risks of the different coxibs and NSAIDs. No increased risk was observed for ibuprofen for the other study endpoints.

Table 1
Estimated rate ratios of cardiovascular outcomes for NSAIDs compared with placebo, as reported by *Trelle et al*

	RR (95% CI)				
	MI	**Stroke**	**CV death**	**All-cause mortality**	**APTC***
Naproxen	0.82 (0.37-1.67)	1.76 (0.91-3.33)	0.98 (0.41-2.37)	1.23 (0.71-2.12)	1.22 (0.78-1.93)
Ibuprofen	1.61 (0.50-5.77)	3.36 (1.00-11.60)	2.39 (0.69-8.64)	1.77 (0.73-4.30)	2.26 (1.11-4.89)
Diclofenac	0.82 (0.29-2.20)	2.86 (1.09-8.36)	3.98 (1.48-12.70)	2.31 (1.00-4.95)	1.60 (0.85-2.99)
Celecoxib	1.35 (0.71-2.72)	1.12 (0.60-2.06)	2.07 (0.98-4.55)	1.50 (0.96-2.54)	1.43 (0.94-2.16)
Etoricoxib	0.75 (0.23-2.39)	2.67 (0.82-8.72)	4.07 (1.23-15.70)	2.29 (0.94-5.71)	1.53 (0.74-3.17)
Rofecoxib	2.12 (1.26-3.56)	1.07 (0.60-1.82)	1.58 (0.88-2.84)	1.56 (1.04-2.23)	1.44 (1.00-1.99)
Lumiracoxib	2.00 (0.71-6.21)	2.81 (1.05-7.48)	1.89 (0.64-7.09)	1.75 (0.78-4.17)	2.04 (1.13-4.24)

**APTC: Antiplatelet Trialists' Collaboration composite outcome; MI: myocardial infarction*

In the **Hernandez-Diaz et al (2006)** meta-analysis of observational studies ibuprofen was associated with a marginally statistically significant increased risk of MI compared to non-NSAID use (RR 1.07, 95% CI 1.02-1.12), although the relative risks were lower for ibuprofen than for diclofenac and rofecoxib. No conclusions could be drawn from either study on the effect of treatment duration or dose.

The results of the meta-analysis of observational studies by **Varas-Lorenzo et al (2011)** did not report a statistically increased risk of stroke for ibuprofen compared to no NSAID use for any of the reported endpoints (all strokes; incident or ischaemic stroke) which is inconsistent with the results of the Trelle et al (2011) meta-analysis of clinical trials for ibuprofen and the risk of stroke. A statistically significant increase in risk was observed for all stroke endpoints for rofecoxib.

Table 2
Relative risk (RR) of stroke associated with various NSAIDs and coxibs, compared to no NSAID use in the various studies included in the meta-analysis by *Varas-Lorenzo et al*

Reference Cases (N)	RR (95% CI)				
	Naproxen	**Ibuprofen**	**Diclofenac**	**Celecoxib**	**Rofecoxib**
Abraham et al -	2.00 (1.49-2.70)	1.70 (1.24-2.32)	NA	1.70 (1.14-2.54)	3.00 (2.04-4.42)
Andersohn et al 684	1.16 (0.80-1.70)	1.12 (0.91-1.37)	1.32 (1.10-1.57)	1.07 (0.79-1.44)	1.71 (1.33-2.18)
Bak et al 158	0.70 (0.44-1.13)	1.30 (1.03-1.64)	1.10 (0.70-1.70)	NA	NA
Haag et al 52	2.63 (1.47-4.72)	1.47 (0.73-3.00)	1.60 (1.00-2.57)	NA	3.38 (1.48-7.74)
Roumie et al 574	0.94 (0.80-1.11)	0.88 (0.73-1.06)	0.94 (0.59-1.49)	1.04 (0.87-1.23)	1.28 (1.06-1.53)
Solomon et al 1904	0.83 (0.67-1.04)	0.95 (0.78-1.16)	0.98 (0.75-1.29)	1.00 (0.92-1.09)	1.15 (1.04-1.26)

NA: not applicable

However, this meta-analysis has a number of important limitations including the possibility of significant residual confounding, the lack of information on concurrent acetylsalicylic acid and/or non-prescription ibuprofen use, significant heterogeneity between studies and a lack of information on dose and duration of treatment.

Two meta-analyses of observational studies investigating cardiovascular risks in association with individual NSAIDs and coxibs have been published by **McGettigan and Henry** in 2006 and 2011. The purpose of the second study was to update the results of the first by including all eligible studies in the intervening time between the two studies. The most commonly reported outcome in the included studies was MI; however, some studies reported on the risks of coronary heart disease (CHD)-related death or a composite of MI and CHD-related death; a minority reported on stroke only. The results of the 2011 study are mixed; an increased risk was reported for high but not low dose ibuprofen although there was significant heterogeneity between the studies included for this result. The pair-wise comparison in this study also found that ibuprofen was associated with a statistically significant decreased risk for MI compared to etoricoxib and diclofenac and a small increased risk compared to naproxen, as shown below.

Table 3
Pair wise comparison of individual drugs for myocardial infarction, ratios of relative risks (RRR) and their corresponding 99% confidence interval in the study by McGettigan and Henry

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

Emboldened results indicate significance at p <0.0033

A total of 7 case-control studies and 14 cohort studies were reviewed, the results of which were inconsistent for ibuprofen. Most of the studies did not report an increased risk with ibuprofen. However, some of the higher quality studies (the Danish registry studies: **Gislason 2006, 2009**) reported a statistically significant increased risk for ibuprofen which was generally lower than that reported for the coxibs. The difference in risk between naproxen and ibuprofen in these two studies was of the same magnitude (approximately 10%) as that reported in the meta-analysis by McGettigan and Henry (2011).

In addition to data published in the literature, the CHMP also considered results from the SOS Project. This project was designed to assess and compare the risk of cardiovascular and gastrointestinal events in users of NSAIDs and coxibs. The programme included two meta-analyses of observational studies – one on the risk of stroke (Varas Lorenzo et al 2011) and one on the risk of MI. The CHMP also considered the unpublished meta-analysis on the risk of MI which since then has been published (Varas-Lorenzo, 2013). In addition to the meta-analyses of existing observational studies, the SOS project conducted four new nested case-control studies to estimate the relative risks of acute MI, heart failure, stroke and upper gastrointestinal (GI) complications associated with current individual NSAID use compared to remote use.

The results of the meta-analysis of observational studies on the risk of MI were generally consistent with the results of the McGettigan and Henry 2011 meta-analysis. The pooled estimate of the relative

risk of acute MI for most commonly prescribed NSAIDs and coxibs and the effect of dose (based on reported low-high definition in each study) on this risk are presented below (table 4). Of the 8 individual studies contributing dose data for ibuprofen, low dose was considered to be ≤1200mg in 5 studies, ≤1600mg in 1 study and ≤1800mg in 1 study. The final study looked at high dose only, defined as doses at or above 1800mg/day.

Table 4
Overall pooled estimates on the relative risk of acute myocardial infarction for most commonly prescribed NSAIDs compared with no NSAID use in the SOS meta-analysis

	Naproxen	Ibuprofen	Diclofenac	Celecoxib	Rofecoxib
Acute Myocardial Infarction					
No of studies	17	13	11	18	18
Random effects	1.06 (0.94-1.20)	1.14 (0.98-1.31)	1.38 (1.26-1.52)	1.12 (1.00-1.24)	1.34 (1.22-1.48)
Fixed effects	1.07 (1.01-1.13)	1.08 (1.04-1.13)	1.40 (1.33-1.47)	1.07 (1.01-1.14)	1.33 (1.25-1.40)
Heterogeneity (p-value)	<0.00001	<0.00001	0.005	<0.0001	0.0005
Dose effect: Low dose					
No of studies	5	6	6	7	9
Random effects	0.93 (0.75-1.16)	0.97 (0.76-1.22)	1.26 (1.03-1.53)	1.14 (0.99-1.31)	1.23 (1.12-1.34)
Fixed effects	0.91 (0.76-1.09)	0.83 (0.77-0.90)	1.25 (1.12-1.40)	1.11 (1.00-1.23)	1.22 (1.12-1.34)
Heterogeneity (p-value)	0.30	0.0001	0.02	0.13	0.42
Dose effect: High dose					
No of studies	6	7	6	8	9
Random effects	0.97 (0.80-1.16)	1.20 (0.99-1.46)	1.32 (1.07-1.63)	1.24 (0.99-1.57)	1.69 (1.39-2.05)
Fixed effects	0.98 (0.87-1.10)	1.11 (0.98-1.25)	1.40 (1.27-1.53)	1.17 (1.00-1.36)	1.69 (1.39-2.05)
Heterogeneity (p-value)	0.21	0.08	0.0007	0.09	0.87

In the four new nested case-control studies odds ratios were calculated for each endpoint (acute MI, heart failure, stroke and upper GI complications) from 6 different EU databases (IPCI; PHARMO; OSSIFF; SISR; GePaRD and THIN). Meta-analysis was performed using both fixed and random effect models. Only results from the random effect analysis are presented below and p-values are provided as a measure of statistical heterogeneity of results between the databases.

Table 5
Odds ratios and 95% CI for acute myocardial infarction and ischaemic stroke for the most commonly studied NSAIDs in the SOS studies compared to remote NSAID use

Database	Naproxen	Ibuprofen	Diclofenac	Celecoxib	Rofecoxib
Acute Myocardial Infarction					
GePaRD	1.87 (1.20-2.89)	1.36 (1.23-1.50)	1.22 (1.13-1.33)	0.79 (0.46-1.37)	-
IPCI	1.27 (0.74-2.17)	1.23 (0.74-2.06)	1.07 (0.79-1.47)	-	-
OSSIF	1.07 (0.83-1.38)	1.02 (0.83-1.25)	1.36 (1.24-1.50)	1.11 (0.98-1.26)	1.27 (1.12-1.44)
PHARMO	1.34 (1.13-1.59)	1.43 (1.24-1.65)	1.44 (1.30-1.59)	1.73 (1.32-2.27)	1.46 (1.17-1.77)
SISR	1.01 (0.81-1.24)	1.23 (1.09-1.39)	1.39 (1.29-1.50)	1.08 (0.97-1.20)	1.16 (1.00-1.35)
THIN	1.12 (0.96-1.32)	1.14 (1.04-1.26)	1.23 (1.14-1.34)	1.10 (0.95-1.28)	1.28 (1.09-1.50)
Pooled	1.19 (1.04-1.37)	1.24 (1.13-1.32)	1.31 (1.26-1.36)	1.09 (1.00-1.32)	1.26 (1.17-1.36)
p-value	0.09	0.018	0.02	0.017	0.41
Ischeaemic stroke					
GePaRD	1.68	1.41	1.37	-	-

	(1.05-2.69)	(1.27-1.55)	(1.26-1.49)		
IPCI	-	-	-	-	-
OSSIF	1.09 (0.76-1.55)	1.11 (0.85-1.46)	1.26 (1.10-1.45)	1.04 (0.88-1.24)	1.13 (0.94-1.36)
PHARMO	-	-	-	-	-
SISR	0.96 (0.70-1.31)	1.07 (0.89-1.28)	1.38 (1.24-1.54)	1.03 (0.89-1.18)	1.22 (1.00-1.48)
THIN	0.88 (0.66-1.19)	1.04 (0.88-1.23)	1.12 (0.96-1.30)	1.08 (0.83-1.41)	1.09 (0.82-1.46)
Pooled	1.06 (0.84-1.35)	1.16 (0.97-1.39)	1.30 (1.19-1.42)	1.02 (0.93-1.13)	1.18 (1.05-1.34)
p-value	0.14	0.0035	0.084	0.42	0.793

Results using the fixed effect model yielded very similar results the only exception being ibuprofen and ischaemic stroke which was in this case higher and statistically significant (OR, 95% CI: 1.24, 1.15-1.34).

Effect of dose on arterial thrombotic risk

The data available on the effect of dose on arterial thrombotic risk of NSAIDs is derived from observational studies since most clinical trials employed only fixed (high) doses of traditional NSAIDs versus variable coxib doses. In addition to the SOS meta-analysis of MI discussed above, two further meta-analyses of observational data reported on dose-effect for cardiovascular risks of traditional NSAIDs, i.e. Garcia-Rodriguez (2008) and McGettigan and Henry (2011).

Garcia-Rodriguez (2008) conducted an analysis on the effect of administered NSAID dose and degree of COX-2 inhibition and cardiovascular risk. Neither low-dose ibuprofen (<1200mg) nor naproxen (>750mg and >75mg) were associated with an increased risk for incident MI.

The results of the **McGettigan and Henry (2011)** dose-analysis are presented below (table 6). As with the SOS meta-analysis, the cut-off definition between "low" and "high" dose was determined by the authors of the individual studies. For rofecoxib and celecoxib high doses were consistently defined in the included studies as > 25mg and >200mg/day respectively. The majority of studies for ibuprofen (8/11) defined high doses as more than 1,200 mg/day, whereas high dose for diclofenac was determined as >100mg/day (in 8 of the 10 studies). High dose definition for naproxen was more varied for naproxen (≥ 500mg/day in 2 studies, ≥ 750/day in four studies and >1000mg/day in 4 studies). Significant heterogeneity in these results was reported for most drugs, especially for high dose ibuprofen and diclofenac.

