

ORIGINAL ARTICLE

Risk of ST versus non-ST elevation myocardial infarction associated with non-steroidal anti-inflammatory drugs

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ABSTRACT

Objective The objective of this study was to explore the association of non-steroidal anti-inflammatory drugs (NSAID) with ST-segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI).

Design, Setting & Patients A matched case-control study comparing patients with incident non-fatal myocardial infarction (MI) collected by cardiologists with controls. Cases were retrieved from the Pharmacoepidemiological General Research on Myocardial Infarction (PGRx-MI) registry, a French nationwide registry consisting of 55 cardiology centres, whereas controls were selected from general practice settings. Both cases and controls were recruited from the same geographically diverse areas across continental France.

Main Outcome Measures The association between NSAID and MI was assessed by matched adjusted OR from conditional logistic regression.

Results Between 2007 and 2009, 1125 incident cases were included (67.3% and 32.7% for STEMI and NSTEMI, respectively), with 2790 controls matched to MI cases by age and sex. Current use (previous 2 months) of either diclofenac or naproxen and other arylpropionic acid NSAID was not associated with STEMI (OR 0.9, 95% CI 0.4 to 1.9 and OR 1.0, 95% CI 0.6 to 1.7, respectively), instead it showed significant association with NSTEMI (OR 2.8, 95% CI 1.2 to 6.4 and OR 0.4, 95% CI 0.2 to 0.9, respectively). Our study confirms results from previously published analyses on the association of MI with NSAID (OR 1.5, 0.9, and 1.0 for diclofenac, naproxen and related NSAID, and all NSAID combined, respectively).

Conclusions Our study shows that the MI risk modification associated with NSAID is limited to NSTEMI.

The cardiac safety of widely used non-steroidal anti-inflammatory drugs (NSAID) remains a topic of current interest, especially after the market withdrawal of rofecoxib, a selective inhibitor of cyclooxygenase 2. Conventional NSAID reversibly block both cyclooxygenase 1 and cyclooxygenase 2 isoforms with varying degrees of selectivity,¹ a mechanism purported to explain differences in reported risks. Diclofenac has been reported to increase the risk of myocardial infarction (MI), and as such remains a subject of debate.²⁻¹³ A

cardioprotective effect of naproxen has been offered as an explanation for the excess cardiovascular risk comparatively observed with rofecoxib,¹⁴ but no such effect has been confirmed in several studies.^{2 3 10 15-18} Ibuprofen, while generally reported to be safe, has been queried as to whether it interacts with aspirin and other antiplatelet agents.^{5 13 19 20} Regrettably, most studies assessing the risks of NSAID also lacked clinical specificity on the diagnosis of MI,²¹ a heterogeneous group of diseases. MI with ST-segment elevation myocardial infarction (STEMI) is usually associated with total coronary occlusion by thrombus, whereas MI with non-ST segment elevation myocardial infarction (NSTEMI) is more likely to be associated with incomplete thrombotic occlusion and more extensive atheromatous disease.^{22 23} The two diseases also affect different types of patients, with STEMI seen more frequently in younger patients that smoke.²⁴ In addition, early hospital mortality in STEMI patients is higher but post-discharge mortality tends to be lower compared with NSTEMI patients.²⁵ NSAID with some cyclooxygenase 2 selectivity are believed to facilitate the development of small platelet thrombi in the vascular surface. Although this may be sufficient to provoke an occlusion in already atheromatous coronaries, it is thought insufficient to produce a complete occlusion of a large epicardial coronary artery, indeed the classic mechanism of STEMI.^{22 26} Previous studies have not analysed the association between the use of NSAID and the risk of acute MI in STEMI and NSTEMI patients. Since completing our study, Bueno *et al*²⁷ also found an effect of diclofenac upon NSTEMI but not on STEMI. Likewise, García Rodríguez *et al*²⁸ have recently noted in a meta-analysis that NSAID use selectively increases the risk of non-fatal MI, with STEMI being known to be more lethal than NSTEMI. Furthermore, evidence to support these findings has also been published over the past year.^{29 30} The present study sought to explore the association of NSAID with STEMI and NSTEMI and to confirm the results of published analyses regarding their association with the risk of MI. The stratification of data into STEMI versus NSTEMI was planned ahead of the analysis, as proposed by one member of the scientific committee (PGS) and the first author (LGB).

