Nonsteroidal Antiinflammatory Drugs and the Risk of Myocardial Infarction in the General Population

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Background—Nonsteroidal antiinflammatory drugs (NSAIDs) are reversible inhibitors of cyclooxygenase (COX)-1 and COX-2. Whether transient and incomplete COX-1 inhibition with NSAIDs other than aspirin will translate into clinical cardioprotection is unclear. Some reports suggest that concurrent aspirin and ibuprofen might be associated with lower cardioprotection than aspirin alone because of a pharmacodynamic interaction.

Methods and Results——We conducted a cohort study with a nested case-control analysis. Overall, 4975 cases of acute myocardial infarction (MI) and death from coronary heart disease (CHD) were identified (January 1997 to December 2000) in the UK. A total of 20 000 controls were randomly sampled, and frequency was matched to cases by age, sex, and calendar year. The incidence rate was 5.0 per 1000 person-years. The multivariate-adjusted OR for current NSAID use compared with nonuse was 1.07 (95% CI, 0.95 to 1.20). Treatment duration or daily dose did not change the results. The effect was similar among patients free of CHD history (1.04; 95% CI, 0.90 to 1.20) and patients with previous history (1.12; 95% CI, 0.91 to 1.38). Estimates for individual NSAIDs were all comparable, with no major effect on the risk of acute MI. Naproxen was associated with an OR of 0.89 (95% CI, 0.64 to 1.24). The OR of aspirin and concurrent NSAIDs use was 1.10 (95% CI, 0.89 to 1.37) compared with aspirin alone. We observed the same result when analyzing ibuprofen and aspirin taken concomitantly.

***Conclusions*—**This study could not demonstrate any detectable risk reduction of NSAIDs on the occurrence of MI. Our results do not support the existence of a clinically meaningful interaction between aspirin and NSAIDs, including ibuprofen. **(*Circulation*. 2004;109:3000-3006.)**

Key Words: myocardial infarction ■ aspirin ■ epidemiology

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely prescribed as analgesics and antiinflammatory drugs. Their mechanism of action includes inhibition of cyclooxygenase (COX) enzymes, both the COX-1 and COX-2 isoenzymes. COX-1 and COX-2 catalyze the conversion of arachidonic acid to eicosanoids, which play an important role in the maintenance of gastrointestinal, renal, and cardiovascular hemostasis. Nonselective NSAIDs inhibit platelets in a reversible and incomplete manner via COX-1 inhibition.[1]

In the Vioxx Gastrointestinal Outcomes Research Study (VIGOR), patients randomized to the COX-2 selective inhibitor rofecoxib showed a significant 4-fold increased risk of myocardial infarction (MI) compared with those randomized to naproxen (a nonselective NSAID).[2] One advanced explanation was the reduction of prostacyclin biosynthesis due to inhibition of COX-2 enzyme.[3] Given the platelet inhibitory and vasodilatory properties of this eicosanoid, unopposed inhibition of COX-2 could translate into an increased cardiovascular risk in certain populations at risk, which could explain the result observed in VIGOR. Others have proposed that it could be a consequence of cardioprotective properties of naproxen (through COX-1 inhibition).[2,4]

Several published observational studies with differing study designs and populations have suggested no overall class effect of NSAIDs on the risk of coronary heart disease (CHD).[4–11] Most of these studies also assessed the effect of individual NSAIDs, and results for naproxen were comparable with no effect or a minor protective effect on cardiovascular events.

The objective of the present study was to provide a precise estimate of the effect, in a broad study base, of nonaspirin NSAIDs on the occurrence of acute myocardial infarction (AMI) and death from CHD and to evaluate whether this class of drugs interferes with the cardioprotection offered by aspirin.

Methods

Data Source

The General Practice Research Database (GPRD) contains computerized medical information entered systematically by general prac-

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titioners (GPs) in the UK and sent anonymously to the Medicines and Healthcare products Regulatory Agency.[12] The information recorded includes demographic data, outpatient clinical diagnoses, consultant referrals and hospital admissions, and prescriptions. More than 90% of all referrals present in the manual records in GPs' offices are entered into computer files with a code that reflects the clinical diagnosis.[13] Prescriptions are generated directly from the GP's computer and entered into the patient's computerized file.