Table 6
Dose response relationship for individual coxibs and NSAIDs included in the meta-analysis by McGettigan et al (2011)

	RR (95%CI)	**p for trend**	**No of studies**	**Cochrane Q, p-value**
≤ 25 mg/d	1.37 (1.20-2.17)	0.0008	16	71.8 <0.0001
Rofecoxib > 25mg/d	2.17 (1.59-2.97)			80.7 <0.0001
≤ 200 mg/d	1.26 (1.09-1.47)	0.197	11	33.7 0.0008
Celecoxib > 200 mg/d	1.69 (1.11-2.57)			119.9 <0.0001
Low	1.05 (0.96-1.15)	0.0004	11	43.3 <0.0001
Ibuprofen High	1.78			221.4

	(1.35-2.34)			<0.0001
Low **Naproxen** High	0.97 (0.87-1.08)	0.433	10	11.7 0.4
	1.05 (0.87-1.24)			29.4 0058
Low **Diclofenac** High	1.22 (1.12-1.33)	0.009	10	16.3 0.1786
	1.98 (1.40-2.82)			437.5 <0.0001

It was concluded that the meta-analysis by McGettigan et al did not provide very robust information on the effect of dose as the high and low dose were pooled using the cut-off values of the individual studies, rather than predefined dose levels. As a result defining a safe dose for the different NSAIDs was difficult.

The results indicate that low dose ibuprofen is not associated with an increased risk for cardiovascular events. Low dose ibuprofen is a mixture ≤1200mg in 6 studies, ≤1600mg in two studies, and <1800mg in 2 studies. Hence, ≤1200mg ibuprofen may be regarded as a safe dose (bearing in mind the other limitations of the study). High dose ibuprofen was associated with a statistically significantly increased risk for MI, although this was lower than was seen for high dose rofecoxib and high dose diclofenac.

Effect of duration of treatment on arterial thrombotic risk

There are limited data available on the effect of duration of NSAID treatment on arterial thrombotic risk. There is one cohort study (**Schjerning Olsen et al 2011**) in which hazard ratios were estimated according to duration of NSAID treatment; the endpoints were all-cause mortality and a composite of recurrent MI and mortality. Data were collected from individual-level linkage of nationwide registries with drug dispensing in Denmark. The results of this study are generally consistent with previous regulatory conclusions that the risk increases with increasing duration of use. Diclofenac and rofecoxib but not ibuprofen, celecoxib or naproxen, were associated with a statistically increased risk of death from the beginning of treatment (0-7 days). Ibuprofen but not celecoxib or naproxen, was associated with an increased risk from 7-14 days of treatment. The authors acknowledge the lack of information on potential confounding factors.

Overall, the PRAC acknowledged the conclusions of the previous reviews that whilst clinical trial data suggested that the thrombotic risk with high-dose (2400mg daily) ibuprofen was similar to that of coxibs, the epidemiological data are inconsistent and suggested a very modest increase in risk, possibly due to the fact that the high doses of ibuprofen used in the clinical trials are not generally used in clinical practice. Epidemiological data also suggest that low dose ibuprofen (≤1200mg/day) is not associated with an increased risk of arterial thrombotic events.

1.2.2. Presentation of new data

Hereinafter a summary of the new relevant data considered within the current review is presented. A total of 15 publications which were not considered in previous reviews were identified for assessment: one systematic review of meta-analyses of randomized controlled trial (RCT) data (Salvo et al, 2011), one meta-analysis of RCT data (CNT Collaboration, 2013), and thirteen epidemiological studies (seven cohort studies, four case-control studies, two case-crossover studies).

Clinical trial data

As part of the SOS Project, **Salvo et al (2011)** performed a detailed systematic review of data from published meta-analyses of clinical trials of NSAIDs. The review included 29 meta-analyses, from which 109 incidence rates for cardiovascular adverse events were estimated. Coxibs were studied in more meta-analyses than tNSAIDs (21 for coxibs vs 7 for tNSAIDs; one studied both).

The table below provides a summary of the cumulative incidence rates for cardiovascular events for coxibs and NSAIDs.

Table 7
Cumulative incidence rates (%) for cardiovascular events for NSAIDs from the SOS systematic review of meta-analyses of RCTs

NSAID	Myocardial Infarction Events	Cerebrovascular Events	Stroke Events	Thromboembolic Events
Coxibs				
Celecoxib	0.12-1.35	0.13-0.93	0.02-0.79	-
Etoricoxib	0.24-0.66	0.08-0.61	-	0.25-1.73
Lumiracoxib	0.09-0.37	0.25-0.34	0.06-0.34	-
Paracoxib/valdecoxib	0.58	0.94	-	-
Rofecoxib	0.3-0.89	0.1-0.94	0.12	-
Valdecoxib	0.11-0.61	0.16-0.18	0.18	-
tNSAIDS				
Diclofenac	0.20-0.74	0.29-0.48	-	0.22-0.81
Ibuprofen	0.00-0.19	0.00-0.24	-	0
Nabumetone	0.39	0	-	-
Naproxen	0.1-0.33	0.13-0.28	0.09-0.24	0.00-0.91
Piroxicam	-	-	-	0.08

The Coxibs and traditional NSAIDs Trialists' **(CNT) Collaboration (2013)** meta-analysis is an extension of the Kearney et al (2006) meta-analysis, considered previously by CHMP. In this network meta-analysis, the CNT aimed to obtain individual participant data on all trials of NSAIDs vs placebo or NSAID vs NSAID, in order to further characterise the vascular and gastrointestinal effects of NSAIDs (e.g. patient risk factors; dose of NSAID; duration of treatment).

Trials were identified through searches of MEDLINE and EMBASE up to January 2009, based on the Cochrane strategy, and periodic scrutiny of clinical trial registers, reference lists and enquiry among collaborators and pharmaceutical companies. All trials with results available prior to January 2011 were eligible for inclusion if they were properly randomised, of at least 4 weeks duration, and: involved a comparison of an NSAID versus placebo (or open control) or one NSAID regimen versus another NSAID regimen; and no other systematic differences in drug treatment between treatment arms were planned. Individual participant data was sought on: pre-randomisation characteristics; randomised allocations and occurrence of clinical outcomes and dates. Wherever possible, outcomes were adjudicated.

Meta-analyses of each comparison were done using standard logrank methods where individual patient data were available or standard methods for 2x2 contingency tables otherwise. Rate ratios for coxibs were obtained directly from coxib (C) vs placebo (P) trials. Rate ratios for tNSAIDs (N) were obtained via direct and indirect comparison. Direct comparisons were: tNSAID vs placebo (vs coxib, usually). Indirect comparisons were: (coxib vs placebo) vs (coxib vs tNSAID), as C/P divided by C/N = N/P.

The overall (combined) estimate of the effect of tNSAID versus placebo was calculated as the inverse variance weighted average of the indirect and direct estimates.

The main outcomes were major vascular events (non-fatal MI, coronary death, MI or CHD death, non-fatal stroke, stroke death, any stroke, and other vascular death); cause-specific mortality (vascular; non-vascular; and unknown cause); heart failure; or upper gastrointestinal complications (perforation, obstruction, or bleed).

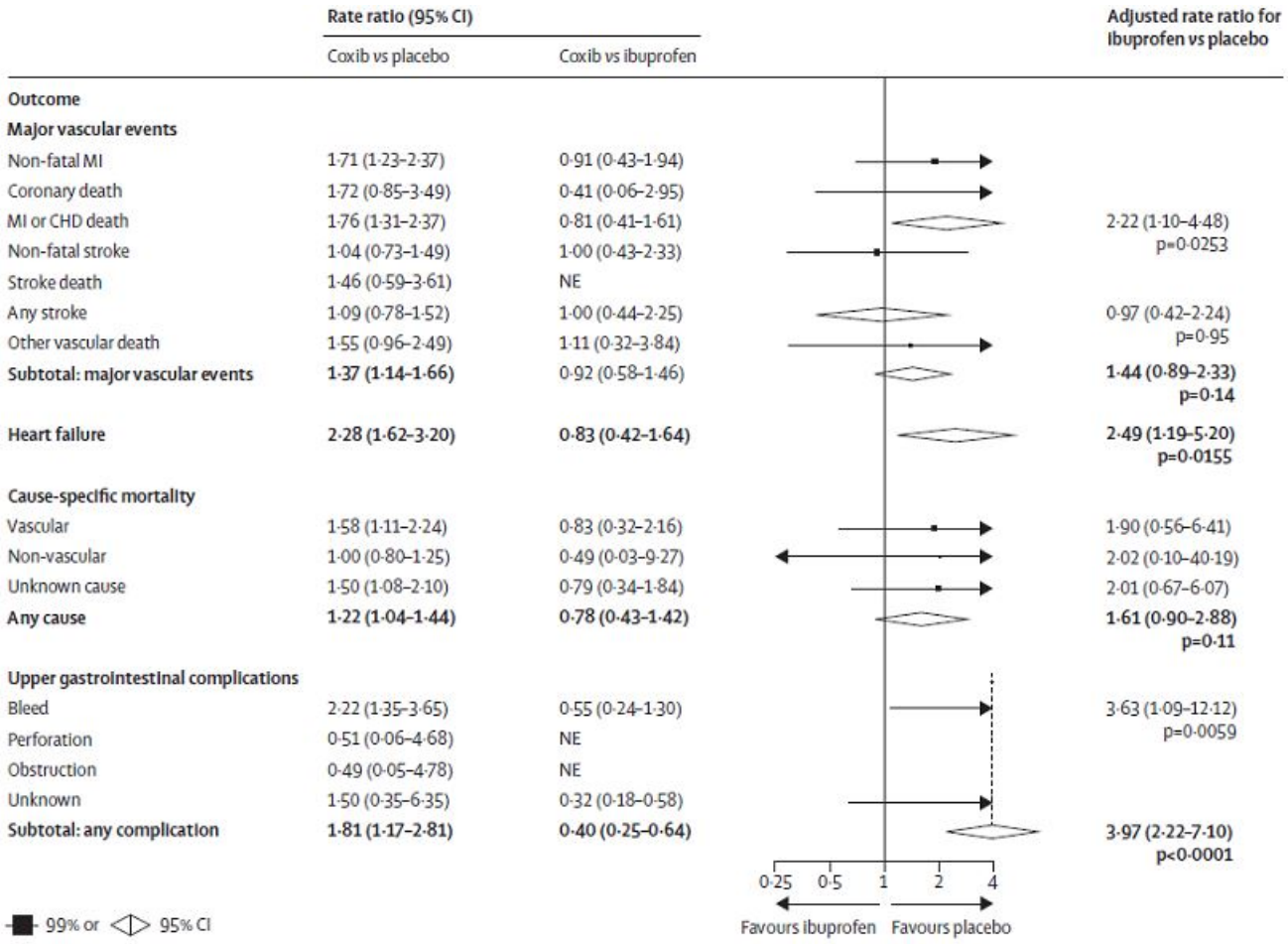
639 trials were included in the analyses. Meta-analyses of 280 trials of NSAIDs vs placebo (124 513 participants, 68 342 person-years) and 474 trials of one NSAID vs another NSAID (229 296 participants, 156 456 person-years) were performed.

Almost all the primary outcomes were reported in trials involving a coxib (rofecoxib, etoricoxib, celecoxib, parecoxib/valdecoxib, lumiracoxib) or high-dose tNSAID (diclofenac 150mg; ibuprofen 2400mg; naproxen 1000mg).

The main findings, as summarised in the published paper by the authors are as follows:

- Major vascular events were increased by about a third by a coxib (rate ratio [RR] 1.37, 95% CI 1.14–1.66; p=0.0009) or diclofenac (1.41, 1.12–1.78; p=0.0036), chiefly due to an increase in major coronary events – MI or CHD death (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), but not major vascular events (1.44, 0.89–2.33).
- Compared with placebo, of 1000 patients allocated to a coxib or diclofenac for a year, three more had major vascular events, one of which was fatal.
- Naproxen did not significantly increase major vascular events (0.93, 0.69–1.27).
- Vascular death was increased significantly by coxibs (1.58, 99% CI 1.00–2.49; p=0.0103) and diclofenac (1.65, 0.95–2.85, p=0.0187), non-significantly by ibuprofen (1.90, 0.56–6.41; p=0.17), but not by naproxen (1.08, 0.48–2.47, p=0.80).
- The proportional effects on major vascular events were independent of baseline characteristics, including vascular risk.
- Heart failure risk was roughly doubled by all NSAIDs.
- All NSAID regimens increased upper gastrointestinal complications (coxibs 1.81, 1.17–2.81, p=0.0070; diclofenac 1.89, 1.16–3.09, p=0.0106; ibuprofen 3.97, 2.22–7.10, p<0.0001; and naproxen 4.22, 2.71–6.56, p<0.0001).

Figure 1
Effects of ibuprofen on major vascular events, heart failure, cause-specific mortality, and upper gastrointestinal complications (indirect comparisons). MI=myocardial infarction. CHD=coronary heart disease. NE=not estimated.



The authors considered 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.

Epidemiological data

An overview of the 13 publications (7 cohort studies, 4 case-control studies and 2 case cross-over studies) that were identified for further analysis is provided in the table below.