METHODS

In this case–control study, patients presenting with a first, non-fatal MI from 55 geographically diverse cardiology centres across France were compared with controls selected from general practice settings, also from the same geographically diverse areas of continental France. All participants (cases and controls) provided informed written consent to participate in the study, were aged 18–79 years, could read French and were capable of answering questions by a qualified telephone interviewer. Cases and controls were excluded from the study if they had a history of MI, percutaneous coronary intervention, coronary artery bypass surgery or any other history of coronary artery disease or heart failure. Cases and controls were also excluded if they were currently taking aspirin or other antiplatelet agents (clopidogrel, ticlopidine or dipyridamole).

Source populations

Cases

We conducted this study using patient data retrieved from the Pharmacoepidemiological General Research on MI (PGRx-MI) registry, a French nationwide registry consisting of 55 acute cardiology centres (13 academic, 25 non-academic public and 17 non-academic private hospitals) across continental France. Clinical research assistants randomly audited the centres for compliance with the study protocol.

Consecutive subjects presenting with incident MI were identified prospectively, independently of any risk factor or drug exposure. They were classified as ‘definite MI’ after a board certified cardiologist rendered a diagnosis based on at least two of the following criteria: (1) characteristic chest pain; (2) electrocardiography (ECG) abnormalities: pathological Q waves and/or ST-T changes in at least two adjacent derivations; (3) elevation of biochemical markers (creatinine kinase, myocardial type and/or troponin) to twice the upper normal limit. Subjects were further categorised as STEMI or NSTEMI after additional analysis of individual ECG. The algorithm used to classify STEMI and NSTEMI subjects had previously been validated by a panel of cardiologists. In addition, a panel of cardiologists validated the classification of STEMI and NSTEMI in case of any doubt. Physicians recorded this information, along with responses to a series of general clinical questions, on a web-based clinical research form. All cases hospitalised between 1 March 2007 and 31 May 2009, fulfilling the inclusion criteria and not meeting any of the exclusion criteria were accepted.

Controls

Four hundred and fifty-seven general practitioners (GPs) from the same regions as the cardiology centres participated in this study. They were randomly selected by region from a national list of GPs in France. The GPs were instructed to identify and recruit the first patient, regardless of his/her reason for consultation, and independent of any morbidity or exposure criteria, by sex and the following age strata (years): 18–34, 35–49, 50–64 (stratum doubled) and 65–79 (stratum doubled). A registry of 5529 subjects was constituted. Among these, controls were randomly selected after matching by age (± 5 years) and sex to the MI cases. Controls were recruited during the same calendar time period as the MI cases. All subjects fulfilling the inclusion criteria and not meeting any of the exclusion criteria were identified independently by the research team. Up to six individually matched controls were sought for cases using an iterative matching process with a control being dropped from the pool after matching.

Physicians were requested to complete an electronic medical data form that included medical information on the patient (chronic diseases and comorbidities, medical risk factors, biological data and current and 2-year past prescriptions).

Exposure classification

All participants recruited from the PGRx-MI registry and the PGRx-GP database authorised their physician(s) to share the information contained in their medical file with the research team and provided written informed consent.

Furthermore, cases and controls agreed to participate in an in-depth, standardised telephone interview covering personal history of diseases, medical history, behavioural risk factors and environmental exposures.

An identical, detailed questionnaire on medicines use was administered to all cases and controls. It spanned a 2-year timeframe before the index date (defined as the date of hospitalisation for cases and the date of recruitment for controls). The interviews of cases and controls were conducted within 45 days of recruitment by trained interviewers from the PGRx database/registry call centre. The interview was derived from methodology previously reported, and covered 85 separate health conditions listed in a detailed interview guide given to the subjects ahead of the interview.³¹ The interview guide contained complete descriptions of medicines, their brand and generic names, along with corresponding packaging images. A total of 300 branded and generic drug descriptions and photographs of their packaging was provided, including all the ambulatory medicines available on the market for 3 years or less and drugs used by 250 000 persons or more per year in France. Subjects were also requested to report spontaneously any other drug use. Validation of the methodology for analysing the agreement between patients’ reports and physicians’ prescriptions has been published elsewhere.³²

Case and control medicine use was categorised into two time frames: ‘current’ (if the drug was taken at any time within the past 8 weeks) or ‘past’ (if the drug was taken at any time before that 8-week period) relative to the respective index dates as indicated above. Current use was retained as the at-risk time frame of interest. NSAID brand name and generic drugs were classified into three categories: diclofenac, arylpropionic acid (AA) NSAID, and miscellaneous. The AA NSAID category was subdivided into two areas: naproxen and related AA NSAID (ketoprofen, flurbiprofen, tiaprofenic acid, alminoprofen, fenoprofen) and ibuprofen. The miscellaneous classification included infrequently used drugs (aceclofenac, celecoxib, etodolac, indometacin, mefenamic acid, meloxicam, nabumetone, niflumic acid, nimesulide, parecoxib, phenylbutazone, piroxicam, sulindac, tenoxicam).