Study Population

We identified all individuals aged 50 to 84 years at January 1, 1997. We started following up patients from the first day after January 1, 1997, once they met the criteria of at least 2 years of enrollment with the GP and 1 year since the first computerized prescription of any drug. That date was their start date. We excluded patients with a diagnosis of cancer before start date. We also removed from the study cohort all persons aged 70 years and older who had a follow-up longer than 1 year and fewer than 2 health contacts during their follow-up period. The resulting cohort consisted of 404 183 subjects.

Case Ascertainment and Validation

We followed up all study cohort members from the start date until the earliest occurrence of one of the following end points: a first-time recorded diagnosis of MI, cancer, death, 85 years of age, date of last practice data collection, or December 31, 2000. We reviewed computerized profiles of all patients with a code of MI. All patient identifiers were suppressed, and information on NSAID use was removed to allow for their blinded review. We excluded patients not admitted to a hospital, as well as those who had been hospitalized for a noncardiac condition in the previous month. We also reviewed all deaths occurring in this cohort.

We used the adapted international standardized diagnostic criteria to consider a patient as a case of AMI or death from CHD.[14,15] We applied methods of case ascertainment and validation described elsewhere.[9,16] In summary, we considered a patient as dying from CHD when there was postmortem evidence of fresh MI or a recent coronary artery occlusion or ante-mortem evidence of CHD in the absence of another cause of death or recorded CHD as the underlying cause of death. After the manual review of the patients' computerized profiles, 4801 were considered cases. For a random sample of 174 patients, we sent a questionnaire to the GPs to confirm the diagnosis and requested all available information related to this episode, including hospital discharge letters, electrocardiograms, myocardial serum enzyme levels, autopsy reports, and death certificates. We received information on 147 patients (response rate, 82%), and because the diagnosis was confirmed in 96%, validation of all remaining cases was not deemed necessary. Overall, 4795 patients were cases, and the date of admission to hospital or date of death was treated as the index date. We considered as fatal cases those who died within the first 30 days after the occurrence of AMI and patients who died from CHD before reaching the hospital. Therefore, in this study, AMI included, if not otherwise stated, fatal and nonfatal cases.

Selection of Controls

A random date within the study period was generated for each of the 404 183 cohort members. All subjects with a random date included in their period of observation (from study entry to end of follow-up) were eligible as controls. A group of 20 000 controls frequency-matched by age, sex, and calendar year was randomly sampled among the study cohort. We applied to the controls the same computer-based exclusion criteria as those applied to cases, using each subject's random date as his or her index date.

Comorbidity and Risk Factor Assessment

Information on coronary risk factors, comorbidities, and drug utilization was obtained from the database. Hypertension, diabetes, hyperlipidemia, smoking, cardiovascular disease (CVD), arthritis, and recent anemia were considered present when these specific diagnostics were registered in the database before the index date. History of CHD was defined by the presence of MI or angina. Cerebrovascular disease was defined by the presence of ischemic or hemorrhagic stroke.

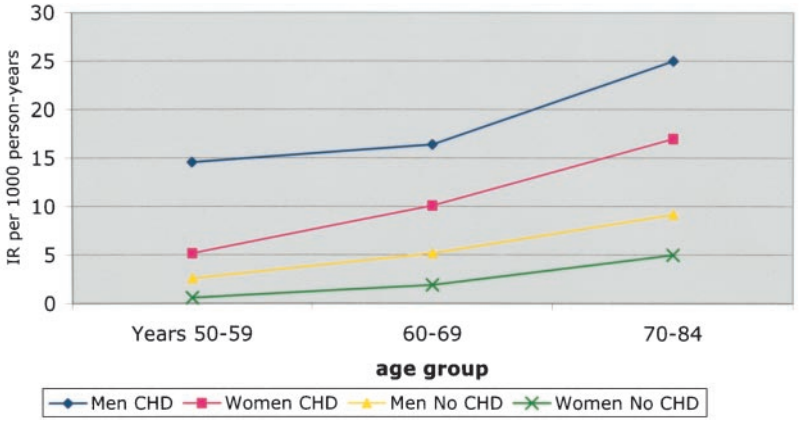
Body mass index, expressed in kilograms per square meter, was calculated from registered height and weight. Alcohol intake was used as directly registered by the GP. Current use of comedications was assessed using the same definition as that used for NSAID use, as follows.

