

# Association Between Naproxen Use and Protection Against Acute Myocardial Infarction

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**Background:** The association between the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and acute myocardial infarction (AMI) is unclear. Nonsteroidal anti-inflammatory drugs vary in their antithrombotic properties, with naproxen having a particularly effective antithrombotic potential.

**Objective:** To compare the effect of naproxen vs other NSAIDs in the prevention of AMI in an older population.

**Methods:** Population-based, matched case-control study. Patients (aged  $\geq 65$  years) in Quebec had been hospitalized for AMI between January 1, 1992, and December 31, 1994. The admission date for AMI was considered the index date. Control subjects were randomly selected from a Quebec drug and physician claims database. For each case, a control was matched with the same index date, age (within 2 years), and sex. Cases and controls were required to have at least 1 year of pharmaceutical and medical records before the index date to identify risk factors for AMI and exposure to naproxen or

other nonaspirin NSAIDs. Concurrent exposure to a medication was defined as exposure to that medication at the index date. Logistic regression analyses were used to evaluate the association between the use of naproxen and other NSAIDs in the prevention of AMI, adjusting for potential confounders.

**Results:** Included in the study were 4163 cases and 14 160 controls. Determinants (adjusted odds ratios [95% confidence intervals]) of AMI included use in the prior year of anticoagulants (0.76 [0.64-0.90]), nitrates (2.01 [1.86-2.17]), antidiabetic agents (1.72 [1.56-1.90]), antihypertensive agents (1.36 [1.28-1.45]), and lipid-lowering agents (0.83 [0.75-0.91]), as well as concurrent exposure to naproxen vs other NSAIDs (0.79 [0.63-0.99]).

**Conclusion:** Compared with other NSAIDs, concurrent exposure to naproxen has a protective effect against AMI.

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**N**ONSTEROIDAL anti-inflammatory drugs (NSAIDs) are effective for the management of inflammatory and arthritic conditions and have been one of the most widely used classes of drugs worldwide.<sup>1-5</sup> In vivo investigations have shown a beneficial effect of other NSAIDs on platelet functions,<sup>6</sup> suggesting that these agents may prevent the thrombotic complications of cardiovascular diseases, such as myocardial infarction (MI).

*For editorial comment  
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The cyclooxygenase-2 (COX-2) inhibitors, or coxibs, form a group of agents that have the anti-inflammatory effect of NSAIDs, with a lower potential for causing upper gastrointestinal toxicity.<sup>7-14</sup> Coxibs have been associated with MI<sup>7,15</sup>; however, this association remains controversial.<sup>16</sup> The hypothesis that naproxen is a stronger antiplatelet agent compared with other

NSAIDs has been suggested in a study<sup>7</sup> comparing rofecoxib with naproxen.

Given the widespread use of coxibs and NSAIDs among older populations, it is important to examine, at the population level, the association between naproxen and other NSAID exposure and hospitalization for acute MI (AMI). Government health plan databases, such as the database of the Quebec Health Care Fund administered by the *Régie de l'assurance maladie du Québec* (RAMQ), Quebec City, are a source of patient-specific data.<sup>17</sup>

The objective of this study was to compare the effect of naproxen vs other NSAIDs in the prevention of AMI in older persons.

## RESULTS

### PATIENT CHARACTERISTICS

During the study, 14 163 patients had an AMI and formed the case group. The control group comprised 14 160 persons. In the year preceding the index date, more

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## SUBJECTS AND METHODS

### DATA SOURCE

In Quebec, all persons aged 65 years or older are eligible for health care coverage by RAMQ. The fund covers the costs of prescription drugs, outpatient physician visits, and other medical services offered in private clinics or hospitals. The RAMQ database has been described in detail elsewhere.<sup>17,18</sup>

A hospital discharge summary database maintained by *Med-Echo*, a government agency, is also available in Quebec. *Med-Echo* records provide information on hospitalized patients, including discharge diagnosis, comorbid conditions, and dates of admission and discharge. For all Quebecois who are permanent residents, hospitalizations are covered by RAMQ, and the dates are captured in the *Med-Echo* database. The data in the *Med-Echo* and RAMQ databases are linked by patient identification number. The 2 databases have been used in other epidemiological studies.<sup>17-20</sup>

### STUDY POPULATION

The study population was derived from the RAMQ and *Med-Echo* databases, using data recorded for all patients aged 65 years or older between January 1, 1988, and December 31, 1994.