Risk factors, confounders and comorbidities

The following variables were considered as individual risk factors for MI: smoking status (current smoker, past smoker, non-smoker), body mass index (BMI; weight in kilogrammes divided by squared height in centimetres and classified into ≤ 19 , 20–24, 25–29, ≥ 30), amount of physical exercise (at least 30 min per day vs more), history of stroke, hyperlipidaemia, hypertension or diabetes mellitus. Rheumatic diseases and co-medication, including any cardiovascular drug use in the previous 2 years (β -blockers, diuretics, ACE inhibitors, calcium antagonists, angiotensin II receptor antagonists, other antihypertensive drugs and lipid-regulating drugs) were considered as potential confounders. Past exposures to aspirin and other antiplatelet drugs were also included as potential confounders (current users

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of aspirin and other antiplatelet drugs were excluded from the analysis).

Statistical analysis

The distribution of demographic and risk factor variables was compared between cases and controls using Student's *t* test and Pearson's χ^2 test for continuous and categorical variables, respectively. Comparisons of the distribution of cardiovascular risk factors and their association with MI were assessed by matched adjusted OR from conditional logistic regression. The association between NSAID use and MI was analysed by comparing cases with controls for the current use of the drugs of interest and employing conditional logistic regressions that had no NSAID use as the reference and that controlled for past use of the drugs of interest, as well as for the past use of aspirin. Current use of aspirin or other antiplatelet drugs was a criterion for exclusion. All the risk factors and confounders mentioned above, as well as the number of per-patient per-year visits to a physician (placed into four categories: 0–2, 3–6, 7–12, >12 visits) were included in the regression models. The analysis was first performed by including all the MI cases, followed by a stratified analysis into STEMI and NSTEMI diagnoses. The same modelling approach was applied in both cases. To assess potential confounding by indication, the propensity to use the individual NSAID according to the presence of cardiac risk

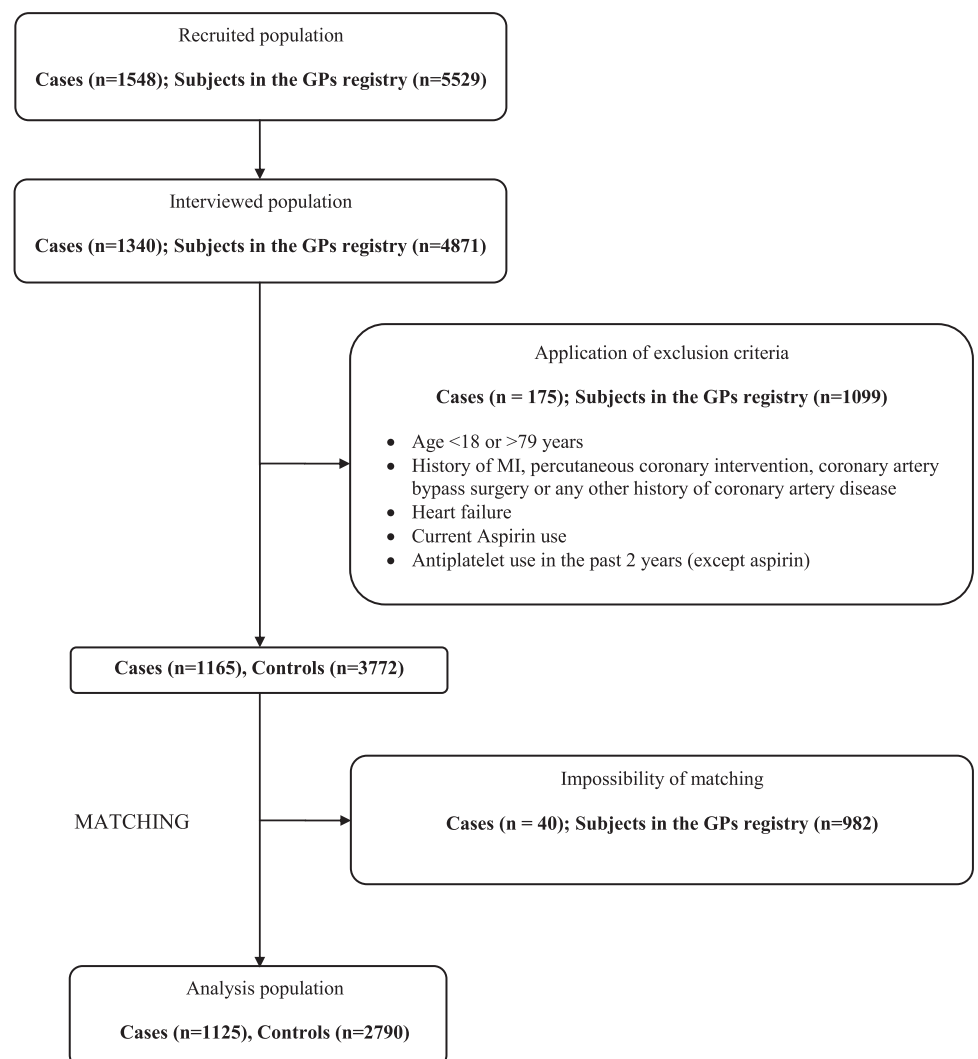
factors (smoking, BMI ≥ 30 , hypertension, hyperlipidaemia, diabetes, stroke) was estimated in controls by multiple logistic regression using all the risk factors and confounders. In the results section, matched adjusted OR are presented with their 95% CI. Matched crude OR were very close to the adjusted OR and are therefore not shown. For each group of NSAID separately (ie, diclofenac, AA NSAID and miscellaneous), heterogeneity of the OR for STEMI and NSTEMI was tested using Wald's test. For the three groups of NSAID considered, overall heterogeneity was tested using the likelihood ratio test.