Exposure Definition

We identified NSAID prescriptions before the index date for cases and controls and categorized exposure to NSAIDs as *current* when the supply of the most recent prescription lasted until index date or ended in the 30 days before the index date, *recent* when it ended between 31 and 180 days before the index date, *past* when it ended between 6 months and 2 years before the index date, and *nonuse* when there was no recorded use in the 2 years before the index date. We also performed a sensitivity analysis using a 7-day time window to define current use. We evaluated duration of use, adding the periods of consecutive prescriptions, defined as an interval of less than 2 months between 2 NSAID prescriptions. Current users were subdivided into current single users and current multiple/switcher users. The latter category included patients who received prescriptions for different NSAIDs with their respective supply ending within the month before the index date. Among current single users, we calculated the OR for individual NSAIDs and the dose-response relation using 2 categories, low–medium and high.[17]

Analysis

A nested case-control analysis was performed to estimate the dose and duration effects of NSAIDs as well as the contribution of other potential risk factors, such as use of other medications, antecedents



Incidence of myocardial infarction by history of CHD, sex, and age groups.

TABLE 1. Association of MI With Risk Factors

	Cases, % (n=4795)	Controls, % (n=20 000)	OR* (95% CI)	Multivariate Adjusted OR† (95% CI)
Smoking				
Never	2352 (49)	11 637 (58)	1	1
Current	1314 (27)	3694 (15)	1.76 (1.63–1.90)	2.05 (1.88–2.23)
Former smoker	566 (12)	2068 (10)	1.35 (1.22–1.50)	1.27 (1.14–1.42)
Unknown	563 (12)	2601 (13)	1.07 (0.99–1.19)	1.26 (1.08–1.47)
Diabetes				
No	4105 (86)	18 645 (93)	1	1
Yes	690 (14)	1355 (7)	2.31 (2.10–2.55)	1.87 (1.69–2.08)
Hypertension				
No	2943 (61)	14 182 (71)	1	1
Yes	1852 (39)	5818 (29)	1.53 (1.44–1.64)	1.30 (1.21–1.40)
Hyperlipidemia				
No	3916 (82)	17 806 (89)	1	1
Yes, without lipid-lowering drugs	517 (11)	1411 (7)	1.67 (1.50–1.85)	1.31 (1.17–1.47)
Yes, with lipid-lowering drugs	362 (8)	783 (4)	2.10 (1.85–2.39)	1.02 (0.89–1.18)
Body mass index, kg/m^2				
<20	138 (3)	686 (3)	0.96 (0.79–1.16)	0.86 (0.70–1.06)
20–24	1197 (25)	5694 (28)	1	1
25–29	1655 (35)	6636 (33)	1.19 (1.09–1.29)	1.14 (1.05–1.24)
≥30	731 (15)	2387 (12)	1.46 (1.31–1.62)	1.22 (1.09–1.36)
Unknown	1074 (22)	4597 (23)	1.11 (1.01–1.22)	1.16 (1.03–1.30)
RA				
No	4660 (97)	19 624 (98)	1	1
Yes	135 (3)	376 (2)	1.51 (1.24–1.85)	1.22 (0.98–1.51)
Osteoarthritis				
No	2977 (62)	13 281 (66)	1	1
Yes	1818 (38)	6719 (34)	1.21 (1.13–1.299	1.01 (0.94–1.10)
Anemia				
No	4678 (98)	19 726 (99)	1	1
Yes	117 (2)	274 (1)	1.80 (1.45–2.24)	1.37 (1.09–1.74)
CHD				
No	2966 (62)	16 698 (83)	1	1
Yes	1829 (38)	3302 (17)	3.12 (2.91–3.34)	2.44 (2.24–2.66)
Cerebrovascular disease				
No	4134 (86)	18 302 (92)	1	1
Yes	661 (14)	1698 (8)	1.72 (1.57–1.90)	1.19 (1.06–1.32)

*Adjusted for matching variables.

