Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data

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ABSTRACT

OBJECTIVE

To characterise the determinants, time course, and risks of acute myocardial infarction associated with use of oral non-steroidal anti-inflammatory drugs (NSAIDs).

DESIGN

Systematic review followed by a one stage bayesian individual patient data meta-analysis.

DATA SOURCES

Studies from Canadian and European healthcare databases.

REVIEW METHODS

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

EXPOSURE AND OUTCOMES

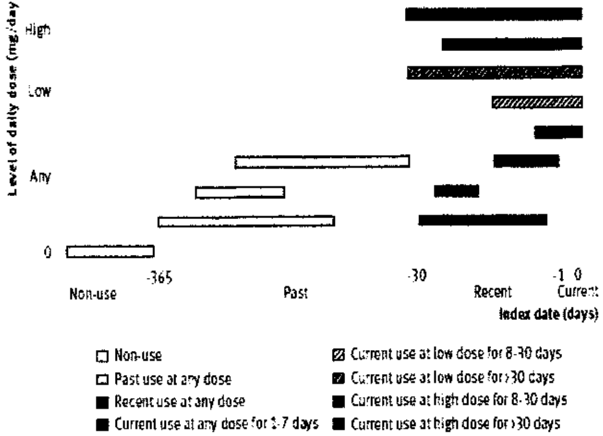
Drug exposure was modelled as an indicator variable incorporating the specific NSAID, its recency, duration of use, and dose. The outcome measures were the summary adjusted odds ratios of first acute myocardial infarction after study entry for each category of NSAID use at index date (date of acute myocardial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

RESULTS

A cohort of 446 763 individuals including 61 460 with acute myocardial infarction was acquired. Taking any dose of NSAIDs for one week, one month, or more than a month was associated with an increased risk of myocardial infarction. With use for one to seven days the probability of increased myocardial infarction risk (posterior probability of odds ratio >1.0) was 92% for celecoxib, 97% for ibuprofen, and 99% for diclofenac, naproxen, and rofecoxib. The corresponding odds ratios (95% credible intervals) were 1.24 (0.91 to 1.82) for celecoxib, 1.48 (1.00 to 2.26) for ibuprofen, 1.50 (1.06 to 2.04) for diclofenac, 1.53 (1.07 to 2.33) for naproxen, and 1.58 (1.07 to 2.17) for rofecoxib. Greater risk of myocardial infarction was documented for higher dose of NSAIDs. With use for longer than one month, risks did not appear to exceed those associated with shorter durations.

CONCLUSIONS

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


Level of daily dose (mg/day)
High
Low
Any
0
-365
-30
-1
0
Non-use
Past
Recent
Current
Index date (days)
☐ Non-use
☐ Past use at any dose
■ Recent use at any dose
■ Current use at any dose for 1-7 days
▨ Current use at low dose for 8-30 days
▨ Current use at low dose for >30 days
■ Current use at high dose for 8-30 days
■ Current use at high dose for >30 days

Celecoxib (low dose ≤200 mg, high dose >200 mg)
Diclofenac (low dose ≤100 mg, high dose >100 mg)
Ibuprofen (low dose ≤1200 mg, high dose >1200 mg)
Naproxen (low dose ≤750 mg, high dose >750 mg)
Rofecoxib (low dose ≤25 mg, high dose >25 mg)

Fig 1 | Multidimensional indicator categories of non-steroidal anti-inflammatory drug (NSAID) use defined by recency of use, daily dose, and duration

Table 1 | Prevalence of confounders for association between exposure to non-steroidal anti-inflammatory drugs and acute myocardial infarction outcome at index date documented in each healthcare database study. Values are numbers (percentages) unless stated otherwise