### DESIGN

The design was a 1:1 matched, population-based, case-control study.<sup>21</sup>

### CASE SELECTION

Medical, demographic, and pharmaceutical records on all patients aged 65 years or older who had a diagnosis of AMI (*International Classification of Diseases, Ninth Revision [ICD-9]*), code 410) between 1988 and 1994 were obtained from RAMQ. All hospital discharge summaries of these patients during the same period were obtained from *Med-Echo*. Those with an AMI discharge diagnosis date

between January 1, 1992, and December 31, 1994, were retained as potential cases. The date of admission for each case was termed the *index date*. For each of these patients, medical records of the 4 years before hospitalization were examined for prior AMI. Those with a prior AMI within that period were excluded. To further exclude cases with preexisting events, *Med-Echo* records for the potential cases were linked to those obtained from RAMQ; the RAMQ records were searched for ICD-9 code 412 ("old" MI diagnoses); and all patients with this diagnosis during the year before their index date were excluded. The remaining patients who had at least 1 year of documented observation in the database before their index date constituted the cases.

### CONTROL SELECTION

Control subjects were selected from a random sample of 82754 patients obtained from the RAMQ database. The sample comprised 10% of all patients who were aged 65 years or older between 1988 and 1994 and who filled at least 1 prescribed drug or had at least 1 medical service during that period. From this sample, we identified, for each case, all subjects who were of the same sex, within 2 years of the same age at the case index date, and who had at least 1 year of medical and pharmaceutical data before the case index date. From these subjects, 1 control was randomly selected for each case. The index date of the case was assigned to its matched control. The control for a case was selected using the method of sampling with replacement. Therefore, a person could serve as a control for more than 1 case. All controls used in the analysis were under observation (ie, active in the RAMQ database and still alive) at the index date.

### POTENTIAL DETERMINANTS OF AMI

Patient demographics and medical and prescription records for cases and controls were searched for data from the year before the index date, to identify potential determinants of MI. The following potential determinants were assessed and included in the analysis:

cases than controls had been hospitalized, had office visits, and had higher chronic disease scores (**Table 1**). In addition, the prevalence of AMI risk factors was higher in cases than in controls. Prescriptions for nitrates, antihypertensive agents, antidiabetic agents, anticoagulants, and aspirin were more frequently filled by cases than by controls. More cases than controls had been diagnosed as having cardiovascular diseases or had visited a cardiologist in the year before the index date. Exposure history to naproxen and other NSAIDs was more common in cases than in controls (**Table 2**).

### ASSOCIATION BETWEEN NAPROXEN USE AND HOSPITALIZATION FOR AMI

**Table 3** displays the results of the primary analysis, which used a conditional logistic regression model to compare the association (odds ratio [95% confidence interval]) between AMI and concurrent-chronic exposure to naproxen

and other NSAIDs, adjusting for baseline factors. Patients who filled prescriptions for nitrates (2.01 [1.86-2.17]), antidiabetic agents (1.72 [1.56-1.90]), and antihypertensive agents (1.36 [1.28-1.45]) were at significantly higher risk for AMI compared with those not prescribed these agents. Patients who were exposed to aspirin at the index date were at higher risk of AMI than those not exposed (1.17 [1.07-1.28]). There was an interaction effect between prior ischemic heart disease and aspirin at the index date. Among those who had ischemic heart disease diagnoses before the index date, those exposed to aspirin had a lower incidence of AMI than those not exposed to aspirin (0.85 [0.77-1.00]). Patients who were dispensed lipid-lowering agents (0.83 [0.75-0.91]) and those dispensed anticoagulants (0.76 [0.64-0.90]) had a lower incidence of AMI than those not dispensed these agents. Concurrent-chronic users of naproxen had a lower incidence of AMI than concurrent-chronic users of other NSAIDs (0.64 [0.48-0.86]).

## Medications

Prior use of anticoagulants, nitrates, lipid-lowering agents, antidiabetic agents, and antihypertensive agents was documented.

## Existing Cardiovascular Disease

Ischemic heart disease (ICD-9 codes 410-414), congestive heart failure (codes 428-429), prior visits to cardiologists, and prior diagnoses of cerebrovascular diseases (codes 430-438) were indicative of existing cardiovascular disease.