†Estimates of OR were obtained from a logistic model including all variables in this table in addition to age, sex, calendar year, alcohol intake, and use of steroids, aspirin, anticoagulants, paracetamol, and NSAIDs.

of CVD, and comorbidity, to the risk of MI. We calculated the ORs and 95% CIs of MI associated with NSAID use compared with nonuse using unconditional logistic regression.

Results

After a mean follow-up time of 2 years, 4 months, the overall incidence rate of AMI (first event during study period) in our source population aged 50 to 84 years was 5.0 per 1000 person-years (Figure). The incidence rate was considerably higher among people with history of CHD (17.2 per 1000 person-years) than among those free of CHD history (3.5 per 1000 person-years), irrespective of sex and age groups. Among men with history of CHD, the rates ranged from 14.6 per 1000 person-years in those aged 50 to 59 years to 25 per 1000 person-years in those aged 70 to 84 years. Among women, the corresponding figures ranged from 5.2 to 17 per 1000 person-years.

Overall, 65% of MI cases were men, 55% were aged 70 years or older, and 44% (n=1914) were fatal. A total of 61% of cases (n=2917) and 59% of controls (n=11 791) were exposed to NSAIDs at any time during the last 2 years before the index date, whereas 12% (n=580) of cases and 10%

TABLE 2. Association of MI With NSAID Use

	Cases, % (n=4795)	Controls, % (n=20 000)	OR* (95% CI)	Multivariate Adjusted OR† (95% CI)
Nonuse	1878 (39)	8209 (41)	1	1
Current use (0–30 days)	580 (12)	1989 (10)	1.28 (1.15–1.42)	1.07 (0.95–1.20)
Recent use (31–180 days)	365 (8)	1385 (7)	1.15 (1.02–1.31)	0.98 (0.85–1.12)
Past use (>180 days)	1972 (41)	8417 (42)	1.02 (0.96–1.10)	0.89 (0.82–0.96)
Current use				
Single	553	1936	1.25 (1.12–1.39)	1.05 (0.93–1.18)
Multiple/switcher	27	53	2.23 (1.40–3.55)	1.52 (0.93–2.49)
Current use by form				
Oral plain	436	1547	1.23 (1.10–1.39)	1.02 (0.90–1.17)
Slow release	117	389	1.05 (0.98–1.12)	1.14 (0.91–1.44)
Current use by duration				
≤60 days	177	602	1.29 (1.08–1.53)	1.14 (0.94–1.37)
>60 days	376	1334	1.23 (1.09–1.40)	1.01 (0.87–1.16)
Current use by dose				
Low–medium	312	1097	1.24 (1.09–1.429	1.07 (0.92–1.24)
High	241	839	1.26 (1.08–1.46)	1.02 (0.86–1.20)

*Adjusted for matching variables.

†Estimates of OR were obtained from a logistic model including all variables in this table in addition to age, sex, calendar year, alcohol intake, and use of steroids, aspirin, anticoagulants, paracetamol, and NSAIDs.

(n=1989) of controls were current users of NSAIDs. We examined the distribution of potential risk factors among controls by NSAID exposure. Current NSAID users were more likely to be women and older than the group of nonusers (data not shown). In addition, current users more frequently had hypertension and arthritis compared with nonusers of NSAIDs (data not shown).

