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Assessment report for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and cardiovascular risk

Review under Article 5(3) of **Regulation (EC) No 726/2004**

Procedure no: EMEA/H/A-5(3)/1319

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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1. Background information on the procedure

The cardiovascular (CV) safety of non-steroidal anti-inflammatory drugs (NSAIDs) has been continuously reviewed over the last years.

In 2004, concerns were raised for rofecoxib when results from clinical trials suggested an increased risk of thrombotic events. This led to the voluntary withdrawal of this product by the respective marketing authorisation holder (MAH). The withdrawal, in conjunction with post-marketing reports of serious thrombotic events for celecoxib, prompted a class review of the cardiovascular safety for all cyclo-oxigenase-2 inhibitors (coxibs) by the CHMP. The review concluded that coxibs, as a class, are associated with an increased risk of thrombotic events which is dose and duration dependent.

The focus of the review was subsequently expanded to examine data related to non-selective NSAIDs. In 2005, the CHMP concluded that NSAIDs as a class of drugs are associated with cardiorenal events which could impact negatively on the long-term cardiovascular risk for these drugs.

In 2006, in the context of a formal review for NSAIDs under Article 5(3) of Regulation (EC) No 726/2004, the CHMP reviewed clinical and epidemiological studies on the cardiovascular safety of non-selective NSAIDs[1]. The Committee concluded that the overall benefit-risk balance remained positive, but a potential increase in the absolute risk for thrombotic events could not be excluded for NSAIDs as a class, especially when used at high-doses and for long-term treatment. In particular, the review suggested that the overall thrombotic risk for diclofenac (150mg daily) could be of the same magnitude as perceived for the cyclo-oxygenase-2 (Cox-2) inhibitors (also referred as coxibs), and that diclofenac, particularly at high dose (150mg daily), could be associated with an increased risk of arterial thrombotic events (for example myocardial infarction (MI) or stroke). Regarding ketorolac, no new data had emerged at the time of the previous review. The Committee noted that the data was still insufficient to conclude on thrombotic risk for indomethacin.

Further epidemiological studies were needed to obtain additional data on pertinent safety aspects of NSAIDs and therefore the Agency recommended in 2006 that the European Commission fund an independent epidemiological study to further explore the risk of gastrointestinal and cardiovascular toxicity of these medicines. Since 2006, a number of new studies on the cardiovascular safety of NSAIDs have been published. In addition, results from the independent research project 'safety of non-steroidal anti-inflammatory drugs' (SOS) funded by the European Commission under the Seventh Framework Programme to evaluate the safety of NSAIDs, have also become available.

In view of the availability of new data, on 19 October 2011 the Medicines and Healthcare Regulatory Agency (MHRA) requested the CHMP, in accordance with Article 5(3) of Regulation (EC) No 726/2004, to give its opinion on the cardiovascular risks of non-selective NSAIDs.

2. Scientific discussion

2.1. Introduction

Non-selective non-steroidal anti-inflammatory drugs are indicated in the relief of all grades of pain and inflammation in a wide range of conditions, including arthritic conditions, acute musculo-skeletal disorders and other painful conditions resulting from trauma. The adverse event profile of NSAIDs, including Cox-2 inhibitors, is known. Gastrointestinal adverse events, including serious events of PUB (perforation, ulcer, bleeding) are one main reason for discontinuation of treatment with NSAIDs. Other events such as hypersensitivity or skin reactions, cardiorenal effects and hepatotoxicity are class effects, although the exact incidence may vary between products.

[1] The 2006 opinion of the Committee can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/01/WC500054342.pdf. The assessment report can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500054344.pdf.

Epidemiological and clinical trial data were previously considered by the CHMP. In the 2006 review the Committee concluded that a small increase in the absolute risk of thrombotic events could not be excluded for NSAIDs as a class, especially when used at high-doses and long-term therapy. Further epidemiological studies were needed to obtain additional data on pertinent safety aspects of NSAIDs. The present review focus on the cardiovascular safety of NSAIDs and the data that became available since the previous review. An overview of the published evidence from meta-analysis of clinical trials and observational studies, and also epidemiological studies, available to date was considered for the assessment. Only relevant information for the discussion is presented hereinafter and therefore only the corresponding references are included in the text. For a full list of references please see section 5. Of note, as with the data reviewed previously by CHMP, most of the evidence on thrombotic risks from newly available studies relate to naproxen, ibuprofen and diclofenac.

2.2. Meta-analysis of clinical trials

Chen and Ashcroft (2007)[14]

The risk of myocardial infarction associated with various coxibs and NSAIDs was investigated in a meta-analysis of randomised controlled trials conducted by Chen and Ashcroft. This study was similar to the meta-analysis by Kearney et al (2006)[32], but reported only on the risk of myocardial infarction and excluded trials with no events. In addition, the trials included in the two meta-analyses were different. The most noticeable differences were the omission of the MEDAL programme results[2] in the analysis by Chen and Ashcroft (only the EDGE component of the programme was included) and the relatively small number of trials including ibuprofen (6 compared to 24 in the Kearney study), which might have resulted in the slightly higher risk for ibuprofen reported in this study. Both meta-analyses included trials of varying durations (in this case between 4-208 weeks) and differing doses which were conducted in a number of different indications.

The study pooled the events observed in the coxibs treatment arms which while increasing statistical power also assumes in the interpretation of the results that the effects of coxibs are similar which might not be the case. The different doses of NSAIDs/coxibs employed in the various studies were not taken into account in the analysis. Heterogeneity between trials was not detected with the tests performed for any of the pooled comparisons included in the analysis.
Coxibs were associated with a statistical significant increased risk of myocardial infarction compared to placebo, OR, 95%CI: 1.46 (1.02-2.09), even though comparisons of individual coxibs (except celecoxib at doses higher than 200mg) with placebo did not reach statistical significance.

[2] For more details on the MEDAL programme, including the EDGE component please refer to the previous CHMP opinion at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/01/WC500054342.pdf. The assessment report can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500054344.pdf.

The results from the coxibs pooled analysis compared to individual NSAIDs are shown below.

Table 1
Risk of myocardial infarction of coxibs compared to individual NSAIDs in the Chen and Ashcroft meta-analysis

OR (95% CI) Coxib vs			
Naproxen	**Ibuprofen**	**Diclofenac**	**Non-naproxen**
1.93 (1.22-3.05)	1.29 (0.65-2.59)	1.06 (0.70-1.62)	1.16 (0.80-1.66)

Pair-wise comparisons of individual drugs were also calculated but the only statistical significant differences observed were for rofecoxib compared to naproxen: OR, 95% CI: 5.39 (2.08, 14.02) and for valdecoxib compared to diclofenac OR, 95% CI: 0.14 (0.03, 0.73). However, these individual comparisons are limited by the small number of events, e.g. one event in the valdecoxib arm in the valdecoxib-diclofenac trials and should be interpreted with caution.

Trelle et al (2011)[59]

The study investigated the cardiovascular safety of NSAIDs using a network meta-analysis approach. All large randomised controlled trials (defined as trials with at least 100 patient years of follow up) which compared NSAIDs against each other, paracetamol or against placebo were included in this study. Trials in patients with cancer were excluded from the analysis.

The pre-specified primary endpoint was myocardial infarction (fatal and non-fatal), but only studies reporting a minimum of 10 events in the active arm of all eligible trials were included in the analysis. Secondary outcomes were haemorrhagic or ischaemic fatal or non-fatal stroke; cardiovascular death; death of unknown cause; death from any cause and the Antiplatelet Trialists' Collaboration composite outcome (APTC) of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. Etoricoxib and diclofenac had the longest number of patient year follow up, greater than 26 000 patient years (largely due to inclusion of the MEDAL study), and ibuprofen the lowest, with approximately 4800 patient years. Drugs were taken for at least one year in the majority of trials, however a number of relatively short trials were also included (duration between 12-14 weeks).

The main results from the study are presented in the table below:

Table 2
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*

The design of the study also allowed for pair-wise comparisons between two NSAIDs. Statistical heterogeneity across the comparisons performed was generally low with the exception of myocardial infarction (τ^2, 95%CI: 0.12, 0-0.79). However, the authors noted that heterogeneity could not be

excluded given the low number of events. This is also reflected in the reported confidence intervals which for most drug-event combination are quite wide, especially for myocardial infarction (n=554 across all trials), stroke (377), cardiovascular death (312) and all-cause mortality (676). The uncertainty over the Antiplatelet Trialists' Collaboration composite endpoint is smaller but is limited by the fact that it included non-thrombotic events. The authors also considered that the results of their analysis was limited by the quality of available information on the individual trials, noting that not all events were adjudicated and that the number of events in certain trials was not consistently reported in all the available sources of information.

