Eur J Clin Pharmacol (2012) 68:1533–1540
DOI 10.1007/s00228-012-1283-9

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

# Non-steroidal anti-inflammatory drugs (NSAIDs) and hypertension treatment intensification: a population-based cohort study

**Jean-Pascal Fournier · Agnès Sommet · Robert Bourrel · Stéphane Oustric · Atul Pathak · Maryse Lapeyre-Mestre · Jean-Louis Montastruc**

Received: 12 December 2011 / Accepted: 20 March 2012 / Published online: 15 April 2012


**Abstract**
*Purpose* Non-steroidal anti-inflammatory drugs (NSAIDs) are known to antagonize the effects of antihypertensive drugs, and these associations can lead to an increase in arterial blood pressure. However, the impact of NSAIDs on hypertension treatment management in large-scale populations remains poorly evaluated. We examined whether the introduction of NSAID into the treatment regimen would induce an intensification of hypertension treatment (defined as the introduction of a new antihypertensive drug).
*Methods* We conducted a cohort study involving 5,710 hypertensive subjects included in the French health insurance system database who had been treated and stabilized with their antihypertensive therapy and not exposed to any NSAID between 1 April 2005 and 1 April 2006. The maximum follow-up duration was 4 years.
*Results* Adjusted hazard ratios (HR) for hypertension treatment intensification were 1.34 [95% confidence interval (CI) 1.05–1.71] for NSAIDs in general, 1.79 (95% CI 1.15–2.78) for diclofenac and 2.02 (95% CI:1.09–3.77) for piroxicam. There were significant interactions between NSAIDs and angiotensin converting enzyme inhibitors (ACEIs; HR 4.09, 95% CI 2.02–8.27) or angiotensin receptor blockers (ARBs; HR3.62, 95% CI 1.80–7.31), but not with other antihypertensive drugs.
*Conclusions* Exposure to NSAIDs leads to an intensification of hypertension treatment, especially in patients treated with ACEIs or ARBs. Renin–angiotensin system blockers should be avoided whenever NSAIDs are prescribed.

**Keywords** Anti-inflammatory agents, non-steroidal · Antihypertensive agents · Cohort studies · Drug interactions · Insurance, health, reimbursement · Pharmacoepidemiology

J.-P. Fournier (✉) · A. Sommet · A. Pathak · M. Lapeyre-Mestre · J.-L. Montastruc
Laboratoire de Pharmacologie Médicale et Clinique,
Faculté de Médecine, Université Paul Sabatier,
37 allées Jules Guesde,
31000, Toulouse, France
e-mail: jean-pascal.fournier@univ-tlse3.fr

J.-P. Fournier · A. Sommet · M. Lapeyre-Mestre · J.-L. Montastruc
INSERM, UMR1027,
Toulouse, France

J.-P. Fournier · S. Oustric
Département Universitaire de Médecine Générale,
Faculté de Médecine, Université Paul Sabatier,
Toulouse, France

A. Sommet · A. Pathak · M. Lapeyre-Mestre · J.-L. Montastruc
Service de Pharmacologie Clinique, Centre Midi-Pyrénées de Pharmacovigilance, de Pharmacoépidémiologie et d'Information sur le Médicament, Centre Hospitalier Universitaire de Toulouse,
Toulouse, France

R. Bourrel
Direction Régionale du Service Médical Midi-Pyrénées (CNAMTS),
Toulouse, France

A. Pathak
INSERM UMR1048,
Toulouse, France

## Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) can antagonize the effects of antihypertensive drugs by inhibiting cyclooxygenase (COX) and prostaglandin synthesis [1, 2]. This can lead to an increase in arterial blood pressure, as has been fully described in several clinical trials and meta-

analyses [3], and partly explain the increase in cardiovascular morbidity and mortality associated with this class of drugs. This risk has been underscored by several "dear doctors letters" sent by European Medicines Agency to all potential prescribers in recent years [4].

The increase in blood pressure can be limited by hypertension treatment intensification (addition of a new antihypertensive or increase in dosage) [5, 6]. The effect of intensifying hypertension treatment has also been suggested to be beneficial for patients with suboptimal adherence [7]. Several studies have demonstrated that the main factors leading to hypertension treatment intensification among uncontrolled patients are systolic and diastolic blood pressure, respectively [8–11]. Blood pressure levels remains the main target in hypertension treatment management.

