

# Ibuprofen May Abrogate the Benefits of Aspirin When Used for Secondary Prevention of Myocardial Infarction

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**ABSTRACT.** *Objective.* To determine whether patients taking aspirin for secondary prevention of myocardial infarction are at increased risk of recurrent disease when they take concomitant ibuprofen.

*Methods.* In this population based, retrospective cohort study using governmental databases, patients  $\geq 66$  years of age, hospitalized for an index acute myocardial infarction (AMI) between January 1992 and March 1999 and taking ASA throughout the period of followup were identified. The main exposure was the concomitant use of ibuprofen and ASA after the index AMI. The outcome of interest was recurrent AMI. Subjects were followed to one year after the index AMI.

*Results.* A total of 18,503 patients met the study entry criteria. Of these, 372 patients were dispensed a prescription for ibuprofen (exposed) and 14,424 patients were not dispensed a prescription for any non-steroidal antiinflammatory drug (NSAID) (unexposed). Patients dispensed prescriptions for any NSAID ( $n = 4079$ ), naproxen ( $n = 1239$ ), and diclofenac ( $n = 1474$ ) were analyzed separately. There was a trend to an increase in the rate of recurrent AMI in patients taking ibuprofen and ASA compared to those taking ASA alone as the duration of exposure increased [hazard ratios for ever,  $\geq 30$  days, and  $\geq 60$  days exposed were 1.01 (95% CI 0.58–1.76), 1.13 (95% CI 0.54–2.39), and 1.83 (95% CI 0.76–4.42), respectively]. In contrast, subjects taking prolonged naproxen and ASA had a trend toward a lower rate of recurrent AMI compared to those taking ASA alone.

*Conclusion.* The results are consistent with data that suggest that regular, but not intermittent, ibuprofen may abrogate the benefits of aspirin when used for the secondary prevention of AMI. There may be differences in the risk of heart disease with various NSAID. (J Rheumatol 2005;32:1589–93)

## Key Indexing Terms:

IBUPROFEN  
ASPIRIN  
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NONSTEROIDAL ANTIINFLAMMATORY DRUG  
SECONDARY PREVENTION

Nonsteroidal antiinflammatory drugs (NSAID), including aspirin (ASA), are widely used for the treatment of pain and arthritis<sup>1</sup>. ASA is also effective for the primary and secondary prevention of cardiovascular disease<sup>2</sup>. However, the cardiovascular risks and benefits of NSAID are controversial. Studies have produced conflicting results. Three case-control studies published simultaneously from Canada<sup>3</sup>, the United States<sup>4</sup>, and the United Kingdom<sup>5</sup> concluded that the rates of myocardial infarction (MI) among patients taking naproxen

were lower than the rates among patients not taking NSAID and those taking other NSAID. An observational study<sup>6</sup> suggested that NSAID as a group were cardioprotective. However, 2 observational studies<sup>7,8</sup> failed to demonstrate a cardioprotective effect of NSAID. Indeed, in the large, population based cohort study involving over 130,000 patients<sup>7</sup>, NSAID as a group were found to have no effect on the risk of cardiovascular disease, but subgroups of ibuprofen users were at increased risk of serious cardiovascular disease compared to nonusers. Recently, 2 studies have suggested that naproxen may in fact increase the risk of ischemic heart disease<sup>9,10</sup>.

There are few data on the cardiovascular effects of the concurrent use of NSAID and ASA. An *ex vivo* study suggested that coadministration of ASA and rofecoxib and ASA and diclofenac did not interfere with the antiplatelet effect of ASA, but that administration of ibuprofen antagonized the irreversible platelet inhibition induced by ASA<sup>11</sup>. The clinical correlates of that study have yielded contradictory results. In a retrospective cohort study of elderly patients with known cardiovascular disease, those taking ASA plus ibuprofen had an increased risk of all-cause mortality and cardiovascular mortality compared to those who used ASA alone<sup>12</sup>. Similarly, a *post hoc* analysis of the Physicians' Health Study suggested

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that the regular use of NSAID (defined as  $\geq 60$  days/year) in combination with ASA was associated with an increased risk of first AMI<sup>13</sup>. During the study period, ibuprofen was a widely used NSAID. By contrast, a retrospective study in a cohort of elderly patients with a history of MI found no adverse interaction between aspirin and ibuprofen. Patients prescribed ASA and ibuprofen had a similar risk of death compared to those prescribed ASA alone<sup>14</sup>.