2.3. Meta-analysis of observational studies

Varas-Lorenzo et al (2011)[63]

The Varas-Lorenzo et al meta-analysis of observational studies considered observational cohort or case-control studies published in English in peer-reviewed journals between January 1st 1990 and November 30th 2008. Studies were included in the meta-analysis if they provided a measure of association of the risk of acute ischaemic and/or haemorrhagic stroke between users of individual NSAIDs and non-NSAID users. Of the 3,203 articles identified, only 75 met the inclusion criteria for study design or study medication. However, most of these studies did not contain sufficient data to calculate measures of association for individual NSAIDs or investigated cardiovascular endpoints other than stroke, and so only 6 studies were included in the meta-analysis for stroke. Data from one of these studies by *Solomon et al*[30], have been considered by the CHMP in the past during the cardiovascular review of NSAIDs.

Odds ratios (OR) from case-control studies and relative risks (RR) from cohort studies were pooled to provide RR of stroke and 95% confidence intervals (CI) for incident and recurrent cases combined, incident cases only and for all users (prevalent and new) of NSAIDs combined as well as for new users of NSAIDs. Both random and fixed effect models were used in the meta-analysis but forest plots were constructed based on the random effect model. The relative risk for stroke as reported for each individual NSAID for the studies included in the meta-analysis is summarised below:

Table 3
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

The authors of the meta-analysis calculated the pooled RR and 95%CI for all types of strokes using data from all analysed studies associated with individual NSAIDs relative to no use. Relative risks were also provided for incident stroke from the four studies that provided this type of information[3,5,26,48] and for ischaemic stroke from studies which distinguished between ischaemic and haemorrhagic stroke[3,5,26,53]. Data from this analysis are summarised in the table below, showing results for the random effects model (the fixed effects models yielded very similar results).

Table 4
Pooled Relative Risk (RR) of stroke, incident stroke and ischaemic stroke associated with various NSAIDs and coxibs, compared to no NSAID use, adapted from *Varas-Lorenzo et al*

RR (95% CI)				
Naproxen	**Ibuprofen**	**Diclofenac**	**Celecoxib**	**Rofecoxib**
Stroke				
1.19 (0.85-1.65)	1.15 (0.95-1.39)	1.17 (0.98-1.40)	1.08 (0.93-1.25)	**1.70 (1.25-2.31)**
Incident stroke				
1.14 (0.76-1.69)	1.10 (0.89-1.36)	**1.27 (1.08-1.48)**	1.04 (0.90-1.21)	**1.64 (1.15-2.33)**
Ischaemic stroke				
1.05 (0.71-1.55)	1.10 (0.95-1.27)	1.20 (0.99-1.45)	-	**1.82 (1.09-3.04)**

Only the heterogeneity analysis for the diclofenac results (and for ibuprofen for ischaemic stroke) did not show statistical significant heterogeneity (p-value <0.10) for stroke, incident stroke and ischaemic stroke. For all other NSAIDs and coxibs the test indicated that the results were statistically heterogeneous. A sensitivity analysis was performed to reduce heterogeneity by removing the study that reported high RR for naproxen[15], but these results were not presented as exclusion of this study did not resolve heterogeneity. Removal of the study which included only men and which had the longest window of exposure to define current use[1], reduced heterogeneity (data not shown) and only the RR for rofecoxib was presented (RR, 95%CI: **1.32, 1.07-1.62**) without however specifying if this result referred to incident, ischaemic or all strokes.

A number of important limitations in the study by *Varas-Lorenzo et al* need to be considered. The comparison between NSAID users versus non-NSAID users is quite possibly subject to significant confounding which cannot be adjusted for by logistic regression. Information on over the counter medication relevant to the issue, especially aspirin and ibuprofen is lacking. There was significant heterogeneity between the studies, especially with regards to naproxen and rofecoxib. This study also did not provide any information on the effect of dose and treatment duration on the possible association with stroke as this was provided only in 2 of the studies[3,48] included in the meta-analysis.

McGettigan and Henry (2006, 2011)[38,39]

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 respectively. 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. As the first meta-analysis included studies that have been considered during the previous CHMP review, details of the most recent meta-analysis are presented in this report.

Eligible studies in the second meta-analysis were cohort or case-control studies published between 1st January 1985 and November 30th 2010. All major electronic databases were searched using the generic names of individual drugs, therapeutic classes and modes of action, cardiovascular and cerebrovascular events with no language restrictions. This search identified 5,391 potentially relevant titles. Following screening to exclude non observational studies, duplicate entries, studies not reporting cardiovascular outcomes and studies with no data on individual NSAIDs, 51 studies were included in the analysis: 30 case control studies and 21 cohort studies (of these, 18 case control and 6 cohort studies had been included in the first meta-analysis by the same authors). The most commonly reported outcome in the included studies was acute myocardial infarction; however some studies reported on the risks of coronary heart disease–related death or a composite of myocardial infarction and coronary heart disease death; a minority reported on stroke only.

Current NSAID use was defined as within a week or less of the index day. The authors noted that important variables not adjusted for in the majority of the studies were the use of aspirin and over the counter use of NSAIDs, smoking, alcohol consumption and body mass index. The main results of the study, including patient exposure per drug and studies per drug are summarised in the table below.

Table 5
Summary of studies included in the meta-analysis by McGettigan and Henry, patient exposure per drug and the estimated pooled relative risk of cardioavascular events for individual drugs compared to non-use or remote use[39]

Drug	Case-Control Studies		Cohort Studies		Total Number of Studies	Pooled RR (95% CI)
	Number of Studies	Number of Exposed Cases/ Controls	Number of Studies	Number of Person-Years of Exposure		
Naproxen	24	3,103/24,468	17	159,824	41	1.09 (1.02, 1.16)
Ibuprofen	21	5,716/37,207	17	255,621	38	1.18 (1.11, 1.25)
Celecoxib	20	1,496/12,755	15	179,479	35	1.17 (1.08, 1.27)
Rofecoxib	19	1,662/10,827	15	126,219	34	1.45 (1.33, 1.59)
Diclofenac	16	3,181/13,523	13	50,736	29	1.40 (1.27, 1.55)
Indomethacin	11	788/4,406	3	9,350	14	1.30 (1.19, 1.41)
Piroxicam	7	288/1,216	1	0[a]	8	1.08 (0.91, 1.30)
Meloxicam	6	240/714	1	0[a]	7	1.20 (1.07, 1.33)
Etodolac	4	464/4,115	1	8,994	5	1.55 (1.28, 1.87)
Etoricoxib	4	60/116	0	0	4	2.05 (1.45, 2.88)
Valdecoxib	1	2/2	4	5,629	5	1.05 (0.81, 1.36)

Where possible the authors also conducted an analysis for the dose effect. 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 1,200mg/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, ≥750mg/day in four studies and >1000mg/day in 4 studies). The effect of dose on the cardiovascular risk for these drugs is summarised in the table below. 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 and Henry[39]

	RR (95%CI)	p for trend	No of studies	Cochrane Q, p-value
≤ 25 mg/d **Rofecoxib**	**1.37 (1.20-2.17)**	**0.0008**	16	71.8, <0.0001
> 25mg/d	**2.17 (1.59-2.97)**			80.7, <0.0001
≤ 200 mg/d **Celecoxib**	**1.26 (1.09-1.47)**	0.197	11	33.7, 0.0008
> 200 mg/d	**1.69 (1.11-2.57)**			119.9, <0.0001
Low **Ibuprofen**	1.05 (0.96-1.15)	**0.0004**	11	43.3, <0.0001
High	**1.78 (1.35-2.34)**			221.4, <0.0001
Low **Naproxen**	0.97 (0.87-1.08)	0.433	10	**11.7, 0.4**
High	1.05 (0.87-1.24)			**29.4, 0058**
Low **Diclofenac**	**1.22 (1.12-1.33)**	**0.009**	10	**16.3, 0.1786**
High	**1.98 (1.40-2.82)**			437.5, <0.0001

It is also important to note (and acknowledged by the authors) that significant heterogeneity ($I^2 \geq 50\%$) was detected between the included trials for most of the drugs analysed. This was especially true for the most extensively studied drugs (defined as included in 10 or more studies). The explanation offered by the authors was that this was due to the fact that the individual relative risks for these drugs were more precise compared to the less studied drugs resulting in significant heterogeneity even though the differences of the estimates between studies were relatively small.

A similar analysis was performed for these drugs in high and low risk populations based on definitions from the individual studies. The authors suggested that high risk patients in general "had experienced prior ischaemic events" without providing further details. No statistical significant difference in the risk of cardiovascular events between the high and low risk populations was found for any of the drugs investigated.

In order to account for possible differential effect of treatments across different studies, additional analyses were performed by the authors by carrying out a series of pair-wise comparisons of drugs that had been included in some studies. A ratio of the relative risks (RRR) for myocardial infarction and their corresponding 99% CI were calculated for selective pairs (see below).

