European Heart Journal (2006) **27**, 1657–1663
doi:10.1093/eurheartj/ehl053

NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case–control study from Finland

Arja Helin-Salmivaara[1]*, Arja Virtanen[2], Risto Vesalainen[3], Juha M. Grönroos[4], Timo Klaukka[5], Juhana E. Idänpään-Heikkilä[6], and Risto Huupponen[7]

[1] *Centre for Pharmacotherapy Development and Postgraduate School of Clinical Drug Research, University of Turku, PB 55, FIN-00301 Helsinki, Finland;* [2] *Research Department, Social Insurance Institution, Peltolantie 2, FIN-20720 Turku, Finland;* [3] *Department of Medicine, Turku University Hospital, PB 52, FIN-20521 Turku, Finland;* [4] *Department of Emergency, Turku University Hospital and Department of Surgery, University of Turku, PB 52, FIN-20521 Turku, Finland;* [5] *Research Department, Social Insurance Institution, PB 450, FIN-00101 Helsinki, Finland;* [6] *Council for International Organizations of Medical Sciences, c/o WHO, CH-1211, Geneva 27, Switzerland; and* [7] *Department of Pharmacology and Clinical Pharmacology, University of Turku and Department of Pharmacology and Toxicology, University of Kuopio and Kuopio University Hospital, PB 1627, FIN-70211 Kuopio, Finland*

Received 20 February 2006; revised 4 May 2006; accepted 6 May 2006; online publish-ahead-of-print 26 May 2006

See page 1635 for the editorial comment on this article (doi:10.1093/eurheartj/ehl090)

KEYWORDS
Risk;
Non-steroidal anti-inflammatory drugs;
Myocardial infarction;
Case–control

Aims To evaluate the risk of first myocardial infarction (MI) associated with the use of various non-steroidal anti-inflammatory drugs (NSAIDs) in the general population.
Methods and results We conducted a population-based matched case–control study over the years 2000–3 in outpatient residents of Finland. In the nationwide Hospital Discharge Register 33 309 persons with first time MI were identified. A total of 138 949 controls individually matched for age, gender, hospital catchment area, and index day were selected from the Population Register. For combined NSAIDs, the adjusted odds ratio for the risk of first MI with current use was 1.40 (95% CI, 1.33–1.48). The risk was similar for conventional (1.34; 1.26–1.43), semi-selective (etodolac, nabumetone, nimesulide, and meloxicam) (1.50; 1.32–1.71), and cyclo-oxygenase-2 (COX-2) selective NSAIDs (rofecoxib, celecoxib, valdecoxib, and etoricoxib) (1.31; 1.13–1.50). Age of current user did not consistently modify the risk. No NSAID was associated with an MI-protective effect. All durations from 1 to 180 days of conventional NSAIDs and from 31 to 90 days duration of COX-2 selective NSAIDs were associated with an elevated risk of MI.
Conclusion Current use of all NSAIDs is associated with a modest risk of first time MI.

Introduction

The accumulating data on the cardiovascular risks associated with the use of cyclo-oxygenase-2 (COX-2) selective NSAIDs also call into question the cardiovascular safety of the conventional non-steroidal anti-inflammatory drugs (NSAIDs). The earlier randomized controlled trials (RCT) designed to study efficacy and safety of conventional NSAIDs focused on gastrointestinal adverse effects and were generally underpowered to find rare hazards, such as myocardial infarction (MI). Results suggesting an association between cardiovascular risk and the use of various conventional NSAIDs have recently emerged from some observational studies,[1,2] although not all such reports have confirmed these findings.[3–10]

Information on the effects of duration of NSAID therapy and age of the user on potential cardiovascular risk is either controversial or lacking. We therefore conducted a nationwide case–control study in the general Finnish population on the risk of first time MI associated with the use of various NSAIDs, considering both duration and the age of the user. Non-selective conventional NSAIDs, those with some COX-2 selectivity (semi-selective), as well as COX-2 selective NSAIDs were included in the analysis.

Methods

We conducted a population-based matched case–control study in persons living in the community, based on historical data. The outcome was first MI requiring hospitalization. The cases were identified using the Finnish Hospital Discharge Register from 1 January 2000 to 31 December 2003. Up to five control patients to each case were identified from the Population Register and matched for age at the end of the calendar year, sex, and hospital catchment area. The index day of the case (day of hospitalization) was assigned to its controls. The use of medication and co-morbidity associated with the risk of MI were obtained by linking the personal

* Corresponding author. Tel: +358 9 4733 4429; fax: +358 9 4733 4431.
E-mail address: arja.helin-salmivaara@rohto.fi

identity codes of the cases and controls with their data in the Finnish Prescription Register and the Special Reimbursement Register. Using the Anatomical Therapeutic Chemical (ATC) codes,[11] we located any and all prescriptions for NSAIDs for each person and the dates they were written during the 2 years prior to the index day. For each prescription the amount of NSAID was then assigned according to the defined daily dose coding (DDD; defined as the standard dose per 24 h for an adult taking the drug for its main indication) as suggested by WHO.[11] The amount of DDD was used as a proxy for supply.