The question of whether ibuprofen interferes with the cardioprotection of ASA is of public health importance given the prevalence of cardiovascular disease and the use of ASA, as well as the widespread use of ibuprofen, which is available over the counter. Given this background, we investigated whether ibuprofen increases the risk of recurrent acute myocardial infarction (AMI) in patients already taking ASA for the secondary prevention of heart disease.

## MATERIALS AND METHODS

**Study design and population.** We designed a population based, retrospective cohort study using administrative databases. Cohort members were identified from the hospital discharge summary database of the Province of Quebec, Canada. This database provides information on all hospital admissions for the entire province, including discharge diagnosis and comorbid conditions. Subjects were included if (1) they had been diagnosed with a new AMI [as defined in the *International Classification of Diseases*, 9th revision (ICD), code 410] between January 1, 1992, and March 31, 1999 (the index AMI); (2) they were taking ASA; and (3) they were  $\geq 66$  years of age at the time of their AMI. New AMI was defined as the absence of a diagnosis of AMI during the year before the index AMI. The age cutoff was determined on the basis of the availability of prescription records (see below). We identified all patients who had a recurrent AMI within one year of discharge from the index AMI. All other patients were censored at the earlier of death or 365 days after discharge from their index AMI. Patients who had at least one prescription for an NSAID during this time were classified as exposed. All the others were classified as unexposed.

**Medication exposure.** We used the prescription drug claims database to determine exposure to medications. The Quebec provincial government covers the costs and keeps records of all outpatient prescriptions for persons aged  $\geq 65$  years. The data in the discharge summary and drug claims databases are linkable by patient identification number. The 2 databases have been validated for AMI identification and accuracy of prescription claims<sup>15,16</sup>. The information in the prescription drug database includes drug name, dispensation date, dosage, drug form, duration, and quantity of the drug dispensed for all prescribed medications. We used the dispensation date to identify the time of first prescription (time zero). We summed the number and duration of all prescriptions for any given medication to calculate the number of prescriptions and the total duration of use of that medication.

Subjects were included only if they were taking ASA. We assumed that subjects were taking ASA if (1) they had filled a prescription for ASA in the 30 days following the index AMI; (2) they had filled at least 2 consecutive prescriptions for ASA during the followup period; and (3) they had prescriptions for ASA for a total duration of at least 60 days during the followup period. A second prescription filled within 7 days of expiration of a first prescription was considered to be consecutive.

The main exposure was filling of at least one prescription for ibuprofen, for any length of time, in the first year after the index AMI. Subgroups of exposure were defined for those with one or more prescriptions totaling  $\geq 30$  days' and  $\geq 60$  days' duration at any time during the period of followup. Similar analyses were also performed for all NSAID, as well as diclofenac and naproxen separately. Exposure to one NSAID did not have to be exclusive of other NSAID. NSAID were those included on the provincial drug for-

mulary of all the drugs approved for therapeutic purposes by the Ministry of Health, during the study period. The selective cyclooxygenase-2 (COX-2) inhibitors were included on the provincial formulary in late 1999 and early 2000. The study ended in March 2000. Thus, we did not specify a separate category for them. NSAID nonusers were defined as subjects who did not fill a prescription for any NSAID at any time after their index AMI or during the period of followup.

**Study outcome.** The study outcome was recurrent AMI, defined as having an admission with a primary diagnosis of AMI (ICD code 410) after the index admission. This was assessed using the hospital discharge database described above. Patients with recurrent AMI who died before reaching the hospital were not recorded under our definition of outcome, whereas patients who died in the course of their admission were included. Thus, the outcome of recurrent AMI includes some fatal and nonfatal AMI.

**Followup.** We followed the patients starting at time zero. For each exposed, time zero was the time of first prescription for ibuprofen or an NSAID of interest. The nonexposed were assigned the value of time zero of a randomly selected exposed patient. This random matching on time zero was designed to reduce the possibility of a survival bias in favor of the exposed, who had to have lived long enough to fill a first prescription. The nonexposed assigned a time zero after a study outcome had already occurred were excluded from the study cohort. Followup ended with the occurrence of a recurrent AMI, or death, or at most 365 days after the index AMI.

**Statistical analysis.** Cox proportional hazards modeling was performed to compare time to outcome between the exposed and the nonexposed. The model was adjusted for age, sex, comorbidities assessed in the year prior to the index AMI (diabetes mellitus, chronic renal failure, congestive heart failure, cerebrovascular disease), cardiac procedures in the year after the index AMI (coronary angiography, percutaneous transluminal coronary angioplasty, and coronary artery bypass grafting), the use of certain cardiac drugs in the 90 days after the index AMI (beta-blockers and angiotensin-converting enzyme inhibitors), the type of institution (rural, university, with or without an angiography suite), and time to first prescription or time to time zero, depending on exposure status. Since acetaminophen may be used instead of NSAID in patients at greater cardiac risk, we also adjusted for acetaminophen use during the period of followup to reduce the possibility of confounding by indication.