NSAID exposure in resuscitated patients was examined in an attempt to evaluate a potential underestimation of the risk between surviving compared with deceased patients. Sample size was calculated to allow the detection of an OR greater than or equal to 1.5 with 80% power for all MI. All analyses were performed using SAS software version 9.1.

RESULTS

Between 1 April 2007 and 31 May 2009, 1548 individuals (cases) with a first lifetime occurrence of MI were recruited from the PGRx-MI registry. Figure 1 displays the selection process of cases and controls collated from the registries. Initially, 814 STEMI cases meeting the inclusion criteria were recruited, among whom 57 (7%) were current aspirin users and were excluded;

Figure 1 Flow diagram of the selection of cases and controls. GP, general practitioner; MI, myocardial infarction.



409 NSTEMI cases were recruited, among whom 41 (10%) were current aspirin users and were excluded ($p=0.07$). Seventy-seven MI cases were not eligible (age or non-incident MI cases), and were therefore excluded. These cases were not characterised for their status as STEMI or NSTEMI. After applying all inclusion and exclusion criteria, 1125 cases were retained, of whom 78.1% were men. The mean age was 56.8 years (SD 11.4). Cases excluded because of current aspirin use were older than cases finally retained, but this was not differential according to STEMI or NSTEMI; indeed, retained STEMI and NSTEMI cases were 56.2 years old (SD 11.3) and 57.9 years old (SD 11.7), respectively, on average, while excluded STEMI and NSTEMI were 61.8 years old (SD 10.7) and 63.2 years old (SD 9.0), respectively. Finally, the proportion of retained cases classified as STEMI was 67.3%. Table 1 presents the clinical characteristics of the cases included. A total of 2790 patients passed inclusion and exclusion criteria and matched a case. Of these, 48.2% were men (one to three matched controls were found per male case and one to six per female case) and their mean age was 57.7 years (SD 12.5). Table 2 presents the distribution of cardiac risk factors for cases and controls and their corresponding adjusted OR. OR were 4.3 (95% CI 3.4 to 5.5) for current smokers versus those that never smoked, OR 1.7 (95% CI 1.4 to 2.1) for minimal physical exercise (≤ 30 min/day), OR 1.7 (95% CI 1.3 to 2.4) for BMI of 30 or greater, OR 1.3 (95% CI 0.9 to 1.8) for diabetes mellitus, OR 1.2 (95% CI 0.9 to 1.5) for treated or untreated hypertension, OR 1.4 (95% CI 1.2 to 1.8) for treated or untreated hyperlipidaemia and OR 1.3 (95% CI 0.7 to 2.6) for stroke. An assessment of potential confounders by indication by modelling the propensity to use individual NSAID according to the presence of cardiac risk factors revealed no significant differences.