The proximity of NSAID therapy to the MI was defined as the most recent supply of a prescription before the index day. The users were classified in three mutually exclusive categories: (a) current users: the supply of the prescription started before and extended beyond the index day; (b) recent users: the supply of the prescription ended 1–30 days before the index day; and (c) past users: the supply of the prescription ended 31 days to 2 years before the index day. If a person had prescriptions with different NSAIDs inside a time category, he or she was classified as a multiple NSAID user. Persons with no prescriptions of NSAIDs during the 2 years prior to the index day were classified as non-users.

Further description of the methods is presented in the Supplementary data.

Statistical analysis

Conditional logistic regression models taking into account the 1:5 matching were used to estimate the associations between NSAID categories or individual NSAIDs and the risk of MI. The matching factors were age, gender, hospital catchment area, and index day. Because of the matching procedure, the effect of age and gender could not be examined in the models, as their distributions of the controls matched those of the cases. Therefore, the contribution of age and gender were examined by conditional logistic regression models taking into account the interaction terms of age, gender, and NSAID category.

Use of any of the following drugs during the 120 days preceding the index day was considered as a confounder for MI, and was included in the adjusted analysis of the risk ratio: statins (ATC code C10AA), β-adrenoceptor blocking drugs alone (C07A) or in combination with diuretics (C07B) or with other substances (C07F), clopidogrel (B01AC04), or post-menopausal hormone therapy (G03CA, G03DC05, G03F). Furthermore, co-morbidity with rheumatoid arthritis, hypertension, diabetes, or coronary artery disease (CAD) present on the index day, as reflected by the person's inclusion in the Special Reimbursement Register for that disease, was used as an adjusting factor in the statistical analysis.

The OR and corresponding 95% CI were estimated using the PHreg procedure in the SAS package (version 8.2; SAS Institute Inc., Cary, NC, USA).

Ethics

This study was approved by the National Research and Development Centre for Welfare and Health, the Social Insurance Institution, and the Office of the Data Protection Ombudsman.

Results

We identified 33 309 persons with MI and 138 949 individually matched controls (*Table 1*). At least three controls could be identified for 91.9% of the cases; the number of controls per case declined with advancing age. MI was slightly more prevalent in males. When compared with matched controls, a significantly larger proportion of cases had some predisposing factor for MI (diabetes, hypertension, rheumatoid arthritis, CAD). Similarly, with the exception of hormone replacement therapy, the use of drugs modifying the risk of MI was more prevalent among cases than control persons.

Table 1 Baseline patient characteristics

	Cases (%) $n = 33\,309$	Controls (%) $n = 138\,949$
Age (years)		
≤35	131 (0.4)	645 (0.5)
36–45	966 (2.9)	4 750 (3.4)
46–55	3 987 (12.0)	19 350 (13.9)
56–65	6 173 (18.5)	29 213 (21.0)
66–75	9 014 (27.1)	39 318 (28.3)
76–85	9 437 (28.3)	34 848 (25.1)
≥86	3 601 (10.8)	10 825 (7.8)
Females	13 181 (39.6)	51 835 (37.3)
Diabetes mellitus[a]	4 820 (14.5)	8 091 (5.8)
Rheumatoid arthritis[a]	1 434 (4.3)	3 747 (2.7)
Hypertension[a]	11 406 (34.2)	33 304 (24.0)
CAD[a]	15 897 (47.7)	14 104 (10.2)
Other medication used 4 months prior the index day		
β-blocker	11 664 (35.0)	29 161 (21.0)
HMG-CoA-reductase inhibitor	4 885 (14.6)	14 331 (10.3)
Hormone replacement therapy in females	1 306 (3.9)	7 508 (5.4)
Clopidogrel	96 (0.3)	76 (0.1)

[a]Valid at the index day in the Special Reimbursement Register of the Social Insurance Institution.