For the analysis with  $\geq 30$  days of exposure, we calculated the number of days it took each exposed patient to accumulate 30 days of exposure after discharge and defined that as time zero, which we called  $t_{30}$ . Again, to minimize the possibility of a survival bias, each nonexposed patient who had survived at least 30 days since discharge was assigned the  $t_{30}$  of a randomly chosen exposed patient. The nonexposed patients assigned a  $t_{30}$  after the occurrence of the study outcome or death were excluded from the analysis. We repeated this for those with  $\geq 60$  days of prescription.

All analyses were performed using SAS statistical software, version 8.2 (SAS Institute, Cary, NC, USA).

## RESULTS

An initial cohort of 21,684 patients who had an AMI between January 1, 1992, and March 31, 1999 (the index AMI), was identified. We excluded 11.6% of this cohort because they failed to take ASA as defined throughout the study period. Another 6.8% of the nonexposed were excluded because they were assigned a random time zero after they had already had a study outcome. A final cohort of 18,503 subjects was obtained. Of these, 372 patients were dispensed a prescription for ibuprofen (exposed) and 14,424 patients were not dispensed any NSAID (unexposed) during the period of interest.

The 3 most commonly used NSAID were ibuprofen (9.1%), naproxen (30.4%), and diclofenac (36.1%). Other

NSAID less frequently used during the study period included indomethacin, phenylbutazone, fenoprofen, tolmetine, ketoprofen, sulindac, piroxicam, diflunisal, mefenamic acid, flurbiprofen, tiaprofenic acid, tenoxicam, nabumetone, salsalate, etodolac, celecoxib, and rofecoxib. The exposed had a mean number of NSAID prescriptions of 2.4 and a mean total duration of prescriptions of 47.9 days.

The exposed and nonexposed groups were well balanced in terms of baseline characteristics (Table 1). The mean time of followup was 239.7 days (median 256.5) for the exposed and 235.1 days (median 264) for the nonexposed. During this time, 3.7% of the cohort had a recurrent AMI.

In subjects exposed to ibuprofen and ASA, there was a trend toward an increase in the rate of recurrent AMI compared to those taking ASA alone as the duration of exposure increased from ever-users (hazard ratio 1.01, 95% confidence interval 0.58–1.76), to  $\geq 30$  days (HR 1.13, 95% CI 0.54–2.39) and to  $\geq 60$  days (HR 1.83, 95% CI 0.76–4.42; Table 2). The rate of recurrent AMI was similar in those dispensed a prescription for any NSAID and ASA compared to those taking ASA alone. Finally, there was a trend toward a decrease in the rate of recurrent AMI in those dispensed  $\geq 60$  days of naproxen and ASA compared to those taking ASA alone.

Table 1. Demographic and clinical characteristics of acute myocardial infarction (AMI) in patients taking aspirin who were prescribed NSAID.

Characteristics	Unexposed	NSAID (all)	Ibuprofen	Naproxen	Diclofenac	Other NSAID*
No. of patients (n = 18,503)	14,424	4079	372	1239	1474	1670
Median age, yrs	74	74	73	73	74	74
Male, %	57.7	54.9	57.8	53.6	53.0	54.2
Comorbidities, %						
Congestive heart failure	23.0	18.9	19.4	18.2	17.4	19.6
Diabetes	21.3	21.3	21.0	20.6	21.0	21.1
Cardiac dysrhythmias	17.3	15.4	15.9	16.1	14.7	15.3
Cerebrovascular disease	6.5	5.6	4.8	5.3	5.2	5.9
Chronic renal failure	6.4	6.6	7.8	5.7	5.9	8.1
Shock	1.0	1.0	2.2	1.4	0.5	0.9
Procedures (1 year post-AMI), %						
Catheterization	24.2	23.8	26.1	24.9	24.6	22.3
PTCA	9.7	9.5	10.2	10.1	10.2	8.7
CABG	4.4	4.2	4.6	4.6	4.6	3.7
Other medications (< 90 days after discharge), %						
Beta-blockers	56.8	56.7	57.8	56.3	59.4	54.7
ACE Inhibitors	43.4	40.7	39.3	39.8	39.6	41.1
Hospital characteristics, %						
University hospital	45.3	43.4	45.4	43.9	43.4	43.5
Rural location	4.6	4.3	4.0	5.0	3.7	4.4
Hospital with angiography suite	25.2	23.6	28.5	22.5	23.0	25.0
No. of recurrent AMI (%)	535 (3.7)	147 (3.6)	13 (3.5)	41 (3.3)	49 (3.3)	65 (3.9)

\* Sum for individual NSAID is greater than for the total because exposed patients could have been prescribed more than one type of NSAID. PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass grafting; ACE: angiotensin-converting enzyme.