## Comorbidity Factors

All hospitalizations and the number of medical encounters during the year before the index date and the chronic disease score were assessed. The chronic disease score for a patient was derived from a weighted summation of the number of drugs filled during the year before the index date.<sup>22</sup> Classes of drugs were assigned scores (0 to 5) according to the severity of the disease for which they were prescribed, with higher scores indicating more severe conditions. The sum of the scores of drugs the patient took during the year preceding the index date was the chronic disease score. Nonsteroidal anti-inflammatory drugs and the drugs listed as key variables in the "Medications" subsection were excluded from the calculation of the chronic disease score (to prevent colinearity).

## EXPOSURE CLASSIFICATION

Medical records preceding the index date were searched for filled prescriptions for naproxen, nonaspirin NSAIDs (excluding naproxen), and aspirin. Each prescription was assigned a duration, using the number of days' supply as indicated in the database. Four exposure types were assessed:

### Concurrent Exposure

Concurrent exposure referred to prescriptions with a duration that covered or overlapped with the index date.

## Chronic Exposure

Chronic exposure referred to prescriptions filled at least twice and with 60 or more consecutive days of prescription duration. For this category, patients were considered to be exposed for 125% days' supply as recorded in the database<sup>23</sup> to allow for a gap between prescriptions not exceeding 25% of the duration of the first one (**Figure**).

### Concurrent-Chronic Exposure

Concurrent-chronic exposure was chronic exposure and exposure at the index date. This category was the subject of the primary analysis.

### Interrupted-Chronic Exposure

Interrupted-chronic exposure was chronic exposure without exposure at the index date.

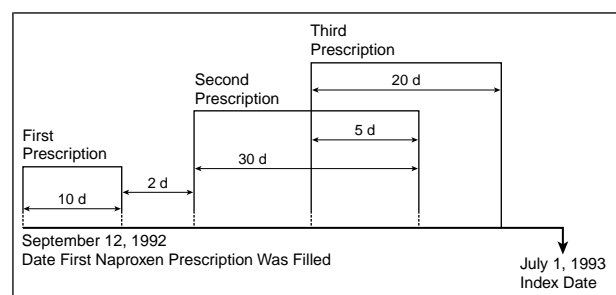
## STATISTICAL ANALYSIS

Descriptive statistics (means and proportions) were used to evaluate patient characteristics at the index date. The association between use of naproxen and other NSAIDs (excluding naproxen) and hospitalization for AMI was assessed using 3 conditional logistic regression analyses appropriate for 1:1 matched case-control studies,<sup>24</sup> adjusting for the same potential confounders. The primary analysis examined the effect of concurrent-chronic exposure to naproxen vs other NSAIDs (excluding naproxen) on outcomes. Additional analyses examined the effects of (1) concurrent exposure to naproxen and any concurrent NSAID (excluding naproxen) and (2) interrupted-chronic exposure to naproxen vs other NSAIDs (excluding naproxen). The potential confounders adjusted for in the models included prior use of anticoagulants, nitrates, lipid-lowering agents, antidiabetic agents, or antihypertensive agents; prior cardiovascular diseases; and the presence of comorbidity factors. Commercially available statistical software (SAS, version 8; SAS Institute, Cary, NC) was used to carry out the analyses.

Secondary analyses showed that (1) the incidence of AMI association with interrupted-chronic exposure to naproxen was not significantly different from that of interrupted-chronic exposure to other NSAIDs (0.98 [0.73-1.33]) and (2) the incidence of AMI in concurrent users of naproxen was significantly lower than that of concurrent users of other NSAIDs (0.79 [0.63-0.99]). In these secondary analyses, estimates of the effect of baseline factors on AMI were similar to those in the primary analysis for all baseline factors.