NSAID use and risk of MI by proximity of the last prescription

In all NSAID categories current use was statistically significantly associated with MI. The mean adjusted odds ratios (AOR) were in the range of 1.3–1.5 with no obvious differences between the categories (*Table 2*). Among individual substances, the AOR associated with the current use of nimesulide was 1.69 (95% CI 1.43–1.99), with indomethacin 1.56 (1.21–2.03), with rofecoxib 1.44 (1.20–1.72), with ibuprofen 1.41 (1.28–1.55), with diclofenac 1.35 (1.18–1.54), and with naproxen 1.19 (1.02–1.38) (*Table 3*). In the case of etoricoxib, the point estimate of AOR was 2.21 but the CI was wide from 1.18 to 4.14. None of the NSAIDs had a protective effect against MI among current users.

In the sensitivity analysis, assuming that the actual NSAID dose had been twice of that indicated by DDD, the ORs of any current NSAID use turned out to be the same (unadjusted OR 1.57; 1.48–1.66, AOR 1.43; 1.34–1.53) as in the original analysis (*Table 2*). If only half of the DDD dose was supposed to be taken, the ORs remained highly significant (unadjusted OR 1.45, 1.40–1.51; AOR 1.32; 1.27–1.38).

With increasing time between discontinuation of NSAID therapy and index day the mean AORs tended to decrease in all NSAID categories, although the association was statistically significant in the users of conventional NSAIDs only (*Table 2*). A similar trend emerged when the analysis was repeated on a substance-by-substance basis (*Table 3*).

Table 2 Risk of first time MI by proximity and category of the last prescription

	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Non-users	20 645	92 524	1.00 (Reference)	1.00 (Reference)
Any NSAID				
Current[b]	2 979	8 076	1.60 (1.53–1.67)	1.40 (1.33–1.48)
Recent[c]	1 204	4 132	1.28 (1.20–1.37)	1.16 (1.07–1.25)
Past[d]	8 481	34 217	1.12 (1.08–1.15)	1.01 (0.98–1.04)
Conventional NSAIDs[e]				
Current	1 985	5 572	1.50 (1.42–1.59)	1.34 (1.26–1.43)
Recent	794	2 702	1.25 (1.15–1.36)	1.15 (1.04–1.26)
Past	4 347	17 202	1.11 (1.07–1.15)	1.04 (1.00–1.09)
Semi-selective NSAIDs[f]				
Current	459	1 103	1.66 (1.48–1.85)	1.50 (1.32–1.71)
Recent	258	873	1.21 (1.05–1.39)	1.10 (0.94–1.30)
Past	1 635	6 885	0.99 (0.93–1.04)	0.91 (0.85–0.97)
COX-2 selective NSAIDs[g]				
Current	380	1 016	1.47 (1.30–1.66)	1.31 (1.13–1.50)
Recent	118	441	1.11 (0.90–1.36)	1.13 (0.89–1.43)
Past	375	1 653	0.93 (0.83–1.04)	0.86 (0.76–0.98)

[a]Adjusted for diabetes mellitus, rheumatoid arthritis, CAD, hypertension, and the use of a β-blocker, a statin, hormone replacement therapy, and clopidogrel 4 months prior the index day.
[b]'Current' use denotes the supply of the last prescription, counted in DDD, covered the index day.
[c]'Recent' denotes the supply ended in the days 1–30 prior the index day.
[d]'Past' denotes the supply ended 31 days prior the index day.
[e]Conventional NSAIDs: diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, mefenamic acid, piroxicam, tenoxicam, tolfenamic acid, aceclofenac, tiaprofenic acid, and mefenamic acid.
[f]Semi-selective NSAIDs: etodolac, nabumetone, nimesulide, and meloxicam.
[g]COX-2 selective NSAIDs: rofecoxib, celecoxib, valdecoxib, and etoricoxib.

Duration of therapy among current users of NSAIDs

In the users of conventional NSAIDs, the OR for MI were constantly elevated regardless of the length of use (*Table 4*). Similar results emerged when the analysis was repeated on a substance-by-substance basis (not shown in the tables). Among persons on semi-selective NSAIDs the risk was significant for other durations than from 2 to 4 weeks, and among persons on COX-2 selective NSAIDs the risk was significant only for 2–3 months of use (*Table 4*). During that period, rofecoxib was mostly responsible for the AOR among COX-2 inhibitors (1.77; 1.08–2.90); the AOR for rofecoxib was also elevated for longer use (1.55; 1.04–2.30) of the therapy.

Age

Age or gender in the current users did not modify the risk of MI in any NSAID category (all interaction *P*-values >0.07). However, when analysing individual NSAIDs a different finding emerged. In the users of indomethacin, diclofenac, naproxen, nimesulide, or rofecoxib, an elevated risk of MI (AORs ranging from 1.31 to 1.79) was observed only in persons aged 76 years or more (data not shown).

