Selective Cyclooxygenase-2 Inhibitors
Population-based analysis of use in France over a three-year period and comparison with randomized clinical trials

Guy-Robert Auleley, Jean Deligne, Catherine Hantson, Claudine Blum-Boisgard

Résumé

Objectifs L'utilisation des inhibiteurs sélectifs de la cyclo-oxygénase 2 (coxibs) est actuellement contestée, en particulier en raison des risques cardiovasculaires. Peu de travaux ont évalué leurs conditions réelles d'utilisation. Cette étude avait pour but de mesurer l'évolution des conditions réelles d'utilisation des coxibs en France et de les comparer à celles des essais cliniques randomisés.

Méthodes La base de données des bénéficiaires du régime d'assurance maladie des professions indépendantes a permis d'identifier les patients par leur remboursement de célocoxib ou de rofécoxib entre novembre 2000 et octobre 2003, leur morbidité par l'existence des affections de longue durée prises en charge à 100 %, l'existence de grossesses par le paiement d'honoraires ou allocations pour accouchement et le paiement aux cliniques pour naissance, et les médicaments concomitants par leurs remboursements. Les caractéristiques démographiques des patients, la prévalence de la morbidité et des grossesses, et la fréquence d'utilisation des médicaments concomitants ont été comparées à celles estimées à partir des essais cliniques randomisés (ECR) rapportant l'efficacité de célocoxib ou de rofécoxib et publiés en langue anglaise ou française avant novembre 2003.

Résultats À l'exception de l'âge moyen des patients (passant de 64,2 à 62,9 ans), de la proportion des femmes (passant de 56,7 à 54,7 %) et de la fréquence d'utilisation des protecteurs gastriques (passant de 18,2 à 28,4 % des patients), les conditions réelles d'utilisation des coxibs ont peu varié au cours des 3 années étudiées. L'âge moyen des patients était supérieur de plus à 10 ans à celui des ECR. La proportion des femmes était inférieure de 15 % à celle des ECR. Par ailleurs, 0,02 % des femmes traitées dans les conditions réelles d'utilisation et 0,09 % dans les ECR étaient enceintes. Les fréquences de remboursements d'accessoires de longue durée étaient systématiquement plus élevées parmi les patients traités par coxibs dans les conditions réelles d'utilisation que dans les ECR, sauf pour la polyarthrite rhumatoïde. Il y avait en particulier plus de patients souffrant de maladies cardiovasculaires ou de diabète (environ 15 %) que dans les ECR (environ 6 %). Enfin, la fréquence d'utilisation de 9 des 14 classes médicamenteuses de la classification ATC ("Anatomical Therapeutic Chemical") était plus élevée dans les conditions réelles d'utilisation des coxibs que dans les ECR: elles étaient respectivement de 55 et 5 % environ pour les médicaments du système cardiovasculaire.

Conclusion Les conditions réelles d'utilisation des coxibs en France ont peu évolué au cours des 3 années qui ont suivi leur commercialisation. Elles différaient de celles des ECR en particulier par des patients plus âgés, proportionnellement moins de femmes et une morbidité, notamment cardiovasculaire, plus élevée. La survenue d'accidents cardiovasculaires parmi les utilisateurs de coxibs dans les conditions réelles en France doit être évaluée.

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Original Article

N onosteroideal antiinflammatory drugs (NSAIDs) are commonly used to treat pain and febrile or inflammatory conditions. Their efficacy has been demonstrated for rheumatoid arthritis, headaches, dysmenorrhea, and dental and postoperative pain. However, they can cause gastrointestinal bleeding. The wide spectrum of diseases for which coxibs can be used as antiinflammatory agents and recommendations for their use in almost all situations requiring NSAIDs have contributed to their “off-label” use outside approved indications. Despite knowledge of the possible risks associated with coxibs and advances in “evidence-based medicine”, which relies on randomized studies of drug treatments, these drugs have been widely used in situations not yet addressed by clinical trials. The differences between how coxibs are currently used and their use in...
randomized drug trials have not been carefully studied. In any case, whatever the actual indications of coxib use were, these may well have changed over time in view of the debate they have provoked. Although several studies have described the use of coxibs in daily practice in France, particularly in situations that may be associated with risk of side effects, they have been very limited in scope. The aim of this study was therefore to measure changes in characteristics, morbidity, pregnancy, and concomitant prescriptions of patients in France taking celecoxib and rofecoxib on a daily basis and to compare these with those in randomized clinical trials (RCTs) for efficacy and tolerance.

