Use of nonsteroidal anti-inflammatory drugs and the risk of first-time acute myocardial infarction

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Aims Aspirin decreases the risk of clinical manifestations of atherothrombosis. This effect is mainly due to inhibition of platelet aggregation and potentially due to anti-inflammatory properties of aspirin. To evaluate whether use of non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) may also be associated with a decreased risk of first-time acute myocardial infarction (AMI), we performed a population-based case-control analysis using the United Kingdom-based General Practice Research Database (GPRD)

Methods We identified first-time AMI-patients free of preexisting diagnosed cardiovascular or metabolic diseases. We compared use of NSAIDs prior to the index date between cases and control patients who were matched to cases on age, gender, practice and calendar time.

Results A total of 3319 cases (≤75 years) with a diagnosis of first-time AMI between 1992 and 1997 and 13 139 controls (matched to cases on age, sex, general practice attended, calendar time, years of prior history in the GPRD) were included. Overall, the relative risk estimate of AMI (adjusted for smoking, body mass index, hormone replacement therapy and aspirin) in current NSAID users was 1.17 (95% CI 0.99, 1.37). Long-term current NSAID use (≥30 prescriptions) yielded an adjusted odds ratio (OR) of 1.20 (95% CI 0.94, 1.55). Stratification by age (<65 years *vs* ≥65 years) and sex did not materially change the results.

Conclusions Our findings indicate that current NSAID exposure in patients free of diagnosed cardiovascular or metabolic conditions predisposing to cardiovascular diseases does not decrease the risk of AMI.

Keywords: aspirin, case-control study, inflammation, myocardial infarction, nonsteroidal anti-inflammatory agents

Introduction

Aspirin has been thoroughly evaluated as an antiplatelet drug to prevent or treat atherothrombosis [1]. It has been found to prevent vascular death by about 15% and non-fatal vascular events by about 30% in a recent meta-analysis of more than 50 secondary prevention trials [2]. The antiplatelet effect of aspirin is due to irreversible inhibition of cyclooxygenase-1 (COX-1) in platelets. This results in an inhibition of platelet thromboxane A_2 (TXA_2) production, a potent inducer of platelet aggregation [3]. Additionally, anti-inflammatory effects by inhibition of cyclooxygenase-2 (COX-2) activity have been suggested as a potential additional mechanism of aspirin for preventing ischaemic heart disease [4, 5]. Studies have indicated that the baseline plasma concentration of C-reactive protein (CRP), a systemic marker for underlying inflammation, may predict the risk of future acute myocardial infarction (AMI) [5, 6] and that the risk reduction associated with aspirin use appears directly related to the CRP level [5]. Thus, it has been suggested that anti-inflammatory agents other than aspirin may also have a role in preventing cardiovascular disease [5].

Non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in a variety of disorders associated with inflammation and acute or chronic pain. The principal pharmacological mechanism by which NSAIDs exert their therapeutic effect is by reversible, competitive COX-inhibition. With the exception of newer, more selective COX-inhibitors [7], most currently used

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NSAIDs inhibit COX-1 and COX-2 nonselectively [8]. By reversible inhibition of COX-1, NSAIDs too may decrease the production of TXA_2 in platelets and inhibit platelet aggregation [1, 9]. In addition, due to their anti-inflammatory effects NSAIDs might also reduce the risk of AMI through reduction of chronic systemic inflammation. However, information is scarce whether nonaspirin NSAIDs may have beneficial cardioprotective effects of clinical relevance. In a recent nested case-control analysis exposure to nonaspirin NSAIDs did not alter the risk of first-time myocardial infarction in postmenopausal women compared with nonusers of NSAIDs [10]. The study included women with major risk factors for myocardial infarction such as diabetes mellitus, hypertension, and family history of coronary heart disease [10]. Another recent epidemiological study in patients 50–84 years of age including patients with preexisting cardiovascular disease found no evidence that exposure to nonaspirin NSAIDs reduces the risk of serious coronary heart disease events [11].

The aim of the present study was to evaluate further whether current and/or long-term exposure to nonaspirin NSAIDs may modify the risk of first-time AMI in both men and women 75 years of age or younger who are free of diagnosed cardiovascular or metabolic conditions predisposing to cardiovascular disease.