## COMMENT

This study was designed to examine the association between naproxen use and hospitalization for AMI in comparison with other NSAIDs, using a database of older Quebecois. We used a case-control design that included all those who had been hospitalized for AMI (14 163 patients) during 3 years. Given the same risk susceptibil-



Example of a patient's interrupted-long-term exposure to naproxen 12 months before the index date. The patient had 62 (10+2+[30-5]+20+20/4) consecutive days of exposure but was not exposed at the index date.

ity, exposure to naproxen had a protective effect against AMI compared with the other nonaspirin NSAIDs. This effect seemed to be present only with concurrent naproxen exposure and was strongest in chronic users. This is consistent with the fact that the antiplatelet effect of naproxen

**Table 1. Patient Characteristics at Index Date\***

Characteristic	Case (n = 14 163)	Control (n = 14 160)
Age, mean ± SD, y	75.7 ± 6.6	76.0 ± 6.7
Male sex	52.8	52.8
Prior all-cause hospitalizations		
In prior 2-7 d	11.0	2.6
In prior 8-365 d	39.1	35.1
Chronic disease score in prior year		
0	42.9	62.6
1-3	32.1	24.5
>3	25.0	12.9
No. of medical visits in prior year		
0	3.1	12.6
1-11	39.2	46.3
>11	57.7	41.1
Prior medication use		
Aspirin		
In prior year	31.7	20.5
At index date	20.1	12.4
Nitrates in prior year	33.6	14.2
Anticoagulants in prior year	3.1	2.2
Antidiabetic agents in prior year	12.4	5.1
Antihypertensive agents in prior year	63.2	42.4
Lipid-lowering agents in prior year	8.6	7.6
Cerebrovascular disease diagnosis in prior year	2.3	1.6
Cardiovascular disease diagnosis or visits to cardiologists in prior year	36.1	21.3

\*Data are given as percentages unless otherwise indicated.

**Table 2. Exposure to Naproxen or Other Nonsteroidal Anti-inflammatory Drugs (NSAIDs)\***

Exposure	Case (n = 14 163)	Control (n = 14 160)
NSAID in prior year	22.6	17.6
Concurrent users	7.5	5.1
Chronic users	8.9	6.0
Concurrent-chronic users	5.1	3.2
Naproxen in prior year	8.9	7.5
Concurrent users	1.8	1.5
Chronic users	2.1	1.7
Concurrent-chronic users	1.0	0.9

\*Data are given as percentages.

is brief and suggests that persistent use is required for cardioprotection.

Conventional NSAIDs inhibit 2 forms of COX, COX-1 and COX-2.<sup>10</sup> Cyclooxygenase-1 is constitutively expressed in platelets, gastric mucosa, and most tissues, where it maintains physiological functions such as vascular homeostasis and gastric cytoprotection. Cyclooxygenase-2 is predominantly induced at sites of inflammation throughout the body to generate prostaglandin, believed to mediate pathologic processes such as pain and inflammation.<sup>25,26</sup> Naproxen, but not aspirin, meclizolam sodium, or indomethacin, has been found to protect ischemic myocardium caused by coronary occlusion in animals.<sup>27</sup> In contrast, another study<sup>28</sup> found no association between nonaspirin NSAID use and reduced risk for AMI among women.

**Table 3. Conditional Logistic Regression Model to Determine the Factors Associated With Hospitalization for Acute Myocardial Infarction\***

Factor	Odds Ratio (95% Confidence Interval)
Exposure in prior years to	
Nitrates	2.01 (1.86-2.17)
Anticoagulants	0.76 (0.64-0.90)
Antidiabetic agents	1.72 (1.56-1.90)
Antihypertensive agents	1.36 (1.28-1.45)
Lipid-lowering agents	0.83 (0.75-0.91)
All-cause hospitalizations	
0	Reference
In prior 2-7 d	3.42 (3.00-3.91)
In prior 8-385 d	0.93 (0.88-0.99)
No. of medical visits in prior year	
0	Reference
1-11	2.37 (2.10-2.67)
>11	2.60 (2.29-2.97)
Chronic disease score in prior year	
0	Reference
1-3	1.41 (1.32-1.50)
>3	1.74 (1.61-1.88)
Concurrent aspirin	1.17 (1.07-1.28)
Ischemic heart disease diagnosis in prior year	1.14 (1.03-1.25)
Ischemic heart disease diagnosis and aspirin at index date	0.75 (0.64-0.89)
Association with AMI	
Concurrent-chronic NSAIDs (excluding naproxen)	Reference
Concurrent-chronic naproxen	0.64 (0.48-0.86)
No concurrent-chronic exposure to naproxen or the other NSAIDs	0.75 (0.65-0.86)

\*AMI indicates acute myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs.