Methods

Data sources and collection

The characteristics of coxib use we studied included patient demographics, chronic disease, pregnancy, and concomitant medications.

We obtained data on the number of celecoxib and rofecoxib prescriptions written, filled, and reimbursed from the French National Health Insurance Fund AMPI database of self-employed workers in nonagricultural occupations, which were available through the OCAPI observatory (information center). The AMPI fund insures self-employed nonagricultural workers and their covered family members through 31 local units (regional insurance funds): 29 in metropolitan France, one in the West Indies and French Guyana, and another for Reunion (island belonging to France). In 2003, AMPI covered approximately 3 million beneficiaries. Each treatment reimbursed or service provided to a beneficiary is recorded in AMPI’s computer system with a specific identification code. Similarly, the system records the official diagnosis of any ALD-30 disease; that is, any of 30 groups of listed chronic diseases for which all care (procedures and treatments) is reimbursed at 100% during the study period and various services or allocations to AMPI beneficiaries. We could therefore collect information about all reimbursements of prescriptions for celecoxib and rofecoxib filled between November 2000 and October 2003 for outpatients, including the date they were filled. Other information included the physician’s (private or public) status and specialty. Information collected about the patients included age, sex, chronic disease diagnoses (those approved for reimbursement at 100%) at the time the coxib prescription was filled, and any payment of physician or hospital fees for delivery or of maternity benefits.

Data on all outpatient prescriptions filled at the same time as the coxibs and reimbursed were also collected and classified according to the “Anatomical Therapeutic Chemical” (ATC) classification system, as updated by the World Health Organization collaborating center for drug statistics methodology. We arbitrarily decided to sample concomitant drug use, rather than study the use of all such drugs over the entire study period. Specifically, we analyzed the concomitant drugs for which prescriptions were filled during the third week of the months during the coxib study period (November 2000 through October 2003). At the same time, we collected information about these facts during the coxib period. We searched the medical literature systematically through to a two-stage process.

- First, an automated Medline search (without restricting language of publication) identified all RCTs assessing coxib effects. We searched for different combinations of the following terms: “cyclo-oxygenase 2 inhibitors”, “COX-2 inhibitors”, “celecoxib”, “rofecoxib”, “Celebrex®”, “Vioxx®”, “randomized controlled trials”, and “clinical trials”. Only references with a summary or abstract were used and each was systematically read.

- We then conducted a manual search of secondary sources, including article reference lists, reviews, and meta-analyses of coxibs, regardless of publication date, to find potentially relevant RCTs. Only RCTs, reviews, and meta-analyses were obtained in full. Our inclusion criteria were publication before November 2003, in either English or French, and reporting on at least one efficacy criterion for the coxibs tested. To avoid the repeated use of the same RCTs, we rigorously analyzed the reference lists, authors, and affiliations. Nonetheless, to take into account all available information, we decided to collect all relevant data from these RCTs, even if published elsewhere. Accordingly, RCT meta-analyses were also used if they included relevant data not reported in the original articles. We did not include subgroup analyses, articles reporting follow-ups of previous RCTs, articles reporting coxib effects in animals or healthy subjects, articles published after October 2003 or abstracts from scientific conferences.

As we collected data from the RCTs, we paid particular attention to the sections on “Patients and methods” and “Results” for each study. The following information was collected for the study groups receiving coxib treatment: number of patients included, number or percentage of patients with each explicitly reported disease, number or percentage of patients receiving the drug, administration or authorization of all explicitly mentioned concomitant drug use, frequency or mean value, and standard deviation for each patient characteristic (age, sex, disease).