Table 2. Hazard ratios (CI) of recurrent acute myocardial infarction (compared to nonexposed subjects).

	All NSAID	Ibuprofen	Naproxen	Diclofenac	Others
Ever exposed					
N	4079	372	1239	1474	1670
Crude	1.00 (0.83, 1.20)	0.92 (0.53, 1.59)	0.91 (0.67, 1.26)	0.90 (0.67, 1.21)	1.05 (0.81, 1.35)
Adjusted*	1.09 (0.90, 1.31)	1.01 (0.58, 1.76)	1.04 (0.58, 1.76)	0.99 (0.74, 1.33)	0.99 (0.74, 1.33)
Exposure $\geq 30$ days					
N	2440	160	592	829	1046
Crude	0.84 (0.67, 1.06)	1.05 (0.50, 2.20)	0.87 (0.57, 1.35)	0.73 (0.49, 1.08)	0.79 (0.56, 1.12)
Adjusted*	0.93 (0.74, 1.16)	1.13 (0.54, 2.39)	1.13 (0.54, 2.39)	0.80 (0.54, 1.20)	0.80 (0.54, 1.20)
Exposure $\geq 60$ days					
N	1547	90	336	517	633
Crude	0.93 (0.69, 1.25)	1.68 (0.70, 4.06)	0.72 (0.36, 1.44)	0.92 (0.56, 1.51)	0.80 (0.50, 1.30)
Adjusted*	1.01 (0.75, 1.36)	1.83 (0.76, 4.42)	1.83 (0.76, 4.42)	1.00 (0.61, 1.65)	1.00 (0.61, 1.65)

\* Adjusted for age, sex, congestive heart failure, diabetes mellitus, chronic renal failure, cerebrovascular disease, cardiac procedures (angiography, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting), time to time zero, acetaminophen use, university or rural hospital, hospital with an angiography suite, use of a beta-blocker within 90 days of discharge, and use of an ACE inhibitor within 90 days of discharge.

All patients were assumed to be taking ASA. To test this assumption, a sensitivity analysis was performed. In the 365 days after discharge from their index AMI, the exposed and nonexposed filled an average of 11.1 and 11.0 prescriptions for ASA, had an average of 313.5 and 313.1 days of ASA on record, and had a median time to last prescription of 347 and 346 days, respectively. These numbers are consistent with high rates of persistence and support the assumption concerning ASA use.

## DISCUSSION

In this study of over 18,000 elderly patients with a previous AMI, patients taking ASA who filled prescriptions for ibuprofen had a trend toward an increasing rate of recurrent AMI as the duration of exposure to ibuprofen increased. Those who filled prescriptions for any NSAID had similar rates of recurrent AMI compared to those taking ASA only, and those who filled prescriptions for  $\geq 60$  days of naproxen had a trend toward a lower rate of recurrent AMI.

There is evidence to suggest that ibuprofen may increase the risk of cardiovascular disease, alone and in combination with ASA. Alone, there was an increase in the risk of serious cardiovascular disease in subgroups of ibuprofen users compared to NSAID nonusers in the Tennessee cohort<sup>7</sup>. In combination, ibuprofen has been shown to interfere with the antiplatelet effect of ASA both *in vitro*<sup>17,18</sup> and *ex vivo*<sup>11</sup>. ASA and ibuprofen share a common docking site in the COX-1 enzyme. Thus, ibuprofen has the ability to interfere with the antiplatelet action of ASA by competitive inhibition. Spatial differences in binding sites, pharmacokinetic differences, and differences in affinity for the COX-1 enzyme could explain that ibuprofen, but not diclofenac, has the potential to blunt the antiplatelet effect of ASA<sup>11</sup>.