Methods

Study population and data source

Data were derived from the United Kingdom-based General Practice Research Database (GPRD), which has been previously described in detail elsewhere [12–14]. Since 1987, more than 3 million residents in England and Wales have been registered with selected general practitioners (GPs) who have agreed to provide data for research purposes to the GPRD. The age- and sex-distribution of the patients enrolled is representative of the entire UK-population. The information recorded includes patient demographics and characteristics (e.g. height, weight, smoking status), symptoms, clinical diagnoses, consultant referrals, hospitalizations, and drug prescriptions. A coded drug dictionary based on the UK Prescription Pricing Authority dictionary is used for recording prescriptions including information on the route of administration, dose, and number of tablets for each prescription. The GPs generate prescriptions directly from the computer and they are recorded in each patient's computerized profile. On request, hospital discharge and referral letters are available for review to validate the diagnoses recorded in the computer record.

The GPRD is administered by the Medicines Control Agency. The database currently encompasses some 30 million person-years of follow-up; it has been the source for numerous epidemiological studies in recent years, and the accuracy and completeness of these data have been well documented and validated [15, 16]. GPRD data have been used in several recent studies investigating risk factors for AMI [17–20] or effects of NSAIDs [21, 22].

Case definition and ascertainment

Potential cases were selected on the basis of a first-time diagnosis of AMI (by computer-recorded Oxford Medical Information System [OXMIS] codes, mapped onto *International Classification of Diseases [ICD]* codes) between January 1, 1992, and October 31, 1997. We restricted the study to patients who were ≤ 75 years of age at the time of the diagnosis of AMI (index date), and who were free of metabolic or cardiovascular diseases predisposing to AMI. Therefore, all patients with a diagnosis of AMI, angina pectoris, unexplained chest pain, cardiac arrhythmias, congestive heart failure, stroke, intermittent claudication, venous thromboembolism, chronic renal disease, hypertension, hyperlipidaemia, diabetes mellitus, or connective-tissue disorders recorded >60 days before the AMI were excluded. All cases had to be registered on the database for at least 3 years before the index date. Any information with regard to exposure to NSAIDs was concealed when the records were reviewed to identify potential cases.

In previous studies using GPRD data [17–20], the computer-recorded diagnosis of a first AMI was validated for a random sample of approximately 450 patients by reviewing hospital discharge letters. The validity of the AMI-diagnosis was confirmed for a high percentage ($>90\%$) of cases identified on computer and after review of computer records by at least two of the following documented diagnostic criteria: Characteristic chest pain, characteristic changes in the electrocardiogram, characteristic serial rises in the concentrations of cardiac enzymes, an arteriogram documenting a recent coronary occlusion, or fibrinolytic therapy. Therefore, we decided to include all the potential cases that we identified through a manual review of computerized patient records.

Controls

Four controls were matched to each case on age (same year of birth), sex, the practice attended, and calendar time by using the same index date (i.e. the date of the AMI-diagnosis of the corresponding case) for matched controls as for cases. The same exclusion criteria were applied to controls as to cases (i.e. recorded history on the GPRD of less than 3 years, and/or circulatory or

metabolic diseases predisposing for AMI recorded >60 days before the index date).

Exposure definition

For each case and control the exposure history to NSAIDs (i.e. acemetacin, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, naproxen, piroxicam, sulindac, tenoxicam and tiaprofenic acid) was assessed. A patient was defined as 'current user' if the supply of the last prescription for an NSAID prior to the index date ended at or after the index date. Subjects were defined as 'recent users' when the supply ended between 1 and 29 days and as 'past users' when the supply ended 30 or more days prior to the index date; 'nonusers' were defined as patients who had no prescription for an NSAID in the medical record before the index date.

Statistical analysis

We conducted a matched analysis (conditional logistic regression model) using the software program SAS, Version 6.12 (SAS Institute Inc., Cary, NC). Relative risk estimates (odds ratios, OR) are presented with 95% confidence intervals (95% CI).

For each case and control, the potential confounders body mass index (BMI) (<25, 25–29.9, ≥30 kg m^{-2}, unknown) and smoking status (never, ex, current, unknown) were assessed from the patient profiles. We also assessed aspirin use and longer-term use of hormone replacement therapy and adjusted the final multivariate models for these covariates. By doing stratified regression analyses, we further evaluated potential effect modification by age (<65 years, ≥65 years) and sex.