Independent Risk Factors of MI

Smoking, diabetes, and prior history of CHD were the major risk factors associated with the risk of having an AMI during the study period (Table 1). Rheumatoid arthritis (RA) was associated with a 20% increase in the risk of AMI after adjusting by coronary risk factors and the use of selected medications. However, although this risk was not increased among men (OR, 0.98; 95% CI, 0.72 to 1.34), women with RA were at a higher risk of MI compared with those without the disease (OR, 1.50; 95% CI, 1.11 to 2.03).

NSAID Use and Risk of MI

The estimated relative risk of AMI associated with current use of NSAIDs was 1.07 (95% CI, 0.95 to 1.20) compared with nonuse (Table 2). No material difference was observed either by duration of use (≤60 days: OR, 1.14; 95% CI, 0.94 to 1.37; >60 days: OR, 1.01; 95% CI, 0.87 to 1.16), by dose, or when a more strict definition of current use (supply of the most recent prescription ended in the week before the index date) was applied (data not shown). Sex and age did not modify the risk of AMI associated with current use of NSAIDs (results not shown). We assessed the potential for confounding by indication among short-term users by taking into account the indication for which NSAIDs were prescribed. The most frequent indication was osteoarthritis, and within this subgroup, NSAID use was not associated with an increased risk (OR, 1.03; 95% CI, 0.83 to 1.29). However, in the small subgroup of patients who were prescribed NSAIDs to treat ill-defined chest pain, the risk of MI was markedly increased (OR, 6.33; 95% CI, 1.37 to 29.30). The effect was no different between patients free of CHD history (1.04; 95% CI, 0.90 to 1.20) and patients with previous history (1.12; 95% CI, 0.91 to 1.38). The effect of current NSAID exposure was similar whether the outcome was fatal (OR, 1.00; 95% CI, 0.84 to 1.20) or nonfatal (OR, 1.10; 95% CI, 0.84 to 1.44).

Effect of Individual NSAIDs

We estimated the relative risk of AMI associated with the use of individual NSAIDs (Table 3). Estimates for the 3 most widely used NSAIDs were all comparable, with no major effect on the risk of MI, as follows: naproxen: OR, 0.89; 95% CI, 0.64 to 1.24; ibuprofen: OR, 1.06; 95% CI, 0.87 to 1.29; and diclofenac: OR, 1.18; 95% CI, 0.99 to 1.40. We also estimated the effect of these 3 NSAIDs on the risk of AMI according to prior history of CHD and found no significant effect modification with any of these NSAIDs (Table 4).

Interaction Between Aspirin and NSAIDs

Current use of aspirin was observed among 27% of cases and 14% of controls (data not shown). Among them, 87% of cases and 89% of controls used low doses (≤150 mg/d). The use of aspirin was greater among cases and controls with prior history of CHD and cerebrovascular disease by 50% and 44%, respectively.

The effect of concomitant use of aspirin and NSAIDs was similar to that when aspirin was taken alone (OR, 1.10; 95% CI, 0.89 to 1.37). Among fatal cases, the corresponding OR was 1.25 (95% CI, 0.94 to 1.66). The results shown in Table 5 did not suggest a major interaction between the concomitant use of aspirin and any of the 3 most widely used NSAIDs.

TABLE 3. Association of MI With Current Use of Individual NSAIDs

	Cases (n=4795)	Controls (n=20 000)	OR* (95% CI)	Multivariate Adjusted OR† (95% CI)
Nonuse	1878	8209	1	1
Use				
Naproxen	49	206	1.04 (0.76–1.43)	0.89 (0.64–1.24)
Ibuprofen	155	575	1.18 (0.98–1.42)	1.06 (0.87–1.29)
Diclofenac	213	679	1.37 (1.17–1.61)	1.18 (0.99–1.40)
Ketoprofen	16	56	1.25 (0.72–2.18)	1.08 (0.59–1.96)
Meloxicam	25	81	1.35 (0.86–2.12)	0.97 (0.60–1.56)
Piroxicam	16	52	1.35 (0.77–2.36)	1.25 (0.69–2.25)
Indomethacin	29	114	1.11 (0.74–1.68)	0.86 (0.56–1.32)
Other NSAIDs	50	173	1.26 (0.92–1.74)	0.89 (0.63–1.25)

*Adjusted for matching variables.