Our findings indirectly support the results of Van Hecken et al,<sup>6</sup> showing that naproxen is a stronger inhibitor of COX-1 than either diclofenac or ibuprofen. Our results partially explain the discrepancy between the findings by Bombardier et al,<sup>7</sup> in which the incidence of MI was higher in rofecoxib users than in naproxen users, and studies by Day<sup>8</sup> and Cannon<sup>9</sup> and their colleagues, in which the incidence of MI in rofecoxib users was similar to that in ibuprofen or diclofenac users. Another case-control study<sup>28</sup> has found no cardioprotective effect of NSAIDs. This study used a nested case-control design in women after menopause. Our study design differed in that it compared patients concurrently exposed to naproxen with those concurrently exposed to other NSAIDs, thus reducing the selection bias that is present in the comparison between NSAID users and nonusers.

The beneficial effect of aspirin in the prevention of MI is well known.<sup>29-31</sup> Patients who have had an MI or who are considered at risk for such an event should be prescribed a daily low dosage of aspirin. Aspirin use can therefore be a marker for the presence of MI risk factors and is also an effect modifier for that risk factor. The beneficial effect of aspirin to prevent MI is immediate. Therefore, only concurrent exposure to aspirin was considered in this study. Unlike aspirin, the effect of nonaspirin NSAIDs on MI is unknown, and patients prescribed

naproxen are not expected to differ from those prescribed other nonaspirin NSAIDs (excluding naproxen) in MI risk susceptibility. Therefore, any difference in AMI occurrence between the 2 groups was attributed to exposure to naproxen or other NSAIDs.

This analysis was conducted using a large population-based, validated medical database. Patients with uncontrolled hypertension or those at high risk for MI are typically excluded from clinical trial research.<sup>16</sup> Use of administrative databases provide the advantage of a large sample size, generalizability, and the broad inclusion of patients with multiple AMI risk factors, who are typically excluded from clinical trials.

This study had several limitations. First, important risk factors such as cigarette smoking and obesity could not be assessed. These factors could be differential between users and nonusers of NSAIDs. In addition, cardiovascular morbidity is increased in autoimmune diseases such as rheumatoid arthritis that necessitate chronic use of NSAIDs.<sup>16</sup> Therefore, a direct comparison between NSAID users and nonusers was not performed. However, in theory, naproxen and other NSAID users should not differ in AMI risk susceptibility. By comparing the AMI risk in those exposed to naproxen with that of those exposed to other NSAIDs, we have controlled for factors that are nondifferential between the 2 groups, including cigarette smoking and obesity. Second, patients who died of MI before reaching the hospital are not captured in the *Med-Echo* database. However, we have no reason to believe that those exposed to naproxen were at greater risk of dying of MI before reaching the hospital than those exposed to the other nonaspirin NSAIDs. Other potential limitations of the study include uncertainty about actual medications taken and unknown concurrent use of over-the-counter drugs (especially aspirin, naproxen, and ibuprofen). However, *Santé Québec* (a government public health agency [written communication, 1992-1993]) reports that, during the years of the study, older Quebecois acquired the following agents over the counter (given as proportions of the total numbers of those who used the agents): acetaminophen (5.5%), NSAIDs (90.5%), and aspirin (0.3%).

In summary, concurrent exposure to naproxen was cardioprotective compared with other nonaspirin NSAIDs. Our study design did not permit direct comparison of the effect of aspirin vs naproxen on AMI. Therefore, our results apply only to patients in need of NSAID therapy and do not support the use of naproxen as a primary cardiovascular prophylaxis. Given the widespread use of NSAIDs among older populations, these patients may require close monitoring when using these drugs. In a population such as the one included in this study, physicians should weigh the cardiac benefit of naproxen vs its gastrointestinal toxicity.

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### Correction

**Error in Text.** In the Original Investigation by Rahme et al titled “Association Between Naproxen Use and Protection Against Acute Myocardial Infarction,” published in the May 27 issue of the ARCHIVES (2002;162:1111-1115), an error occurred in the “Comment” section on page 1115. The last sentence of the third paragraph on that page should have read as follows: “However, *Santé Québec* (a government public health agency [written communication, 1992-1993]) reports that, during the years of the study, older Quebecois acquired the following agents over the counter (given as proportions of the total numbers of those who used the agents): acetaminophen (5.5%), NSAIDs (0.5%), and aspirin (0.3%).” The journal regrets the error.