However, the clinical implications of the pharmacological interaction between ASA and ibuprofen remain uncertain. A retrospective study in Scottish patients reported that patients with cardiovascular disease prescribed ASA and ibuprofen at the time of discharge from hospital were at increased risk of all-cause mortality and cardiovascular mortality compared to patients prescribed ASA alone (HR 1.73, 95% CI 1.05–2.84)<sup>12</sup>. Similarly, in a recent *post hoc* analysis of data from the Physicians' Health Study<sup>13</sup>, the regular use of NSAID (defined as  $\geq 60$  days/year) in combination with ASA was associated with an increased risk of first AMI (relative risk 2.86, 95% CI 1.25–6.56). However, the intermittent use of NSAID (defined as 1–59 days per year) was not associated with an increased risk of MI (relative risk 1.21, 95% CI 0.78–1.87). Although the authors did not have information on the types of NSAID used, they comment that ibuprofen was a widely used NSAID during the study period. By contrast, a retrospective study in a large cohort of elderly patients with a history of MI compared patients discharged taking ASA alone, ASA and ibuprofen, and ASA and other NSAID. In adjusted analysis, the risk of death was similar in patients taking ASA

and ibuprofen compared to patients taking ASA alone (HR 0.84, 95% CI 0.70–1.01) and compared to patients taking ASA and other NSAID (HR 0.96, 95% CI 0.86–1.06)<sup>14</sup>. The authors concluded that the pharmacodynamic interaction between ASA and ibuprofen did not translate into significant clinical events.

Our results are consistent with this literature. We found a trend toward an increase in the rate of recurrent AMI in patients taking ASA and ibuprofen compared to those taking ASA alone as the duration of exposure to ibuprofen increased. Thus, at the clinical level, it is possible that ibuprofen interferes with the cardioprotective effect of ASA when used chronically, but not intermittently. Our study has several strengths compared to the available studies on the possible interaction between ASA and ibuprofen. In the 2 retrospective studies, patients were defined as exposed to ASA and ibuprofen based on medications prescribed at the time of discharge from hospital. However, patients may have ceased to take either of those medications or started to take a number of others during the period of followup. Moreover, the influence of duration of exposure was not assessed. The report from the Physicians' Health Study was a *post hoc* analysis<sup>13</sup>. There were very few events in the exposed group and this contributed to wide confidence intervals. Finally, the authors had no information on the types of NSAID used, and could only assume that ibuprofen accounted for much of the NSAID use because it was widely used during their study period. We assessed exposure over time, examined the effect of intermittent and prolonged exposure, and had specific information on the type of NSAID prescribed.

There are data to suggest that naproxen alone may be cardioprotective<sup>3–5</sup>, although this has recently been the subject of controversy<sup>9,10</sup>. However, there is a paucity of data on the cardiovascular effects of concomitant naproxen and ASA. Our findings suggest that prolonged naproxen use may afford cardioprotection over and above that provided by ASA.

There are inherent limitations to using claims databases for epidemiological research. First, there may be residual confounding resulting from unavailable or unmeasurable variables, such as exercise capacity, body mass index, or smoking status. Second, the results may have been affected by a misclassification bias. Indeed, there is no way to verify that patients who were prescribed ibuprofen were compliant. Thus, noncompliant patients may have been classified as exposed when they were not. On the other hand, patients who were classified as unexposed may have been taking over-the-counter (OTC) ibuprofen. A survey conducted by Santé Québec, a provincial public health agency, in 1998 showed that 17.0% of the elderly who consumed NSAID acquired them OTC<sup>19</sup>. Thus, patients may have been misclassified on exposure, and the effect of this may, in the former case, have been to bias the results away from and, in the latter case, towards the null. The net effect of a possible misclassification bias in this study cannot be determined with certainty. Third, our definition of the



main exposure requiring ever-exposure is crude. In particular, it does not capture details about the timing of exposure, whether current, recent, or remote in relation to the outcome of interest. Finally, our definition of outcome required an admission for recurrent AMI. Patients with recurrent AMI who died before reaching the hospital were not included. Thus, our results are generalizable only to patients with recurrent AMI who survived long enough to reach the hospital.

On the other hand, the questions asked in this study could only be answered with great difficulty. A randomized trial would be expensive and the results would not be available for some time. As for other observational databases, most do not account for compliance or OTC medication use, nor do they have extensive information on individual patient attributes (weight, exercise capacity, smoking) or other important confounders. Nevertheless, heart disease is prevalent, aspirin is commonly used in secondary prevention, and ibuprofen is readily available. The risk of an interaction, if real, has the potential to have substantial public health consequences. We believe that our high quality administrative databases, our design, and our methods have allowed us to approach an important question that could otherwise not be readily answered. Our results should be viewed in the context of accumulating evidence that ibuprofen may interfere with the cardioprotective effect of aspirin.

We believe clinicians should be aware that prolonged use of ibuprofen may interfere with the cardioprotective effect of aspirin. They should be cautious when using the 2 drugs in combination, particularly in elderly patients with known heart disease. Until definitive data are available, they should consider using alternative medications when possible.

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