Table 8
Summary of observational studies reporting of arterial thrombotic risk of ibuprofen, published since the previous CHMP review

Author (Publication year)	Source population	Study design	Study population	Outcome definition	Exposure/ comparator definition	Time period	Estimate for risk of cardiovascular events
deAbajo (2014)	National Primary Care Database, Spain	Nested case-control	Subjects aged 40-90 years; age, sex and calendar year matched controls	Non-fatal MI	Study drug use within 30-days of index date Vs non-use	2001-2007	tNSAIDs (group): 1.08 (0.95-1.24) Aceclofenac: 1.59 (1.26-2.58) Desoxibuprofen: 1.77 (0.77-4.07) Diclofenac: 1.14 (0.88-1.47) Ibuprofen: 0.95 (0.78-1.16) Indomethacin: 1.11 (0.57-2.13) Ketorolac: 0.90 (0.40-1.98) Lornoxicam: 1.54 (0.68-3.46) Meloxicam: 1.13 (0.67-1.91) Naproxen: 0.98 (0.57-1.69) Piroxicam: 0.87 (0.50-1.52)
Bavry (2014)	Women's Health Initiative, US	Cohort	Post-menopausal women aged 59-70 years	Cardiovascular death, non-fatal MI or non-fatal stroke	Regular users vs non-users of NSAIDs	2005-2010	Celecoxib: 1.13 (1.04-1.23) Rofecoxib: 1.13 (1.01-1.27) Naproxen: 1.22 (1.12-1.34) Diclofenac: 1.15 (0.99-1.35) Ibuprofen: 1.00 (0.93-1.07) Nabumetone: 1.14 (0.97-1.34) Etodolac: 1.01 (0.78-1.30) Piroxicam: 1.19 (0.93-1.53) Sulindac: 1.15 (0.89-1.47) Ketorolac: 1.86 (1.14-3.04) Ketoprofen: 1.47 (1.08-1.99) Indomethacin: 1.23 (0.89-1.69) Flurbiprofen: 1.66 (1.03-2.67)
Caughey (2011)	Veterans database, Australia	Cohort	Veterans; AVG age 76 years (SD±7.9); 60% men.	Stroke hospitalization; Ischaemic stroke; Haemorrhagic stroke.	Incident NSAID dispensing VS non-use	2001-2008	(Risk of stroke - after sensitivity analysis) Any NSAID: 1.85 (1.66-2.05) Ibuprofen: 1.74 (1.15-2.65) Naproxen: 1.39 (0.80-2.40) Indomethacin: 1.53 (0.97-2.41) Piroxicam: 3.13 (1.27-7.72) Meloxicam: 1.51 (1.12-2.03) Diclofenac: 1.96 (1.39-2.78) Celecoxib: 1.71 (1.42-2.07) Rofecoxib: 1.95 (1.55-2.45)
FosbØl (2012)	Nationwide record linkage, Denmark	Case crossover	Healthy individuals aged ≥10 years	Fatal or non-fatal ischaemic or haemorrhagic stroke	≥1 NSAID prescription Index date: date of outcome of interest	1997-2005	Ischaemic stroke High dose ibuprofen: 2.15 (1.66-2.79) High dose diclofenac: 2.37 (1.99-2.81) Haemorrhagic stroke High dose diclofenac: Increased (numbers not

					Case period: 0-30 days before index Control period: 60-90 and 90-120 days before index		provided) Naproxen: 2.15 (1.35-3.42) (see Figures 2 and 3 below)
Grimaldi-Bensouda (2011)	National registries, France	Case-control	Consecutive subjects (18-79 years) presenting with incident MI to PGRx-MI registry; Age and sex matched controls from GP practices	Incident non-fatal MI	Current NSAID use (within past 8-weeks)	2007-2009	<u>MI</u> Diclofenac: 1.47 (0.87-2.48) Ibuprofen: 0.91 (0.65-1.27) Naproxen & other AA* NSAID: 0.72 (0.45-1.16) All NSAIDs: 0.96 (0.75-1.23) <u>STEMI</u> Diclofenac: 0.90 (0.43-1.87) Ibuprofen: 0.98 (0.65-1.48) Naproxen & other AA* NSAID: 0.97 (0.55-1.68) All NSAIDs: 0.95 (0.70-1.28) <u>NSTEMI</u> Diclofenac: 2.82 (1.23-6.48) Ibuprofen: 0.75 (0.41-1.38) Naproxen & other AA* NSAID: 0.37 (0.15-0.91) All NSAIDs: 0.96 (0.63-1.46)
Gudbjornsson (2010)	Nationwide registries, Iceland	Cohort	Icelandic population	MI; Unstable angina; cerebral infarction and death due to cardiac arrest	NSAID/coxib exposure Vs diclofenac	2001-2003	<u>MI</u> Ibuprofen: 1.10 (0.84-1.45) Naproxen: 1.46 (1.03-2.07) Celecoxib: 1.19 (0.75-1.90) Rofecoxib: 1.77 (1.34-2.32) <u>Unstable angina pectoris</u> Ibuprofen: 0.63 (0.40-1.0) Naproxen: 1.02 (0.58-1.80) Celecoxib: 1.23 (0.63-2.42) Rofecoxib: 1.52 (1.01-2.30) <u>Cerebral infarction</u> Ibuprofen: 1.09 (0.76-1.54) Naproxen: 1.18 (0.73-1.92) Celecoxib: 1.52 (0.90-2.60) Rofecoxib: 2.13 (1.54-2.97)
Lamberts (2012)	Nationwide record linkage, Denmark	Cohort	Subjects aged ≥30 years hospitalised with first time MI	All-cause mortality within 30 days of admission to hospital with first-time MI All-cause mortality or re-MI within 1 year of admission to hospital with first-time MI.	NSAID prescription Vs non-use	1997-2006	<u>Mortality within 30 days</u> Any NSAID: 1.03 (0.96-1.08) Rofecoxib: 1.43 (1.22-1.68) Celecoxib: 1.23 (1.03-1.47) Other NSAID: 1.11 (1.02-1.22) Naproxen: 1.14 (0.94-1.39) Diclofenac:0.98 (0.88-1.09) Ibuprofen:0.91 (0.84-0.98)

							Mortality or re-MI within 1 year Any NSAID: 1.05 (1.02-1.09) Rofecoxib: 1.15 (1.04-1.27) Celecoxib: 1.13 (1.01-2.26) Other NSAID: 1.03 (0.97-1.09) Naproxen: 1.07 (0.94-1.22) Diclofenac: 1.12 (1.04-1.20) Ibuprofen:1.02 (0.98-1.07)
Lindhardsen (2013)	Nationwide record linkage, Denmark	Cohort	RA patients; (4:1) age and sex matched controls	MI, stroke or cardiovascular mortality	NSAID exposure vs non-exposure	1997-2009	Any NSAID RA: 1.22 (1.09-1.37) Controls: 1.51 (1.36-1.66) Ibuprofen RA: 1.16 (0.96-1.41) Controls: 1.54 (1.33-1.78) Diclofenac RA: 1.35 (1.11-1.64) Controls: 1.58 (1.31-1.90) Etodolac RA: 1.11 (0.83-1.47) Controls: 1.36 (1.00-1.86) Celecoxib RA: 1.12 (0.82-1.52) Controls: 1.28 (0.85-1.92) Rofecoxib RA: 1.57 (1.16-2.12) Controls: 2.19 (1.57-3.05) Piroxicam RA: 1.22 (0.61-2.44) Controls: 1.76 (1.06-2.92) Naproxen RA: 0.98 (0.47-2.06) Controls: 0.73 (0.37-1.47) Ketoprofen RA: 0.76 (0.36-1.60) Controls: 1.12 (0.56-2.24) Nabumetone RA: 0.86 (0.46-1.60) Controls: 0.99 (0.47-2.09)
Mangoni (2010a)	Veterans database, Australia	Nested case-control	Subjects aged ≥65 years; age, sex, and Australian state matched controls	Incident MI; Heart failure; All-cause mortality	NSAID prescription in last 2 years Vs non-use	2002-2006	Estimates given per frequency of NSAID use. No estimates for overall use per individual NSAID provided.
Mangoni (2010b)	Veterans database, Australia	Case-control	Subjects aged ≥65 years; age, sex, and Australian state matched controls	Intracerebral haemorrhage; Cerebral infarction	NSAID prescription in last 2 years Vs non-use	2002-2006	Estimates given per frequency of NSAID use. No estimates for overall use per individual NSAID provided.

Schjerning Olsen (2012)	Nationwide record linkage, Denmark	Cohort	Subjects aged ≥30 years, admitted with first MI	All-cause death; Composite of coronary death and non-fatal re-MI	NSAID use Vs non-use	1997-2009	No estimates for overall use per individual NSAID provided. Hazard ratios presented per year over 5-years for each study drug – see figure 3.
Schjerning Olsen (2013)	Nationwide record linkage, Denmark	Cohort	Subjects aged ≥30 years, admitted with first MI	CV death; Coronary death and non-fatal MI; Fatal and non-fatal stroke	NSAID use vs non-user	1997-2009	<u>CV death</u> Any use: 1.42 (1.36-1.49) Rofecoxib: 1.66 (1.44-1.90) Diclofenac: 1.96 (1.79-2.15) <u>Coronary death and non-fatal MI</u> Any use: 1.37 (1.32-1.43) Rofecoxib: 1.65 (1.44-1.90) Diclofenac: 1.66 (1.51-1.81) <u>Fatal and non-fatal stroke</u> Diclofenac: 1.21 (1.00-1.48) Ibuprofen: 1.23 (1.10-1.38) Other estimates are not provided and are presented in figures only (see figures 6 and 7)
Shau (2012)	Taiwan	Case crossover	Subjects hospitalised for new acute MI.	New acute MI hospitalisation	Index date: date of AMI hospitalisation Case period: 1-30days prior to index Control period: 91-120 days prior to index	2006	<u>Oral</u> Celecoxib: 1.36 (0.95-1.96) Ketorolac: 2.02 (1.00-4.09) Flurbiprofen: 1.71 (1.06-2.74) Ibuprofen: 1.45 (1.19-1.76) Sulindac: 1.44 (1.02-2.03) Diclofenac: 1.29 (1.13-1.47) Naproxen: 1.26 (0.88-1.81) Ketoprofen: 1.17 (0.64-2.11) <u>Parenteral</u> Diclofenac: 1.88 (0.95-3.75) Ketorolac: 4.27 (2.90-6.29) Ketoprofen: 2.34 (1.31-4.19)

* AA: arylpropionic acid; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST elevation myocardial infarction.

Cohort studies

The aim of the study by **Schjerning Olsen et al, 2012** was to examine whether the cardiovascular risk seen with NSAIDs was associated with the time elapsed following first-time myocardial infarction (MI). Patients aged 30 years or older admitted with first-time MI between 1997 and 2009 and subsequent NSAID use were identified by individual-level linkage of nationwide registries of hospitalisation and drug dispensing from pharmacies in Denmark. Incidence rates of death were calculated and a composite end point of coronary death or nonfatal recurrent MIs associated with NSAID use in 1-year time intervals up to 5 years after inclusion was used. Adjusted time-dependent COX proportional hazards models were used to calculate comparative risk estimates. Of the 99,187 patients included, 43,608 (44%) were prescribed NSAIDs after the index MI. There were 36,747 deaths and 28,693 coronary deaths or nonfatal recurrent MIs during the 5 years of follow-up.

The study reported that the use of NSAIDs was associated with a persistently increased cardiovascular risk in the years following MI. The authors state that the incidence rates show persistent increased absolute risks during the 5 years among the patients taking any NSAID, whereas the risk among the patients not taking NSAIDs declines. The risk of coronary death or MI associated with NSAID treatment after MI was significantly increased for rofecoxib, celecoxib, diclofenac and ibuprofen at all time points. In accordance with previous studies, the risk was highest for rofecoxib and diclofenac and lowest for naproxen (the increased risk for naproxen was statistically significant at the 1 year and 5 year time points only).

The aim of the study by **Lindhardsen et al, 2013** was to examine the incidence of adverse cardiovascular events in a nationwide cohort of rheumatoid arthritis (RA) patients according to their NSAID use between 1997 and 2009.

A longitudinal cohort study was conducted using Danish nationwide individual-level registry data on inpatient and outpatient treatment, pharmacotherapy and income. 17,320 RA patients were identified and matched with 69,280 controls (4:1) by age and sex. NSAID-associated risk of major cardiovascular disease defined as the combined endpoint of MI, stroke or cardiovascular mortality was assessed in multivariable survival models.

During follow-up (median 4.9 years) 6,283 events occurred. The cardiovascular risk associated with overall NSAID use was significantly lower in RA patients than in controls (Hazard Ratio (HR)=1.22, 95% CI: 1.09 to 1.37)) versus 1.51 (1.36 to 1.66). The pattern of lower NSAID-associated risk in RA patients was generally found with the individual NSAIDs investigated. While use of rofecoxib (HR=1.57, 95% CI: 1.16 to 2.12) and diclofenac (HR=1.35, 95% CI: 1.11 to 1.64) was associated with increased cardiovascular risk in RA patients, there was no significant risk associated with the use of any of the other NSAIDs in these patients.

The cardiovascular risk associated with NSAID use in RA patients was modest and significantly lower than in non-RA individuals. Only a few of the individual NSAIDs were associated with increased cardiovascular risk. With the exception of naproxen, the risk estimates consistently increased with higher daily dosages of NSAIDs in both RA patients and controls. The HRs with low NSAID dosages were very close to 1 in both groups, while high dosages generally were associated with more pronounced increased risk in controls than in RA patients.

The aim of this study by **Schjerning Olsen et al, 2013** was to examine cause-specific mortality and morbidity associated with NSAIDs in a nationwide cohort of MI patients.

By individual-level linkage of nationwide registries of hospitalization and drug dispensing from pharmacies in Denmark, patients aged 30 years admitted with first-time MI during 1997–2009 and their subsequent NSAID use were identified. The risk of three cardiovascular specific endpoints:

cardiovascular death, the composite of coronary death and nonfatal MI, and the composite of fatal and nonfatal stroke, associated with NSAID use was analysed by COX proportional hazard models. Of the 97,698 patients included, 44.0% received NSAIDs during follow-up. Overall use of NSAIDs was associated with an increased risk of cardiovascular death (HR=1.42, 95% CI: 1.36 to 1.49). In particular use of the nonselective NSAID diclofenac and the selective COX-2 inhibitor rofecoxib was associated with increased risk of cardiovascular death (HR=1.96, 95% CI: 1.79 to 2.15) and (HR=1.66, 95% CI: 1.44 to 1.91) respectively with a dose dependent increase in risk. For celecoxib, there was a lower, but still increased risk of cardiovascular death, coronary death and stroke relative to rofecoxib. Use of naproxen was associated with the lowest risk of the examined endpoints, albeit with dose-dependent increased risk in the Cox models. Use of ibuprofen was associated with increased risk of cardiovascular death (HR=1.34, 95% CI: 1.26 to 1.44).