The impact of NSAIDs on hypertension treatment management in large-scale populations remains poorly evaluated. Identification and quantification of the potential association between NSAIDs and hypertension treatment intensification could increase the awareness of doctors and patients and lead to changes in prescribing patterns. Thus, we conducted a cohort study on subjects treated and stabilized with their antihypertensive drugs to investigate if the introduction of NSAIDs into their treatment regimen could induce an intensification of their antihypertensive therapeutic regimen.

## Methods

### Study design

This study is a pharmacoepidemiological retrospective cohort study.

### Data sources

In France, a publicly funded healthcare system covers all of the population. The French health insurance system database collects information on the French population and categorizes this information into four categories: demographic characteristics of users, characteristics of health professionals, data concerning health facilities and reimbursement data (drug, laboratory, radiology, medical acts) [12]. For the category drug dispensing, the database contains information on the date of dispensing, quantity of dispensed drug expressed in defined daily doses (DDDs), and prescriber. Drugs are classified according to the Anatomical Therapeutic Chemical system [13]. Only information on drugs prescribed and reimbursed by the French health system are recorded in the database (thus excluding drugs not reimbursed, delivered during hospitalizations or sold over-the-counter).

### Study population

We extracted a random sample (sample rate: 5%, as provided by the French health insurance system database) of adults living in the Midi-Pyrénées area (2,600,000 inhabitants) between 1 April 2005 and 1 April 2006 and having at least two reimbursements of the same antihypertensive drug during this period; individuals receiving any NSAID (including topical, injectable and oral forms) during this period were excluded. Antihypertensive drugs included beta-blocking agents, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics (except eplerenone), calcium channel blockers (except bepridil) and other drugs (centrally acting antihypertensive drugs, minoxidil and dihydralazine). Fixed combinations were analyzed as separate drugs. Patients undergoing an intensification of their hypertension treatment in the 6 months before inclusion (between 1 October 2005 and 1 April 2006) were excluded. Inclusion in the study was determined on 1 April 2006 for all patients, and the maximal follow-up was 4 years (until 31 March 2010). Patients were considered lost to follow-up when there was no drug reimbursement for more than 3 months. Data were extracted and analyzed anonymously in conformity with the French Law of Privacy [14].

### Drugs and morbidity

For each patient, exposure to each antihypertensive drug was defined as the period between the first and the last month of reimbursement for this drug. For NSAIDs, exposure started on the first reimbursement date. The duration of NSAID treatment was estimated from the number of DDDs, corresponding by definition to the number of days under treatment. In the case of overlapping NSAID reimbursements, we extended the treatment duration with the number of overlapping days. Only exposure to oral and injectable NSAIDS marketed in France during the period of study were taken into account. Topical NSAIDs (gels and ophthalmic solutions) were excluded from the analysis.

Several drugs (platelet aggregation inhibitors, blood glucose lowering drugs, lipid modifying agents and antineoplasic and immunomodulating agents) were used as proxies of comorbidities. Cardiovascular morbidity was defined by the number of cardiology consultations and hospitalizations during the 6 months before inclusion.

### Outcome measure

The most recent guidelines recommend the use of several antihypertensive drugs to achieve the blood pressure target rather than increasing doses of previously used drugs [5, 6]. Thus, we defined the primary outcome of our study

(hypertension treatment intensification) as the introduction of a new antihypertensive drug into the treatment regimen compared to the previous month.

### Statistic methods

Kaplan–Meier curves were used to illustrate the time to an event according to exposure. We used the Cox proportional hazard regression model, including exposure to drugs of interest as time-dependent covariates (model 1). The model was then adjusted (model 2) for potential confounding factors, associated with the outcome in univariate analysis (log-rank test, $p<0.2$). The potential confounding factors considered were age, gender, antihypertensive classes and comorbidities. In the final model (model 3), we tested all potential NSAID/antihypertensive drug interactions. For the analysis, $p<0.05$ was considered to be statistically significant. Statistical analyses were performed using Stata® ver. 11.0 (StataCorp LP, College Station, TX).

## Results

A sample of 6,983 patients who met the selection criteria was extracted from the French health insurance system database; of these, 1,273 were excluded (Fig. 1). Baseline characteristics of the 5,710 patients included in the study cohort are shown in Table 1. During the study period, 2,492 subjects (43.6%) had at least one NSAID reimbursement. Among these, 1,193 subjects (47.9%) were exposed to more than one NSAID (maximum 8) during the follow-up. In comparison with those unexposed to NSAIDs during the same period, these patients were younger and had less cardiovascular morbidity. The characteristics of the antihypertensive drugs used at baseline are shown in Table 1, and the duration of treatment for each specific NSAID is listed in Table 2.