Confounders	RAMQ (n=233 816)	Finland (n=172 219)	GPRD (n=17 561)	Saskatchewan (n=23 167)
Mean (SD) age at index date (years)	77.8 (6.1)	68.9 (12.7)	70.2 (11.5)	58.1 (12.8)
Median (interquartile range) age at index date (years)	78 (73-83)	70 (60-78)	71 (62-79)	56 (47-69)
Male sex	118 492 (50.7)	107 225 (62.3)	10 349 (58.9)	11 831 (51.1)
Comorbidities:				
Diabetes	40 812 (17.5)	12 911 (7.5)	1933 (11.0)	1663 (7.2)
Hyperlipidaemia	72 008 (30.8)	19 212 (11.2)	2397 (13.7)	6738 (29.1)
Hypertension	108 916 (46.6)	44 702 (26.0)	5944 (33.9)	9181 (39.6)
Previous myocardial infarction	17 025 (7.3)	NA	NA	1154 (5.0)
Coronary heart disease	79 466 (34.0)	29 998 (17.4)	3731 (21.3)	4972 (21.5)
Congestive heart failure	19 602 (8.4)	NA	NA	1722 (7.4)
Cerebrovascular disease	22 203 (9.5)	NA	1480 (8.4)	1798 (7.8)
Peripheral vascular disease	15 833 (6.8)	NA	NA	706 (3.1)
Chronic obstructive pulmonary disease	53 465 (22.9)	NA	NA	2546 (11.0)
Gastrointestinal ulcer disease	68 062 (29.1)	NA	NA	9419 (40.7)
Gastrointestinal bleed	5696 (2.4)	NA	NA	1039 (4.5)
Acute or chronic renal failure	4102 (1.8)	NA	NA	143 (0.6)
Rheumatoid arthritis	4245 (1.8)	5180 (3.0)	574 (3.3)	1277 (5.5)
Concomitant drug treatment:				
Oral corticosteroids	5301 (2.3)	NA	NA	NA
Clopidogrel	4007 (1.7)	172 (0.1)	NA	NA
Cardioprotective aspirin	53 738 (23.0)	NA	NA	NA

NA=systematically missing in original study

Table 2 | Risk of acute myocardial infarction with various non-steroidal anti-inflammatory drug (NSAID) multidimensional indicator categories of use defined by recency of use, daily dose, and duration in each healthcare database study and in pooled studies

	RAMQ (n=233 816) (21 256 cases)		Finland (n=172 219) (33 309 cases)		GPRD (n=17 560) (3463 cases)		Saskatchewan (n=23 167) (3252 cases)		Pooled studies (n=446 763) (61 460 cases)
Variables*†	No (%) of individuals	Adjusted odds ratio‡ (95% CrI)	No (%) of individuals	Adjusted odds ratio‡ (95% CrI)	No (%) of individuals	Adjusted odds ratio‡ (95% CrI)	No (%) of individuals	Adjusted odds ratio‡ (95% CrI)	Adjusted odds ratio (95% CrI)
Non-use									
No NSAID in year PID	[illegible] (73.8)	1 (reference)	[illegible]	1 (reference)	[illegible]	1 (reference)	[illegible] (81.9)	1 (reference)	1 (reference)
Celecoxib									
Past									
Ended 31-365 days PID	[illegible]	1.05 ([illegible])	2575 ([illegible])	1.01 (0.93 to 1.10)	[illegible]	1.04 (0.91 to 1.20)	[illegible]	[illegible]	[illegible]
Recent									
Ended 1-30 days PID	[illegible]	[illegible]	[illegible]	[illegible]	NA	[illegible]	[illegible]	[illegible]	[illegible]
Current									
Any dose for 1-7 days	[illegible]	[illegible]	NA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
≤200 mg/day for 8-30 days	[illegible]	[illegible]	155 ([illegible])	[illegible]	[illegible]	[illegible]	[illegible]	1.26 (0.97 to 1.94)	[illegible]
>200 mg/day for 8-30 days	[illegible]	[illegible]	NA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
≤200 mg/day for >30 days	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
>200 mg/day for >30 days	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Diclofenac									
Past									
Ended 31-365 days PID	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Recent									
Ended 1-30 days PID	[illegible]	[illegible]	[illegible]	[illegible]	NA	[illegible]	[illegible]	[illegible]	[illegible]
Current									
Any dose for 1-7 days	[illegible]	[illegible]	NA	[illegible]	[illegible]	1.44 (0.97 to 1.96)	[illegible]	[illegible]	[illegible]
≤100 mg/day for 8-30 days	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
>100 mg/day for 8-30 days	[illegible]	[illegible]	NA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
≤100 mg/day for >30 days	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
>100 mg/day for >30 days	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Ibuprofen									
Past									
Ended 31-365 days PID	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Recent									
Ended 1-30 days PID	[illegible]	[illegible]	[illegible]	[illegible]	NA	[illegible]	[illegible]	[illegible]	[illegible]
Current									
Any dose for 1-7 days	[illegible]	[illegible]	NA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
≤1200 mg/day for 8-30 days	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
>1200 mg/day for 8-30 days	[illegible]	[illegible]	NA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
≤1200 mg/day for >30 days	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
>1200 mg/day for >30 days	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Naproxen									
Past									
Ended 31-365 days PID	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Recent									
Ended 1-30 days PID	[illegible]	[illegible]	[illegible]	[illegible]	NA	[illegible]	[illegible]	[illegible]	[illegible]
Current									
Any dose for 1-7 days	[illegible]	[illegible]	NA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
≤750 mg/day for 8-30 days	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
>750 mg/day for 8-30 days	[illegible]	[illegible]	NA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
≤750 mg/day for >30 days	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
>750 mg/day for >30 days	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Rofecoxib									
Past									
Ended 31-365 days PID	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Recent									
Ended 1-30 days PID	[illegible]	[illegible]	[illegible]	[illegible]	NA	[illegible]	[illegible]	[illegible]	[illegible]
Current									
Any dose for 1-7 days	[illegible]	[illegible]	NA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
≤25 mg/day for 8-30 days	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
>25 mg/day for 8-30 days	[illegible]	[illegible]	NA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
≤25 mg/day for >30 days	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
>25 mg/day for >30 days	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