Association between NSAID and MI

Figure 2 presents the distribution of current use (within 8 weeks) of NSAID in case and matched control subjects and the corresponding estimation of the adjusted OR of non-fatal MI. Current use of diclofenac was associated with MI, albeit not significantly, revealing an OR of 1.47 (95% CI 0.87 to 2.48). The OR for MI and the current use of AA NSAID was 0.85 (95% CI 0.64 to 1.12); 0.91 (95% CI 0.65 to 1.27) for the current use of ibuprofen and 0.73 (95% CI 0.45 to 1.16) for the current use of naproxen and related AA NSAID. The OR was 1.08 (95% CI 0.71 to 1.65) for the current use of a group of infrequently used NSAID, which we have identified as 'miscellaneous NSAID' (figure 1, legend). Lack of sufficient data did not permit the estimation of OR for the individual drugs in this group.

Table 1 Clinical presentation of MI case subjects

Clinical feature	Proportion with feature (N=1125)
STEMI	67.3%
Coronary occlusion: number, site	
1	64.6%
≥ 2	34.2%
Left circumflex coronary artery	30.2%
Left anterior descending interventricular coronary artery	50.0%
Right coronary artery	45.2%
Resuscitation after cardiac arrest*	2.5%

*At any time after myocardial infarction (MI) occurrence and before case reporting. STEMI, ST-segment elevation myocardial infarction.

Table 2 Cardiac risk factors in incident cases and controls, and adjusted OR for MI with their 95% CI

	Cases* (n=1125) % with item	Controls* (n=2790) % with item	Adjusted OR† for MI (95% CI)
	n=1125	n=2790	
Age, years, mean (SD)	56.8 (11.4)	57.7 (12.5)	—
Sex (men, %)	78.1%	48.2%	—
Medical risk factors (n=1125) (n=2790)			
Hypertension (treated or not treated)	32.4%	37.2%	1.2 (0.9 to 1.5)
Hyperlipidaemia (treated or not treated)	29.5%	23.9%	1.4 (1.2 to 1.8)
Diabetes mellitus (treated or not treated)	10.2%	9.3%	1.3 (0.9 to 1.8)
Stroke	1.6%	1.6%	1.3 (0.7 to 2.6)
Smoking‡ (n=1125) (n=2790)			
Current	47.8%	19.5%	4.3 (3.4 to 5.5)
Past	26.2%	30.9%	1.1 (0.9 to 1.4)
Never	25.2%	48.8%	1.0
BMI (n=1125) (n=2790)			
<25	39.3%	43.9%	1.0
25–29	43.8%	39.9%	1.1 (0.9 to 1.3)
≥ 30	16.9%	16.1%	1.7 (1.3 to 2.4)
Alcohol drinking (n=1119) (n=2784)			
Every day or several times per week	48.7%	39.9%	0.8 (0.7 to 1.0)
Occasionally/never	51.1%	59.4%	1.0
Physical exercise (n=1111) (n=2732)			
<0.5 h/day	22.2%	30.1%	1.7 (1.4 to 2.1)
>0.5 h/day	77.8%	69.9%	1.0

*Non-aspirin users before index date.

†OR estimated by multivariable conditional logistic regression including smoking (current, past, never), body mass index (BMI) (<25, 25–29, ≥ 30), history (yes, no) of treated or untreated hyperlipidaemia, hypertension or diabetes, history (yes, no) of stroke, rheumatic disorders, previous use (yes, no) of any cardiovascular drug, number of visits to a physician per year (four classes: 0–2, 3–6, 7–12, >12 visits).

‡Missing in 30 subjects: each missing information was attributed the mean estimate for the variable in the case or referent patients of the same sex and age group.

MI, myocardial infarction.

Of the 28 resuscitated subjects included in the study, 14.3% had current NSAID exposure compared with 15.2% from the entire study sample of MI cases.