Results

We included 3315 cases with AMI and 13 139 controls in the analysis. Table 1 shows the characteristics of cases and controls including age, sex, smoking status and body mass index. Overall, cases were predominantly male, and the majority (57%) was under the age of 65. Current smoking status and high BMI (≥30) were substantially more prevalent in cases than controls. Current use of aspirin at the index date (OR 0.6, 95% CI 0.4, 1.0) and longer-term use (≥10 prescriptions prior to the index date) of hormone replacement therapy in women (OR 0.6, 95% CI 0.4, 0.9) were also associated with altered risk estimates for AMI.

The relative risk estimates (odds ratios, OR) of developing a first-time AMI in relation to current, recent past or past exposure to NSAIDs are shown in Table 2. Overall, current exposure to NSAIDs was not associated with a reduced risk of AMI compared with the reference group of nonusers (adjusted OR 1.17; 95% CI 0.99, 1.37). Stratification by duration of exposure did not yield materially different results in current users. Long-term NSAID use (≥30 prescriptions) yielded an adjusted relative risk estimate of 1.21 (95% CI 0.94, 1.55). Stratification by dose indicated that patients currently exposed to high NSAID doses may even have a slightly increased risk of AMI (adjusted OR 1.29; 95% CI 1.05, 1.58).

We also observed a suggestion of an increased relative risk estimate of first-time AMI in the group of recent past users of NSAIDs (adjusted OR 1.26; 95% CI 1.01, 1.57). The stratification by duration of therapy indicated that this association was based on the subset of cases and controls with ≥30 prescriptions (adjusted OR 2.71; 95% CI 1.75, 4.22). For past users, stratification by duration again showed an increased risk in the subgroup of patients with ≥30 prescriptions (adjusted OR 2.33; 95% CI 1.57, 3.46), but not for those who used less NSAIDs. These results were very similar in different age groups (<65 years of age *vs* ≥65 years of age) and in both genders.

We additionally explored the risk of AMI associated with current exposure to individual NSAIDs (Table 3). None of the individual agents was associated with a

Table 1 Characteristics of cases and controls in relation to risk of developing acute myocardial infarction (AMI).

Characteristics	*Cases, Number (%) (n = 3315)*	*Controls, Number (%) (n = 13 139)*	*Adjusted⋆ odds ratio (95% CI)*
Age (years)			
<40	91 (2.8)	367 (2.8)	
40–49	417 (12.6)	1656 (12.6)	
50–59	830 (25.0)	3314 (25.2)	
60–69	1227 (37.0)	4832 (36.8)	
70–75	750 (22.6)	2970 (22.6)	
Sex			
Male	2452 (74.0)	9715 (73.9)	
Female	863 (26.0)	3424 (26.1)	
Smoking status			
Non	1079 (32.6)	6204 (47.2)	1.0 (Referent)
Current	1100 (33.2)	2574 (19.6)	2.7 (2.4–2.9)
Ex	376 (11.3)	1353 (10.3)	1.6 (1.4–1.9)
Unknown	760 (22.9)	3008 (22.9)	1.5 (1.3–1.7)
Body mass index (kg m^{-2})			
<25	885 (26.7)	4240 (32.3)	1.0 (Referent)
25–29.9	1100 (33.2)	4004 (30.5)	1.4 (1.3–1.6)
≥ 30	387 (11.7)	1208 (9.2)	1.7 (1.4–1.9)
Unknown	943 (28.4)	3687 (28.0)	1.2 (1.1–1.4)
Died from AMI†	467 (14.1)	–	

⋆ adjusted for all covariates in the table in the same multivariate model
† autopsy finding (patient did not reach hospital alive)

Table 2 Risk of first-time acute myocardial infarction associated with current, recent past or past exposure to anti-inflammatory drugs (NSAIDs) stratified by duration of NSAID therapy (expressed as number of prescriptions) and dose.