### Cox proportional hazard analyses

During the follow-up, a new antihypertensive drug was reimbursed to 2,399 patients (incidence rate 165.1 per 1,000 person-years). Exposure to NSAIDs [adjusted hazard ratio (HR) 1.34, 95% confidence interval (CI) 1.05–1.71; $p=0.020$] was associated with more antihypertensive treatment intensifications. Diclofenac (adjusted HR 1.79, 95% CI 1.15–2.78; $p=0.010$) and piroxicam (adjusted HR 2.02, 95% CI 1.09–3.77; $p=0.026$) were the only specific NSAIDs associated with the outcome in the multivariate analysis (Table 2).

### Interactions between NSAIDs and antihypertensive drugs

There were statistically significant interactions between NSAIDs and ACEIs or ARBs, but not with other antihypertensive drugs (Table 3). HR associated with NSAID exposure decreased when these two interactions were taken into account. Similar interactions were found for diclofenac and piroxicam (data not shown).

## Discussion

The aim of our study was to evaluate the association between NSAIDs and hypertension treatment intensification in a population of treated patients who were unexposed to

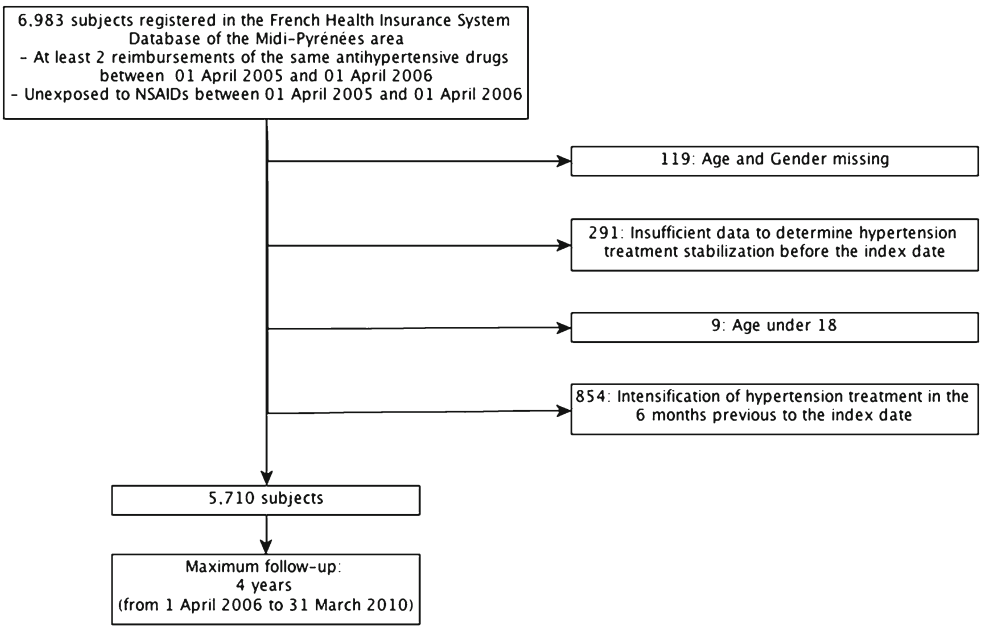


**Fig. 1** Selection of the cohort sample of 6,001 subjects. *NSAIDS* Non-steroidal anti-inflammatory steroids

**Table 1** Characteristics of the cohort according to exposure group

| Characteristics | No NSAID[a] | NSAIDs |
|---|---|---|
| Number of subjects, *n* | 3,218 | 2,492 |
| Median age (IQR), years | 74.1 (64.0-81.3) | 68.3 (58.3-76.4)* |
| Gender (female) | 1,541 (47.9) | 1,155 (46.3) |
| Drug exposure | | |
| Platelet aggregation inhibitors[b] | 980 (30.4) | 658 (26.4) § |
| Blood glucose lowering drugs[b] | 594 (18.5) | 444 (17.8) |
| Lipid modifying agents[b] | 1,339 (41.6) | 1,189 (47.7) § |
| Antineoplasic and immunomodulating agents[b] | 97 (3.0) | 56 (2.2) |
| Number of antihypertensive drugs | | |
| 1 | 1,145 (35.6) | 973 (39.0) § |
| 2 | 1,197 (37.2) | 921 (37.0) |
| More than 2 | 876 (27.2) | 598 (24.0) § |
| Antihypertensive classes[c] | | |
| Diuretics | 1,762 (54.7) | 1,251 (50.2) § |
| Beta-blocking agents | 1,191 (37.0) | 986 (39.6) § |
| Calcium channel blockers | 1,049 (32.6) | 726 (29.1) § |
| ARBs | 1,011 (31.4) | 773 (31.0) |
| ACEIs | 931 (28.9) | 661 (26.5) § |
| Alpha blocking agents | 74 (2.3) | 53 (2.1) |
| Other antihypertensives | 128 (4.0) | 72 (2.9) § |
| Cardiovascular morbidity | | |
| One cardiology consultation and more[d] | 266 (8.3) | 156 (6.3) § |
| One cardiology hospitalization and more[d] | 58 (1.8) | 18 (0.7) § |