Table 7
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[39]

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

Emboldened results indicate significance at p <0.0033

This meta-analysis of observational studies includes all the important studies published on this issue until December 2010. The authors have also presented and analysed as thoroughly as possible the effects of the dose on the cardiovascular risks highlighting the limitations of the available data, primarily due to the heterogeneity of the included studies. However, the study reported the risks on "major cardiovascular events" rather than more specific endpoints. The authors stated that the most commonly reported outcome in the included studies was acute myocardial infarction but that some studies also reported on cardiovascular death, stroke or a composite endpoint of cardiovascular death and myocardial infarction. The pooled relative risks were based on different outcomes, and this approach limits the validity of the overall results. Nevertheless, this limitation does not apply to the pair-wise comparison of individual drugs which focused on the risk of myocardial infarction. On the other hand it is worth pointing out that some of these comparisons were based on a relatively small number of studies and limited drug exposure (e.g. the etoricoxib comparisons).

2.4. Individual epidemiological studies

A number of case-control and cohort studies have been published since the last cardiovascular review of NSAIDs. A brief summary of these studies are presented in this section.

Case-control studies

Ten case-control studies have been published since 2006. The results of these studies for the primary endpoints are summarised in the tables below, however it should be noted that a number of studies reported on more than one endpoint or included additional analyses (e.g. subpopulation or dose effect analysis). The main disadvantage of these studies is the exposure classification. The majority of the studies reported on the risk of myocardial infarction, but ischaemic stroke and acute coronary syndrome was the selected endpoint in some studies. Inability to adjust for over the counter aspirin and NSAID use was recognised by most investigators as a potential problem in the reported results. As has been the case in the past, the most common NSAIDs included in these studies were naproxen, ibuprofen and diclofenac but a few studies also included indomethacin (4 studies) and etodolac (3 studies). Drugs such as nabumetone, piroxicam and suldinac were included only in one study. A summary of the data for each individual NSAID from these studies is presented below.

Ibuprofen

Of the 7 case-control studies including ibuprofen, a statistical significant increase in the risk of cardiovascular events was reported in 2 studies[33,60]. Of particular interest is the study by *Lee et al*[33], which included 2 cohort populations: one with pre-existing coronary artery diseases and one without. The results in the table below are for patients without a history of coronary artery disease in which ibuprofen was associated with a modest increase in the composite risk of cardiovascular and cerebrovascular events, but not individually with cardiovascular or cerebrovascular events. Interestingly, in patients with a history of coronary artery disease, ibuprofen was the only one of the included drugs in this study to be associated with a statistical significant increase in the composite risk of cardiovascular and cerebrovascular events (OR, 95% CI: 1.27 (1.15-1.42)), and this appeared to be driven by an increased risk for cardiovascular events (OR, 95% CI: 1.45(1.26-1.67)).

Diclofenac

Results on diclofenac were reported in 7 studies. A statistical significant association between an increased risk of cardiovascular events and diclofenac use was reported in 4 studies, but it should be noted that in 2 further studies[11,13], the lower end of the reported 95%CI for diclofenac approached unity (0.98 and 0.99 respectively). The other study in which diclofenac was not associated with a statistical significant increased risk[62], failed to demonstrate an increased risk for any of the included drugs (including rofecoxib). Only the results for naproxen in that study approached statistical significance (lower end of 95% CI: 0.98) which contradicts results from all other sources.

Naproxen

Naproxen, as has been suggested by previous studies is most likely to be associated with the least cardiovascular risks of the 3 most commonly used NSAIDs. Nine studies reported on naproxen, which was found to be associated with a statistical significant increased risk in 2 studies[,13,33]. In the study by *Cheetam et al*[13], the statistical significance was borderline (OR, 95% CI: 1.14 (1.00-1.30)) and the authors of the study acknowledged that possible unmeasured confounding could have an effect on the reported excessive risk and the level of significance. The results by *Lee et al*[33], showed an increased risk in both cardiovascular (OR, 95%CI: 1.21(1.04-1.40)) and cerebrovascular events (OR, 95%CI: 1.15 (1.01-1.31)) in patients without relevant medical history, and a similar increase in the risk of cerebrovascular events only in patients with prior history of coronary artery disease (OR, 95%CI: 1.20 (1.01-1.43)).

Other NSAIDs

Of the other, less commonly used NSAIDs, indomethacin and etodolac were associated with statistical significant increases in one study each. In both of these studies[13,33], naproxen was reported to be one of the drugs associated with the highest risks. It would therefore be difficult to reach conclusions regarding the risks associated with these drugs from these results alone.

Cox-2 Inhibitors

Of the selective Cox-2 inhibitors, celecoxib and rofecoxib were the ones most commonly included in these studies (10 and 9 studies respectively). Celecoxib was associated with a statistical significant increase in 3 of those studies, and in two of these the reported risk was the highest amongst all

included drugs[11,60]. However, in one of these[11] the magnitude of the reported risk and the very wide confidence intervals (OR, 95% CI: 4.96 (1.09-22.47)) cast some doubt about the validity of this result. Rofecoxib was associated with a statistical significant increase in 5 studies, while doses over 25mg were also associated with a significant increase in the risk in one more study. In most of these studies the reported risk with rofecoxib was amongst the highest compared to the other drugs investigated in the studies. Finally, etoricoxib was included only in one study[3] and was found to be associated with the highest risk of the drugs included. However, the number of cases for etroricoxib in this study (10) was considerably lower than those for any of the other drugs.

Effect of dose effect and degree of Cox-2 inhibition on cardiovascular risk

An interesting analysis was conducted by Garcia-Rodriguez[21] on the effect of the administered NSAID dose and degree of Cox-2 inhibition and the reported cardiovascular risk. This analysis showed a dose-response effect for diclofenac (p for trend <0.0001) with a statistical significant risk for myocardial infarction in patients receiving 100mg/day (OR: 95% CI: 1.65, 1.26-2.18) or 150mg/day (OR: 95% CI: 1.80, 1.49-2.18). For patients receiving lower doses the risk did not reach statistical significance (50mg/day, OR 95% CI: 1.12, 0.57-2.19 and 75mg/day OR, 95%CI: 1.31, 0.8-2.16).

The authors also reported a statistically significant correlation (r^2=0.7458, p= 0.0027) between the degree of inhibition of whole blood Cox-2 *in vitro* produced by average circulating therapeutic concentrations and the relative risk of MI associated with individual NSAIDs. Grouping individual NSAIDs with a degree of Cox-2 inhibition <90% at therapeutic dose (ibuprofen, meloxicam, celecoxib, and etoricoxib), users of these NSAIDs presented an RR of 1.18 (95% CI: 1.02 to 1.38), whereas users of rofecoxib, indomethacin, diclofenac, and piroxicam (Cox-2 inhibition ≥90%) had an RR of 1.60 (95% CI: 1.41 to 1.81, p for interaction=0.01). Naproxen was excluded from this analysis as it was considered that it significantly inhibits platelet function.

Table 8
Summary of new case-control studies published since the last CHMP review reporting on cardiovascular risk of NSAIDs and coxibs

Study	Endpoints	Cases/controls (n)	Non-adjusted factors	OR 95%CI)
Mc Gettigan[37]	Non-fatal MI Unstable angina	328/478 Patients admitted to 3 Australian hospitals with diagnosis of ACS (cases) or other acute conditions (ctrls)	BMI	Acute coronary syndrome Celecoxib: 1.11 (0.59-2.11) Rofecoxib: 0.63 (0.31-1.28)
Andershon[3]	Ischaemic stroke	3094/11859 Nested case-control within UK GPRD with at least 1 prescription for NSAID	Prescribed aspirin use, OTC NSAID/aspirin, lifestyle factors; socio-economic status	**Rofecoxib: 1.71 (1.33-2.18)** **Etroricoxib: 2.38 (1.10-5.13)** Celecoxib: 1.07 (0.79-1.44) **Diclofenac: 1.32 (1.10-1.57)** Ibuprofen: 1.12 (0.91-1.37) Naproxen:1.16 (0.80-1.70)
Suissa[58]	First MI	558*/5580 *Only 82 cases for NSAIDs Nested case-control within a cohort of patients with RA from a US claims database	OTC aspirin /NSAIDs, smoking, alcohol	Rofecoxib: 1.26 (0.89-1.80) Celecoxib: 1.03 (0.75-1.40) Naproxen:0.98 (0.59-1.64)
Brophy[10]	MI	3423/68456 Nested case-control of elderly patients treated with NSAIDs from health databases in Quebec.	Intermittent NSAID use, OTC aspirin or NSAIDs, smoking, alcohol, BMI, socio-economic status	**Rofecoxib: 1.28 (1.10-1.49)** Celecoxib: 1.08 (0.94-1.25) Naproxen: 1.24 (0.83-1.84) Meloxicam: 0.78 (0.36-1.68)
Lee[33]	Non-fatal cardio- or cerebrovascular event	28781/32675 Nested case control in patients with a diagnosis of osteoarthrits within US Veteran Health Administration	OTC aspirin /NSAIDs	**Rofecoxib: 1.32 (1.04-1.67)** Celecoxib: 0.91 (0.69-1.22) **Diclofenac: 1.32 (1.08-1.62)** **Ibuprofen: 1.11 (1.02-1.22)** **Naproxen: 1.18 (1.07-1.30)** **Etodolac: 1.33 (1.10-1.62)** Indomethacin: 1.11 (0.89-1.39)
Cheetam[13]	Acute MI	8143/31496 Nested case-control within a US health care organization with at least one prescription for a NSAID.	Prescribed aspirin, OTC aspirin /NSAIDs, smoking, alcohol, BMI, socio-economic status:	Rofecoxib: ≤ 25 mg: 1.23 (0.89-1.74) **>25 mg: 3.01 (1.10-8.31)** Celecoxib: 0.87 (0.69-1.08) Diclofenac: 1.72 (0.98-3.01) Ibuprofen: 1.08 (0.97-1.20) **Naproxen: 1.14 (1.00-1.30)** Etodolac: 1.34 (0.91-1.98) **Indomethacin: 1.27 (1.04-1.56)**
Garcia-Rodriguez[21]	Non-fatal MI	8852/20000 Nested case-control within UK THIN database with a diagnosis of MI	OTC aspirin /NSAIDs, alcohol	**Rofecoxib: 1.46 (1.10-1.92)** **Celecoxib: 1.33 (1.00-1.77)** **Diclofenac:1.67 (1.44-1.94)** Ibuprofen:1.06 (0.86-1.30) Naproxen: 1.04 (0.74-1.45) Etodolac:1.32 (0.69-2.5) Indomethacin: 1.47 (0.90-2.41) Meloxicam: 1.30 (0.90-1.82)