Association between individual NSAID and STEMI and NSTEMI

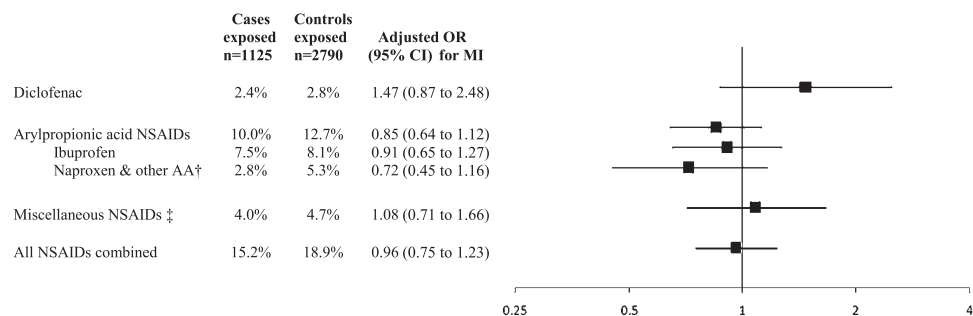
Figure 3 presents the OR for the use of individual NSAID and STEMI and NSTEMI separately. The use of all NSAID combined was not associated with MI, either with or without ST elevation. The current use of diclofenac did not appear to be associated with STEMI but was associated with NSTEMI. The OR of diclofenac and STEMI was significantly different from that with NSTEMI (Wald's heterogeneity test, $p=0.025$). The AA NSAID also displayed no association with STEMI and a trend towards association with NSTEMI, albeit negatively. For the current use of naproxen and related AA NSAID, the OR of STEMI did not differ from unity but was statistically significant for NSTEMI. OR for ibuprofen did not differ significantly from unity for STEMI and NSTEMI. Heterogeneity between STEMI and NSTEMI OR associated with AA NSAID or with each other individual AA NSAID was not significant. However, overall heterogeneity between the OR of STEMI and NSTEMI for the main groups of NSAID was statistically significant (likelihood ratio heterogeneity test, $p=0.02$).

The use of propensity scores rather than individual risk factors or confounders in the multiple logistic regressions did not change the results substantially.

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Figure 2 Adjusted OR (with 95% CI) for myocardial infarction (MI) and recent use* of non-aspirin non-steroidal anti-inflammatory drugs (NSAID).

*Recent use: use in the 8 weeks before the index date. †Naproxen and other arylpropionic acid (AA): ketoprofen (22 cases, 112 controls), naproxen (five cases, 18 controls), flurbiprofen (two, nine), tiaprofenic acid (two, 10), alminoprofen (zero, zero), fenoprofen (zero, zero). ‡Miscellaneous NSAID: aceclofenac (four cases, 11 controls), celecoxib (three, 28), etodolac (one, one), indometacin (zero, one), mefenamic acid (zero, zero), meloxicam (one, three), nabumetone (two, two), niflumic acid (six, seven), nimesulide (five, 33), parecoxib (zero, zero), phenylbutazone (zero, two), piroxicam (22, 42), sulindac (one, zero), tenoxicam (one, three). §OR estimated by multivariable conditional logistic regression including smoking (current, past, non-smoker), body mass index (<25, 25–29, >30), history (yes, no) of treated or untreated hyperlipidaemia, hypertension or diabetes, history (yes, no) of stroke, rheumatic disorders, previous use (yes, no) of any cardiovascular drug, number of visits to a physician per year (four classes: 0–2, 3–6, 7–12, >12 visits).

**DISCUSSION**

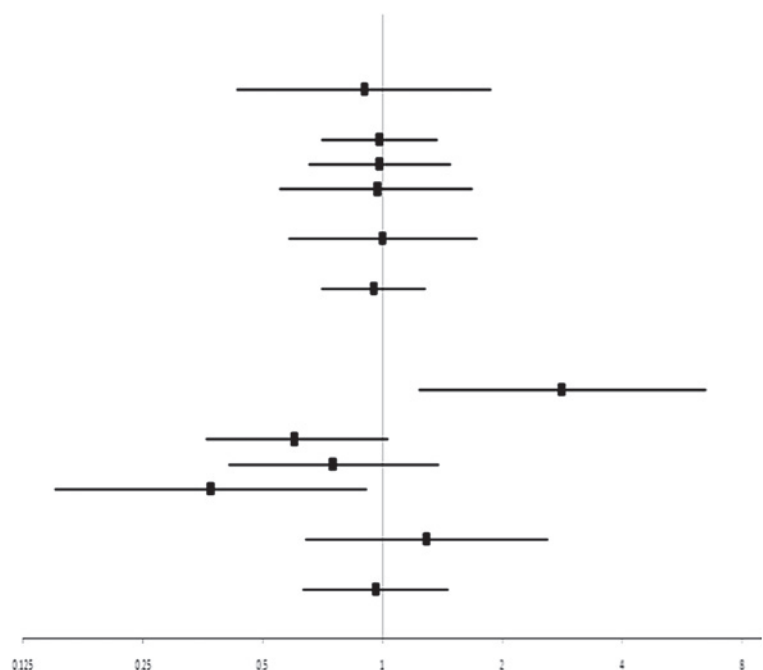
This study presents new data on the relationship between NSAID and MI, and for the first time addressed the association between the use of NSAID and STEMI and NSTEMI. Over-the-counter NSAID use was taken into account along with the exclusion of the use of antiplatelet agents, such as aspirin, which may interact with other NSAID.