Discussion

We found a clear but moderate association (less than two-fold) between first MI and current use of NSAIDs. The associations were present regardless of the NSAID category, and were of similar level for conventional, semi-selective, and COX-2 selective NSAIDs. The risk elevation associated with individual substances varied from 121 (etoricoxib) to 19% (naproxen), compared with non-users of NSAIDs.

The second important finding was the close association of the proximity of NSAID use to MI: the longer the time from NSAID discontinuation the weaker the association. Age of the user did not consistently modify the risk.

When the duration of any NSAID therapy was considered, the risk for MI was elevated regardless of the duration of therapy, although there was a tendency for a bimodal distribution of the risk in NSAID users with a short and extended (over 3 months) exposure showing the highest AORs.

Even if the risk increase was modest, any risk of serious adverse event is important at the population level if a drug is not life-saving and is widely used, as is the case with NSAIDs. The risk level of the MI is clearly lower than the risk of serious upper gastrointestinal events, 2–5-fold when compared with non-users, as confirmed previously.[12–14] Anyhow, MI is attributable to approximately 17 000 hospitalizations annually in 2000's in Finland[15] when compared with that of 2700–3500 attributable to upper gastrointestinal bleeding, perforation, and ulceration (Rusanen J., Hospital Discharge Register, personal communication).

The association between MI and any NSAID use was also observed in a recent population-based database study in Denmark.[1] The researchers observed elevated risk of MI associated with current use of rofecoxib, celecoxib, naproxen, other coxibs (classified as semi-selective in our study), and other NSAIDs as a group. Similarly, in case–control studies in the UK and US, elevated risk ratios across different NSAID subclasses were reported.[2,16]

Table 3 Risk of first time MI with specific NSAIDs by proximity of the last prescription

	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Non-users	20 645	92 524	1.00 (Reference)	1.00 (Reference)
Conventional NSAIDs				
Indomethacin				
Current[b]	108	258	1.70 (1.35–2.13)	1.56 (1.21–2.03)
Recent[c]	52	139	1.51 (1.10–2.09)	1.46 (1.01–2.11)
Past[d]	232	724	1.32 (1.13–1.53)	1.18 (0.99–1.40)
Ibuprofen				
Current	768	1 993	1.59 (1.46–1.74)	1.41 (1.28–1.55)
Recent	282	962	1.19 (1.04–1.36)	1.10 (0.94–1.28)
Past	1 475	5 447	1.15 (1.10–1.23)	1.08 (1.00–1.15)
Diclofenac				
Current	388	1 059	1.48 (1.32–1.67)	1.35 (1.18–1.54)
Recent	174	673	1.07 (0.90–1.26)	0.93 (0.77–1.13)
Past	1 088	4 644	1.00 (0.94–1.07)	0.98 (0.91–1.06)
Naproxen				
Current	300	937	1.33 (1.16–1.51)	1.19 (1.02–1.38)
Recent	97	294	1.40 (1.11–1.77)	1.34 (1.03–1.74)
Past	621	2 622	1.01 (0.92–1.10)	0.98 (0.88–1.08)
Piroxicam				
Current	45	130	1.43 (1.02–2.02)	1.35 (0.92–1.99)
Recent	17	80	0.91 (0.54–1.53)	0.89 (0.49–1.61)
Past	127	516	1.04 (0.85–1.26)	1.00 (0.80–1.25)
Ketoprofen				
Current	249	786	1.26 (1.09–1.45)	1.11 (0.94–1.31)
Recent	106	306	1.43 (1.14–1.79)	1.30 (1.01–1.68)
Past	525	2 090	1.05 (0.95–1.16)	0.98 (0.88–1.09)
Tolfenamic acid				
Current	37	113	1.39 (0.96–2.02)	1.39 (0.90–2.15)
Recent	21	69	1.31 (0.80–2.14)	1.29 (0.74–2.26)
Past	91	394	1.00 (0.80–1.26)	0.94 (0.73–1.22)
Other single conventional NSAIDs[e]				
Current	90	296	1.21 (0.96–1.54)	1.23 (0.94–1.62)
Recent	45	179	1.02 (0.73–1.42)	1.08 (0.74–1.56)
Past	188	765	1.02 (0.87–1.20)	1.03 (0.86–1.24)
Semi-selective NSAIDs				
Nimesulide				
Current	292	648	1.81 (1.58–2.09)	1.69 (1.43–1.99)
Recent	174	588	1.21 (1.02–1.44)	1.11 (0.91–1.35)
Past	1 307	5 397	1.01 (0.95–1.07)	0.93 (0.87–1.00)
Etodolac				
Current	6	16	1.43 (0.55–3.72)	1.35 (0.44–4.17)
Recent	3	12	1.17 (0.33–4.14)	0.95 (0.23–4.00)
Past	2	27	0.33 (0.08–1.38)	0.22 (0.04–1.14)
Nabumetone				
Current	12	37	1.24 (0.64–2.39)	1.26 (0.59–2.69)
Recent	6	10	2.28 (0.82–6.33)	3.01 (0.96–9.43)
Past	22	73	1.13 (0.70–1.84)	1.16 (0.67–2.00)
Meloxicam				
Current	149	402	1.46 (1.20–1.76)	1.24 (0.99–1.55)
Recent	75	263	1.14 (0.88–1.48)	1.03 (0.77–1.40)
Past	304	1 388	0.90 (0.79–1.02)	0.83 (0.72–0.96)
COX-2 selective NSAIDs				
Etoricoxib				
Current	20	40	2.11 (1.22–3.65)	2.21 (1.18–4.14)
Recent	4	26	0.64 (0.22–1.84)	0.79 (0.23–2.71)
Past	7	20	1.47 (0.62–3.49)	1.17 (0.40–3.42)
Rofecoxib				
Current	235	576	1.60 (1.37–1.87)	1.44 (1.20–1.72)
Recent	67	220	1.27 (0.97–1.68)	1.33 (0.98–1.83)
Past	202	892	0.93 (0.79–1.08)	0.83 (0.70–0.99)
Celecoxib				
Current	124	393	1.23 (1.00–1.51)	1.06 (0.83–1.34)