Van der Linden[60]	Acute MI	2165/8653 Nested case-control within the PHARMO linkage system in the Netherlands	OTC aspirin/ NSAIDs, smoking, alcohol, BMI, socio-economic status	**Celecoxib :2.53 (1.53 -4.18),** **Rofecoxib: 1.60 (1.22 -2.10)** **Ibuprofen: 1.56, (1.19 -2.05)** **Diclofenac 1.51 (1.22 -1.87)** Naproxen: 1.21 (0.87-1.68)
Varas-Lorenzo[62]	MI, CV death	3252/20002 Nested case-control of patients aged 40-84 enrolled in Saskatchewan Health Canada	Prescribed aspirin, OTC aspirin /NSAIDs, smoking, alcohol	**MI/CHD** Rofecoxib: 1.32 (0.91-1.91) Celecoxib: 1.11 (0.84-1.47) Diclofenac: 1.02 (0.75-1.38) Ibuprofen: 1.59 (0.88-2.89) Naproxen: 1.57 (0.98-2.52) Indomethacin: 1.34 (0.81-2.19)
Bueno[11]	Acute coronary syndrome	2954/2954 Patients admitted with ACS (cases) in a set of Spanish hospitals and patients visitors (controls).	Alcohol	Diclofenac: 1.56 (0.99-2.45) Ibuprofen: 0.88 (0.68-1.14) Naproxen: 1.30 (0.60-2.82) **Celecoxib:4.96 (1.09-22.47)**

MI: myocardial infarction; CV: cardiovascular; OTC: over the counter, ACS: acute coronary syndrome, CHD: coronary heart disease

Cohort studies

Fifteen cohort studies were identified for inclusion in this review. One of these studies by *Schjerning Olsen et al*[49] is discussed separately as the reported results for individual NSAIDs were stratified by treatment duration. Another study by *Rahme et al*[45] is not further discussed as the only identified reference group was the mixed ibuprofen/diclofenac use which makes interpretation of results very difficult. The tables below provide summaries of the identified retrospective (n=11) and prospective (n=2) cohort studies. Not all results are included as most studies reported results on more than one endpoint while some studies had additional analyses on sub-populations within the study cohort.

Despite the retrospective nature of most of these studies, exposure misclassification is expected to be less problematic compared to the case-control studies, as they were based on databases with good exposure information (Danish national prescription registries [19,20,22,23] or the UK GPRD[61]).

All of the studies included results on individual NSAIDs. As with the case-control studies, the NSAIDs included most commonly were naproxen, ibuprofen and diclofenac but a few studies also included indomethacin, etodolac, nabumetone and meloxicam.

The majority of the studies reported on various composite endpoints which included MI or death, but others reported on recurrent MI, stroke, and out-of-hospital cardiovascular death either as single endpoints or as composites in various combinations.

The patient population examined also differed between the studies. Some examined healthy individuals whilst others looked at specific patient populations including those with osteoarthritis, heart failure or those with previous MI. Other populations were defined by the database used; for example many of the studies using US databases were conducted in frail elderly and/or disabled subjects.

Finally the control/reference groups also varied between studies which adds further complexity to the pooling or direct comparison of data. Most of the better designed studies used non-users of NSAIDs as the reference group; other reference groups included users of other medication (e.g. for glaucoma and thryroid hormones), other NSAIDs (e.g. naproxen), or non-chronically exposed users of NSAIDs (not further defined in the paper).

A summary of the data for each individual NSAID is provided below.

Ibuprofen

All but one of the cohort studies included data on ibuprofen. The results for ibuprofen are inconsistent. Only three of these studies[1,20,22] report an increased risk for any use of ibuprofen for the primary endpoints even though an increased risk is reported in other study for high dose ibuprofen or secondary endpoints. Two of the three studies showing an increased risk for ibuprofen were based on Danish national registries[20,22] which have some advantages compared to other cohort studies included in this section. Selection bias and over the counter 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 in Denmark.

Diclofenac

Results on diclofenac were reported in 12 studies (including both prospective cohort studies) and were associated with a trend for increased risk of the primary cardiovascular endpoint in six of these studies. In five other the risks for other endpoints or the association with high dose diclofenac was also statistically significant. Diclofenac was associated with increased risks in all four studies utilising the Danish national registries[19,20,22,61]. In addition the reported risks in those studies was comparable to that of Cox-2 specific inhibitors, and in one study[44] was associated with the highest risk of death compared to all the drugs investigated.

Naproxen

Results on naproxen are provided in 13/14 studies. An increase in CV risk associated with the use of naproxen was reported in two of these studies (1 retrospective one prospective)[23,26]

The results of the *Haag study*[26] are particularly unusual in that they show an increased risk of stroke with naproxen compared to ibuprofen and diclofenac. However, the reported magnitude of risk for rofecoxib (HR: 5.56) is considerably higher than that reported in any other published study and confidence intervals (for both reofecoxib and naproxen) are quite wide, indicating increased uncertainty over the reported results.

Other NSAIDs
Of the other less commonly used NSAIDs, indomethacin, etodolac, and nabumetone were associated with statistical significant increase in cardiovascular risk in some studies.

Results on etodolac were reported in one retrospective cohort study[1] and were shown to have a statistically significant increased risk of acute myocardial infarction and stroke compared to naproxen. This was also the only study in which results on nabumetone were reported, which was associated with a statistically significant increased risk for myocardial infarction but not for stroke compared to naproxen.

Results on indomethacin were reported in three retrospective cohort studies[47,48,61]. Two of these studies[,47,61] reported statistically significant increases in the risk of CV events in users of indomethacin.

Cox-2 Inhibitors
All but one of these studies included results on rofecoxib. In 12 of the 13 studies, rofecoxib was associated with statistical significant increases in cardiovascular risks and in most cases these were reported to be the highest amongst the included drugs. Celecoxib was also included in most studies, however was associated with an increased risk only in three of these studies. These included two Danish record linkage studies[20,22] while in another study the reported risks with celecoxib also approached statistical significance[19]. Valdecoxib results were reported in three studies, and in two of these its use was associated with a statistical significant increase for the reported endpoints.