NSAID use (number of prescriptions)	*Cases (n = 3315)*	*Controls (n = 13 139)*	*Adjusted⋆ odds ratio (95% CI)*
Non-users	1502	6236	1.0 (Referent)
Current NSAIDs	242	825	1.17 (0.99–1.37)
1–4	34	111	1.30 (0.87–1.93)
5–9	45	157	1.10 (0.78–1.54)
10–19	36	145	0.97 (0.66–1.42)
20–29	38	119	1.31 (0.89–1.91)
30 +	89	293	1.21 (0.94–1.55)
Recent past NSAIDs	118	377	1.26 (1.01–1.57)
1–4	25	105	0.95 (0.61–1.48)
5–9	21	95	0.90 (0.55–1.46)
10–19	23	77	1.13 (0.70–1.83)
20–29	14	44	1.33 (0.72–2.46)
30 +	35	56	2.71 (1.75–4.22)
Past NSAIDs	1453	5701	1.04 (0.96–1.13)
1–4	984	4002	1.02 (0.93–1.12)
5–9	311	1190	1.06 (0.92–1.22)
10–19	91	352	1.00 (0.78–1.28)
20–29	26	82	1.26 (0.80–2.01)
30 +	41	75	2.33 (1.57–3.46)
Current by dose			
Low dose†	98	367	1.02 (0.81–1.29)
High dose‡	144	458	1.29 (1.05–1.58)

⋆ adjusted for smoking status, body mass index, hormone replacement therapy and aspirin

† low dose (dose per tablet): acemetacin 60 mg, diclofenac < 100 mg, diflunisal 250 mg, etodolac 200 mg, fenbufen 300 mg, fenoprofen 300 mg, flurbiprofen 100 mg, ibuprofen ≤ 200 mg, indomethacin ≤ 75 mg, ketoprofen 100 mg, mefenamic acid 250 mg, nabumetone 500 mg, naproxen 275 mg, piroxicam 10 mg, sulindac 100 mg, tenoxicam 20 mg and tiaprofenic acid 200 mg

‡ high dose (dose per tablet): diclofenac 100 mg, diflunisal 500 mg, etodolac 300 mg, fenbufen 450 mg, fenoprofen 600 mg, flurbiprofen 200 mg, ibuprofen > 200 mg, indomethacin 100 mg, ketoprofen 200 mg, mefenamic acid 500 mg, nabumetone 500 mg, naproxen 500 mg, piroxicam 20 mg, and tiaprofenic acid 300 mg

substantially reduced AMI risk. Current naproxen exposure yielded an adjusted OR of 0.68 (95% CI 0.42, 1.13).

Discussion

The present study provides evidence that current exposure to NSAIDs in patients ≤ 75 years of age without a diagnosed prior history of cardiovascular or metabolic disease is not associated with a reduced risk of first-time AMI. Thus, a possible effect of NSAID exposure on platelet aggregation by COX-1 inhibition and/or modification of inflammatory processes does not seem to be of clinical relevance in reducing the AMI risk. The level

Table 3 Risk of first-time acute myocardial infarction in current NSAID users, stratified by individual agents.

NSAID use	*Cases (n = 3315)*	*Controls (n = 13 139)*	*Adjusted⋆ odds ratio (95% CI)*
Non-users	1502	6236	1.0 (Referent)
Individual NSAIDs†			
Ibuprofen	60	204	1.17 (0.87–1.58)
Diclofenac	97	277	1.38 (1.08–1.77)
Piroxicam	10	28	1.65 (0.78–3.49)
Fenbufen	7	13	2.06 (0.80–5.30)
Ketoprofen	15	48	1.39 (0.77–2.51)
Indomethacin	15	56	1.03 (0.58–1.85)
Flurbiprofen	8	14	2.26 (0.93–5.46)
Naproxen	19	105	0.68 (0.42–1.13)

⋆ adjusted for smoking status, body mass index, hormone replacement therapy and aspirin

† only NSAIDs presented with ≥ 5 exposed cases

of COX-1 inhibition by NSAIDs at conventional analgesic dosages may be insufficient to inhibit platelet aggregation *in vivo*.

Our finding of no association with a decreased AMI risk with NSAID exposure is in accordance with a recent follow-up study using Medicaid data from Tennesse. In this study in a high-risk population of people 50 years of age or older (22% of the patients had a diagnosis of a serious cardiovascular disease in the past year before myocardial infarction and 67% used different cardiovascular drugs in the year prior to AMI indicating some kind of pre-existing cardiovascular risk factor) the authors found no evidence for an altered risk of serious coronary heart disease [11]. Multivariate adjusted relative risks for current or former use of nonaspirin NSAIDs were 1.05 (95% CI 0.97, 1.14) and 1.02 (95% CI 0.97, 1.08), respectively. However, there was some indication of an excess risk in association with high dose ibuprofen use.