Continued

Table 3. *Continued*

	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Recent	47	193	0.99 (0.72–1.36)	0.95 (0.65–1.37)
Past	166	741	0.92 (0.77–1.09)	0.90 (0.74–1.09)
Multiple NSAIDs				
Current	155	385	1.66 (1.37–2.00)	1.56 (1.26–1.94)
Recent	34	116	1.18 (0.80–1.74)	1.03 (0.66–1.61)
Past	2 124	8 477	1.06 (1.01–1.12)	0.97 (0.92–1.03)

[a]Adjusted for diabetes mellitus, rheumatoid arthritis, CAD, hypertension, and the use of a β-blocker, a statin, hormone replacement therapy, and clopidogrel 4 months prior the index day.
[b]Current use denotes the supply of the last prescription, counted in DDD, covered the index day.
[c]Recent denotes the supply ended in the days 1–30 prior the index day.
[d]'Past' denotes the supply ended latest 31 days prior the index day.
[e]Aceclofenac, mefenamic acid, tenoxicam, and tiaprofenic acid.

Table 4 Risk of first time MI among current users of NSAIDs stratified by the duration of continuous therapy (days) in categories

	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Non-users	20 645	92 524	1.00 (Reference)	1.00 (Reference)
Any NSAIDs				
1–14	542	1 509	1.55 (1.39–1.73)	1.39 (1.23–1.58)
15–30	436	1 344	1.37 (1.22–1.54)	1.22 (1.06–1.40)
31–90	670	1 807	1.43 (1.29–1.58)	1.25 (1.11–1.41)
91–180	631	1 551	1.74 (1.57–1.93)	1.54 (1.36–1.74)
Conventional NSAIDs[b]				
1–14	358	1 033	1.49 (1.31–1.70)	1.37 (1.17–1.60)
15–30	313	984	1.36 (1.18–1.56)	1.24 (1.05–1.46)
31–90	474	1 439	1.40 (1.25–1.57)	1.20 (1.05–1.37)
91–180	470	1 179	1.76 (1.56–1.98)	1.58 (1.37–1.82)
Semi-selective NSAIDs[c]				
1–14	125	311	1.79 (1.42–2.25)	1.56 (1.18–2.05)
15–30	68	210	1.45 (1.07–1.97)	1.30 (0.90–1.88)
31–90	72	205	1.54 (1.14–2.09)	1.43 (1.00–2.06)
91–180	68	129	1.93 (1.38–2.69)	1.57 (1.06–2.31)
COX-2 selective NSAIDS[d]				
1–14	59	165	1.56 (1.12–2.17)	1.32 (0.88–1.96)
15–30	55	150	1.22 (0.86–1.73)	0.88 (0.58–1.34)
31–90	61	163	1.74 (1.24–2.44)	1.68 (1.12–2.51)
91–180	93	243	1.41 (1.08–1.84)	1.23 (0.89–1.70)

[a]Adjusted for diabetes mellitus, rheumatoid arthritis, CAD, hypertension, and the use of a β-blocker, a statin, hormone replacement therapy, and clopidogrel 4 months prior the index day.
[b]Conventional NSAIDs: diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, mefenamic acid, piroxicam, tenoxicam, tolfenamic acid, aceclofenac, tiaprofenic acid, and mefenamic acid.
[c]Semi-selective NSAIDs: etodolac, nabumetone, nimesulide, and meloxicam.
[d]COX-2 selective NSAIDs: rofecoxib, celecoxib, valdecoxib, and etoricoxib.