Table 9
Summary of new retrospective cohort studies reporting on cardiovascular risk of NSAIDs and coxibs

Study	Endpoints	Cases (n)	Non-adjusted factors	Results
Gislason[22]	Recurrent AMI Death	Record linkage between Danish national registries Study population: 71,515 patients admitted with first MI between 1995-2002 and alive at discharge. 21,093 claimed >1 prescription for >1 NSAID.	Obesity Smoking Alcohol consumption OTC NSAID use OTC aspirin use	HR (95%CI) for any use vs non-use Re-current AMI **Rofecoxib: 1.63 (1.27-2.10)** **Celecoxib: 1.50 (1.10-2.05)** **Ibuprofen: 1.25 (1.07-1.46)** **Diclofenac: 1.54 (1.23-1.93)** Death **Rofecoxib: 2.80 (2.31-3.25)** **Celecoxib: 2.57 (2.15-3.08)** **Ibuprofen: 1.50 (1.36-1.67)** **Diclofenac: 2.40 (2.09-2.80)**
Rahme[44]	Hospitalisation for acute MI	Population-based healthcare record database: patients aged ≥65 yrs who filled >1 NSAID, coxib, or acetaminophen prescription between April 1999 and December 2002 in Quebec, Canada.	Obesity, Smoking Alcohol OTC use of NSAIDs, aspirin, Non-(compliance) with prescribed medicines	HR (95% CI) vs paracetamol AMI **Rofecoxib: 1.14 (1.00-1.31)** Celecoxib: 0.97 (0.86-1.10) Ibuprofen: 1.04 (0.68-1.59) Diclofenac: 1.17 (0.96-1.43) Naproxen: 1.16 (0.89-1.51)
Abraham[1]	MI CVA	Prescription data linked to Veterans Affairs-Medicare dataset. 384, 322 veterans aged 65-99yrs with filled prescription for NSAID, salicylate (>325mg/day) or coxib for >5 days between 1/1/00-31/12/02.	BMI, tobacco use OTC NSAID/low dose aspirin use Socio-economic status	IDR (95% CI) vs naproxen Acute MI **Rofecoxib: 1.76 (1.34-2.68)** **Celecoxib: 1.04 (1.02-1.08)** **Etodolac: 1.15 (1.06-1.31)** **Nabumetone: 1.13 (1.05-1.27)** **Ibuprofen: 1.12 (1.05-1.24)**
Roumie[48]	Stroke	Tennessee Medicaid program (for people eligible for benefits). 336,906 non-institutionalised patients aged 50 to 84 yrs enrolled between 1/1/1999 and 31/12/2004. 94,456 NSAID users (current and former users) and 242,450 non-users	Smoking status (although proxy of smoking-related illness used) OTC NSAID use BMI Lifestyle factors	Adjusted HR (95% CI) Vs non-users Celecoxib: 1.04 (0.87-1.23) **Rofecoxib: 1.28 (1.06-1.53)** **Valdecoxib: 1.41 (1.04-1.91)** Naproxen: 0.94 (0.80-1.11) Ibuprofen: 0.88 (0.73-1.06) Diclofenac: 0.94 (0.59-1.49) Indomethacin: 1.20 (0.85-1.69)
Cunnington[16]	Hospitalisation for acute MI or ischaemic stroke	Life-link US medical and pharmacy claims database. 80,826 chronic users (>90days) of NSAIDs and coxibs aged ≥40 but ≤80yrs with OA.	Obesity,smoking OTC NSAID or aspirin use, socio-economic status	HR (95%CI) vs non chronic use **Rofecoxib: 1.25 (1.04-1.50)** Celecoxib: 1.05 (0.91-1.22) Naproxen: 0.99 (0.64-1.54)
van Staa[61]	MI	UK General Practice Research Database study. 729294 patients aged 40+ yrs prescribed a NSAID.	OTC use of ibuprofen	Relative Rate (95% CI) Ibuprofen: 1.04 (0.98-1.09) **Diclofenac: 1.21 (1.15-1.28)**

		Controls: 443047 non-users of NSAIDs (disease risk score matched)		Naproxen: 1.03 (0.94-1.13) Mefenamic acid: 1.18 (0.97-1.45) **Indomethacin: 1.27 (1.13-1.43)** Meloxicam: 1.12 (0.94-1.32) Piroxicam: 1.01 (0.84-1.21)
Gislason[23]	Hospitalisation for AMI Death	Record linkage between Danish national registries Study population: 107,092 patients aged >30years who survived first hospitalisation for HF between Jan 1995 and 31 Dec 2004. 36,354 claimed >1 prescription for >1 NSAID.	Obesity Smoking Alcohol consumption OTC NSAID use Indication	HR (95% CI) vs non-use <u>Death</u> **Rofecoxib: 1.70 (1.58-1.82)** **Celecoxib: 1.75 (1.63-1.88)** **Ibuprofen: 1.31 (1.25-1.37)** **Diclofenac: 2.08 (1.95-2.21)** **Naproxen: 1.22 (1.07-1.39)** <u>Hospitalisation (MI)</u> **Rofecoxib: 1.30 (1.07-1.59)** **Celecoxib: 1.38 (1.13-1.69)** **Ibuprofen: 1.33 (1.19-1.50)** **Diclofenac: 1.36 (1.12-1.64)** **Naproxen: 1.52 (1.11-2.06)**
Fosbøl[20]	Composite of death and MI	Record linkage between Danish national registries Healthy individuals aged ≥10 yrs on 1 Jan 2007: No prescription for selected con meds after 1995 until first NSAID (n=1,028,437)	Unregistered use of OTC NSAIDs Adherence to treatment, smoking, alcohol, BP, lipid levels, obesity	HR (95% CI) Vs No use Ibuprofen : 1.01 (0.96-1.07) **Diclofenac:1.63 (1.52-1.76)** **Rofecoxib: 2.13 (1.89-2.41)** Celecoxib: **2.01 (1.78-2.27)** Naproxen: 0.97 (0.83-1.12)
Fosbøl[19]	Cardiovascular death	Record linkage between Danish national registries 1,028,437 Healthy individuals aged ≥10 yrs on 1 Jan 2007 with at least one NSAID prescription: 568,525 non users	adherence to treatment, smoking lipid levels, alcohol obesity, blood pressure	HR (95% CI) Ibuprofen : 0.88 (0.80-0.96) **Diclofenac: 1.20 (1.06-1.38)** **Rofecoxib: 1.64 (1.31-2.05)** Celecoxib: 1.24 (0.997-1.58) Naproxen: 0.86 (0.67-1.10)
Ray[46]	AMI or out of hospital death due to AMI or sudden cardiac death	Data from 3 databases: UK GPRD; Tennessee Medicaid program (US low-income); Saskatchewan Heath databases (Canada) 48,566 patients aged 40-89yrs with CHD (AMI, coronary revascularisation, unstable angina)	LV ejection fraction Self-paid NSAID/ aspirin use and OTC NSAID/aspirin use	IDR (95% CI) Vs non-users <u>MI or CHD death</u> Naproxen: 0.88 (0.66-1.17) Ibuprofen: 1.18 (0.92-1.53) Diclofenac: 1.27 (0.95-1.70) Celecoxib: 1.03 (0.85-1.25) Rofecoxib: 1.19 (0.97-1.47)
Roumie[47]	Composite of AMI, Stroke, or Out of hospital death from coronary heart disease (CHD)	Tennessee Medicaid program (for people eligible for benefits). 610,001 non-institutionalised patients aged 35 to 94 yrs enrolled between 1/1/1999 and 31/12/2005. 525,249 of subjects had no history of CVD at baseline.	Use of OTC NSAIDs/ aspirin	HR (95% CI) vs non-use <u>No CVD history</u> Celecoxib: 1.00 (0.89-1.13) **Rofecoxib: 1.21 (1.07-1.37)** **Valdecoxib: 1.30 (1.04-1.61)** Ibuprofen: 1.03 (0.92-1.15)

				Naproxen: 1.00 (0.91-1.11) **Indomethacin: 1.36 (1.11-1.66)** Diclofenac: 1.02 (0.79-1.33) Past CVD history Celecoxib: 0.92 (0.82-1.03) **Rofecoxib: 1.21 (1.08-1.37)** Valdecoxib: 0.99 (0.79-1.24) Ibuprofen: 1.02 (0.90-1.15) Naproxen: 0.88 (0.79-0.99) Indomethacin: 0.97 (0.75-1.25) Diclofenac: 1.01 (0.76-1.34)

Table 10
Summary of new prospective cohort studies reporting on cardiovascular risk of NSAIDs and coxibs

Study	Endpoints	Subjects (n)	Non-adjusted factors	Results
Solomon[54]	Composite of hospitalisation for MI, stroke or CHF, or out of hospital death attributable to CVD.	Record linkage: subjects were beneficiaries of Medicare and Pharmaceutical Assistance Contract for Elderly (PACE) in Pennsylvania, US or Pharmaceutical Assistance for the Aged and Disabled (PAAD) program. Subjects: new users since 1 Jan 1999 – 2004 of coxibs (76,082), non-selective NSAIDs (53,014). Reference group: 46,558 non-users of NSAIDs	Smoking status Aspirin use, BMI, OTC or other source use of NSAIDs Unmeasured (non) compliance with prescribed meds	HR (95% CI) vs no use Celecoxib: 0.89 (0.83-0.94) **Rofecoxib: 1.22 (1.14-1.30)** Valdecoxib: 0.86 (0.75-0.99) Diclofenac: 0.91 (0.74-1.13) Ibuprofen: 0.96 (0.83-1.10) Naproxen: 0.79 (0.67-0.93) Other nsNSAIDs: 0.87 (0.79-0.96)
Haag[26]	Incident stroke	Record linkage: medical and prescription databases 7637 persons aged 55-yrs or older, free of stroke at baseline and living in Ommoord district of Rotterdam	Socio-economic status OTC NSAID use	HR (95% CI) vs no use Ischaemic Stroke Diclofenac: 1.70 (0.91-3.17) Ibuprofen: 1.02 (0.32-3.32) **Naproxen: 2.65 (1.23-5.69)** **Rofecoxib: 5.56 (2.38-12.9)**