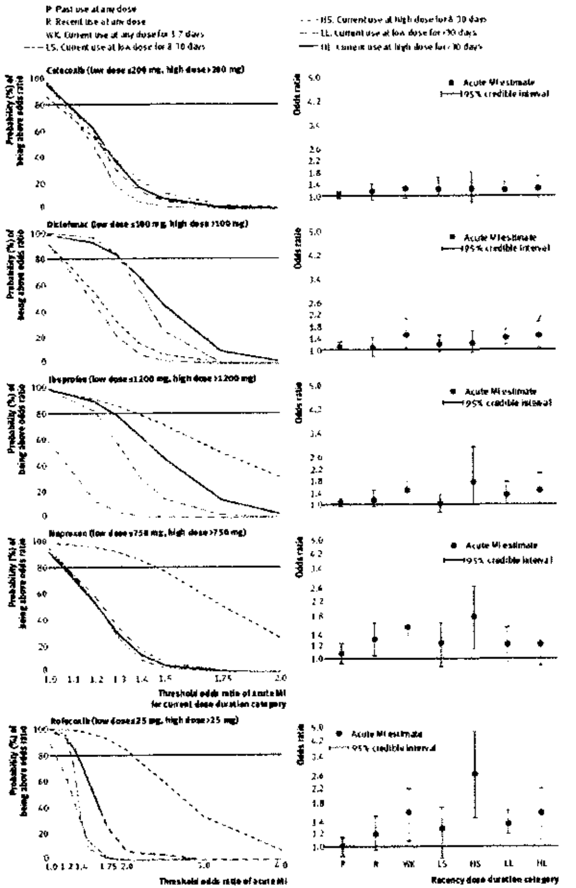


Fig 2 | Plot of probability of exceeding odds ratios of acute myocardial infarction (MI) for exposure categories corresponding to current use for each non-steroidal anti-inflammatory drug (NSAID) versus non-use and corresponding forest plot for risk of acute myocardial infarction for each exposure category in pooled studies

Table 3 | Probability that risk of acute myocardial infarction is increased (odds ratio >1.0) and probability of this risk increase being greater than 50% (odds ratio >1.5) according to dose and duration of non-steroidal anti-inflammatory drug use

	Bayesian posterior probability (%) of summary adjusted odds ratio of acute myocardial infarction	
Current use category	>1.0	>1.5
Celecoxib:		
Any dose for ≤7 days	92.6	17.1
≤200 mg/day for 8-30 days	97.4	6.1
>200 mg/day for 8-30 days	85.8	12.5
≤200 mg/day for >30 days	97.9	1.8
>200 mg/day for >30 days	95.0	8.0
Diclofenac:		
Any dose for ≤7 days	98.6	50.1
≤100 mg/day for 8-30 days	93.3	2.0
>100 mg/day for 8-30 days	92.7	7.0
≤100 mg/day for >30 days	99.9	25.2
>100 mg/day for >30 days	98.8	45.6
Ibuprofen:		
Any dose for ≤7 days	97.1	47.1
≤1200 mg/day for 8-30 days	59.3*	0.6*
>1200 mg/day for 8-30 days	97.5	70.8
≤1200 mg/day for >30 days	98.0	14.5
>1200 mg/day for >30 days	98.3	45.3
Naproxen:		
Any dose for ≤7 days	98.8	54.9
≤750 mg/day for 8-30 days	92.1	7.1
>750 mg/day for 8-30 days	99.2	77.2
≤750 mg/day for >30 days	96.9	3.0
>750 mg/day for >30 days	91.6	5.0
Rofecoxib:		
Any dose for ≤7 days	98.8	63.6
≤25 mg/day for 8-30 days	88.6	14.0
>25 mg/day for 8-30 days	99.8	96.9
≤25 mg/day for >30 days	99.9	9.0
>25 mg/day for >30 days	99.0	59.3

*Sparse data