Though the association between MI and the use of an NSAID appears to be a class effect, the risk level varied between substances. The elevated risk of MI from rofecoxib found in our study (AOR 1.44; 95% CI 1.20–1.72) was at the same level as found in other observational studies that demonstrated a positive relationship.[1,2,9,10,16,17] In the prospective APPROVE trial, the relative risk of all cardiac events reflecting the risk of MI in the users of rofecoxib 25 mg daily compared with placebo was somewhat higher at 2.8 (95% CI 1.44–5.45).[18] In the APC trial, the risk of serious cardiovascular events from celecoxib was dose-related.[19] In accordance with this, our results demonstrated a significant association of MI with rofecoxib, but not with celecoxib at a DDD of 200 mg for celecoxib.

The relatively high risk of MI associated with etoricoxib (2.21; 1.18–4.14) in our study still needs to be interpreted with caution because of the small number of users, and hence the wide CI. However, it is in agreement with a recent cohort study based on the United Kingdom General Practice Research Database where the current (14-day period before the index date) use of etoricoxib was associated with MI by the risk ratio of 2.09 (95% CI 1.10–3.97).[20] Instead, numerous persons were using nimesulide or ibuprofen in our study, the most frequently prescribed NSAIDs in Finland in 2002,[21] resulting in narrow CI and clear statistical significance of the risk association (*Table 3*).

Different observations were made among recent users of NSAIDs. No general trend for an associated risk with MI

could be identified; the only significant associations found were with indomethacin, naproxen, and ketoprofen.

Our results do not support the view that COX-selectivity alone determines the cardiovascular adverse effects of NSAIDs, at least concerning MI. It has been postulated that COX-2 selective NSAIDs might increase the risk of cardiovascular thrombotic events by blocking the formation of vasodilatory prostacyclin and leaving the proaggregatory COX-1-mediated formation of thromboxane relatively unaffected.[22] In addition, according to a study in rabbits, COX-2 is activated in cardiac ischaemia and this has been postulated to have a cardioprotective function; the activation is antagonized by celecoxib.[23] Furthermore, recent findings in mice suggest that adiponectin protects the heart from ischaemia-reperfusion injury by a COX-2-mediated mechanism, and that COX-2 inhibition reverses this protective effect.[24] Both COX-2 selective and non-selective NSAIDs inhibit the formation of COX-2. Hence, if the adverse effects are mediated mainly by inhibition of COX-2, independently on the balance between prostacyclin and thromboxane as suggested by the latter studies, the use of non-selective and COX-2 selective NSAIDs could be equally associated with the risk of MI as found by us. Nevertheless, COX-selectivity is an *in vitro* measure, and *in vivo* pharmacokinetic processes such as metabolism and differences in tissue distribution complicate its interpretation.

We postulate that the risk associated with the long-term duration of NSAID therapy might be mediated by an increase in blood pressure. Both conventional and COX-2 selective NSAIDs have been reported to elevate blood pressure,[25–27] and to expose users to cardiac failure,[28] or aggravate it.[29,30] Both hypertension and cardiac failure may predispose a patient to a cardiac event. The effect of hypertension may be rapid; during the first 6 months of an anti-hypertensive treatment even a modest decrease in the blood pressure has been shown to decrease the risk of MI in patients with cardiovascular risk factors.[31]

An observational study like ours cannot of course define the mechanism behind the association of NSAID use and MI. Whatever the mechanism might be, our findings clearly indicate that the risk is reversible and associated with the presence of the drug in the body; the closer the proximity of the prescription, the larger the effect.

To our knowledge, this is the largest population-based observational study thus far on the cardiovascular risk associated with the NSAIDs. In Finland, both cardiovascular mortality and morbidity are higher than in many western societies,[32] which boosted the event rates in our study. The total consumption of NSAIDs is relatively high in Finland, varying from 63.5 DDDs/1000 inhabitants/day in 2000 to 70 in 2003.[33] Therefore, we were able to evaluate the risk on a substance-by-substance basis. The validity of the Hospital Discharge Register we used has recently been verified.[34] The advantage of using register data is that they reflect routine medical practice for the general population, compared with highly selected patients in clinical trials.