The aim of the study by **Gudbjornsson et al, 2010** was to examine the risk of thromboembolic cardiovascular events in users of coxibs and NSAIDs in a nationwide cohort. Data from three nationwide databases, the Icelandic Medicines Registry (IMR), The Icelandic National Patient Registry (INPR) and the Registry for Causes of Death at Statistics Iceland (RCD) were utilised. The outcomes of interest were MI, unstable angina pectoris, cerebral infarction and death due to cardiac arrest. Diclofenac was used as the comparator drug. Cox proportional hazards and Poisson regression were used to analyse the data.

A total of 108,700 individuals received prescriptions for NSAIDs or coxibs, of whom 78,539 received one drug only (163,406 person-years). Among those receiving only one drug, 426 individuals were discharged from hospital with endpoint diagnoses. In comparison to diclofenac, the incidence ratios adjusted for age and gender, were significantly higher for cerebral infarction (2.13; 95% CI: 1.54 to 2.97; p<0.001), for myocardial infarction (1.77; 95% CI: 1.34 to 2.32; p<0.001) and for unstable angina pectoris (1.52; 95% CI: 1.01 to 2.30; p=0.047) for patients who used rofecoxib. For naproxen users, the incidence ratio was 1.46 for myocardial infarction (95% CI: 1.03 to 2.07; p=0.03), but was reduced in ibuprofen users (0.63; 95% CI: 0.40 to 1.00; p=0.05). Use of ibuprofen was not associated with an increased risk of MI relative to diclofenac (1.10, 95% CI: 0.84 to 1.45, p=0.50) or cerebral infarction (1.09, 95% CI: 0.76 to 1.00, p=0.05). The youngest users of rofecoxib (≤39 years) had the highest hazard ratio for cardiovascular events (8.34; p<0.001), while those ≥60 years had a lower but still significantly elevated HR (1.35; p=0.001).

The aim of the study by **Caughey et al, 2011** was to determine the risk of stroke associated with NSAID use. The study was a retrospective cohort of 162,065 Australian veterans with incident dispensing of an NSAID between 1 January 2001 and 31 December 2008, using prescription event sequence symmetry analysis (SSA). The outcomes of interest were hospitalisation for all stroke, and ischaemic stroke or haemorrhagic stroke as individual endpoints.

The absolute risk of stroke was low: 7.1/1,000 people/year. Incident use of an NSAID was associated with a 1.88 times (95% CI: 1.70 to 2.08) increased risk of hospitalisation for stroke (ischaemic or haemorrhagic). This equates to an increased absolute risk of 13.4 strokes/1,000 people/year. Significant positive associations between starting an NSAID and having a hospitalisation for stroke were found for most NSAIDs.

The adjusted sequence ratios for the risk of first stroke with ibuprofen use are summarised below.

Stroke type	No. of patients	Stroke in 12 months after initiation of ibuprofen use	Stroke in 12 months before initiation of ibuprofen use	Adjusted sequence ratio (ASR) (95% CI)
Incident stroke	345	193	152	1.23 (0.99 to 1.52)
Incident ischaemic	180	92	88	1.03 (0.77 to 1.39)
Incident haemorrhagic	70	41	29	1.35 (0.84 to 2.17)

In comparison, a significantly increased risk of hospitalisation for incident stroke was seen for all other NSAIDs individually. Diclofenac was associated with a 1.72 times (95% CI: 1.34 to 2.21) increased risk of ischaemic stroke and a 1.92 times (95% CI: 1.30 to 2.85) increased of haemorrhagic stroke. Celecoxib was associated with a 1.55 times (95% CI: 1.30 to 1.87) increased risk of ischaemic stroke and a 1.81 times (95% CI: 1.34 to 2.45) increased of haemorrhagic stroke. Rofecoxib was associated with a 1.71 times (95% CI: 1.43 to 2.04) increased risk of ischaemic stroke and a 2.40 times (95% CI: 1.77 to 3.26) increased of haemorrhagic stroke.

The authors also conducted a sensitivity analysis for all incident stroke, limited to incident users of an NSAID within a 12 month period: i.e. no patients who had no previous dispensing of any NSAID for at least 12 months before incident NSAID dispensing. Increased SSA ratios were observed for ibuprofen (1.74, 1.14 to 2.65), piroxicam (3.13, 1.27 to 7.72), meloxicam (1.51, 1.12 to 2.03), diclofenac (1.96, 1.39 to 2.78), celecoxib (1.71, 1.42 to 2.07) and rofecoxib (1.95, 1.55 to 2.45). No association was observed for naproxen or indomethacin.

The aim of the study by **Lamberts et al, 2012** was to examine the effect of ongoing NSAID treatment at the time of admission for myocardial infarction (MI) on prognosis.

Data on patients aged ≥30 years admitted with a first MI between 1997 and 2006 were analysed using individual-level linkage of nationwide registries in Denmark. Ongoing NSAID treatment was defined as the availability of tablets up to 14 days prior to inclusion. The outcomes of interest were all-cause mortality within 30 days and the combined endpoint of all-cause mortality or admission for recurrent MI within 1 year. Non-use of NSAIDs was used as the comparator group. Concomitant drug use in the 3 month period prior to admission was also analysed. Comorbidity was defined using diagnoses from hospital admission in the one year period prior to the first MI. Logistic regression and COX proportional hazards models were used.

Relative to no NSAID use, rofexcoxib, celecoxib and other NSAIDs were associated with a significant increased risk of death within 30 days from admission (ORs of 1.43 (95% CI: 1.22 to 1.68), 1.23 (95% CI: 1.03 to 1.47) and 1.15 (1.02 to 1.22) respectively). Naproxen showed a non-significant increased risk of death (OR of 1.14 (95% CI: 0.94 to 1.39)) while no association was found for diclofenac (OR of 0.98 (95% CI: 0.88 to 1.09)). Ongoing treatment with ibuprofen showed a decreased risk (OR=0.91, 95% CI: 0.84 to 0.98).

For death within 1 year from admission, rofecoxib, celecoxib and diclofenac were associated with an increased risk with HRs of 1.18 (95% CI: 1.05 to 1.32), 1.17 (95% CI: 1.04 to 1.32) and 1.13 (95% CI: 1.04 to 1.22) respectively. Statistically significant increased risks of the combined endpoint of mortality or recurrent MI was observed for rofecoxib, celecoxib and diclofenac with HRs of 1.15 (95% CI: 1.04 to 1.27), 1.13 (95% CI: 1.01 to 1.26) and 1.12 (95% CI: 1.04 to 1.20) respectively. No association was observed for naproxen or ibuprofen.

The primary objective of the study by **Bavry et al, 2014** was to evaluate the association between regular NSAID use and adverse cardiovascular outcomes among a large cohort of post-menopausal women. The secondary objective was to evaluate whether the risk of cardiovascular adverse events was associated with the relative COX-1 vs COX-2 selectivity of individual NSAIDs.

Postmenopausal women enrolled in the Women's Health Initiative (WHI) were classified as regular or non-users of non-acetylsalicylic acid NSAIDs. COX regression examined NSAID use as a time-varying covariate and its association with the primary outcome of total cardiovascular disease defined as cardiovascular death, nonfatal myocardial infarction or nonfatal stroke. Secondary analyses considered the association of selective COX-2 inhibitors (e.g. celecoxib), nonselective agents with COX-2>COX-1 inhibition (e.g. naproxen) and nonselective agents with COX-1>COX-2 inhibition (e.g. ibuprofen) with the primary outcome. Overall, 160,802 participants were available for analysis (mean follow-up 11.2 years). Regular NSAID use at some point in time was reported by 53,142 participants. Regular NSAID use was associated with an increased hazard for cardiovascular events versus no NSAID use (HR=1.10, 95% CI: 1.06 to 1.15), p<0.001). Selective COX-2 inhibitors were associated with a modest increased hazard for cardiovascular events (HR=1.13, 95% CI: 1.04 to 1.23, p=0.004) and celecoxib only (HR=1.13, 95% CI: 1.01 to 1.27, p=0.031). Among acetylsalicylic acid users, concomitant selective COX-2 inhibitor use was no longer associated with an increased hazard for cardiovascular events. There was an increased risk for agents with COX-2>COX-1 inhibition (HR=1.17, 95% CI: 1.10 to 1.24, p<0.001) and naproxen only (HR=1.22, 95% CI: 1.12 to 1.34, p<0.001). This harmful association remained among concomitant acetylsalicylic acid users. No increased risk was observed for agents with COX-1>COX-2 inhibition (HR=1.01, 95% CI: 0.95 to 1.07, p=0.884) and ibuprofen only (HR=1.00, 95% CI: 0.93 to 1.07, p=0.996).

Regular use of selective COX-2 inhibitors and nonselective NSAIDs with COX-2>COX-1 inhibition showed a modestly increased hazard for cardiovascular events. Nonselective agents with COX-1>COX-2 inhibition were not associated with an increased cardiovascular risk.

Case-control studies

The aim of the study by **de Abajo et al, 2014** was to estimate the risk of nonfatal acute myocardial infarction (AMI) associated with tNSAIDs, non-narcotic analgesics (paracetamol and metamizole), and symptomatic slow-acting drugs in osteoarthritis (SYSADOAs) both overall and in different subgroups of patients according to background cardiovascular risk.

A nested case-control study using a Primary Care Database (BIFAP) was conducted over the study period, 2001–2007. Patients aged 40–90 years were included, with nonfatal AMI and were matched on age, sex and calendar year with randomly selected controls. Exposure to drugs was assessed within a 30-day window before the index date (the first nonfatal AMI event). Patients with a record of cancer were excluded.

No association was found for nonfatal AMI in patients at low-intermediate background cardiovascular risk (OR=0.92; 95% CI: 0.76 to 1.12), whereas there was a moderate significant association among those at high risk (1.28; 1.06 to 1.54) or when tNSAIDs were used for longer than 365 days (1.43; 1.12 to 1.82). Low-dose acetylsalicylic acid did not modify the risk profile showed by any of the

individual tNSAIDs examined. The effect of dose, duration, background cardiovascular risk and concomitant low-dose acetylsalicylic acid use were evaluated. No risk was observed with ibuprofen for any of the effects of dose, duration, background CV risk or concomitant acetylsalicylic acid use. A significantly increased risk was seen with high dose aceclofenac (>150mg/day) but not with high dose diclofenac (>100 mg/day) or ibuprofen (>1200 mg/day).

The aim of this study by **Mangoni et al, 2010a** was to examine the relationship between the use of NSAIDs and their main subclasses, non-selective NSAIDs (ns-NSAIDs) and selective COX-2 inhibitors and the risk of incident myocardial infarction (MI), heart failure (HF) and all-cause mortality. The study population was the Australian veteran community which comprises all Australian war veterans, spouses and dependents aged 65 and older.

A retrospective nested case-control was conducted using nationwide hospital admission and pharmacy dispensing data. For the three primary outcomes of interest, a total of 83,623 cases and 1,662,099 matched controls (1:20) contributing 3,862,931 person-years of observation were identified.

The unadjusted risk of MI was marginally increased with use at least once within the previous 2 years of either ns-NSAIDs (OR 1.05, 95% CI 1.00-1.11), selective COX-2 inhibitors (OR 1.008 95% CI 1.04-1.13), or any NSAID (OR 1.06 95% CI 1.02-1.11). However, these associations disappeared after adjustment for potential confounders. There was no apparent increased risk (aOR) for any of the outcomes with increasing number of prescriptions of ibuprofen or any other of the individual NSAIDs. However, for diclofenac and meloxicam, there appeared to be a reduced risk of all-cause mortality with increasing supply of the respective NSAID.

The aim of the study by **Mangoni et al, 2010b** was to assess the association between the use of non-selective ns-NSAIDs, selective COX-2 inhibitors, or either of these NSAIDs, and the incidence of stroke-related hospitalization in elderly subjects.

A retrospective nested case-control study on Australian veterans using nationwide hospital admission and pharmacy dispensing data was conducted. This study used the same population as the study above. The primary outcomes of interest were intracerebral haemorrhage or cerebral infarction. Conditional logistic regression analysis was used to estimate both crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) for the risk of events for different frequencies of use over the last 2 years. For all of the individual NSAIDs, there appeared to be little evidence of an increased risk of hospitalisation for ischaemic or haemorrhagic stroke.

The aim of the study by **Grimaldi-Bensouda et al, 2011** was to explore the association of NSAIDs with ST-segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI). A matched case-control study was conducted where cases were recruited by cardiologists and consisted of patients with incident non-fatal MI. Cases were retrieved from the Pharmacoepidemiological General Research on Myocardial Infarction (PGRx-MI) registry, a French nationwide registry consisting of 55 cardiology centres, whereas controls were selected from general practice settings. Both cases and controls were recruited from the same geographically diverse areas across continental France. The association between NSAID and MI was assessed using conditional logistic regression.

Between 2007 and 2009, 1,125 incident cases were included (67.3% and 32.7% for STEMI and NSTEMI, respectively), with 2790 controls matched to MI cases by age and sex. Current use (previous 2 months) of either diclofenac (aOR=0.90, 95% CI: 0.43 to 1.87), ibuprofen (aOR=0.90, 95% CI: 0.43 to 1.87) or naproxen and other arylpropionic acid NSAIDs (aOR=0.97, 95% CI: 0.55 to 1.68) was not associated with STEMI. However, an increased risk of non-STEMI was observed for diclofenac (aOR=2.82, 95% CI: 1.23 to 6.48), a reduced risk for naproxen and other arylpropionic acid NSAIDs

(aOR=0.37, 95% CI: 0.15 to 0.91), while no association was observed for ibuprofen (aOR=0.75, 95% CI: 0.41 to 1.38).

Case-crossover studies

The aim of the study by **Fosbøl et al, 2012** was to examine the risk of ischaemic and haemorrhagic stroke associated with the use of NSAIDs in healthy people.

Individual-level linkage of nationwide administrative registers in Denmark, information on hospital admissions, prescription claims, vital status, and cause of death were used for analysis. A cohort of healthy people without hospital admissions for five-years and no important prescription claims for two-years was selected. Case crossover and COX proportional hazard models were used to analyse the relationship between NSAID use and specific cerebrovascular risk (fatal or non-fatal ischaemic or haemorrhagic stroke).