*Statistically significant difference with the group unexposed to NSAID ($p$ <0.05), Mann–Whitney test; § statistically significant difference with the no-NSAID group ($p$<0.05), chi-square test

IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs

Data are presented as the number, with the percentage given in parenthesis unless otherwise stated

[a] NSAIDs included: arylcarboxylic acids (aceclofenac, alminoprofen, diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, nabumetone, tiaprofenic acid), oxicams (meloxicam, piroxicam, tenoxicam), coxibs (celecoxib), acetylsalicylic acid (excluding anti-platelet dose) and others (indometacin, sulindac, phenylbutazone, nimesulide, mefenamic acid, morniflumate, niflumic acid)

[b] According to Anatomical Therapeutic Chemical classification

[c] ARBs, Angiotensin receptor blockers; ACEIs, angiotensin converter enzyme inhibitors; other antihypertensives: centrally acting antihypertensives, minoxidil and dihydralazine

[d] In the 6 months before inclusion

NSAIDs for at least 1 year. Our results show that the use of NSAIDs in general (and diclofenac and piroxicam in particular) was associated with an increased number of antihypertensive treatment intensifications. This study underlines the importance of NSAID interactions in clinical practice with two specific pharmacological classes: ACEIs and ARBs.

To the best of our knowledge, our study is the first to show the clinical impact of NSAID exposure in arterial hypertension management as all the previous studies have only investigated the consequences on the level of arterial blood pressure. The meta-analysis of Johnson et al. [15] found that NSAID exposure increases blood pressure by 5.4 mm Hg (95% CI 1.2–9.6 mm Hg) in previously controlled hypertensive subjects. Pope et al. [16] found an increase in blood pressure in the range 3.5–6.2 mm Hg for indomethacin, naproxen or piroxicam. Even if this increase in blood pressure appears to be slight, our study suggests it has a significant clinical impact in daily practice.

In our study, diclofenac and piroxicam were the only NSAIDs statistically associated with hypertension treatment intensification. Pope et al. [16] demonstrated that piroxicam is the NSAID associated with the greatest increase in blood pressure (+6.2 mm Hg; 95% CI, 0.8–11.5 mm Hg). The effects of piroxicam in hypertension management can be explained by its longer half-life compared to other NSAIDs [17]. The association found for diclofenac in our study needs to be explored in future

**Table 2** NSAIDs and outcome according to exposure group

| NSAIDs | Number of subjects | Treatment duration (days)[a] | Exposure time (person-years) | Number of intensifications of hypertension treatment | Incidence rate (per 1,000 person-years) | HR[b] univariate | *p* | HR adjusted[c] | *p* |
|---|---|---|---|---|---|---|---|---|---|
| Not exposed | 5,710 | 1,021 (15–1,461) | 14,122 | 2,333 | 165.2 | 1 | . | 1 | . |
| NSAIDs (all) | 2492 | 34 (1–1,227) | 409.1 | 66 | 161.3 | 1.29 (1.01–1.65) | 0.039* | 1.34 (1.05–1.71) | 0.020* |
| Ibuprofen | 831 | 21 (1–322) | 64.3 | 5 | 77.8 | 0.90 (0.37–2.16) | 0.813 | . | . |
| Ketoprofen | 678 | 31 (1–658) | 65.9 | 13 | 197.3 | 1.37 (0.80–2.37) | 0.254 | | |
| Diclofenac | 666 | 30 (1–605) | 75.5 | 20 | 264.7 | 1.84 (1.18–2.87) | 0.006* | 1.79 (1.15–2.78) | 0.010* |
| Piroxicam | 485 | 30 (1–281) | 41.1 | 10 | 243.5 | 1.90 (1.02–3.54) | 0.042* | 2.02 (1.09–3.77) | 0.026* |
| Naproxen | 220 | 30 (1–245) | 19.0 | 2 | 105.2 | 0.72 (0.18–2.87) | 0.638 | . | . |

*$p < 0.05$

HR, Hazard ratio

[a] Data given as the median (days), with the minimum–maximum given in parenthesis

[b] Determined by univariate analysis, with the 95 % confidence interval (CI) given in parenthesis

[c] Adjusted for age, exposure to platelet aggregation inhibitors, lipid modifying agents, antineoplasic and immunomodulating agents, NSAIDs and different classes of antihypertensive drugs

studies as we do not have specific explanations for this result. Nevertheless, our data suggest that prescriptions of NSAIDs in hypertensive patients should be carefully weighed. If necessary, ibuprofen and naproxen seem to be the safer NSAIDs for hypertension treatment management. One should keep in mind that if paracetamol is considered to be the safer alternative, its potential for increasing the blood pressure is also currently under discussion [18].