For all MI, the results from this study are consistent with those published in 2006 by McGettigan and Henry.²¹ Their review estimated a summary OR of 1.40 for MI in patients treated with diclofenac versus 1.47 in this study. Here, naproxen and related AA NSAID displayed an OR of 0.97 for MI as a whole, which was also consistent with the estimated summary relative risk of 0.97 presented for naproxen in the review by McGettigan and Henry.²¹ This study confirms the general observations mainly derived from electronic healthcare database analyses. This is of importance because these databases are widely used for pharmacoepidemiological research.²¹

In addition, it also provides insight into a significant differential effect of NSAID on STEMI and NSTEMI. A positive, significant association was found between diclofenac and NSTEMI, while no such association was seen with STEMI. Symmetrically, the AA NSAID tended to decrease the risk of NSTEMI, mainly influenced by the results on naproxen and related AA NSAID, which was significant. The overall heterogeneity was statistically significant between STEMI and NSTEMI, suggesting that the observable effects, whether positive or negative, of NSAID differ between STEMI and NSTEMI and are limited to NSTEMI.

This is of interest because it is also consistent with the conceptual framework proposed by FitzGerald³³ concerning the mechanism of action of individual NSAID on the one hand, and the physiopathology of STEMI and NSTEMI on the other.^{22 23} Diclofenac displays some preferential inhibition of the cyclooxygenase isoenzyme 2, which is believed to favour atheroma-induced thrombosis.²⁶ The combination of atheroma and thrombosis is characteristic of NSTEMI.

	Cases Exposed	Controls Exposed	Adjusted OR (95% CI) for MI
STEMI			
	N=757	N=1884	
Diclofenac	1.7%	2.9%	0.90 (0.43 to 1.87)
Arylpropionic acid NSAIDs	11.0%	13.0%	0.98 (0.70 to 1.37)
Ibuprofen	8.2%	8.2%	0.98 (0.65 to 1.48)
Naproxen & other AA†	3.0%	5.5%	0.97 (0.55 to 1.68)
Miscellaneous NSAIDs ‡	3.7%	4.8%	1.00 (0.58 to 1.73)
All NSAIDs combined	15.5%	18.9%	0.95 (0.70 to 1.28)
NON-STEMI			
	N=368	N=906	
Diclofenac	3.8%	2.6%	2.82 (1.23 to 6.48)
Arylpropionic acid NSAIDs	7.9%	12.3%	0.6 (0.36 to 1.03)
Ibuprofen	6.0%	7.8%	0.75 (0.41 to 1.38)
Naproxen & other AA†	2.2%	5.1%	0.37 (0.15 to 0.91)
Miscellaneous NSAIDs ‡	4.6%	4.5%	1.29 (0.64 to 2.60)
All NSAIDs combined	14.7%	18.7%	0.96 (0.63 to 1.46)

**Figure 3** Adjusted OR and 95% CI for the use of individual non-aspirin non-steroidal anti-inflammatory drugs (NSAID) and either ST-segment elevation myocardial infarction (STEMI) or non-ST segment elevation myocardial infarction (NSTEMI). AA, arylpropionic acid; MI, myocardial infarction.

Several studies, and some pharmacological arguments, militate for a protective effect of naproxen and related drugs.^{4–7 12 19 34–36} This was not found in all of the reports.^{2 3 10 15–19} Differences may be attributed partly to study designs, some having controlled for aspirin use and others not, and presenting with varying degrees of clinical specificity. According to our results, naproxen and related AA NSAID, with antiplatelet properties due to preferential cyclooxygenase 1 inhibition, may act on the limited thrombosis seen in NSTEMI but may not be sufficient to prevent the massive thrombosis seen in STEMI. If this is the case, cardiac prevention by aspirin should be maintained in patients at risk also taking naproxen and related AA NSAID. Because this is the first study to address the relationship between NSAID and STEMI and NSTEMI separately, and as it is also the first observation of a differential effect of NSAID on these outcomes, confirmation through additional research is required.