Analysis

Descriptive indicators were used to measure actual use of coxibs in daily practice and changes in use for the following periods: November 2000 to October 2001, November 2001 to October 2002 and November 2002 to October 2003. We then compared the indicators of age, sex, chronic disease, and concomitant drugs with those from RCT data. Patient age is expressed as mean age with standard devia-
ation and as the proportion of patients younger than 18, older than 65, and between the ages of 18 and 65. We also calculated the distribution of patients according to sex and chronic disease (reimbursed at 100% in France). The number and duration of pregnancies during which reimbursement for a coxib occurred at least once were also estimated. Specifically, we considered the prescriptions filled until the 36th week of pregnancy. Moreover, frequency of concomitant use of each drug class, defined from the first two levels of the ATC classification, was calculated as the proportion of patients taking at least one drug from that drug class. We therefore used the number of patients receiving a concomitant drug to estimate the frequency with which drugs of that class were used. On the other hand, when this number was not available for an RCT, we assumed that all patients included in this RCT had taken that drug. Accordingly, we assumed that for the RCT testing the effects of these coxibs in surgical procedures, all patients included had received the anesthetic reported. Moreover, when an RCT mentioned the administration, authorization, or availability of a drug class - for example, antacids - without specifying the list, we assumed that the patients in this study took any of the drugs in this class. In order to compare coxib use in daily practice in France with that in RCTs, the indicators taken from the RCTs were weighted according to the size of each RCT, thus giving more weight to large RCTs.

Finally, the prescribing frequency of coxibs according to physician specialty was reported only for daily practice in France.

**Results**

**PATIENT AND PRESCRIBER CHARACTERISTICS**

Between November 2000 and October 2001, 300,593 prescriptions for celecoxib and rofecoxib were reimbursed; between November 2001 and October 2002, 360,830; and between November 2002 and October 2003, 359,822. These drugs were mainly prescribed (97%) in the private sector. General practitioners were responsible for approximately 84.1% of prescriptions (table 1), and rheumatologists and orthopedists for approximately 10%. The distribution of coxib prescriptions according to public or private sector on the one hand and according to type of practice (general or specialized) on the other varied little during these periods.

During these periods, 155,722, 161,160, and 154,271 patients were identified. Mean age exceeded 62 years (table 1). It dropped by slightly more than one year during the study period, and the proportion of elderly patients, especially those older than 85 years, fell as the proportion of younger patients progressively increased.

In the 72 RCTs, 19,188 patients, including 15,192 with osteoarthritis or RA (in 29 RCTs), were treated with celecoxib or rofecoxib*. Regardless of period considered, the mean age of the patients treated in daily clinical practice in France was nearly 10 years older than that of the patients in RCTs (mean age reported in 45 [62.5%] RCTs). The difference was smaller in the RCTs testing coxibs for osteoarthritis or RA (mean age reported in 17 [60.7%] RCTs). Most patients were women (table 1). In our study of daily prac-