Our analysis shows that the association between NSAIDs and hypertensive treatment intensification in model 2 is mainly explained by statistical interactions with ACEis or ARBs (model 3). These statistical interactions can be supported by the pharmacodynamic properties of NSAIDs. By inhibiting renal prostaglandin synthesis, NSAIDs induce vasoconstriction of the afferent renal arterioles. Reduction in renal blood flow leads to activation of the renin–angiotensin system, thus antagonizing the effects of ACEIs and ARBs. This in turn can lead to an increase in arterial blood pressure, thereby explaining the need for intensification of the antihypertensive treatment. An increase in arterial blood pressure has been observed in patients treated by ACEIs or ARBs when exposed to NSAIDs [19–21]. The lack of a statistically significant interaction found with beta-blocking agents could be due to the multifactorial origin of their antihypertensive effect [22], although in one study NSAIDs were found to reduce the blood pressure effects of beta-blocking agents [15]. A similar explanation has been proposed for the lack of interaction found with diuretics (previously described with traditional NSAIDs [15] or coxibs [23]).

A number of pharmacoepidemiological studies have evaluated the cardiovascular risk associated to NSAIDs in coronary disease [24, 25] or heart failure [26, 27]. A recent review of population-based observational studies attempted to evaluate the cardiovascular safety of NSAIDs [28]. The authors came to the conclusion that naproxen and low-dose ibuprofen seemed to be the least harmful NSAIDs in this clinical context; in contrast, diclofenac (both in high and low doses) was associated with the greatest increase in risk. Our data confirm that ibuprofen and naproxen should be preferred to diclofenac (and to a certain extent to piroxicam) in hypertensive patients.

To the best of our knowledge, potential interactions with antihypertensive drugs were not taken into account in these earlier studies. Therefore, these interactions (and especially those with ACEIs and ARBs) could explain the discrepancies observed across studies, particularly in heart failure. Further investigations are required to evaluate the clinical impact of NSAID interactions with antihypertensive drugs, particularly on cardiovascular morbidity and mortality.

**Table 3** Hazard ratios for intensification[a] of hypertension treatment associated with NSAID exposure (univariate, adjusted and adjusted with interactions models)

| Factors | Model 1: univariate HR | *p* value | Model 2: adjusted HR[b] | *p* value | Model 3: adjusted with interactions HR[b] | *p* value |
|---|---|---|---|---|---|---|
| NSAIDs | 1.29 (1.01–1.65) | 0.039* | 1.34 (1.05–1.71) | 0.020 | 0.40 (0.20–0.80) | 0.010 |
| NSAIDs: diuretics | | | | | 0.98 (0.53–1.84) | 0.962 |
| NSAIDs: beta-blocking agents | | | | | 1.07 (0.65–1.77) | 0.776 |
| NSAIDs: calcium channel blockers | | | | | 1.08 (0.66–1.77) | 0.754 |
| NSAIDs: ARBs | | | | | 3.62 (1.80–7.31) | <0.001* |
| NSAIDs: ACEIs | | | | | 4.09 (2.02–8.27) | <0.001* |
| NSAIDs: alpha blocking agents | | | | | 0.40 (0.06–2.96) | 0.373 |
| NSAIDs: other antihypertensives | | | | | 1.44 (0.45–4.70) | 0.538 |

*$p < 0.05$

Data for the models are presented as the HR, with the 95 % CI in parenthesis

ARBs, Angiotensin receptor blockers; ACEIs, angiotensin converter enzyme inhibitors; Other antihypertensives: centrally acting antihypertensives, minoxidil and dihydralazine

[a] Defined as the introduction of a new antihypertensive drug

[b] Adjusted for age, exposure to platelet aggregation inhibitors, lipid modifying agents, antineoplasic and immunomodulating agents, NSAIDs and different classes of antihypertensives

## Strengths and limitations

The main strength of our study is the representativeness of our cohort. The main characteristics of our cohort (specifically prevalence of use of antihypertensive drugs) are similar to those presented by the French National Healthcare System in a recent report on hypertensive treatment in France [29], with the exception of age and gender proportion (our study included younger subjects and fewer women). These differences could be explained by our selection of subjects unexposed to NSAIDs for 1 year, which would result in the exclusion of relatively more women and elderly patients as the elderly are more likely to be chronically on NSAIDs [30]. Moreover, Fosbøl et al. [31] found that people treated for more than 3 consecutive months were more frequently women (59.4 vs. 49.0% for people treated less than 3 months) and older (mean age 51.6 years vs. 41.4).