As for all observational, non-randomised studies, ours may not be free of residual confounding. Nevertheless, the impact of individual behavioural and medical risk factors was controlled for by matching and adjusted using multivariable conditional logistic regression. Comorbidities were described by physicians and considered for every case or control subject. In-depth interview allowed for the documentation of behavioural and some familial risk factors. This has also helped to identify over-the-counter and non-prescription uses of aspirin and other NSAID, which Kimmel *et al*¹⁹ have shown to be of paramount importance in the study of NSAID and MI. Despite in-depth documentation of more than 4000 subjects, this study did not have the statistical power to conclude on certain individual NSAID. It should be noted that rofecoxib was withdrawn from the market in 2001, 2 years before the first subject was included in the present study. Celecoxib is available in France, but is infrequently prescribed. It was therefore reported under the ‘miscellaneous NSAID’ category in the figures. Our proportion of NSAID users was found to be within the lower average limit of the published figures in other case–control studies on the same topic.^{2 15 36–38} The French population uses much more ibuprofen and ketoprofen (the latter is almost not used in Anglo-Saxon populations) and less diclofenac; and overall the French population uses fewer NSAID. The thorough clinical work-up of cases and referents allowed for better specificity of results on medical parameters, including MI diagnosis and medical history. The higher proportion of STEMI is expected in incident MI cases, as opposed to secondary MI, in which NSTEMI are more frequent due to better survival compared with STEMI.³⁸ Most series report both incident and prevalent cases, or are unable to exclude non-incident cases completely (database research), which explains why the proportions of STEMI versus NSTEMI reported in other studies present a different balance of electrical findings.

The database’s systematic and routine collection and documentation of patient information reduced the risk of selection bias feared in ad-hoc case–control studies devised to address specific drug risk concerns. Indeed, the cases excluded because of current aspirin use were effectively older than the cases finally retained for the analysis; however, this was not differential according to STEMI or NSTEMI. These differences are unlikely to have notably biased the results. As the same exclusion criterion was applied to controls, the results are not biased but it does limit the scope of our conclusions to current non-aspirin users.

It is not clear to us how confounding by indication would explain the diverging results on STEMI and NSTEMI. For the overall effect, it is possible that patients at risk are prescribed

different NSAID; as diclofenac appears to increase the risk of MI, it is unlikely that it would be prescribed more readily to persons at risk. So if anything, confounding by indication may have biased the results towards the null. Protopathic bias (reverse causality in which the drug would be prescribed after the first symptoms of the disease) is also unlikely as only incident cases of MI were recruited and exposures on the same day as the MI occurrence were not considered.

CONCLUSION

Our study adds to the evidence that diclofenac tends to increase the risk of MI and does increase the risk of NSTEMI in current non-aspirin users. Symmetrically, naproxen and related AA NSAID display a decrease in the risk of NSTEMI. The modification of MI risk associated with NSAID appears limited to NSTEMI.

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Competing interests LGB was the recipient of a research fellowship from INSERM at the time of the study and is currently employed by LA-SER together with MR. PGS’s institution has received a research grant from Servier (2009–14), and PGS has received consulting and speaker’s fees from Astellas Pharma, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, Daiichi Sankyo-Lilly, GSK, Medtronic, MSD, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier and The Medicines Company. PGS declares being a stockholder in Aterovax. MR, ND, PGB, MO, YC, EAL and JB declare having no conflicts of interest. LA is a stockowner and chairman of LA-SER, the company conducting the study.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the PGRx-MI and PGRx-GP registries and the study protocols were submitted to the ethics committee of Paris-Ile de France III and have been approved by CNIL, the French Data Protection Authority (Commission Nationale de l’Informatique et des Libertés).

Contributors The work presented here was carried out with the involvement of every author. All collaborating authors have contributed to the conception of the research theme. All authors participated in the conception, design and interpretation of results. LGB, MR, JB and LA participated in the statistical analysis. LGB, MR and LA had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The PGRx-Myocardial Infarction Study Group contributing members collected the data. LGB and LA co-wrote the article. All collaborating authors have contributed to, read and approved the final manuscript.

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APPENDIX 1

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Risk of ST versus non-ST elevation myocardial infarction associated with non-steroidal anti-inflammatory drugs

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