Additonally, our finding are quite similar to the results of a recent nested case-control analysis looking at NSAID exposure and AMI in postmenopausal women [10]. As in the study by Garcia Rodriguez *et al.* [10], the results of our study indicate that current NSAID use was not associated with a reduced AMI risk; additionally, we also found some tendency towards a slightly increased AMI risk associated with current use of NSAIDs especially in users of high NSAID doses. Statistically significantly increased risk estimates around 2.5 were unexpectedly found in subjects who used NSAIDs on a long-term basis (i.e. ≥ 30 prescriptions) but who stopped NSAID use at some point in time before the index date. Based on the available data we cannot tell whether this is a chance finding, the result of some unknown bias or confounding, or a causal relationship. The latter would

raise the hypothesis that subjects with chronic inflammation, who used NSAIDs for a long time but stopped the therapy for whatever reason, may be at an increased AMI-risk. If this finding were real, it may mean that chronic NSAID use indeed does reduce the AMI risk by suppression of inflammation; thus, current exposure to NSAIDs in subjects with chronic inflammation (i.e. those who regularly take NSAIDs) would reduce the risk from around 3 to 1, but not below 1, leading to an erroneous conclusion that NSAIDs do not lower the AMI risk. This hypothesis is purely speculative and needs further evaluation in future studies.

However, it has been shown that atherosclerosis is a process with inflammatory features [23] and that COX-2 is expressed in human atherosclerotic lesions [4, 24, 25]. It was hypothesized that products of COX-2 may be important in the pathogenesis of atherosclerosis [24], and selective COX-2 inhibitors may potentially have antiatherogenic effects [26].

A recent analysis of randomized trials suggested that current exposure to rofecoxib, a selective COX-2 inhibitor, may increase the risk of AMI as compared with use of naproxen [26]. In one of these studies, the incidence of AMI was lower in the naproxen group than in the rofecoxib group (0.1% *vs* 0.4%; relative risk, 0.2; 95% CI 0.1, 0.7) [27]. If this difference were real, COX-2 inhibitors either increase the AMI risk, or naproxen lowers it. In our study, we had no information on the selective COX-2 inhibitors rofecoxib and celecoxib. However, we compared the AMI risk of current naproxen users to nonusers of any NSAIDs; there was a suggestion of a reduced AMI-risk in naproxen users (OR 0.68, 95% CI 0.42, 1.13), although not statistically significant. Naproxen has been shown to inhibit thromboxane production particularly strongly (by approximately 95%) and platelet aggregation by 88% in healthy volunteers, an effect that is maintained throughout the dosing interval [9]. In addition, naproxen has a particularly long elimination half-life of approximately 14 h [28].

In our study, we were not able to adjust for socioeconomic status or life style habits such as physical activity or dietary information, because this information is not routinely recorded in the GPRD. Since such factors are associated with an altered risk of cardiovascular diseases, they may in theory also be related to NSAID use and thereby potentially confound the association between NSAID use and AMI. Furthermore, we only studied the effect of NSAIDs on the AMI risk in patients without recorded previous cardiovascular or metabolic diseases. This was done because the effect of drugs on the risk of developing a first-time diagnosis of an outcome of interest can best be studied in subjects who are free of clinical risk factors for the disease [29], since preexisting diseases (e.g. hypertension) may both influence the likelihood of using NSAIDs as well as the AMI risk. In addition, it has been shown that use of NSAIDs can elevate blood pressure by about 5 mmHg [30] which might be associated with an increased risk of developing myocardial infarction. This risk elevation may in theory have counterbalanced some risk reduction exerted by NSAIDs, leading to the null result. This theoretically possible pathway – even though speculative – was another reason to exclude a priori subjects with recorded hypertension since we would most likely expect a relevant NSAID effect on blood pressure in subjects with preexisting hypertension.

In summary, we have found evidence that both current use of NSAIDs as well as longer-term use of these drugs does not seem to be associated with a substantially altered risk of developing a first-time diagnosis of AMI in subjects free of recorded clinical risk factors for AMI.

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