†Estimates of OR were obtained from a logistic model including all variables in Table 1 in addition to age, sex, calendar year, alcohol intake, and use of steroids, aspirin, anticoagulants, paracetamol, and NSAIDs.

The results were virtually the same when only duration longer than 1 month for both aspirin and NSAIDs was considered (data not shown). When stratifying NSAIDs according to daily dose, the estimate of interaction was slightly higher for high dose compared with low–medium dose.

Discussion

In this study, we found that nonaspirin NSAIDs have no overall effect on the risk of AMI. The same conclusion holds for every individual NSAID analyzed with sufficient information. Our results are compatible with the overall effects from published studies that indicate no protective effect of NSAIDs.[4–10]

A recent report confirmed that low-dose aspirin reduces the risk of AMI by approximately one third.[18] This protection is widely accepted to be mediated by the complete and irreversible inhibition of platelet COX-1 that translates into inhibition of thromboxane A_2–mediated platelet aggregation.[1] NSAIDs inhibit the 2 COX isoforms, but none of the NSAIDs share the same pharmacokinetic and pharmacodynamic characteristics as low-dose aspirin. Our study supports that these unique features of aspirin, not shared by NSAIDs, might be the basis for not detecting a similar cardioprotection in patients taking NSAIDs in a general population setting.

Our findings were negative, irrespective of the NSAID dose used. We observed a slightly increased risk among subjects newly started on NSAIDs. This could be attributable in part to early symptoms of AMI that could have induced the prescription of an NSAID. We assessed NSAID use according to the various treatment indications among new users. Those receiving NSAIDs to treat osteoarthritis showed no increased risk of MI. This contrasts with a small subgroup of patients who were prescribed NSAIDs to treat ill-defined chest pain (<1% of NSAID users) and whose risk was particularly increased. This finding supports the existence of an indication bias in this subgroup of new users of NSAIDs.[19]

We found RA to be an independent risk factor for AMI in women but not in men. These results are consistent with the more pronounced excess cardiovascular mortality in women compared with men with RA observed in prior epidemiological studies as well as in more recent studies.[20–22]

To assess whether pharmaceutical form modifies the effect of NSAIDs, we analyzed slow-release and regular formulations individually and saw no difference between these forms. Additionally, we analyzed separately the effect of NSAIDs among subjects with and without history of CHD and did not find a suggestion of effect modification. Although we tried to control for all potential bias and confounding, this can never be perfect in nonexperimental studies, and our estimates could still be compatible with a small effect (eg, a 10% to 20% lower or higher risk of MI).

An in vivo study showed that ibuprofen can interact with aspirin, antagonizing the irreversible platelet inhibition induced by aspirin.[23] This interaction could translate into a decreased cardioprotection in those patients using aspirin and ibuprofen concomitantly. One study found that patients with

TABLE 4. Association of MI With Current Use of Individual NSAIDs According to Antecedents of CHD

	Multivariate Adjusted* OR (95% CI)				
	Single Use of any NSAID	Ibuprofen	Naproxen	Diclofenac	Other NSAIDs
All	1.05 (0.93–1.18)	1.06 (0.87–1.29)	0.89 (0.64–1.24)	1.18 (0.98–1.40)	0.95 (0.77–1.18)
Stratified by prior history of CHD					
No	1.04 (0.90–1.21)	1.03 (0.81–1.30)	0.86 (0.57–1.31)	1.19 (0.96–1.47)	0.92 (0.70–1.20)
Yes	1.09 (0.88–1.35)	1.15 (0.81–1.63)	0.91 (0.51–1.61)	1.13 (0.83–1.55)	1.03 (0.72–1.47)

*Estimates of OR were obtained from a logistic model including all variables in Table 1 in addition to age, sex, calendar year, alcohol intake, and use of steroids, aspirin, anticoagulants, and paracetamol.