The French health insurance database has already been efficiently used in several pharmacoepidemiological studies [12]. Indeed, reimbursement data have been found to be highly correlated with drug consumption, especially for chronically used drugs [32]. However, as for any automated generated database, its use implies certain limitations [33]. This is an administrative reimbursement database, and thus we had only information on total drug doses delivered to patients—and not on daily-prescribed doses. In terms of NSAID exposure, we chose an average dose of 1 DDD, which corresponds to the anti-inflammatory activity of these drugs. However, some NSAIDs (ibuprofen, aspirin) can be used at smaller doses (analgesic effect), which could affect the validity of the results for these drugs. A second limitation is that we did not have access to morbidity data nor the indications for the initiation of NSAID treatment. The disease necessitating the prescription of a NSAID could alone be a condition interfering with antihypertensive treatment management. Moreover, exposure to ibuprofen may have been underestimated, as this specific NSAID (as aspirin) can be sold over-the-counter in France. Self-medication with reimbursed NSAIDs is also not recorded in the database. Finally, as the database does not associate drug reimbursements with their medical indications, it was not possible to assess if the drugs investigated were used only for arterial hypertension—and not for other cardiovascular diseases (e.g. chronic heart failure). To ensure the robustness of our results, we performed the analysis on the subgroup of patients treated with only one antihypertensive drug; similar associations were found (Table 4), although some of these were no longer statistically significant due to an insufficient sample size.

Our main outcome was defined by the addition of a new antihypertensive drug, and therefore we could have captured switches in antihypertensive drugs (regardless of their indication: inefficacy, onset of adverse drug reactions or if the prescriber identified the potential risk of interaction) if the patients discontinued their antihypertensive treatment for a few days. Moreover, hypertension treatment intensification could in fact be related to a worsening of a cardiovascular disease (e.g. heart failure, as explained above). Thus, we performed a second analysis with a stricter outcome (addition of a new

**Table 4** Sensitivity analyses: HR for analyses within the group of patients treated with only one antihypertensive at inclusion, and a stricter outcome[a]

| Change made in model | Model 1: univariate HR | | *p* value | Model 2: adjusted HR[b] | | *p* value | Model 3: adjusted with interactions HR[b] | | *p* value |
|---|---|---|---|---|---|---|---|---|---|
| Patients treated with only one antihypertensive at inclusion | NSAIDs | 1.13 (0.73–1.73) | 0.592 | NSAIDs | 1.18 (0.76–1.84) | 0.456 | NSAIDs | 0.43 (0.14–1.35) | 0.151 |
| | | | | | | | NSAIDs: ARBs | 4.36 (1.20–15.9) | 0.026 |
| | | | | | | | NSAIDs: ACEIs | 3.30 (0.83–13.1) | 0.089 |
| Stricter outcome | NSAIDs | 1.16 (0.86–1.56) | 0.332 | NSAIDs | 1.21 (0.90–1.63) | 0.217 | NSAIDs | 0.32 (0.13–0.76) | 0.010 |
| | | | | | | | NSAIDs: ARBs | 4.02 (1.68–9.60) | 0.002 |
| | | | | | | | NSAIDs: ACEIs | 5.07 (2.12–12.12) | 0.000 |

Data for the models are presented as the HR, with the 95 % CI in parenthesis

[a] Stricter outcome was the addition of a new antihypertensive with maintenance for at least 1 month

[b] Adjusted for age, exposure to platelet aggregation inhibitors, lipid modifying agents, antineoplasic and immunomodulating agents, NSAIDs and different classes of antihypertensives

antihypertensive with maintenance for at least 1 month); similar results were found in the final model with interactions (Table 4). We were able to identify intensifications of antihypertensive treatment corresponding only to an increase in dosage of antihypertensive drugs. However, a recent study carried out in the same area among general practitioners found that the addition of a new antihypertensive drug was the main therapeutic option chosen when an intensification of antihypertensive treatment was considered to be necessary [34], which suggests that our main outcome reflects the reality of clinical practice.