As in observational studies in general, there may have been significant unmeasured confounding factors in our study, too. We could not control for the dose, over-the-counter use of aspirin (neither the use for cardioprotection nor pain), ibuprofen or ketoprofen, and the use of non-reimbursed low-price packages of some conventional prescription NSAIDs. Over-the-counter NSAIDs accounted for some 30% of total NSAID consumption in Finland during the study.[35,36] Furthermore, we were unable to adjust for some substantial confounders of MI, such as low-dose aspirin use, smoking, and obesity. However, the findings of a US study indicate that omission of five potential confounders (smoking, aspirin use, obesity, educational attainment, and income level) that are independently associated with MI was not likely to change the interpretation of risk estimates based on health care utilization data when studying the association between COX-2 inhibitors and MI in the elderly.[37]

We could not rule out a protopathic bias, i.e. an inadvertent prescribing of NSAIDs for an early manifestation of MI, or chest pain. Theoretically, this may weaken our conclusion of an observed association, especially when considering the short-term use of NSAIDs. However, we found the risk level to be constantly elevated regardless of the length of use (*Table 4*).

Only MI cases admitted to hospitals were included in our analysis to ensure the validity of diagnosis, and thus fatal MIs outside hospitals and non-fatal MIs cared in health centres were excluded. Missing events due to silent MI and sudden death could have resulted in incomplete case ascertainment, affecting cases and controls similarly.

Our study has several clinical implications. First, as NSAIDs are very widely used, the risks, although modest at the individual level, have to be considered seriously at the population level. NSAIDs are mostly used for symptom relief, which places even more emphasis on their safety profiles. Secondly, choosing a NSAID for patients with several comorbidities becomes a challenging situation for clinicians. Although COX-2 selective NSAIDs seem not to be worse than conventional ones in terms of cardiovascular safety, their gastrointestinal safety in the general population has been challenged.[38] Thirdly, as clinical trials on various NSAIDs large enough to be able to detect rare hazards are hardly realistic, replications of studies similar to ours in other populations are needed.

In conclusion, the present large population-based case–control study demonstrated a modest association of MI with current use of all NSAIDs.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

We thank Hilkka Ruuska and Kristiina Tyrkkö, the Social Insurance Institution, for their data management skills.

Conflict of interest: R. Huupponen has received grants from Kuopio University Pharmacy for the development of web-based clinical pharmacy teaching, and for pharmacokinetic studies in the elderly. T. K.'s employer, the Social Insurance Institution, is the financer and organizer of the national sickness insurance scheme, including drug reimbursements. Other authors have declared no conflict of interests.