TABLE 5. Association of Myocardial Infarction With Concomitant Aspirin and NSAID Use

Current ASA and NSAID Use	Cases (n=1293)	Controls (n=2712)	OR* (95% CI)	Multivariate Adjusted OR† (95% CI)
ASA alone	1119	2396	1	1
ASA plus NSAIDs	163	303	1.15 (0.94–1.41)	1.10 (0.89–1.37)
NSAIDs by dose				
ASA plus low-medium	85	186	0.98 (0.75–1.28)	0.95 (0.72–1.26)
ASA plus high	78	117	1.43 (1.06–1.92)	1.33 (0.97–1.82)
Individual NSAIDs				
ASA plus ibuprofen	46	86	1.15 (0.80–1.65)	1.08 (0.74–1.58)
ASA plus diclofenac	57	102	1.20 (0.86–1.67)	1.16 (0.82–1.65)
ASA plus naproxen	14	32	0.94 (0.50–1.76)	0.96 (0.49–1.86)
ASA plus other NSAIDs	46	83	1.19 (0.82–1.71)	1.10 (0.75–1.62)

ASA indicates aspirin.

*Adjusted for matching variables.

†Estimates of OR were obtained from a logistic model including all variables in Table 1 in addition to age, sex, calendar year, alcohol intake, and use of steroids, anticoagulants, paracetamol, and NSAIDs.

CVD taking low-dose aspirin and ibuprofen had an increased all-cause and CVD mortality compared with those who used low-dose aspirin alone.[24] More recently, a report of the Physicians' Health Study presented a subanalysis of self-reported use of NSAIDs after the termination of the controlled trial.[25] Exposure was assessed with some degree of imprecision, because it was based on the use within the last 30 days at baseline and in each follow-up questionnaire but not on the date of the event of interest. An increased risk of AMI was observed among those randomized to aspirin and who, apparently, used NSAIDs ≥60 days at least during 1 year compared with those only randomized to aspirin. In our study, which included patients with and without history of CVD, the risk of AMI in patients taking aspirin and ibuprofen was similar to that of patients taking aspirin alone. In addition, the absence of a negative interaction extends to the other 2 individual NSAIDs evaluated, although our results could still be compatible with a minor blunting effect of nonaspirin NSAIDs on the cardioprotection offered by aspirin. We also looked at the effect with different numbers of NSAID doses taken per day and found no major variation between 1 a day versus 2 or more (data not shown).

In our study, over-the-counter use of NSAIDs was not captured. However, only ibuprofen could be purchased without a prescription in the UK during the study period, so we expect little misclassification of the overall NSAID exposure variable. This misclassification would tend to be nondifferential among cases and controls, which, given the small magnitude of the observed association, would have little or no effect in our results. Also, we did not have information on over-the-counter use of aspirin (mainly short-term use for pain relief). On the other hand, it is unlikely that patients take prophylactic aspirin for cardiovascular prevention in the UK without a prescription from their GP, particularly among elderly, as reflected by the prevalence of daily users in our control series (14%).

Myocardial infarction cases were identified through careful review of computerized files. We pursued validation in a random sample. Among 147 questionnaires received from the GPs, only 6 cases were not confirmed (positive predictive value of 96%). Therefore, we do not expect a misclassification rate greater than 5% in our whole-case series. It is also unlikely that a significant number of cases remained undetected because of the nature of the outcome being studied. The overall incidence of AMI (first-ever and recurrent events) in our source population was 4.97 per 1000 person-years, in line with rates reported in previous studies.[26]

The results of our study confirm that NSAIDs lack the protective effect against MI afforded by aspirin. Even if we consider that naproxen had a true effect of an approximately 10% to 20% reduction on the incidence of MI, there would be no place for this drug in the therapeutic armamentarium for cardioprotection given the worse risk/benefit profile of naproxen compared with low-dose aspirin, the current standard therapy. Also, we found little evidence for a noticeable clinical interaction that would affect the cardioprotection provided by aspirin when concurrently taking an NSAID.

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