## Conclusions

The results of this observational study highlight the impact of NSAIDs in arterial hypertension management. They also underline the importance of their interactions with ACEIs or ARBs since patients treated with ACEIs or ARBs are more likely to receive a treatment intensification when exposed to NSAIDs. One practical implication is that patients treated or in need of NSAIDs would preferentially require antihypertensive drugs not interfering with the renin–angiotensin system. Further studies are necessary to evaluate the consequences of NSAID interactions with ACEIs or ARBs on cardiovascular morbidity and mortality.

**Acknowledgments** Jean-Pascal Fournier was a beneficiary of the "Année-Recherche" funding of the French Ministry of Research and Education (Faculty of Medicine, University of Toulouse, France). The authors thank Carole Suarez of the Health Insurance System of Midi-Pyrénées for her kind help during the data extraction, and Jane Phillips and Julie Dupouy for corrections of the manuscript.

**Competing interests** None.

## References

1. Olyaei AJ, Whelton A, Sturmer T, Porter GA (2008) Non-steroidal anti-inflammatory drugs. In: de Broe ME, Porter GA (eds) Clinical nephrotoxins: renal injury from drugs and chemicals, 3rd edn. Revue Prescrire, Paris, pp 419–457
2. Maas R, Böger RH (2003) Antihypertensive therapy: special focus on drug interactions. Expert Opin Drug Saf 2(6):549–579
3. Snowden S, Nelson R (2011) The effects of nonsteroidal anti-inflammatory drugs on blood pressure in hypertensive patients. Cardiol Rev 19(4):184–191
4. European Medicines Agency/Committee for Medicinal Products for Human Use (EMA/CHMP) (2011) European Medicines Agency starts new review of cardiovascular risks of non-selective NSAIDs. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/10/WC500116887.pdf Accessed 05 Nov 2011

5. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ (2003) The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 289(19):2560–2572, 21
6. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HAS, Zanchetti (2007) A 2007 ESH-ESC Practice guidelines for the management of arterial hypertension: ESH-ESC Task Force on the management of arterial hypertension. J Hypertens 25(9):1751–1762
7. Rose AJ, Berlowitz DR, Manze M, Orner MB, Kressin NR (2009) Intensifying therapy for hypertension despite suboptimal adherence. Hypertension 54(3):524–529
8. Berlowitz DR, Ash AS, Hickey EC, Friedman RH, Glickman M, Kader B, Moskowitz MA (1998) Inadequate management of blood pressure in a hypertensive population. N Engl J Med 339 (27):1957–1963
9. Hicks PC, Westfall JM, Van Vorst RF, Bublitz Emsermann C, Dickinson LM, Pace W, Parnes B (2006) Action or inaction? Decision making in patients with diabetes and elevated blood pressure in primary care. Diabetes Care 29(12):2580–2585
10. Bolen SD, Samuels TA, Yeh H-C, Marinopoulos SS, McGuire M, Abuid M, Brancati FL (2008) Failure to intensify antihypertensive treatment by primary care providers: a cohort study in adults with diabetes mellitus and hypertension. J Gen Intern Med 23(5):543–550
11. Oliveria SA, Lapuerta P, McCarthy BD, L'Italien GJ, Berlowitz DR, Asch SM (2002) Physician-related barriers to the effective management of uncontrolled hypertension. Arch Intern Med 162 (4):413–420
12. Martin-Latry K, Bégaud B (2010) Pharmacoepidemiological research using French reimbursement databases: yes we can! Pharmacoepidemiol Drug Saf 19(3):256–265
13. WHO Collaborating Centre for Drug Statistics Methodology (2011) ATC/DDD Index 2011. Available at: http://www.whocc.no/atc_ddd_index/. Accessed 5 Nov 2011
14. Le Gouvernement Francais (1978) Loi n°78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés.. Available at: http://www.legifrance.gouv.fr/. Accessed 05 Nov 2011
15. Johnson AG, Nguyen TV, Day RO (1994) Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 121(4):289–300
16. Pope JE, Anderson JJ, Felson DT (1993) A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. Arch Intern Med 153(4):477–484
17. Olkkola KT, Brunetto AV, Mattila MJ (1994) Pharmacokinetics of oxicam nonsteroidal anti-inflammatory agents. Clin Pharmacokinet 26(2):107–120
18. Sudano I, Flammer AJ, Périat D, Enseleit F, Hermann M, Wolfrum M, Hirt A, Kaiser P, Hurlimann D, Neidhart M, Gay S, Holzmeister J, Nussberger J, Mocharla P, Landmesser U, Haile SR, Corti R, Vanhoutte PM, Lüscher TF, Noll G, Ruschitzka F (2010) Acetaminophen increases blood pressure in patients with coronary artery disease. Circulation 122(18):1789–1796
19. Wilson SL, Poulter NR (2006) The effect of non-steroidal anti-inflammatory drugs and other commonly used non-narcotic analgesics on blood pressure level in adults. J Hypertens 24(8):1457–1469
20. Conlin PR, Moore TJ, Swartz SL, Barr E, Gazdick L, Fletcher C, DeLucca P, Demopoulos L (2000) Effect of indomethacin on blood pressure lowering by captopril and losartan in hypertensive patients. Hypertension 36(3):461–465
21. Fogari R, Zoppi A, Carretta R, Veglio F, Salvetti A (2002) Effect of indomethacin on the antihypertensive efficacy of valsartan and lisinopril: a multicentre study. J Hypertens 20(5):1007–1014
22. Manrique C, Giles TD, Ferdinand KC, Sowers JR (2009) Realities of newer beta-blockers for the management of hypertension. J Clin Hypertens 11(7):369–375
23. Whelton A, White WB, Bello AE, Puma JA, Fort JG (2002) Effects of celecoxib and rofecoxib on blood pressure and edema in patients > or =65 years of age with systemic hypertension and osteoarthritis. Am J Cardiol 90(9):959–963, 1
24. Ray WA, Stein CM, Hall K, Daugherty JR, Griffin MR (2002) Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study. Lancet 359 (9301):118–123
25. Fosbøl EL, Gislason GH, Jacobsen S, Folke F, Hansen ML, Schramm TK, Sørensen R, Rasmussen JN, Andersen SS, Abildstrom SZ, Traerup J, Poulsen HE, Rasmussen S, Køber L, Torp-Pedersen C (2009) Risk of myocardial infarction and death associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) among healthy individuals: a nationwide cohort study. Clin Pharmacol Ther 85(2):190–197
26. Gislason GH, Rasmussen JN, Abildstrom SZ, Schramm TK, Hansen ML, Fosbøl EL, Sørensen R, Folke F, Buch P, Gadsbøll N, Rasmussen S, Poulsen HE, Køber L, Madsen M, Torp-Pedersen C (2009) Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. Arch Intern Med 169(2):141–149, 26
27. Mangoni AA, Woodman RJ, Gaganis P, Gilbert AL, Knights KM (2010) Use of non-steroidal anti-inflammatory drugs and risk of incident myocardial infarction and heart failure, and all-cause mortality in the Australian veteran community. Br J Clin Pharmacol 69(6):689–700
28. McGettigan P, Henry D (2011) Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. PLoS Med 8 (9):e1001098
29. Samson S, Ricordeau P, Pépin S (2007) Hypertension artérielle et facteurs de risque associés: évolutions des traitements entre 2000 et 2006. Points Repère 10:1–8
30. Rossignol M, Abouelfath A, Lassalle R, Merlière Y, Droz C, Bégaud B, Depont F, Moride Y, Blin P, Moore N, Fourrier-Réglat A (2009) The CADEUS study: burden of nonsteroidal anti-inflammatory drug (NSAID) utilization for musculoskeletal disorders in blue collar workers. Br J Clin Pharmacol 67(1):118–124
31. Fosbøl EL, Gislason GH, Jacobsen S, Abildstrom SZ, Hansen ML, Schramm TK, Folke F, Sørensen R, Rasmussen JN, Køber L, Madsen M, Torp-Pedersen C (2008) The pattern of use of non-steroidal anti-inflammatory drugs (NSAIDs) from 1997 to 2005: a nationwide study on 4.6 million people. Pharmacoepidemiol Drug Saf 17(8):822–833
32. Noize P, Bazin F, Dufouil C, Lechevallier-Michel N, Ancelin M-L, Dartigues J-F, Tzourio C, Moore N, Fourrier-Réglat (2009) A Comparison of health insurance claims and patient interviews in assessing drug use: data from the Three-City (3C) Study. Pharmacoepidemiol Drug Saf 18(4):310–319
33. Takahashi Y, Nishida Y, Asai S (2012) Utilization of health care databases for pharmacoepidemiology. Eur J Clin Pharmacol 68:123–129. doi:10.1007/s00228-011-1088-2
34. Nicodème R, Albessard A, Amar J, Chamontin B, Lang T (2009) Poor blood pressure control in general practice: in search of explanations. Arch Cardiovasc Dis 102(6–7):477–483