AMI: Acute myocardial infarction, CVA: cerebrovascular accident, IDR: incidence density ratio

Effect of NSAID dose on cardiovascular risk

Six of the identified cohort studies also investigated the association of administered NSAID dose and cardiovascular risks. *Gislason et al*[22] reported a dose dependent statistical significant increased risk of death with ibuprofen and diclofenac. However only diclofenac was also associated with an increased risk of recurrent MI. In the study by *Van Staa et al*[61] ibuprofen was not associated with an increased risk of MI overall, but the association was significant for patients receiving 1200mg of ibuprofen or more per day. In this study diclofenac was associated with an increased risk for any use, but also with a slightly increased risk for patients receiving 150mg diclofenac/day. The second study by *Gislason et al*[23] largely confirmed their previous findings[22] with regards to ibuprofen and diclofenac with a statistically significant increase of death associated with higher doses (>500 mg/day) of naproxen. Similar findings for ibuprofen and diclofenac were reported in another Danish cohort study[20]. *Ray et al*[46] reported an inverse dose correlation between diclofenac and the risks of serious coronary heart disease and serious cardiovascular disease or death. Finally, *Fosbøl* et al[19] reported a dose effect in the association between diclofenac, but not ibuprofen or naproxen, and cardiovascular death, coronary death or non-fatal myocardial infarction and stroke, which was increased in patients receiving 100≥mg/day. In this study, low (≤1200mg/day) but not high dose ibuprofen was associated with a statistical significant increased risk for the composite endpoint of coronary death or non-fatal myocardial infarction.

It is noted that the studies of *Gislason et al*[22,23], *Schjerning Olsen et al*[49], and *Ray et al*[46] were restricted to patients with underlying cardiovascular morbidities (previous MI, heart failure, coronary heart disease) and hence not generalisable to the general population. In the healthy populations studied[19,20,61] diclofenac <100 mg appears to be safer than ≥100mg, but up to 2-fold increased risks cannot be ruled out with the low doses given the upper 95% confidence limits. In addition, Ibuprofen ≤1200mg appears to be safe in healthy populations. Naproxen shows no clear dose response effect. Duration of use was not taken into account in detail in either of these studies.

***Schjerning Olsen et al* (2011)[49]**

This was a cohort study investigating the cardiovascular effect of NSAIDs in patients hospitalised with first time MI. Data were collected from individual-level linkage of nationwide registries with drug dispensing from pharmacies in Denmark. The endpoints for this study were all cause mortality and a composite of recurrent MI and mortality. Hazard ratios were estimated according to duration of NSAID treatment by multivariable time-stratified Cox proportional-hazard models.

The study identified 83,677 patients which had been hospitalised and subsequently discharged in Denmark for a first episode of MI between 1997 and 2006. Of these patients, 42.3% received at least one prescription for a NSAIDs during follow-up, and there were 35 257 death and myocardial infarctions (42.1%) and 29 234 deaths (35.0%) registered during the observation period.

The authors acknowledged the lack of information on various potential confounding factors (blood pressure, body mass index, smoking). On the other hand, the reported results are based on nation-wide data in a country where only low dose ibuprofen and at a limited quantity were available over the counter during the study period which should minimise possible confounding of non-prescribed NSAID use. The results of this study suggest that diclofenac is associated with a high level of risk, in contrast to the other drugs, from the beginning of the treatment. Of particular concern is the fact the reported risk for diclofenac is consistently higher than that associated with rofecoxib regardless of duration of treatment.

The reported risks for the composite endpoint and for death were very similar and are presented below.

Table 11
Time dependent hazard analysis of risk of death for various NSAIDs as reported by Schjerning Olsen et al

	HR (95% CI)				
	0-7 days	**7-14 days**	**14-30 days**	**30-90 days**	**>90 days**
Naproxen	1.63 (088-3.03)	1.60 (0.83-3.08)	1.22 (0.71-2.10)	1.31 (0.90-1.91)	**1.55 (1.10-2.17)**
Ibuprofen	0.92 (0.71-1.20)	**1.57 (1.27-1.94)**	**1.43 (1.22-1.67)**	**1.91 (1.73-2.11)**	**1.52 (1.38-1.69)**
Diclofenac	**3.52 (2.93-4.20)**	**2.57 (2.03-3.24)**	**2.08 (1.71-2.53)**	**2.61 (2.25-3.02)**	**2.02 (1.73-2.36)**
Celecoxib	1.10 (0.71-1.68)	1.39 (0.90-2.13)	**2.33 (1.79-3.02)**	**1.74 (1.42-2.13)**	**1.71 (1.47-1.99)**
Rofecoxib	**1.04 (1.29-1.53)**	**2.57 (1.91-3.46)**	**2.11 (1.62-2.75)**	**1.97 (1.62-2.41)**	**1.57 (1.30-1.88)**

The study was restricted to patients with previous MI and hence not generalisable to the general population. Nevertheless, the increased CV risk associated with NSAIDs among these high risk patients appeared to be consistent with the other studies in high risk populations. The analyses for duration were not adjusted for dose.

2.5. SOS project

The Safety Of non-Steroidal anti-inflammatory drugs (SOS) project was designed to assess and compare the risk of cardiovascular and gastrointestinal events in users of NSAIDs and coxibs. The project was funded under the VII Framework Programme.

A meta-analysis on the risk of stroke in association with NSAIDs use had already been published[63] by the investigators of this project and considered in this review. Additional studies, including a meta-analysis on the risk of myocardial infarction and case-control studies on the risks of stroke, myocardial infarction, heart failure and upper gastrointestinal complications have also been conducted. A summary of the results from the meta-analysis which have been submitted for publication and preliminary results from the case-control studies are also presented in this section of the report.

Meta-analysis of observational studies for myocardial infarction

Eligible studies for inclusion in this analysis were cohort or case-control studies reporting on rates of cardiovascular events in association with individual NSAIDs and published in peer-reviewed journals from 1 January 1990 to 4 May 2011. Studies were identified from a systematic literature search on the Medline database. Of the 3,829 articles initially retrieved, 65 met the inclusion criteria for study design and study medications but 20 of these were excluded because of inappropriate endpoint selection. The main analysis was limited to 18 studies, following further exclusion of studies either due to the lack of appropriate comparator groups (other NSAIDs, remote NSAID use or non-NSAID users) or because they reported on the same source population as other studies included in the analysis. Data from 7 additional studies were included in the sub-group analyses. Almost all studies included in this meta-analysis were also included in the meta-analysis by *McGettigan and Henry*[39], the only exception being the more recent study by *Schjerning Olsen et al*[49] which was included only in the SOS meta-analysis.

The pooled estimate of the relative risk of acute myocardial infarction for most commonly prescribed NSAIDs and coxibs and the effect of NSAID dose (based on reported low-high definition in each study) on this risk are presented in the table below. Random and fixed effect models were used in the meta-analysis which, in most cases, yielded very similar results.

Table 12
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

The investigators conducted further analyses to estimate relative risks for high risk populations (defined as those with prior cardiovascular medical history) and the effect of high dose or long duration of treatment (over 3 months) in this subset of patients. However, as these sub-analyses included only a small number of studies (between 2 and 5) it was not possible to draw firm conclusions from them.

Results on the RR of acute myocardial infarction were also presented for other NSAIDs but without any information on number of studies included for these drugs or level of heterogeneity. These results are summarised in the table below:

Table 13
Relative Risk of acute myocardial infarction for various NSAIDs compared to no NSAID use, as reported in the SOS meta-analysis

Drug	RR (95% CI)
Meloxicam	**1.25 (1.04-1.4)**
Indomethacin	**1.40 (1.21-1.62)**
Etodolac	**1.55 (1.16-2.06)**
Etoricoxib	**1.97 (1.35-2.89)**

Overall, the results of this study largely confirm the findings of the meta-analysis by *McGettigan and Henry*[39] with regards to the level of risk for the most commonly studied NSAIDs, despite restricting the analysis only to studies reporting on the risk of myocardial infarction.

Preliminary results from the individual epidemiological SOS studies
In addition to the meta-analysis of existing observational studies the SOS project conducted four new nested case-control studies to estimate the relative risks of acute myocardial infarction, heart failure, stroke and upper gastrointestinal complications associated with current individual NSAID use compared to remote use which was defined as at least 6 months before the index date of the event of interest.

Odds ratios were calculated for each endpoint from six different databases (IPCI, PHARMO, in the Netherlands; OSSIFF, SISR in Italy; GePaRD in Germany; and THIN in the UK), for a total of 8.56×10^6 NSAIDs users. Results for individual drugs were calculated in each database if there were at least 10 cases for the drug within the database.