### Table 1

**Patient and prescriber characteristics in daily practice and randomized clinical trials**

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>All clinical trials</th>
<th>Clinical trials of RA and osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients, number</strong></td>
<td>155,722</td>
<td>161,160</td>
<td>154,271</td>
<td>191,118</td>
<td>15,192</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (years)</td>
<td>64.2 ± 15.1</td>
<td>63.4 ± 15.1</td>
<td>62.9 ± 15.1</td>
<td>55.4 ± 9.1</td>
<td>60.4 ± 9.3</td>
</tr>
<tr>
<td>&lt; 18 years (%)</td>
<td>0.07</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>18-65 years (%)</td>
<td>42.2</td>
<td>44.8</td>
<td>48.4</td>
<td>48.4</td>
<td>48.4</td>
</tr>
<tr>
<td>&gt; 65 years (%)</td>
<td>57.7</td>
<td>55.1</td>
<td>51.5</td>
<td>51.5</td>
<td>51.5</td>
</tr>
<tr>
<td>&gt; 85 years (%)</td>
<td>11.1</td>
<td>8.9</td>
<td>6.9</td>
<td>6.9</td>
<td>6.9</td>
</tr>
<tr>
<td><strong>Sex, women (%)</strong></td>
<td>56.3</td>
<td>55.2</td>
<td>54.7</td>
<td>70.8</td>
<td>68.5</td>
</tr>
<tr>
<td><strong>Prescribing physicians</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital or employees</td>
<td>3.0</td>
<td>3.2</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Private practice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General practitioner</td>
<td>84.5</td>
<td>84.1</td>
<td>83.9</td>
<td>83.9</td>
<td>83.9</td>
</tr>
<tr>
<td>Rheumatologists</td>
<td>8.6</td>
<td>8.6</td>
<td>8.3</td>
<td>8.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Orthopedists</td>
<td>1.1</td>
<td>1.1</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Other</td>
<td>2.8</td>
<td>3.0</td>
<td>3.2</td>
<td>3.2</td>
<td>3.2</td>
</tr>
</tbody>
</table>

*The list of RCTs included is available from the authors on request.*

* Year 1: 01/11/2000 to 31/10/2001; year 2: 01/11/2001 to 31/10/2002; year 3: 01/11/2002 to 31/10/2003; RA: rheumatoid arthritis; SD: standard deviation
tice, the proportion of women progressively decreased over the study period. It was 14.5% less than those of all RCTs (66 [91.7%] RCTs reported distribution according to sex) and 12.2% less than those in the RCTs for osteoarthritis or RA alone (29 [100%] RCTs reported distribution according to sex).

**CHRONIC DISEASES**

Patients treated with coxibs in daily clinical practice in France were diagnosed with diseases from all 30 groups of chronic diseases reimbursed at 100%. The distribution of these diseases varied little over the study period (table 2). Inversely, patients in RCTs had diseases listed in only 8 of these 30 groups. The prevalence of the other 22 groups among French patients in our study was low, however, ranging from 0.0007 to 0.6%. Regardless of the year considered, the prevalence of chronic progressive arterial disease, severe hypertension, malignant tumors, diabetes, and mental retardation or psychosis, was greater among our study patients than in RCT patients. Cardiovascular conditions and diabetes were 2.5 times more frequent than in the RCTs. Inversely, RA was diagnosed in 30-40% of patients included in the RCTs and in only 1-2% of patients receiving coxibs in daily practice in France.

**PRESCRIPTION OF COXIBS DURING PREGNANCY**

Among those patients with at least one coxib reimbursement, 45 (0.02%) were pregnant. The weighted percentage of pregnant women taking a coxib in the RCTs was higher – 0.09 % (all women included in an RCT to test the preventive effect of celecoxib in threatened preterm delivery, between the 24th and 34th weeks of pregnancy).

**CONCOMITANT DRUGS**

In conditions of daily clinical practice, all drug classes were prescribed for concomitant use with coxibs (table 3). The frequency of their use varied little during the 3 study years, except for gastroprotective agents (antisecretory, antacid, and anti-ulcer agents, with annual frequencies estimated at 18.2, 25.2, and 28.4%). Antifungives for systemic use, antineoplastic or immunomodulating agents, or antiparasitic products were prescribed for 0.1 to 7.5% of patients treated with coxibs in our study. No RCT reported the administration, authorization, or availability of drugs in these classes. The use of drugs affecting the nervous system was very common, but involved a lower proportion of patients in our study (approximately two-thirds of the patients) than in the RCTs (nearly 90%). On the other hand, more than half the patients used drugs for the cardiovascu-