1,028,437 healthy individuals (median age 39 years) were eligible for analysis. At least one NSAID was claimed by 44.7% of the study population, and the drugs were generally used for a short period of time and in low doses. High-dose ibuprofen and diclofenac were associated with an increased risk of ischaemic stroke (HR=2.15 (95% CI: 1.66 to 2.79)) and (HR=2.37 (95% CI: 1.99 to 2.81)), respectively. Diclofenac was also associated with increased risk of haemorrhagic stroke (HR=2.15, 95% CI: 1.35 to 3.42). However, in this study, naproxen which has consistently been shown to have the most favourable cardiovascular risk profile of the NSAIDs, was associated with a significantly increased risk of haemorrhagic stroke (HR: 2.15 (1.35-3.42)), which may reflect its greater selectivity for COX-1. Finally, although a dose-response is observed (see Figures 2 and 3), the confidence intervals are wide limiting the conclusions that can be drawn.

Figure 2

Ischaemic stroke. Odds and hazard ratios derived from case-crossover and Cox models, respectively. Strokes: strokes during treatment. NNH: unadjusted number-needed-to-harm per year of treatment

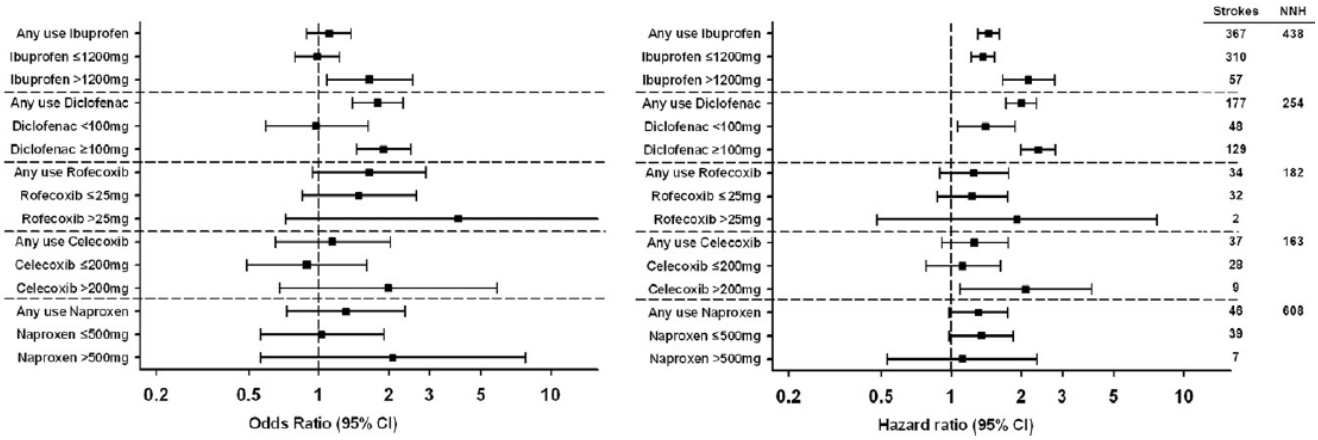
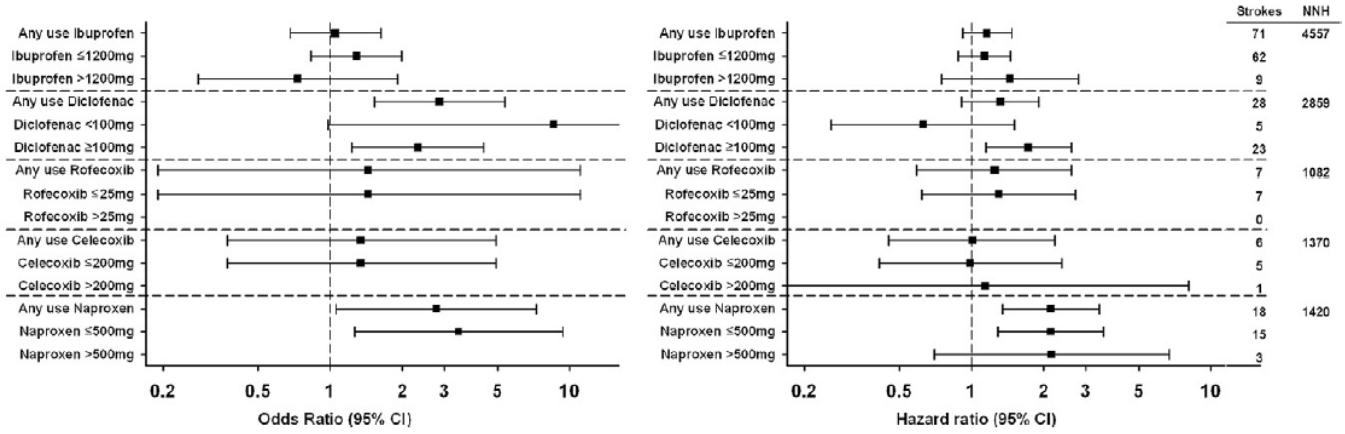


Figure 3

Haemorrhagic stroke. Odds and hazard ratios derived from case-crossover and Cox models, respectively. Strokes: strokes during treatment. NNH: unadjusted number-needed-to-harm per year of treatment



The study by **Shau et al, 2012** examined the risk of new acute myocardial infarction (AMI) hospitalization with current use of a variety of oral and parenteral NSAIDs in a nationwide population.

A case-crossover study was conducted using Taiwan's National Health Insurance claim database, in which patients who were hospitalised for a first AMI in 2006 were identified. The index date was the first AMI hospitalisation. The 1-30 days and 91-120 days prior to the admission were defined as the case and matched control period for each patient, respectively. Use of NSAIDs during the respective periods was compared using conditional logistic regression and adjusted for the use of co-medications.

8,354 new AMI hospitalization patients fulfilled the study criteria. The adjusted odds ratio, aOR (95% confidence interval), for risk of AMI and use of oral and parenteral non-selective NSAIDs were 1.42 (1.29 to 1.56) and 3.35 (2.50 to 4.47), respectively, and significantly greater for parenteral than oral drugs (p for interaction < 0.01). Ketorolac was associated with the highest AMI risk among oral and parenteral NSAIDs studied, the aORs were 2.02 (1.00 to 4.09) and 4.27 (2.90 to 6.29) respectively. Use of oral flurbiprofen (1.71, 1.06 to 2.74), ibuprofen (1.45, 1.19 to 1.76), sulindac (1.44, 1.02 to 2.03), diclofenac (1.29, 1.13 to 1.47) and parenteral ketoprofen (2.34, 1.13 to 4.19) were also significantly associated with increased AMI risk.

The majority of the concerned marketing authorisation holders (MAHs) confirmed that they do not hold any additional unpublished study data regarding the arterial thrombotic risk of ibuprofen/dexibuprofen other than those already under consideration by the PRAC. However, reviews of the published literature were submitted by six ibuprofen MAHs and by one dexibuprofen MAH. A number of these responses also contained reviews of MAH clinical trial data, spontaneous reporting data and/or PSUR data. Only one additional publication was provided (Rafiq et al, 2014) which did not study ibuprofen alone, but only as part of a multi-modal treatment arm. All the data provided by the MAHs were taken into account by the PRAC in its final conclusions.

1.2.3. Additional information

Two drug utilization studies were performed by the Spanish Agency on Medicines and Medical Devices (AEMPS) and by the European Medicines Agency (EMA) to evaluate the use of ibuprofen/dexibuprofen across some member states.

The first one was carried out using the Spanish Database BIFAP. It was concluded that the prevalence of use of prescribed ibuprofen at any dose in the study period is approximately 100 fold greater than the use of dexibuprofen (the incidence of use of ibuprofen was 78 fold greater than that of dexibuprofen). It also highlighted that only a small proportion of ibuprofen users are prescribed doses >1800 mg/day (1%). The study of incident users (first prescription) showed that doses >1800 mg/day of ibuprofen are prescribed for short term duration regimens (up to 10 days) and generally linked to a respiratory and skeletal muscle diagnostic code. Of the patients receiving these doses of ibuprofen, the proportion of patients with cardiovascular disease was very small (1.63%). However almost half of the dexibuprofen users received doses >900 mg/day. The study of incident prescriptions of dexibuprofen showed that it is used also in short term duration regimens (up to 10 days) and similar to ibuprofen for respiratory conditions, although skeletal muscle conditions were more frequent when compared to ibuprofen. It was noted that for patients receiving dexibuprofen doses >900 mg/day the proportion of patients with history of cardiovascular disease is small but is twice that seen for dose of ibuprofen >1800 mg/day.

The second study performed by the EMA included information on the use of ibuprofen/dexibuprofen from three member states (United Kingdom, France and Germany) using two different data sources (the Health Improvement Network (THIN) Database and IMS Health). From counts of intended prescribed dosages in all 3 datasets (UK, FR and DE), prescriptions of 2400 mg of ibuprofen would appear to account for < 1% of all prescriptions. Further preliminary analyses in the THIN dataset suggest that usage has continued to decrease since 01 Jan 2013. An additional analysis of IMS data in France showed that prescriptions of ibuprofen doses ≥ 2400 mg/day in the adult population accounts for 0.36% of all ibuprofen prescriptions over the entire dataset. Results from 2013 suggest such use is declining with only 0.28% of all ibuprofen prescriptions in 2013 accounting for doses ≥ 2400 mg/day. When used at these doses, ibuprofen was usually taken for short period of time (96% of prescriptions were for two weeks or less).

1.2.4. Discussion

Regarding the study by Salvo et al, 2011 the PRAC commented that the incidence rates presented should be interpreted with caution given the heterogeneity between studies included in the reviewed meta-analyses (indication, treatment duration, dose, study population). In addition, the authors also noted that the estimates retrieved from the different meta-analyses are unlikely to be fully independent, due to duplication of trials across meta-analyses. Furthermore, the tNSAIDs diclofenac, ibuprofen, piroxicam and naproxen were not drugs of interest in the selected meta-analyses, therefore the data on these reference NSAIDs are not the result of a systematic retrieval process. The authors note the fact that there are substantially more clinical trial data for the coxibs than for the older tNSAIDs, and the resulting imbalance in the nature of the safety evaluation that can be performed.

In the results of the CNT Collaboration's network meta-analysis, high doses of ibuprofen (2400mg/day) significantly increased major coronary events (MCE) (MI or coronary heart disease (CHD) death) but not major vascular events (MVE) (non-fatal MI, coronary death, MI or CHD death, non-fatal stroke, stroke death, any stroke, and other vascular death). The adjusted rate ratio for ibuprofen vs placebo for MCE and MVE were 2.22 (1.10-4.48) and 1.44 (0.89-2.33), respectively. In the coxib vs ibuprofen comparisons the rate ratios favoured coxibs for both MCE and MVE (i.e. slightly increased risk with ibuprofen vs coxibs group) but these were not statistically significant.

In the initial PRAC consideration of the CNT collaboration network meta-analyses, a number of important questions regarding statistical methodology were raised which were considered to limit the interpretation of the results in particular for the tNSAIDs, including ibuprofen. Consequently, further clarifications from the CNT Collaboration were requested around the use of indirect comparisons for

tNSAIDs, the handling of zero event trials and shorter than average follow-up for ibuprofen trials that could bias the results upwards for ibuprofen.

The CNT Collaboration's responses to the PRAC questions confirmed that zero event trials and possible unequal randomisation are unlikely to have introduced any significant bias to the results of the network meta-analysis for ibuprofen. The responses also confirmed that there is very little randomised evidence directly comparing ibuprofen to placebo and that the results of the network meta-analysis are primarily derived from studies that directly compared coxibs with ibuprofen. The PRAC was of the view that this makes it difficult to judge the size of any biases which may have been introduced by any differences in study population and study duration.

The CNT Collaboration's responses also confirmed that the trials that compared ibuprofen with placebo were shorter in duration than the trials that compared ibuprofen with coxibs and thus there is the possibility that including the trials that compared ibuprofen with placebo in the network meta-analysis could inflate the treatment effect. The data provided by ibuprofen vs placebo trials are too limited to draw any conclusions on the risk.

Given the outstanding uncertainties regarding the size of potential biases in the network meta-analysis and the paucity of information available directly comparing ibuprofen with placebo, the PRAC was of the view that any conclusions on the magnitude of the CV risk of ibuprofen drawn from this meta-analysis should be based on the results of studies that compared ibuprofen with coxibs and not the indirect comparisons derived from the network meta-analysis.

Overall, the PRAC was of the opinion that the data from the coxib vs ibuprofen trials indicate that the CV risks of high dose ibuprofen may be similar to that for coxibs.

Regarding the epidemiological data, the PRAC noted that each study has strengths and limitations which should be borne in mind when interpreting the results. Such limitations included exposure misclassification, non-prescription NSAID/acetylsalicylic acid use, missing data, confounding by indication, channelling, inability to control for lifestyle factors. In all studies the inability to adjust for the possibility of residual confounding was recognised as a potential problem but the PRAC considered that some of the Danish studies were least likely to suffer from this problem.

Furthermore, the exclusion criteria or population specific analysis (either by country or medical history) were also considered to limit the generalizability of the results. Differences between individual studies (study endpoints; doses; study population, comparator) also make it difficult to directly compare the results.

A number of studies reported on more than one endpoint or included additional analyses (e.g. subpopulation, and dose or duration of treatment effect analyses).

Five of the thirteen studies reported on the risk of acute myocardial infarction; 5 on the risk of stroke; 2 on all-cause mortality; and 4 on various composite endpoints which included MI or death. Some examined healthy populations whilst others looked at specific patient populations including those with previous MI (Schjerning-Olsen et al, 2012 & 2013; Lamberts et al, 2012) or rheumatoid arthritis (RA) (Lindhardsen et al, 2013). Other populations were defined by the databases used; for example the studies using Australian databases were conducted in elderly veterans with multiple co-morbidities (Mangoni et al, 2010a & 2010b; Caughey et al, 2011).