Patients were included in the study if they were at least 18 years old and had been enrolled in the database for at least 12 months before the initial prescription of an NSAID. The only exclusion criterion was a diagnosis of malignant cancer with the exception of non-melanoma skin cancers. For each case up to 100 sex and age matched controls were selected from the same database. The investigators identified a number of potential confounders which included demographic and lifestyle information (age, sex, smoking, alcohol abuse, obesity), co-morbidities and concomitant medication. Information on prescribed daily dose was available only in the IPCI, PHARMO and THIN databases, however dose (and duration of treatment) sub-analyses are currently not available.

Conditional logistic regression was used to adjust for potential confounders but the investigators employed different strategies to collect relevant information for each database as it was acknowledged that the databases contain different types of information and level of detail.

Most commonly studied drugs
Results for acute myocardial infarction and ischaemic stroke were provided for 18 and 13 individual drugs respectively. Results were also presented for combination products for diclofenac, ibuprofen and ketoprofen. The number of events for the combination products was very small compared to the events for the single constituent products in most databases and therefore this is not discussed further in this report. Results are presented for the most commonly studied NSAIDs and coxibs separately.

Of the two endpoints of interest, the number of cases and controls for the most commonly studied NSAIDs in each database are presented in the table below together with their respective weighting in the pooled results.

Table 14
Number of acute myocardial infarction and ischaemic stroke cases and controls for most commonly studied NSAIDS in the databases included in the SOS studies

Database	**Naproxen**	**Ibuprofen**	**Diclofenac**	**Celecoxib**	**Rofecoxib**
	Cases/Controls (weighting %)	Cases/Controls (weighting %)	Cases/Controls (weighting %)	Cases/Controls (weighting %)	Cases/Controls (weighting %)

Acute Myocardial Infarction					
GePaRD	21/1009 (4.3)	504/35593 (28.6)	771/64062 (21.5)	13/1446 (1.6)	-/-
IPCI	16/463 (2.8)	18/556 (1.1)	58/2454 (1.5)	3/94 (-)	4/43 (-)
OSSIF	62/5628 (12.9)	91/8126 (6.7)	446/31053 (15.8)	267/22673 (29.6)	259/19430 (37.9)
PHARMO	144/9838 (28.6)	207/14065 (13.8)	420/26381 (14.1)	54/2553 (6.4)	83/4974 (12)
SISR	87/8332 (18.4)	272/20588 (19.1)	720/52244 (25.1)	366/24595 (41.3)	180//16002 (26.6)
THIN	156/13389 (32.9)	472/40291 (30.6)	649/54019 (21.9)	183/14771 (21.1)	164/11225 (23.5)
Ischaemic stroke					
GePaRD	18/974 (13.3)	473/1878 (55.9)	741/54999 (44)	9/1409 (3.1)	-/-
OSSIF	31/2759 (23.1)	54/4412 (7.6)	210/15947 (16.2)	139/12842 (33.4)	126/10777 (44.3)
SISR	41/4181 (29.8)	121/10852 (16.8)	360/25966 (26.3)	198/19694 (49.4)	109/9109 (39.4)
THIN	46/4706 (33.8)	151/13389 (19.8)	187/16300 (14.5)	59/4815 (14)	44/3125 (16.3)

A 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 15
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 (1.05-2.69)**	**1.41 (1.27-1.55)**	**1.37 (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, except ibuprofen and ischaemic stroke which was in this case higher and statistically significant (OR, 95% CI: **1.24, 1.15-1.34**).

Other NSAIDs

Results for most of the other drugs included in the SOS studies were limited to two or three databases. For aceclofenac, dexibuprofen, ketoprofen, ketorolac, lornoxicam, nimesulide and tenoxicam results were presented only for the two Italian databases. Results for nabumetone were provided in three databases and were not statistically significant in any case. Ketoprofen and nimesulide were associated with small statistically significant increased risks of approximately 10% for myocardial infarction. Nimesulide was also associated with a similar increased risk for ischaemic stroke. Of these drugs ketorolac was the only one for which very high risks were seen as summarised in the table below.

Table 16
Risk of acute myocardial infarction and ischaemic stroke in association with ketorolac use compared to remote use from the SOS studies

	Acute MI	Ischaemic stroke
Database		
OSSIF	**2.13 (1.79-2.55)**	**1.39 (1.01-1.89)**
SISR	**1.99 (1.70-2.35)**	**1.52 (1.17-1.99)**
Pooled	**2.05 (1.82-2.31)**	**1.46 (1.20-1.79)**
p-value	0. 578	0.652

Data for meloxicam, piroxicam and indomethacin were available from five or six of the databases. Meloxicam and piroxicam were associated with a statistically significant increased risk of approximately 20% for myocardial infarction. Piroxicam, but not meloxicam was also associated with a statistically significant increased risk for ischaemic stroke of 13%. The level of risk for indomethacin was statistically significant only for myocardial infarction but was also increased for ischaemic stroke in most databases as summarised below.

Table 17
Risk of acute myocardial infarction and ischaemic stroke in association with indomethacin use compared to remote use from the SOS studies

	Acute MI	Ischaemic stroke
Database		
GePaRD	**1.71 (1.13-2.56)**	1.01 (0.57-1.80)
OSSIF	**1.59 (1.16-2.20)**	1.39 (0.87-2.22)
PHARMO	**1.61 (1.06-2.44)**	-
SISR	**1.33 (1.02-1.75)**	1.09 (0.72-1.67)
THIN	**1.36 (1.02-1.82)**	1.26 (0.71-2.24)
Pooled	**1.47 (1.27-1.70)**	1.18 (0.92-1.52)
p-value	0.782	0.822

Etoricoxib was associated with a statistically significant increased risk for myocardial infarction (RR, 95% CI: **1.29, 1.16-1.44**). The risk of ischaemic stroke for etoricoxib did not reach statistical significance (RR, 95%CI: 1.11, 0.97-1.27).

The evaluation of the SOS results was hindered by the lack of detailed usage data for all NSAIDs per database. Nevertheless, the SOS was considered a very important study due to its size and the use of databases which have provided significant information for drugs that have previously not been studied extensively.
Some important inconsistencies across the databases were observed and merit further discussion. The results from GePaRD suggest a considerably higher level of risk for non-selective NSAIDs compared to the selective Cox-2 inhibitors (celecoxib and etoricoxib), which is not consistent with the majority of available randomised clinical trial and observational data. A parameter that needs to be considered in the interpretation of these results is the time period covered in GePaRD which predominantly coincides with the period following the conclusion of the previous CHMP review on the thrombotic risks of coxibs. It is possible that results in this database are more prone to channelling of higher risk patients to treatments perceived as safer alternatives to coxibs than in other databases included in this study which cover wider periods. Available exposure data from this database show that most patients were treated with either diclofenac or ibuprofen but interestingly naproxen exposure was very limited (as also illustrated by the very small number of cases of stroke in naproxen treated patients). It would also appear that the characteristics of patients in GePaRD are quite different to those of the patients in other databases. For example for ischaemic stroke, 15.2% of the cases and 4.7% of controls had a prior history of stroke compared to approximately of 2% of the cases and 0.5% of the controls in the other databases.

For all the above reasons, the GePaRD results should probably be considered separately to the other databases. The influence of the GePaRD results is particularly important for ibuprofen (which also has the most heterogeneous results amongst the most frequently studied drugs) as the weight of the GePaRD data for the ibuprofen meta-analysis is 28.6 and 55.9 for myocardial infarction and ischaemic stroke respectively. If these results were removed, the reported level of risk for ibuprofen would have been considerably lower.

Results from the PHARMO database are also difficult to interpret given the consistently high values for all 5 drugs and the risk of myocardial infarction, which is also not consistent with previous evidence. However, the effect of the PHARMO data on the meta-analysis is limited, with the exception of naproxen (weight 28.9).

Considering all the above, the most consistent results across all databases and for both endpoints, and in line with results from other epidemiological sources, are the levels of risk reported for diclofenac and rofecoxib which are the highest amongst the most commonly studied (and used) NSAIDs.

Of the other drugs investigated in the SOS study, an increased risk was noted for indomethacin and ketorolac.
The increased risk for indomethacin has also been reported by *McGettigan and Henry*[39]. In the SOS study the increased risk appears to be consistent across all databases with low levels of heterogeneity. However, the confidence intervals of the relative risk for acute myocardial infarction in most databases are wide as they are based on relatively few events (167 across all 4 databases). Furthermore for ischaemic stroke the risk does not reach statistical significance and it was based on a small number of events (64 across all 4 databases).
The reported risk for ketorolac was the highest amongst all NSAIDs for both myocardial infarction and ischaemic stroke in the study. However, this was based on results from the two Italian databases, and even in those databases exposure to ketorolac was relatively limited.