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**Tableau 2**

**Frequency of listed chronic diseases reimbursed at 100% (ALD 30) among patients taking at least one coxib**

<table>
<thead>
<tr>
<th>Diseases (%)</th>
<th>Year 1 (n=155722)</th>
<th>Year 2 (n=161160)</th>
<th>Year 3 (n=154271)</th>
<th>RTC included (n=19118)</th>
<th>RTC RA or osteoarthritis (n=15192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial disease, chronic and progressive</td>
<td>7,0</td>
<td>7,1</td>
<td>6,7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>5,6</td>
<td>5,8</td>
<td>5,5</td>
<td>1,6</td>
<td>2,0</td>
</tr>
<tr>
<td>Malignant tumor</td>
<td>5,9</td>
<td>6,3</td>
<td>6,3</td>
<td>0,1</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5,0</td>
<td>5,4</td>
<td>5,4</td>
<td>1,3</td>
<td>0,3</td>
</tr>
<tr>
<td>Progressive RA</td>
<td>1,5</td>
<td>1,4</td>
<td>1,4</td>
<td>32,2</td>
<td>40,5</td>
</tr>
<tr>
<td>Psychosis, mental retardation</td>
<td>2,2</td>
<td>2,3</td>
<td>2,2</td>
<td>0,6</td>
<td>0,8</td>
</tr>
<tr>
<td>Heart disease, heart failure</td>
<td>2,2</td>
<td>2,3</td>
<td>2,1</td>
<td>2,8</td>
<td>3,7</td>
</tr>
<tr>
<td>Chronic respiratory failure</td>
<td>1,3</td>
<td>1,3</td>
<td>1,2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CVA, disabling</td>
<td>1,0</td>
<td>1,0</td>
<td>1,0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ASP</td>
<td>0,5</td>
<td>0,4</td>
<td>0,5</td>
<td>0,4</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction within the past 6 months</td>
<td>0,7</td>
<td>0,7</td>
<td>0,7</td>
<td>0,7</td>
<td>0,8</td>
</tr>
<tr>
<td>No listed chronic disease</td>
<td>77,5</td>
<td>77,4</td>
<td>77,8</td>
<td>63,3</td>
<td>51,9</td>
</tr>
</tbody>
</table>

CVA: cerebrovascular accident; RCT randomized clinical trials; HTA: hypertension; RA: rheumatoid arthritis; ASP: ankylosing spondylitis
A patient might have multiple conditions listed in different chronic disease groups (ALD 30).
The complete ALD 30 list includes 30 groups of diseases.
Source: www.canam.fr/docs/imprim/2d323ps-.htm
lar system in our study, compared with only 4-5% of the RCT patients.

Drugs for the respiratory and genitourinary (including sex hormones) systems, skin, and sensory organs were prescribed less frequently. Nonetheless, their frequency of use among French patients in daily practice exceeded rates in RCTs by 0.4 to more than 8%. Inversely, the frequency of use of drugs for the musculoskeletal system and for blood and hematopoietic organs, as well as of systemic hormones (sex hormones excluded) was 10-30% lower in actual practice.

More specifically, in the actual use of coxibs, a lower proportion of patients also took analgesics (50% compared with 86%), low-dose aspirin, (7.1%—3.9% for its anti-thrombotic effect—compared with 26.4%, and 29% in the RCTs for osteoarthritis or RA), systemic corticosteroids (5.3% compared with 32.8% overall, and 40.3% of RCTs with osteoarthritis or RA), or gastroprotective agents (23.9% compared with 29.8% overall, 36.9% in RCTs for osteoarthritis or RA).

Inversely, the proportion of traditional NSAID use was higher in daily practice (annual mean 13%) than in RCTs (0.6%; not in any RCTs for osteoarthritis or RA).

### Discussion

This study shows that coxib use in daily practice, determined from health insurance data, differs substantially from its use in RCTs, particularly in its higher use by patients with cardiovascular, diabetic, cancer, and psychiatric morbidity. This use has not changed in the years following coxib approval, except for a reduction in the proportion of very elderly patients and of women and an increase in the frequency of concomitant use of gastroprotective agents.

In this study, the characteristics of patients included in coxib RCTs differed from those of patients treated in the daily clinical setting in France. Similar findings have been reported for other drugs; although RCTs are considered to be the methodological tool of reference for proving the efficacy and tolerance of drugs before their approval for sale\textsuperscript{20}, they usually include fewer subjects who are elderly, pregnant, members of ethnic minorities, or have complex health problems associated with multiple diseases, or are taking concomitant drugs\textsuperscript{21-30}. Moreover, these RCTs are often performed in university hospital centers where patient management often differs from that in private practice\textsuperscript{21}.