Twelve of the thirteen new studies provide risk estimates for cardiovascular endpoints for ibuprofen versus non-use or remote use; diclofenac-use was the comparator in the remaining study (Gudbjornsson et al, 2012).

Seven studies did not show a statistically significant increased risk for ibuprofen for: acute MI (de Abajo et al, 2014; Grimaldi-Bensouda et al, 2011, Mangoni et al, 2010a); the risk of stroke (Caughey et al, 2011; Mangoni et al, 2010b); mortality within 30 days of admission with MI and the composite of mortality or re-MI within one year (Lamberts et al, 2012); and the risk of the composite endpoint of CV death or non-fatal MI or non-fatal stroke (Bavry et al, 2014).

One further study showed conflicting results depending on the method of analysis used (Fosbol et al, 2012), which highlighted the difficulties of comparing studies using different methodologies (in this case COX analysis vs case-control).

Five studies showed a statistically significant but modest increase in risk for ibuprofen versus non-use or remote use: (Shau et al, 2012); (Fosbol et al, 2012 – for the case-control analysis only); (Lindhardsen et al, 2013); (Scherning Olsen et al, 2012 & 2013). In both Scherning Olsen studies, the increase in risk reported for ibuprofen was lower than for rofecoxib and diclofenac (for risk estimates see table 8 above). Interestingly Lindhardsen et al (2013) reported an increased cardiovascular risk (combined endpoint of myocardial infarction, stroke or cardiovascular mortality) for ibuprofen in controls but not in patients with RA. Rofecoxib and diclofenac were however associated with an increased risk in both controls and RA patients.

Four of the five studies which showed an increased risk for ibuprofen versus non-use or remote use, were based on Danish national registries (Schjerning Olsen et al, 2012 & 2013; Lindhardsen et al, 2012 and Fosbol et al, 2012) which have some advantages compared to other studies included. Selection bias and non-prescription NSAID use is expected to be minimal in these studies, as they include data for the entire country and unlike most countries, only ibuprofen is available over the counter (OTC) in Denmark. However, two of these studies were conducted in patients with previous-MI and thus the results may not be generalizable (Schjerning Olsen et al, 2012 & 2013) and the authors of Lindhardsen et al note that there is the possibility that the results for ibuprofen and naproxen may be inflated due to possible channelling, and also the fact that ibuprofen changed from a prescription only medicine (POM) to being available without prescription during the period of the study.

Regarding the CV risk for ibuprofen versus other NSAIDs, Gudbjornssen et al (2010) did not show an increased risk for ibuprofen versus diclofenac; the risk of cardiovascular events was increased for rofecoxib and naproxen relative to diclofenac. The increased risk with naproxen is inconsistent with most other studies; important confounders were not adjusted for in this study.

Dose

De Abajo et al (2014) did not report an increased risk with ibuprofen overall, or at doses lower than 1200mg or higher than 1200mg. Schjerning Olsen et al (2013) reported a dose-dependent increase in risk for ibuprofen but did not present the hazard ratios for the dose categories.

In the case-control model, Fosbol et al (2012) reported a statistically significant increased risk for ibuprofen doses above 1200mg but not at doses at or below 1200mg/day. In the Cox model, any use, low dose and high dose ibuprofen was associated with a statistically significant increase in risk; the confidence intervals do not overlap for the low and high dose risk estimates (risk with high dose is greater than for low dose). Lindhardsen et al (2012) found a statistically significant increase in risk with doses of ibuprofen above 800mg/day but not below 800mg/day. The Lindhardsen results are inconsistent with those of two meta-analyses of observational studies which indicate that low dose ibuprofen is not associated with an increased risk for cardiovascular events (McGettigan and Henry, 2011; Varas Lorenzo et al, 2011). In the McGettigan and Henry meta-analysis low dose ibuprofen is a mixture ≤1200mg in 6 studies, ≤1600mg in two studies, and <1800mg in 2 studies. In the Varas-

Lorenzo et al (2011) meta-analysis, neither low dose nor high dose ibuprofen was associated with a significantly increased risk of stroke.

Duration

Schjerning Olsen et al (2012) reported that the use of NSAIDs, including ibuprofen was associated with a persistently increased cardiovascular risk in the years following MI. The authors state that the incidence rates show persistent increased absolute risks during the first 5 years among the patients taking any NSAID, whereas the risk among the patients not taking NSAIDs declines. The risk of coronary death or MI associated with NSAID treatment after MI was significantly increased for rofecoxib, celecoxib, diclofenac and ibuprofen at every time point. In accordance with previous studies, the risk was highest for rofecoxib and diclofenac and lowest for naproxen (the increased risk for naproxen was statistically significant at the 1 year and 5 year time points only).

The published results of the meta-analyses of observational studies from the SOS project (Varas-Lorenzo et al, 2013) provide some limited information on risk of MI stratified by duration of treatment. However, few studies reported on the effects of treatment duration and where information was reported no consistent pattern was observed across studies.

Potential mechanism

Available data on possible mechanisms is not yet sufficient to determine with certainty exactly how the cardiovascular risks of individual NSAIDs are mediated, or why/how the risks differ between products. Examples of potential mechanisms are the imbalance between vasodilatory and prothrombotic prostanoids, selectivity for COX-1 and COX-2, inhibition of platelet thromboxane A2 (TXA2), cardio renal effects of NSAIDs. The PRAC noted that no single mechanism appears to explain all the observed results from clinical trials and epidemiological studies, and thus it appears likely that the thrombotic risks associated with NSAIDs in general, and with ibuprofen in particular, are due to the combination of more than one of these mechanisms. Based on the current knowledge the pathophysiology underlying NSAID-induced, and in particular ibuprofen-induced arterial thrombotic risks, remains speculative.

1.3. Interaction between ibuprofen/dexibuprofen and acetylsalicylic acid

Acetylsalicylic acid is commonly used in adults for its analgesic and anti-inflammatory properties in 'high doses' (typically 300-600mg 4-6 hourly) for the short-term treatment of minor ailments. In addition, at lower doses (typically 75mg daily), acetylsalicylic acid has proven benefits in the long-term primary and secondary prevention of thrombotic cardiovascular events.

Low-dose acetylsalicylic acid is highly selective for COX-1, leading to decreased thromboxane B2 (TXB2) and decreased platelet aggregation. The anti-platelet effect of acetylsalicylic acid is achieved through irreversible acetylation, and thereby inhibition, of platelet COX-1. Unlike acetylsalicylic acid, NSAIDs such as ibuprofen are reversible inhibitors of COX-1/COX-2, leading to impaired platelet function for only a portion of the dosing interval.

The suspected mechanism underlying the observed interaction between ibuprofen and acetylsalicylic acid in human ex vivo studies is the competitive inhibition of the acetylation site of COX in the platelet. Both ibuprofen and acetylsalicylic acid occupy nearby sites on COX in such a way that the presence of ibuprofen interferes with the binding of acetylsalicylic acid, attenuating the acetylsalicylic acid-mediated irreversible inhibition of TXB2 production.

The most recent EU-wide review of the possible interaction between acetylsalicylic acid and ibuprofen was completed by the CHMP Pharmacovigilance Working Party (PhVWP) in 2008. At that time, studies of ex-vivo platelet aggregation and TXB2 suggested the potential for ibuprofen to reduce the anti-

platelet effects of acetylsalicylic acid (Catella-Lawson *et al*, 2001; Cryer *et al*, 2005); however, evidence of a clinically important effect had not been convincingly demonstrated in either pharmacoepidemiological studies or clinical trials. As a result of this review, PhVWP recommended that the product information for acetylsalicylic acid and ibuprofen be updated to include a warning reflecting the data available at the time.

1.3.1. Summary of evidence from previous reviews

A possible interaction between dexibuprofen and acetylsalicylic acid has not previously been reviewed at an EU-level, thus the data discussed in this section relate to ibuprofen only.

The PhVWP has reviewed data relating to the possible interaction between ibuprofen and acetylsalicylic acid on a number of occasions previously; in 2005, 2006 and most recently in 2008. Some of the previously considered data included platelet function studies, clinical trial data, epidemiological data and literature reviews.

Regarding the platelet function studies, **Catella-Lawson *et al,* 2001** conducted randomised cross-over studies to examine the effect of different combinations of NSAIDs and acetylsalicylic acid on platelet function. The study measured *ex-vivo* platelet aggregation, serum TXB2 levels (a marker for COX-1 activity) and serum urinary markers of COX-2 activity. For 6 days, patients were administered 81mg immediate release acetylsalicylic acid 2 hours before 400mg ibuprofen, 1000mg paracetamol or 25mg rofecoxib (and the same doses in the reverse order), or 81mg enteric-coated acetylsalicylic acid followed by 400mg ibuprofen tid or 75mg diclofenac bid (and the same doses in reverse order). The results showed that inhibition of serum TXB2 formation and platelet aggregation by acetylsalicylic acid was reduced when a single daily dose of ibuprofen was given before acetylsalicylic acid, as well as when multiple daily doses of ibuprofen were given. The authors concluded that concomitant administration of ibuprofen but not rofecoxib, paracetamol or diclofenac antagonised the irreversible platelet inhibition induced by acetylsalicylic acid; suggesting that treatment with ibuprofen in patients with cardiovascular risk may limit the cardioprotective effects of acetylsalicylic acid.

Cryer *et al*, 2005 conducted a prospective, multiple dose, single-centre, double-blind, randomised, parallel, placebo-controlled study, in which subjects received 81mg immediate release acetylsalicylic acid for 8 days, and were then randomised to either ibuprofen 400mg TID, or placebo TID for 10 days. Measurements of TXB2 were taken on days 0, 1, 3 7 and 10 following randomisation. The authors found that on days 1, 3, 7 and 10 of the study period, mean TXB2 inhibitions were 99.24%, 98.88%, 97.75% and 98.17% for ibuprofen and 98.82%, 98.93%, 98.75% and 98.83% for placebo. Although a statistically significant difference was seen on day 7, the TXB2 inhibition was near complete in the ibuprofen arm, and the authors concluded that "*no clinically meaningful loss of cardioprotection was found*".

At the time of the last PhVWP review, no large randomized clinical trials had been conducted that were designed to specifically examine the possible ibuprofen/acetylsalicylic acid interaction. However, post-hoc subgroup data from the Celecoxib Long-Term Arthritis Safety Study (CLASS) and Therapeutic Arthritis Research and Gastrointestinal Trial (TARGET) studies provided some information relevant to a possible interaction between acetylsalicylic acid and ibuprofen.

CLASS (White *et al*, 2002)

CLASS compared the incidence of serious cardiovascular thromboembolic events in 3,987 patients randomised to celecoxib with 3,981 patients randomised to either ibuprofen or diclofenac for up to 12

months. Overall CLASS reported a similar cardiovascular risk for celecoxib versus the combined ibuprofen and naproxen group.

Acetylsalicylic acid use was allowed and results were presented for acetylsalicylic acid users and non-acetylsalicylic acid users for celecoxib, ibuprofen and diclofenac and NSAIDs.

The incidence of all serious CV thromboembolic events (cardiac, cerebrovascular or peripheral vascular events) in patients taking ibuprofen was presented for all patients and separately for patients taking ibuprofen and not taking acetylsalicylic acid, which made it possible to deduce incidence for patients using acetylsalicylic acid. The main findings were:

Table 9
Incidence of CV thromboembolic events (MI, unstable angina, fatal MI, other cardiac death, cardiac arrest/sudden cardiac death) for users of ibuprofen and diclofenac in CLASS.

	Ibuprofen 800mg tid		**Diclofenac 75mg bd**		**Celecoxib 400mg bid**	
	Number of patients	Cases (incidence)	Number of patients	Cases (incidence)	Number of patients	Cases (incidence)
CV thromboembolic events - non-users of acetylsalicylic acid	1573	7 (0.4%)	1551	16 (1.0%)	3105	25 (0.8%)
CV thromboembolic events – acetylsalicylic acid users	412	14 (3.4%)	445	12 (2.7%)	882	27 (3.06%)
CV thromboembolic events – all patients	1985	21 (1.06%)	1996	28 (1.40%)	3987	52 (1.3%)

TARGET (Faroukh *et al,* 2004)

TARGET was designed to assess the gastrointestinal safety of lumiracoxib compared with naproxen and ibuprofen, but prospective adjudication of cardiovascular events allowed for evaluation of CV safety alongside GI safety. The primary CV endpoint was incidence of the APTC endpoint of non-fatal and silent myocardial infarction, stroke, or cardiovascular death. Randomisation was stratified by age and acetylsalicylic acid use. Of 18,325 patients ≥ 50 years, 9,156 were randomised to lumiracoxib, 4,754 to naproxen and 4,415 to ibuprofen. Patients used study drugs for up to 12 months. Overall TARGET did not demonstrate any significant differences in the incidence of cardiovascular events between lumiracoxib and ibuprofen or naproxen. However, only a small number of cardiovascular events were reported in this study which limits the strength of its conclusions.

Subgroup analysis for use and non-use of acetylsalicylic acid was conducted for the incidence of the APTC endpoint, for the incidence of MI and the incidence of ischaemic events.