2.6. Discussion

The cardiovascular safety of NSAIDs has been continuously reviewed over the last years. Following the last review of the cardiovascular risks associated with NSAIDs in 2006, a number of additional studies have been published to investigate this issue. Whilst no new clinical trials have been conducted in the intervening time, two meta-analyses of data from older trials have been published including a novel network meta-analysis. Two new meta-analyses of observational studies have also been performed[39,63] including an analysis specific to the risk of stroke for which information was previously lacking. In addition, a substantial number of observational studies have also been published further enhancing knowledge on this topic. As with previous reviews, the majority of the data focuses on naproxen, ibuprofen and diclofenac, although some of the newly conducted studies included other medicinal products (e.g. indomethacin and etodolac).
In addition to the above mentioned meta-analysis and observational studies, important information on the thrombotic risks of NSAIDs has been provided by the large SOS study. The results of the SOS seem to confirm those of other epidemiological studies with regards to the risks of the most commonly studied NSAIDs, naproxen, ibuprofen and diclofenac. In addition, this study also considered the risks of less used NSAIDs, such as indomethacin and ketorolac.

Naproxen
Most of the new evidence available on naproxen was in agreement with the conclusions of the previous review which suggested that naproxen is associated with less thrombotic risks than selective Cox-2 inhibitors. The meta-analysis by *Chen and Ashcroft*[14], similar to the analysis by *Kearney et al*[32], compared non-selective NSAIDs with the Cox-2 inhibitor class. Naproxen was the only one of the three studied NSAIDs that was associated with a statistical significant decreased risk. Similarly, in the network meta-analysis by *Trelle et al*[59] naproxen was the only investigated drug not associated with a statistical significant increased risk for any of the endpoints in the study. Both meta-analyses of observational studies also found naproxen to be the drug associated with the lowest thrombotic risks, even though in one a small overall increased risk was detected[39]. This relatively low level of risk was also reflected in the small number of individual observational studies, mostly showing a relatively small increased risk for naproxen[13,33] compared to the other drugs. The SOS study also indicated a relatively low level of risk overall for naproxen.

Ibuprofen

In line with the previous reviews, information on the cardiovascular safety of ibuprofen produces inconsistent results. The meta-analysis by *Chen and Ashcroft*[14] did not report a statistical difference between ibuprofen and coxibs, but this meta-analysis contained a small number of trials compared to *Kearney et al*[32] (6 compared to 24), and this might have resulted in the slightly higher risk reported in this study. In the network meta-analysis[59], ibuprofen was associated with a marginal statistical significant increased risk for stroke. There was no evidence of an increased risk of the other endpoints in this study (myocardial infarction, cardiovascular death or all-cause mortality), except for the composite APTC endpoint. On the other hand, in the meta-analysis of observational studies on the risk of stroke[63], ibuprofen was not associated with a statically significant increase with any of the reported endpoints (all strokes, incident or ischaemic stroke). Results from the observational meta-analyses *by McGettigan et al*[39] are also mixed, and an increased risk was reported for high but not low doses of ibuprofen although there was significant heterogeneity between the studies included for this result. It has to be noted that the pair-wise comparison in this study also found that ibuprofen was associated with a statistical significant decreased risk compared to etoricoxib and diclofenac, and a small increased risk compared to naproxen. This is in line with the findings of previous reviews.

On an individual study level most of the studies did not find an increased cardiovascular risk associated with ibuprofen. However some studies[20,22] reported a statistical significant increased risk which was generally lower than that reported for the coxibs. The difference in the 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 et al*[39].

The results of the SOS studies on the risk of ibuprofen are also inconsistent and the overall reported risk could possibly be the result of channelling bias especially in GePaRD. The fact that the dose was not taken into account in the analyses, and especially in the observational studies, may play an important role. Of note, available information on dose-response effects of ibuprofen is still limited, and ibuprofen daily doses of 1200 mg and less appear to be safer than higher doses in the observational studies that assessed dose effects.

Diclofenac

In line with the previous reviews, the results for diclofenac point towards an increased cardiovascular risk which is generally higher than the other non-selective NSAIDs and similar to those reported for some of the coxibs.

In the study by Chen and Ashcroft[14], diclofenac was associated with similar levels of risk to the grouped coxib group, despite the exclusion of the results of the MEDAL study. The network meta-analysis[59] largely confirmed the conclusions of the MEDAL study, which first suggested that the cardiovascular risks associated with etoricoxib and diclofenac were very similar. This was confirmed for each individual cardiovascular endpoint investigated.

In terms of observational studies, the risk of stroke with diclofenac in the meta-analysis by Varas-Lorenzo[63] was second to that of rofecoxib and exceeded that reported for celecoxib. In the meta-analysis by *McGettigan et al*, the risks associated with diclofenac were indistinguishable from those associated with rofecoxib and higher than those reported for celecoxib or other non-selective NSAIDs. However the number of studies included in this analysis for etoricoxib was limited to only three. When considering the overall risks, diclofenac was not associated with a statistical significant difference when compared to etoricoxib.

In the individual observational studies an increased risk was reported for diclofenac in several studies[19,20,22,23,61]. An increased risk with diclofenac was also observed in the SOS nested-cases control studies across all databases and for both myocardial infarction and ischaemic stroke. In common with other epidemiological studies, the level of risk reported for diclofenac was the highest together with rofecoxib. Furthermore, the only study that provided risks in relation to duration of exposure[49] found that the risks associated with diclofenac were very similar to that of rofecoxib and higher than that reported for both naproxen and ibuprofen at all time points.

Available information on the dose effect of diclofenac is fairly limited but appears to point towards a dose dependency for the thrombotic risks associated with diclofenac use. It is difficult to establish a clear cut-off dose above which the risks become significantly increased as the various studies use different definitions of low and high doses of diclofenac. Of note, one of the most detailed studies with respect to the dose effect[21] showed that doses above 75mg/day are associated with progressively higher thrombotic risks. The effect of duration of treatment was only studied in patients with underlying heart disease, and therefore may not be applicable to the general population.

Other NSAIDs
Evidence of risk for other NSAIDs is limited. For ketorolac available evidence of risk is limited to the SOS studies. For indomethacin, a number of observational studies[47,61] have suggested an increased cardiovascular risk associated with its use, which appears to be in line with the SOS data, even though the risk in this study does not appear to extend to ischaemic stroke. The meta-analysis by *McGettigan et al*[39] has also suggested an increased risk for indomethacin, even though the endpoint in that analysis was a composite of endpoints.

3. Overall conclusion

Non-selective NSAIDs are indicated in the relief of all grades of pain and inflammation in a wide range of conditions, and are important treatments for arthritic conditions, acute musculo-skeletal disorders and other painful conditions resulting from trauma. The adverse event profile of NSAIDs, including Cox-2 inhibitors, is known. Gastrointestinal adverse events, including serious events of PUB (perforation, ulcer, bleeding) are one main reason for discontinuation of treatment with NSAIDs. Other events such as hypersensitivity or skin reactions, cardiorenal effects and hepatotoxicity are class effects, although the exact incidence may vary between products.

With regards to the cardiovascular safety profile, results from review in 2006 led to the conclusion that it cannot be excluded that non-selective NSAIDs may be associated with a small increase in the absolute risk for thrombotic events, especially when used at high doses for long-term treatment. This resulted in an update of the product information of the different NSAIDs to reflect available evidence at the time. The CHMP noted that although the benefits of NSAIDs outweighed their risks, they should be used at the lowest effective dose and for the shortest possible treatment duration. In addition, further epidemiological studies should be carried out with regards to the safety of non-selective NSAIDs.

Since 2006, results from the independent research project 'safety of non-steroidal anti-inflammatory drugs' (SOS) funded by the European Commission under the Seventh Framework Programme to evaluate the safety of NSAIDs, have become available. In addition, several epidemiological studies and meta-analysis have been published. The findings of the SOS project, together with a number of other studies provided more evidence on the cardiovascular safety of NSAIDs.

Based on the evidence available to date, the CHMP considers that the findings in relation to the cardiovascular risks for naproxen and ibuprofen are in line with the previous evidence. Overall, data suggest that naproxen may be associated with a lower risk for arterial thrombotic events than Cox-2 inhibitors and other NSAIDs, but a small risk cannot be excluded. Similarly, ibuprofen at high dose may be associated with an increased risk of thrombotic events, and the data do not consistently suggest that low dose ibuprofen is associated with an increased risk of cardiovascular events. The Committee notes that the existing prescribing information reflects the known level of cardiovascular and other risks for these medicines.

Data from previous reviews indicated that diclofenac, particularly at high dose, may be associated with an increased risk of arterial thrombotic events such as myocardial infarction or stroke. The CHMP considered that the evidence to date regarding diclofenac seems to consistently point towards a less favourable cardiovascular risk profile compared to naproxen and ibuprofen, and similar risks as those of Cox-2 inhibitors. The reported increases in the risks for diclofenac rarely exceed a two fold-increase compared to no use, but it cannot be excluded that relatively small increases in risk are likely to have a public health impact. The Committee concluded that, given the results of the available studies it may be appropriate to consider this matter and the need for any regulatory action under a formal referral procedure.

For other non-selective NSAIDs the data were considered insufficient to conclude on thrombotic risk. The CHMP therefore reiterates the previous conclusion that an increased risk for NSAIDs as a class cannot be excluded.

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