### Tableau 3

Proportion of patients taking at least one other drug concomitantly with a coxib, classified according to the “Anatomical Therapeutic Chemical” classification (ATC)

<table>
<thead>
<tr>
<th>Classes (%)</th>
<th>Year 1 (n=7583)</th>
<th>Year 2 (n=7849)</th>
<th>Year 3 (n=7058)</th>
<th>RCT included (n=19118)</th>
<th>RCT of RA or osteoarthritis (n=15192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular system</td>
<td>54,8</td>
<td>54,7</td>
<td>55,8</td>
<td>4,8</td>
<td>4,4</td>
</tr>
<tr>
<td>Nervous system</td>
<td>66,2</td>
<td>66,1</td>
<td>65,7</td>
<td>86,6</td>
<td>88,6</td>
</tr>
<tr>
<td>Alimentary tract and metabolism</td>
<td>38,3</td>
<td>37,3</td>
<td>40,2</td>
<td>32,9</td>
<td>36,9</td>
</tr>
<tr>
<td>Musculo-skeletal system</td>
<td>28,1</td>
<td>28,1</td>
<td>28,0</td>
<td>38,8</td>
<td>44,9</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>8,3</td>
<td>7,9</td>
<td>8,6</td>
<td>0,06</td>
<td>0</td>
</tr>
<tr>
<td>Genitourinary system and sex hormones</td>
<td>8,2</td>
<td>8,6</td>
<td>8,1</td>
<td>0,6</td>
<td>0</td>
</tr>
<tr>
<td>Blood and hematopoietic organs</td>
<td>12,9</td>
<td>12,4</td>
<td>13,3</td>
<td>26,0</td>
<td>28,5</td>
</tr>
<tr>
<td>Dermatologicals</td>
<td>8,8</td>
<td>8,4</td>
<td>8,2</td>
<td>0,08</td>
<td>0</td>
</tr>
<tr>
<td>Systemic hormones, excluding sex hormones</td>
<td>9,9</td>
<td>10,0</td>
<td>10,6</td>
<td>32,1</td>
<td>40,3</td>
</tr>
<tr>
<td>Sensory organs</td>
<td>5,9</td>
<td>6,6</td>
<td>5,6</td>
<td>0,6</td>
<td>0</td>
</tr>
<tr>
<td>Antiinfectives for systemic use</td>
<td>7,2</td>
<td>7,5</td>
<td>6,9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Antineoplastic and immunomodulating agents</td>
<td>1,3</td>
<td>0,8</td>
<td>1,1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Antiparasitic products</td>
<td>0,1</td>
<td>0,2</td>
<td>0,2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diverse</td>
<td>0,5</td>
<td>0,5</td>
<td>0,4</td>
<td>3,9</td>
<td>0</td>
</tr>
</tbody>
</table>

RCT: randomized clinical trials; RA: rheumatoid arthritis

One patient might receive several concomitant drugs belonging to different ATC classes.
Few studies describe the use of coxibs after their approval16,18,31-33. Only one, conducted in France, explicitly measured the discordances between the RCT for celecoxib before its marketing and its use in daily practice16. These studies were limited to the evaluation either of elderly patients31-33, a single coxib16, or several concomitant drugs18. The inclusion criteria for patients in our study differed from those in these studies. While the prevalence of cancer in our study population was astonishingly similar to that observed elsewhere1, our principal results differed from those of other studies. The proportion of women was much higher in the other studies than in ours, perhaps because they limited inclusion to elderly patients31-33. Inversely, the prevalence of RA and cardiovascular diseases was lower in our study than in certain others31,32. Only 15% of the patients in our study had morbidity related to the cardiovascular system or diabetes, although other studies report that the frequency of major cardiovascular conditions can reach 43%31-33. Regardless of the study, the use of concomitant drugs seems to indicate that the overall morbidity of patients treated with coxibs may be higher in daily practice than in RCTs. Accordingly, the prevalence of cardiovascular conditions may exceed the 50% in this study and may reach 87% in the elderly33. Patients receiving coxibs in France may thus have a higher risk of cardiovascular events associated with the use of these drugs than do RCT patients.