Table 10
Incidence of APTC endpoint or confirmed/probable MI (clinical or silent) events for users of ibuprofen and naproxen compared with lumiracoxib in TARGET

	Ibuprofen 800mg tid		Lumiracoxib 400mg od		Naproxen 500mg bd		Lumiracoxib 400mg od	
	Patients	Cases (rate per 100 patient yrs)	Patients	Cases (rate per 100 patient yrs)	Patients	Cases (rate per 100 patient yrs)	Patients	Cases (rate per 100 patient yrs)
APTC incidence Non-ASA	3431	13 (0.54)	3401	13 (0.51)	3537	14 (0.53)	3549	22 (0.8)
APTC incidence ASA	966	10 (1.48)	975	6 (1.48)	1192	13 (1.45)	1193	(2.04)
MI incidence Non-ASA	3431	5 (0.21)	3401	4 (0.16)	3537	4 (0.15)	3549	10 (0.36)
MI incidence ASA	966	2 (0.3)	975	1 (0.14)	1193	6 (0.67)	1193	8 (0.91)

Table 11
Incidence of ischaemic events for users of ibuprofen and naproxen in TARGET

	Ibuprofen 800mg tid		Lumiracoxib 400mg od		Naproxen 50mg bd		Lumiracoxib 400mg od	
	Patients	Cases (incidence)	Patients	Cases (incidence)	Patients	Cases (incidence)	Patients	Cases (incidence)
Ischaemic events – non-ASA	3431	12 (0.35%)	3401	13 (0.38%)	3537	15 (0.42%)	3549	21 (0.59%)
Ischaemic events - ASA	966	9 (0.93%)	975	9 (0.92%)	1193	15 (1.25%)	1192	20 (1.68%)

The data from TARGET were not suggestive of an interaction with acetylsalicylic acid specific to ibuprofen; in users of both naproxen and ibuprofen, the rates of the APTC endpoint and ischaemic events are approximately 3 times higher for patients taking acetylsalicylic acid that those not taking acetylsalicylic acid. These data contrast with findings in CLASS, where the number of CV thromboembolic events is approximately 8-10 times higher for ibuprofen users taking acetylsalicylic acid than those not taking acetylsalicylic acid. The number of events in both studies is very small, however, and it is difficult to establish a clear increase in thrombotic risk for ibuprofen and acetylsalicylic acid compared with ibuprofen alone based on such small numbers.

A total of eight epidemiological studies reporting on a possible interaction between acetylsalicylic acid and ibuprofen were previously considered by PhVWP; all were identified from the published literature. In addition a meta-analysis of observational studies which reported on a possible interaction between acetylsalicylic acid and ibuprofen was considered. The table below provides an overview of these studies. These studies showed a range of outcomes, with one study showing a significantly increased risk of thrombotic events with ibuprofen and acetylsalicylic acid, some a non-significantly increased risk of thrombotic events with ibuprofen and acetylsalicylic acid, some showing no effect and one showing a significant protective effect. The study by MacDonald and Wei, 2003 which showed a statistically significant increased risk suffered a number of limitations, such as relatively small sample sizes and incomplete correction for risk factors (e.g. smoking, BMI, family history) or different doses. Overall, the studies evaluated did not allow firm conclusions to be drawn about the effect of ibuprofen on the protective effect of acetylsalicylic acid, but a decrease of the effect of acetylsalicylic acid by ibuprofen could not be excluded.

Table 12
Summary of observational studies reporting a potential interaction between acetylsalicylic acid (ASA) and ibuprofen (IBU) considered previously by PhVWP

Author (Publication year)	Source population	Study design	Age group (years)	Outcome definition	Exposure definition	Comparator group	Inclusion/ exclusion criteria	Time period	Estimate for risk of cardiovascular events
Curtis (2003)	Medicare	Retrospective cohort	≥65	Death	ASA + IBU on discharge	ASA only	Patients with MI, no repeat admissions, no terminal illness	1994-1996	0.84 (0.70-1.01)
Fischer (2005)	GPRD	Nested case control	≤89	First MI	ASA + IBU on index date/ ASA only	Non users	No Hx MI	1995-2001	0.69 (0.42-1.15) 0.87 (0.75-1.00)◇
Garcia Rodriguez (2004)	GPRD	Nested case control	50-84	Acute MI hospitalization, CHD death	ASA + IBU in 30 days before index date	ASA only	No Hx cancer	1997-2000	1.08 (0.74-1.58)
Hippisley-Cox (2005)	QRESEARCH	Nested case control	25-100	First MI	No information provided, stated only that a 2-way interaction was examined between aspirin & specific NSAIDs and CHD		No Hx MI	2000-2004	No significant interaction
Hudson (2005)	Hospital discharge database, Quebec	Retrospective cohort	≥66	Recurrent MI	ASA + IBU in 1yr after initial MI‡	ASA only	Patients with recent new MI	1992-1999	1.01 (0.58-1.76) 1.13 (0.54-2.38) 1.83 (0.76-4.42)‡
Kimmel (2004)	Hospitals in Philadelphia	Case control	40-75	First MI hospitalisation	ASA + IBU in week before index date†	ASA only	No Hx MI	1998-2001	1.01 (0.47-2.20) 0.60 (0.21-1.66) 2.03 (0.60-6.84)†
MacDonald (2003)	MEMO	Cohort	Any	Cardiovascular mortality	ASA + IBU on discharge	ASA only	Discharged with cardiovascular disease, survival ≥1 month	1989-1997	1.73 (1.05-2.84)
Patel (2004)	Durham Veterans Affairs	Case control	Any	MI	ASA + IBU in month before index date	ASA only	None	1990-2000	0.61 (0.50-0.73)
Hernandez-Diaz (2006)	Observational studies	Meta-analysis	Any	First MI	ASA + IBU use / IBU only	Non-users	Studies that allowed ASA use/ studies that did not allow ASA use	1987-2004	1.10 (1.04-1.16) 0.88 (0.78-1.01)§

◇ Estimates refer to aspirin and ibuprofen vs non users and aspirin alone vs non users respectively
‡ Estimates refer to ever exposure, ≥30 days and ≥60 days respectively
† Estimates refer to all exposure, infrequent ibuprofen (1-3 times/week) and frequent (≥ 4 times/week) ibuprofen respectively
§ Estimates refer to studies that allowed aspirin use and those that did not allow aspirin use respectively

Finally, two published review articles were considered by PhVWP in 2008 (Corman *et al,* 2005 and MacDonald and Wei, 2006). The review by Corman *et al* (2005) concluded that there was insufficient evidence to recommend changes to the prescribing information. Although the review by MacDonald and Wei (2006) concluded that an interaction "was more likely than not" it is worth noting that these were the authors of the only study (out of the nine studies in the table above) that showed results consistent with a clinically significant interaction.

The PRAC acknowledged the outcome of the previous reviews which had concluded that overall the available platelet function studies indicate that a plausible mechanism exists whereby ibuprofen may interfere with the antiplatelet effects of acetylsalicylic acid. However, the clinical significance of the

interaction was unknown; a clinically meaningful interaction had not been convincingly demonstrated in clinical trial or epidemiological studies.

1.3.2. Presentation of new data

A summary of the new relevant data considered within the current review is presented in this section. A total of 12 publications were identified for assessment not considered in previous reviews: eight pharmacodynamic and/or pharmacokinetic studies and four epidemiological studies; no new clinical trial data reporting clinical outcomes were identified.

Pharmacodynamic (PD) and/or pharmacokinetic (PK) data

Yokoyama et al (2013) completed a series of *in vitro* studies investigating the influence of NSAIDs (ibuprofen, loxoprofen, indomethacin, diclofenac, etodolac, mefenamic acid, meloxicam, naproxen and flurbiprofen) on the antiplatelet effect of acetylsalicylic acid. The investigators added each NSAID alone, acetylsalicylic acid alone, acetylsalicylic acid before each NSAID and acetylsalicylic acid after each NSAID to platelet-rich plasma and determined the rate of collagen-induced platelet aggregation. The authors found that if ibuprofen is administered before acetylsalicylic acid it interferes with the antiplatelet effect of acetylsalicylic acid, but not if ibuprofen administration followed that of acetylsalicylic acid. The authors commented that ibuprofen binds reversibly to COX-1, while acetylsalicylic acid binds irreversibly and that the antiplatelet effect could therefore continue for the lifetime of the platelets when acetylsalicylic acid is administered before ibuprofen.

Akaji et al (2009) conducted an *in vivo* study in rats to investigate the influence of a number of NSAIDs (ibuprofen, loxoprofen sodium and etodolac) on the antiplatelet effect of acetylsalicylic acid. Acetylsalicylic acid and/or NSAIDs were administered orally at single or multiple daily doses. The authors found that single doses of ibuprofen inhibited the antiplatelet effect of acetylsalicylic acid only when administered before acetylsalicylic acid and not when administered after acetylsalicylic acid dosing. They also found that prolonged use of multiple daily doses of ibuprofen completely inhibited the antiplatelet effect of low-dose acetylsalicylic acid. The authors propose that if co-administration of NSAIDs with low-dose acetylsalicylic acid is deemed necessary, a selective COX-2 inhibitor should be used.

Gengo et al (2008) conducted an *in vivo* study in normal volunteers to measure the magnitude and duration of inhibition of platelet aggregation following doses of acetylsalicylic acid or ibuprofen alone or taken in combination. The volunteers received acetylsalicylic acid (325 mg) alone, ibuprofen (400 mg) alone and ibuprofen followed by dosing with acetylsalicylic acid 2 hours later. The authors found a significant reduction in both the magnitude and duration of acetylsalicylic acid's inhibitory effect on platelet aggregation when ibuprofen was given prior to acetylsalicylic acid administration. They also reported that during a 27-month period, a cohort of 28 patients took regular daily doses of ibuprofen or naproxen. Of these 28 patients, 18 returned for follow-up testing and none of the 18 patients demonstrated inhibition of platelet aggregation following discontinuation of the NSAID. Notably, 13 of the 18 patients (72%) had experienced a recurrent ischemic episode while taking acetylsalicylic acid and NSAIDs concomitantly. They conclude that the data suggest that ibuprofen prevents the irreversible inhibition of platelet aggregation produced by acetylsalicylic acid needed for secondary stroke prophylaxis and that the interaction can have clinical consequences for patients taking acetylsalicylic acid.

Gladding et al (2008) conducted an *in vivo* study in healthy volunteers to assess the impact of 6 commonly used NSAIDs (naproxen, ibuprofen, celecoxib, indomethacin, tiaprofenic acid and sulindac) on platelet function when given 2 hours before acetylsalicylic acid (300 mg). The study concluded that

ibuprofen, indomethacin, naproxen and tiaprofenic acid all block the antiplatelet effect of acetylsalicylic acid, while sulindac and celcoxib did not demonstrate any significant effect.

Meek et al (2012) conducted a multiple dose study in healthy volunteers to evaluate the interaction on acetylsalicylic acid's antiplatelet effect by naproxen, ibuprofen, meloxicam or etoricoxib taken 2 hours before acetylsalicylic acid over a three-day cycle. The authors found that the COX-1 affinity determines the pharmacodynamic interaction between NSAIDs and acetylsalicylic acid on the adhesion and aggregation of platelets, with ibuprofen and naproxen found to inhibit acetylsalicylic acid's antithrombotic effect, while etoricoxib and meloxicam showed no relevant change.

Saxena et al (2013) conducted an *in vitro* study to examine the interference of common NSAIDs (celecoxib, diclofenac, ibuprofen, flufenamic acid, ketorolac, naproxen, nimesulide, oxaprozin and piroxicam) with the antiplatelet activity of acetylsalicylic acid in human platelet rich plasma. The authors found that all except diclofenac and ketorolac significantly interfere with the antiplatelet activity of acetylsalicylic acid and that the interactions at the COX-1 active site are predictive of this effect.

Schuijt et al (2009) conducted an *in vivo* study in healthy volunteers to investigate whether ibuprofen (800 mg three times daily for 7 days) or diclofenac (50 mg three times daily for 7 days) taken concurrently with acetylsalicylic acid 80 mg (once daily for 7 days) influenced the inhibitory effect of acetylsalicylic acid. The study found no interference of antiplatelet effect when slow release diclofenac was co-administered, but a significant effect when immediate release ibuprofen was co-administered.

Awa et al (2012) conducted a PKPD simulation study aimed to predict the time-course of the antiplatelet effect of low-dose acetylsalicylic acid when ibuprofen is administered as a single dose or repeatedly in combination with acetylsalicylic acid at various time intervals. The authors simulated *ex vivo* platelet aggregation using a previously developed PKPD model. The antiplatelet effect of low-dose acetylsalicylic acid was predicted to be markedly reduced when ibuprofen (200 mg) was administered 1 h or less after acetylsalicylic acid, but not when it was administered more than 2 h after the administration of acetylsalicylic acid. The simulations also predicted that administration of ibuprofen up to 12 h before acetylsalicylic acid would completely abolish the antiplatelet effect of acetylsalicylic acid. The multiple dose scenario evaluated was ibuprofen 200 mg three times daily for three days on a background of continuous low-dose acetylsalicylic acid once daily. The simulations predicted no reduction in the antiplatelet effect of acetylsalicylic acid on day 1, but a reduction from day 2 with no return to the initial level until more than 3 days after discontinuation of ibuprofen.

Epidemiological data

An overview of the observational studies that were identified for further analysis is provided in the below table. None of the studies reported significant evidence of an interaction between ibuprofen and acetylsalicylic acid.

The **de Abajo et al (2014)** study was discussed earlier in this report. Low dose acetylsalicylic acid did not significantly modify the OR of non-fatal MI associated with tNSAIDs as a group (OR 1.16; 95%CI 0.83-1.62 among acetylsalicylic acid users vs 1.04; 95%CI 0.89-1.21 for non-users of acetylsalicylic acid; ROR=1.12; 95%CI 0.77-1.61) nor with any individual tNSAIDs evaluated. For ibuprofen the aOR for AMI for users of acetylsalicylic acid was 0.70 (95%CI 0.40-1.22) vs 0.94 (95%CI 0.75-1.18) for non-users of acetylsalicylic acid. The authors conclude that the data do not support a relevant interaction between tNSAIDs and low dose acetylsalicylic acid and note that for ibuprofen, this is inconsistent with results of pharmacodynamics studies but consistent with the results of other epidemiological studies.