References

1. Johnsen SP, Larsson H, Tarone RE, McLaughlin JK, Norgard B, Friis S, Sorensen HT. Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAIDs: a population-based case–control study. *Arch Intern Med* 2005;**165**:978–984.
2. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case–control analysis. *BMJ* 2005;**330**:1366–1370.
3. Ray WA, Stein CM, Hall K, Daugherty JR, Griffin MR. Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study. *Lancet* 2002;**359**:118–123.
4. Schlienger RG, Jick H, Meier CR. Use of non-steroidal anti-inflammatory drugs and the risk of first-time acute myocardial infarction. *Br J Clin Pharmacol* 2002;**54**:327–332.
5. Solomon DH, Glynn RJ, Levin R, Avorn J. Non-steroidal anti-inflammatory drug use and acute myocardial infarction. *Arch Intern Med* 2002;**162**:1099–1104.
6. Mamdani M, Rochon P, Juurlink DN, Anderson GM, Kopp A, Naglie G, Austin PC, Laupacis A. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. *Arch Intern Med* 2003;**163**:481–486.
7. Garcia Rodriguez LA, Varas-Lorenzo C, Maguire A, Gonzalez-Perez A. Non-steroidal anti-inflammatory drugs and the risk of myocardial infarction in the general population. *Circulation* 2004;**109**:3000–3006.
8. Fischer LM, Schlienger RG, Matter CM, Jick H, Meier CR. Current use of non-steroidal anti-inflammatory drugs and the risk of acute myocardial infarction. *Pharmacotherapy* 2005;**25**:503–510.
9. Graham DJ, Campen D, Hui R, Spence M, Cheetham C, Levy G, Shoor S, Ray WA. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case–control study. *Lancet* 2005;**365**:475–481.
10. Levesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with cyclooxygenase-2 inhibitors: a population study of elderly adults. *Ann Intern Med* 2005;**142**:481–489.
11. ATC/DDD system. WHO. Available at: **http://www.whocc.no/atcddd/ (30 August 2005).**
12. Gabriel S, Jaakkimainen L, Bombardier C. Risk of serious gastrointestinal complications related to use of non-steroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med* 1991;**115**:787–796.
13. Henry D, Lim L-Y, Garcia Rodrigues L, Gutthann S, Carson J, Griffin M, Savage R, Logan R, Moride Y, Hawkey C, Hill S, Fries J. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996;**312**:1563–1566.
14. Hernandez-Diaz S, Rodriguez LA. Association between non-steroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med* 2000;**160**:2093–2099.
15. Www Service of Cardiovascular Diseases. Available at: **http://www.ktl.fi/portal/english/osiot/public_health/monitoring___promotion/registers/cardiovascular_diseases/.**
16. Solomon DH, Schneeweiss S, Glynn RJ, Kiyota Y, Levin R, Mogun H, Avorn J. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation* 2004;**109**:2068–2073.
17. Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet* 2002;**360**:1071–1073.
18. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanas A, Konstam MA, Baron JA. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;**352**:1092–1102.
19. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;**352**:1071–1080.
20. Andersohn F, Suissa S, Garbe E. Use of first- and second-generation cyclooxygenase-2-selective non-steroidal anti-inflammatory drugs and risk of acute myocardial infarction. *Circulation* 2006;**113**:1950–1957.
21. The National Agency for Medicines and the Social Insurance Institution. *Finnish Statistics on Medicines 2002*. Helsinki; 2003.
22. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001;**345**:433–442.
23. Shinmura K, Tang XL, Wang Y, Xuan YT, Liu SQ, Takano H, Bhatnagar A, Bolli R. Cyclooxygenase-2 mediates the cardioprotective effects of the late phase of ischaemic preconditioning in conscious rabbits. *Proc Natl Acad Sci USA* 2000;**97**:10197–10202.
24. Shibata R, Sato K, Pimentel DR, Takemura Y, Kihara S, Ohashi K, Funahashi T, Ouchi N, Walsh K. Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. *Nat Med* 2005;**11**:1096–1103.
25. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of non-steroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* 1993;**153**:477–484.
26. Johnson AG, Nguyen TV, Day RO. Do non-steroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med* 1994;**121**:289–300.
27. Aw TJ, Haas SJ, Liew D, Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. *Arch Intern Med* 2005;**165**:490–496.
28. Mamdani M, Juurlink DN, Lee DS, Rochon PA, Kopp A, Naglie G, Austin PC, Laupacis A, Stukel TA. Cyclo-oxygenase-2 inhibitors vs. non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. *Lancet* 2004;**363**:1751–1756.
29. Feenstra J, Heerdink ER, Grobbee DE, Stricker BH. Association of non-steroidal anti-inflammatory drugs with first occurrence of heart failure and with relapsing heart failure: the Rotterdam Study. *Arch Intern Med* 2002;**162**:265–270.
30. Heerdink ER, Leufkens HG, Herings RM, Ottervanger JP, Stricker BH, Bakker A. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. *Arch Intern Med* 1998;**158**:1108–1112.
31. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;**363**:2022–2031.
32. WHO. WHO Mortality Database. Available at: **http://www3.who.int/whosis/mort/table1_process.cfm (1 January 2006).**
33. Drug consumption statistics in Finland. Available at: **http://www.nam.fi/english/medicines/drug_consumption/index.html (1 January 2006).**
34. Pajunen P, Paakkonen R, Juolevi A, Hamalainen H, Keskimaki I, Laatikainen T, Moltchanov V, Niemi M, Rintanen H, Salomaa V. Trends in fatal and non-fatal coronary heart disease events in Finland during 1991–2001. *Scand Cardiovasc J* 2004;**38**:340–344.
35. The National Agency for Medicines and the Social Insurance Institution. *Finnish Statistics on Medicines 2000*. Helsinki; 2001.
36. The National Agency for Medicines and Social Insurance Institution. *The Finnish Statistics on Medicines 2003*. Helsinki; 2004.
37. Schneeweiss S, Glynn RJ, Tsai EH, Avorn J, Solomon DH. Adjusting for unmeasured confounders in pharmacoepidemiologic claims data using external information: the example of COX2 inhibitors and myocardial infarction. *Epidemiology* 2005;**16**:17–24.
38. Hippisley-Cox J, Coupland C, Logan R. Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case–control analysis. *BMJ* 2005;**331**:1310–1316.