More generally, this study shows that in daily practice in France, coxibs are prescribed concomitantly with all classes of drugs. In this study, at least 7.5% of patients took other drugs concomitantly that were not tested in the coxib RCTs. More than a third of the patients receiving coxibs in France may use such drugs16. Our study probably overestimates the frequency of concomitant use of other drugs in RCTs. In 45 of the 67 RCTs where at least one concomitant drug was reported, we assumed that 100% of patients had taken at least one such drug, since the precise number of patients treated was not reported. We therefore cannot rule out the possibility that the rates of use of various concomitant drugs observed in this study were in reality substantially higher than those in the RCTs. In any case, in daily practice, some patients receiving coxibs in this study were exposed to risks associated with the concomitant use of antithrombotics, corticoids, and traditional NSAIDs. This finding confirms that in France, some patients taking coxibs were also exposed to gastrointestinal risks34. Nonetheless, it appears that physicians took this risk into account by prescribing gastroprotective agents to nearly one third of the patients in this study. The reasons for co-prescription of these agents in France appear to be gastric protection in 10% of cases and the existence of lesions in the gastroduodenal region in 11% of cases18. Coxibs are also contraindicated during pregnancy34. Coxib administration during pregnancy in our study was less common than in the RCTs. The criteria we used to identify pregnancy in our study undoubtedly contributed to an underestimation of this exposure because we could not count pregnancies that did not culminate in delivery. Moreover, this exposure was calculated for all women included and not just for women of child-bearing age. Exposure to coxibs during pregnancy in daily practice may therefore be higher than reported in this study.

To our knowledge, this is the first study reporting trends in the actual use of coxibs since their marketing launch in France, and it shows little change in use over these 3 years. Recommendations for prudence and the controversies surrounding coxib use do not seem to have affected prescribing practices. This finding has also been reported for other drugs35. Accordingly, only months after coxibs became available, various risks associated with their use – especially cardiovascular events – were reported in some patients.

This study has several limitations. On the one hand, use of health insurance data does not allow us to identify morbidity not reimbursed at 100% (that is, not a listed chronic disease). Nonetheless, this morbidity was measured indirectly, though concomitant drug use. On the other hand, all concomitant diseases in the RCTs would have been classified as listed chronic diseases in France. Moreover, although some drugs for which prescriptions were filled might not have been used, data about filled prescriptions is nonetheless a highly used and very cost-effective way to answer questions about drug use.

**WHAT IS ALREADY KNOWN**

- Coxib use is currently controversial because of doubts about cardiovascular issues.
- The gap between coxib use in randomized clinical trials and daily practice in the general population, especially in situations exposing patients to possible drug-related risks, has not been thoroughly studied.
- The changes in actual coxib use in France have not been studied.

**WHAT THIS ARTICLE ADDS**

- Coxib use in daily practice differs substantially from that in randomized clinical trials that studied the efficacy of these drugs; in particular, patients in daily practice have more cardiovascular, diabetic, cancer, and psychiatric morbidity.
- The conditions of real coxib use in the French population have changed little in the 3 years following their approval for marketing.
Another limitation of this study is that the data concern only AMPI beneficiaries. Nonetheless, to our knowledge, although prescribing practices and requests for 100% coverage for listed chronic diseases may differ somewhat according to the specific health insurance fund, no such differences have yet been reported in France. We thus deduce that the results of this study are probably representative of coxib use in daily outpatient practice in France.

This study shows that the use of coxibs in daily practice, determined from health insurance data, differs substantially from use in RCTs, particularly in the higher rates of cardiovascular morbidity, and that this use has varied little.

Studies assessing the association between the use of coxibs in real conditions in France and cardiovascular accidents appear to be needed.

Références

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