Garcia Rodriguez et al (2008) carried out a cohort study with a nested case-control analysis using THIN (The Health Improvement Network) database. The aim was to examine the associated between the frequency, dose and duration of different NSAIDS and the risk of MI in the general population. The study identified 8,852 cases of nonfatal MI in patients 50-84 years old between 2000 and 2005. The results sub-analyses on concurrent use of acetylsalicylic acid were suggestive of a potential reduction of the beneficial effect of acetylsalicylic acid only when taken with ibuprofen, although there was substantial statistical imprecision when examining the presence of this interaction with individual NSAIDs. Overall the authors conclude that their results provide little evidence for a major effect modification of the antiplatelet effect of acetylsalicylic acid among users of NSAIDs.

Risk estimates for ibuprofen were stratified by acetylsalicylic acid use in the meta-analysis of observational studies reporting on acute MI conducted as part of the SOS Project **(Varas-Lorenzo et al, 2013)**. Based on results from 3 studies, pooled RRs (95%) for ibuprofen with or without concomitant use of acetylsalicylic acid were 1.15 (0.88-1.50) and 1.02 (0.79-1.31) respectively. These are similar to the results of the Garcia Rodriguez study using the THIN database in which the aRRs were 1.02 (0.80-1.32) and 1.22 (0.83-1.78) for ibuprofen with or without acetylsalicylic acid use, respectively.

Table 13
Summary of observational studies reporting on a potential interaction between acetylsalicylic acid (ASA) and ibuprofen (IBU) published since 2005

Author (Publication year)	Source population	Study design	Age group (yrs)	Time period	Outcome definition	Aspirin alone RR (95% CI)	Ibuprofen alone RR (95% CI)	Aspirin + Ibuprofen RR (95% CI)	P Value Interaction
de Abajo (2014)	National Primary Care, Spain	Nested case control	40-90	2001-2007	Non-fatal AMI	-	0.70 (0.40-1.22)	0.94 (0.75-1.18)	-
Garcia Rodriguez (2008)	THIN	Nested case-control	50-84	2000-2005	Incident non-fatal MI	1.04 (0.96-1.12)	1.02 (0.80-1.32)	1.22 (0.83-1.78)	0.14
Van Staa (2008)	GPRD	Retrospective cohort	≥40	1987-2006	MI	-	1.12 (1.06-1.19)	1.28 (1.16-1.40)	-
Varas-Lorenzo (2013)	Observational studies	Meta-analysis	Any	1990-2000	Acute MI	-	1.02 (0.79-1.31)	1.15 (0.88-1.50)	-

No published epidemiological studies reporting on a potential interaction between dexibuprofen and acetylsalicylic acid were identified.

The majority of the concerned marketing authorisation holders (MAHs) confirmed that they do not hold any unpublished study data regarding the possible interaction between ibuprofen and low-dose acetylsalicylic acid in addition to that already under consideration by the PRAC. However, reviews of the published literature were submitted by six ibuprofen MAHs and by one dexibuprofen MAH.

In addition, one MAH provided an unpublished study in relation to the interaction between dexibuprofen and low-dose acetylsalicylic acid. This was a double blind, randomized, parallel group, placebo controlled clinical trial of dexibuprofen effects on thromboxane TXB2 concentrations and platelet aggregation in acetylsalicylic acid-treated healthy volunteers. The study involved 72 subjects who, after 8 days of acetylsalicylic acid treatment alone, were allocated to receive 200mg dexibuprofen three times daily + 100mg acetylsalicylic acid once daily, 400mg dexibuprofen twice daily + 100mg acetylsalicylic acid once daily or placebo three times daily + 100mg acetylsalicylic acid once daily for 10 days in a balanced, randomized, cross-over design. The dexibuprofen morning dose was given 2 hours after acetylsalicylic acid. TXB2 inhibition of >90% was considered to correlate with complete inhibition of platelet aggregation. After 10 days of study treatment, placebo+acetylsalicylic acid treatment resulted in 93.93% inhibition of platelet COX-1 activity compared with baseline, as indicated

by TXB2 levels. In comparison, use of dexiburprofen+acetylsalicylic acid resulted in 88.76% and 86.81% inhibition for 200mg tid and 400mg bid dexibuprofen, respectively. It was concluded that whilst co-administration of dexibuprofen with acetylsalicylic acid resulted in inhibition below the pre-defined level of 90%, the interaction is considered to be marginal and of unknown clinical significance. Although dexibuprofen was not compared directly with racemic ibuprofen, the nature of the interaction seems to be common to all forms of ibuprofen. All the data provided by the MAHs were taken into account by the PRAC in its final conclusions.

1.3.3. Discussion

From a number of *in vivo* PK/PD studies, the PRAC was of the view that it is well substantiated that ibuprofen inhibits the antiplatelet effect of acetylsalicylic acid when it is administered concurrently or 2 hours before acetylsalicylic acid dosing. PK/PD simulations predict that this negative impact could be alleviated by dosing ibuprofen 2 hours after acetylsalicylic acid. However, the PRAC commented that it is also predicted that due to the long time-course of ibuprofen effect, after multiple ibuprofen doses, the antiplatelet effect of acetylsalicylic acid will be reduced during and for a number of days following ibuprofen cessation. There are no *in vivo* data that substantiate the positive impact of dose order (ibuprofen 2 h after acetylsalicylic acid) for single doses of ibuprofen or that dose order ceases to mitigate this effect when ibuprofen is taken regularly (e.g. three times a day). Overall, the PK/PD data suggest that the order of dosing and the use of dosing intervals may reduce the deleterious impact of ibuprofen on the antiplatelet effect of acetylsalicylic acid when ibuprofen is administered as a one off single daily dose but do not necessarily suggest that order of dosing and the dosing intervals would have any impact if individuals are taking multiple doses of ibuprofen on a daily basis. The available data would seem to question the implementation of specific dose order and time intervals, at least for low-dose acetylsalicylic acid users who are also chronic, multiple daily dose users of ibuprofen.

The PRAC was of the view that the new epidemiological data were generally of good quality and most attempted to correct for important confounding factors. However, an important limitation of healthcare databases in examining the potential interaction between ibuprofen and acetylsalicylic acid is that the exact timing of drug exposure and the extent of co-administration cannot be determined. Furthermore, exposure misclassification may also occur due to the fact that both ibuprofen and acetylsalicylic acid are widely available without prescription. The PRAC concluded that the results of these studies are consistent with the overall results of epidemiological studies considered in the previous EU-wide review of this issue.

The PRAC commented that the lack of good quality confirmatory evidence of an interaction from large clinical trials and limitations of existing epidemiology mean that it is impossible to reach firm conclusions on the clinical significance of the pharmacodynamic studies. It was noted that two large randomized controlled clinical studies are ongoing and are due to report in the near future. These are: the Standard care versus Celecoxib Outcome Trial (SCOT) study conducted in Scotland, Denmark and the Netherlands, and in which patients aged over 60 years with osteoarthritis or rheumatoid arthritis, free from established cardiovascular disease and requiring chronic NSAID therapy, are randomised to celecoxib or their previous traditional NSAID; and the US Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) trial in the US. The protocols indicate that information about concurrent exposure to acetylsalicylic acid will be collected, thus these trials may provide further useful information about the clinical significance of an interaction between ibuprofen and acetylsalicylic acid.

To conclude the PRAC was of the opinion that based on the currently available data the clinical implications of an interaction between ibuprofen and acetylsalicylic acid are still uncertain, however,

the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded.

1.4. Overall discussion and benefit/risk assessment

Regarding the cardiovascular risk with ibuprofen, the PRAC was of the opinion that clinical trial data suggest that high daily doses of ibuprofen (2400mg/day) are associated with an increased risk of cardiovascular events (MI, stroke), which may be similar to that observed with coxibs or diclofenac. The review of the updated epidemiological data confirms the findings of previous EU reviews and does not suggest that ibuprofen at low doses (≤1200mg/day) is associated with an increased risk of cardiovascular events.

The PRAC noted that there are no or limited data on the arterial thrombotic risk of ibuprofen at doses between 1200mg and 2400mg/day and so it cannot be determined exactly how the risk changes over this dosage range. However the PRAC considered that it is likely that there is a dose-dependent increase in risk with increasing doses between 1200mg and 2400mg/day.

The effect of ibuprofen treatment duration on cardiovascular risk has not been extensively studied and is therefore uncertain.

Cardiovascular risk may be higher in patients with cardiovascular disease, and high ibuprofen doses should be avoided in this population. Similarly, high daily doses should not be recommended to patients with risk factors for cardiovascular disease.

The PRAC considered that, in general terms, the current product information of ibuprofen-containing products already contains meaningful information regarding cardiovascular risks. However, the information about the use of high ibuprofen doses in certain populations with pre-existing cardiovascular disease and/or risk factors for arterial thrombotic events merits further clarification and thus updates should be made to section 4.4 and 4.8.

Although no specific data about cardiovascular risk of dexibuprofen are available, a similar cardiovascular risk to that of high-dose of ibuprofen is expected when dexibuprofen is used at equipotent doses. The MAHs widely supported the definition of dexibuprofen high dose as 50% of the high dose of ibuprofen. The PRAC concluded that dexibuprofen product information should be amended in the same way as ibuprofen product information.

Regarding the interaction between ibuprofen and acetylsalicylic acid, the PRAC was of the opinion that new pharmacodynamic and epidemiological data investigating a possible interaction between ibuprofen and acetylsalicylic acid are consistent with the conclusions of the previous EU-wide review of this issue – that whilst pharmacodynamic studies show that ibuprofen inhibits the antiplatelet effect of acetylsalicylic acid when it is administered concurrently, the clinical implications of such an interaction are still uncertain. The PRAC further concluded that the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded.

The PRAC was of the view that updates should be made to section 4.5 and 5.1 to reflect current data on the potential clinical effect of the pharmacodynamic interaction when ibuprofen is taken with acetylsalicylic acid.

There are limited available data on a potential interaction between dexibuprofen and acetylsalicylic acid. However, the results of a single pharmacodynamic study submitted by one of the MAHs in response to the PRAC questions suggest that dexibuprofen also reduces the antiplatelet effect of acetylsalicylic acid *ex vivo*. The PRAC was of the view that any updates to the ibuprofen product

information should also be applied to the product information for dexibuprofen, taking into consideration any dexibuprofen specific details, e.g equipotent dose.

The recommendation for update of the product information should be applicable to all medicinal products containing ibuprofen and dexibuprofen, regardless of maximum recommended daily dose.

Benefit/risk balance

Having noted all of the above, the PRAC concluded that the benefit-risk balance for ibuprofen and dexibuprofen containing medicinal products (systemic formulations) remains favourable subject to the agreed changes to the product information set out in Annex III of the recommendation.

1.5. Changes to the product information

The PRAC considered all available evidence and recommended the below changes to the product information for all ibuprofen and dexibuprofen containing medicinal products affected by this review.

The cardiovascular risks with high doses of ibuprofen/dexibuprofen were acknowledged and update of the content of the product information was recommended to capture the fact that patients with cardiovascular events (e.g. uncontrolled hypertension, congestive heart failure (New York Heart Association (NYHA) II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease) should only be treated with ibuprofen after careful consideration and that high doses should be avoided as well as that careful consideration should be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) particularly if high doses of ibuprofen are required.

For clarity, the addition of the corresponding class of NYHA Functional Classification in the already existing contraindication for severe heart failure (i.e. NYHA Class IV) was recommended.

Regarding the interaction with acetylsalicylic acid update of the relevant parts of the product information was recommended to reflect the message that although there are uncertainties regarding extrapolation of the available data to the clinical situation, the possibility that regular, long-term use of ibuprofen/dexibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. However, no clinically relevant effect is considered to be likely for occasional ibuprofen use.

The final agreed wording for the relevant sections of the SmPC and PL can be found in Annex III of the recommendation.

2. Overall conclusion and grounds for the recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, for ibuprofen- and dexibuprofen-containing medicinal products (systemic formulations).
- The PRAC considered the totality of the data available in relation to the cardiovascular risk of ibuprofen- and dexibuprofen-containing medicinal products and in relation to the potential interaction between ibuprofen/dexibuprofen and acetylsalicylic acid, acknowledging the conclusions from previous reviews, the submissions by marketing authorisation holders, and additional data from independent researchers.

- The PRAC considered that with regard to the arterial thrombotic risks of ibuprofen, the data available to date from randomised clinical trials, observational studies and individual epidemiological studies, including meta-analysis thereof, supports that ibuprofen at high doses (2400mg or above per day) is associated with an increased risk of arterial thrombotic events. It was observed that this risk may be similar to that of selective COX-2 inhibitors. The available data do not suggest that ibuprofen at low doses (equal to or below 1200mg per day) is associated with an increased risk of arterial thrombotic events.
- The PRAC considered that although no specific data about the cardiovascular risk of dexibuprofen are available, a similar cardiovascular risk to that of high-dose of ibuprofen is expected when dexibuprofen is used at equipotent doses.
- The PRAC considered that with regard to the interaction between ibuprofen/dexibuprofen and acetylsalicylic acid the pharmacodynamic studies available to date show that ibuprofen/dexibuprofen inhibit the antiplatelet effect of acetylsalicylic acid when it is administered concurrently. The epidemiological data available to date, however, do not demonstrate a clinically significant interaction but the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded.
- The PRAC considered that in general terms, the current product information of ibuprofen- and dexibuprofen-containing products already contains meaningful information regarding cardiovascular risks and pharmacodynamic interaction with acetylsalicylic acid. However, the PRAC concluded that information about the risks associated with the use of high doses of ibuprofen/dexibuprofen in certain populations with pre-existing cardiovascular disease and/or risk factors for arterial thrombotic events merits further clarification, as well as some additional information on the potential clinical effect of the pharmacodynamic interaction when taken with acetylsalicylic acid.

The PRAC concluded that the benefit-risk balance for ibuprofen- and dexibuprofen-containing medicinal products (systemic formulations) remains favourable subject to the agreed changes to the product information.

Therefore in accordance with Articles 31 and 32 of Directive 2001/83/EC, the PRAC recommends the variation to the terms of the marketing authorisation for all medicinal products referred to in Annex I and for which the amendments of the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III of the recommendation.

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