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NSAID–antihypertensive drug interactions: Which outpatients are at risk for a rise in systolic blood pressure?

Annemieke Floor-Schreudering[1,2], Peter AGM De Smet[2], Henk Buurma[1], Cornelis Kramers[3,4], P Chris Tromp[5], Svetlana V Belitser[6] and Marcel L Bouvy[1,6]

Abstract

Background: Management guidelines for drug–drug interactions between non-steroidal anti-inflammatory drugs (NSAIDs) and antihypertensives recommend blood pressure monitoring in hypertensive patients. We measured the short-term effect of initiating NSAIDs on systolic blood pressure (SBP) in users of antihypertensives, aiming to investigate which outpatients are at risk for an increase in SBP in daily clinical practice.

Design: A cohort study with a nested case-control design in Dutch community pharmacies.

Methods: Patients with a drug–drug interaction alert for a newly initiated NSAID and antihypertensive were interviewed and their SBP was measured at T0, after one week (T1) and after two weeks (T2). We evaluated risk factors for exceeding a predefined limit of change (PLoC) in SBP ($\geq$10 mmHg to $\geq$140 mmHg) at T1 and T2 versus T0.

Results: For 112 patients the SBP at T0 was measured. Two patients were excluded (T0 SBP $\geq$180 mmHg). PLoC was exceeded in 10 patients (10.4%) at T1 and in seven patients (8.0%) at T2. Patients using etoricoxib (odds ratio (OR), 21.0; 95% confidence interval (CI), 3.7–120.6) and patients using >1 defined daily dose of an NSAID (OR, 3.3; 95% CI, 1.1–10.0) were at increased risk of a rise in SBP.

Conclusions: A newly initiated NSAID has an immediate clinically relevant effect on SBP in some users of antihypertensives. Management guidelines for NSAID-antihypertensive drug–drug interactions should advise SBP monitoring before and after initiation of an NSAID or intensification of NSAID therapy. Monitoring is especially relevant in patients prescribed high dosages of NSAIDs. Etoricoxib should not be used in hypertensive patients.

Keywords

Systolic blood pressure, hypertensive patients, monitoring, drug–drug interactions, NSAIDs, antihypertensive drugs, risk factors

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Introduction

It has been reported that individual patients using antihypertensive drugs may experience substantial elevations of blood pressure (BP) within two weeks after commencement of a non-steroidal anti-inflammatory drug (NSAID).[1–3]

Drug interaction management guidelines advise that NSAIDs should be used with caution in patients using antihypertensive drugs because of a BP destabilizing effect.[4–7] Furthermore, there is abundant evidence that high BP is associated with increased risk of cardiovascular morbidity and mortality.[8–10] The antihypertensive

[1]SIR Institute for Pharmacy Practice and Policy, Leiden, The Netherlands
[2]Departments of Clinical Pharmacy and IQ Healthcare, Radboud University Nijmegen Medical Centre, The Netherlands
[3]Departments of General Internal Medicine and Pharmacology and Toxicology, Radboud University Nijmegen Medical Centre, The Netherlands
[4]Department of Clinical Pharmacy, Canisius Wilhelmina Ziekenhuis, Nijmegen, The Netherlands
[5]Health Base Foundation, Houten, The Netherlands
[6]Division Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, The Netherlands

Corresponding author:
Annemieke Floor-Schreudering, SIR Institute for Pharmacy Practice and Policy, Theda Mansholtstraat 5B, 2331 JE Leiden, The Netherlands.
Email: a.floor@stevenshof.nl

drugs concerned in this drug–drug interaction (DDI) are renin–angiotensin system (RAS) inhibitors (angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-II receptor blockers), beta-blockers or diuretics (loop or thiazide). The interaction does not apply for calcium channel blockers, as they are less affected by NSAIDs.[2]

In daily clinical practice physicians and pharmacists encounter a high frequency of DDI alerts concerning the combination of NSAIDs and antihypertensives.[11] Each alert should be followed by an assessment of whether this combination of drugs is needed. Ideally, BP monitoring should be part of this assessment, keeping in mind that current guidelines on hypertension management and cardiovascular disease prevention aim at a systolic BP (SBP) below 140 mmHg.[6,12–14] The question is whether all patients for which this DDI alert occurs are at risk for a BP elevation and should be routinely monitored.

While several studies have demonstrated that NSAIDs may increase BP in patients treated for hypertension,[2,15–19] only Krum et al. performed a multivariate analysis on potential risk factors predisposing patients to a rise in BP after the start of an NSAID.[20] Their study population, however, was restricted to osteoarthritis and rheumatoid arthritis patients. Moreover, patients with uncontrolled hypertension were excluded, and NSAID use was limited to etoricoxib (60 and 90 mg/day) and diclofenac (150 mg/day). Consequently, the risk factors found may not be applicable to all treated hypertensive patients using an NSAID. Moreover, the changes in BP were only determined after four months of continuous NSAID use, whereas in daily clinical practice NSAIDs are often used intermittently or for a few weeks.

Therefore, the aim of our study was to measure the short-term effect of newly initiated NSAIDs on SBP in outpatients on antihypertensive therapy and to investigate which outpatients are at risk for a rise in SBP in daily clinical practice.

Methods

Setting

A total of 78 Dutch community pharmacies, belonging to the Utrecht University Pharmacy Practice Research Network (UPPER) (which comprises about 50% of all 1976 Dutch pharmacies[21]), were invited to participate in this study from September 2010 to September 2011. Pharmacy master's students from Utrecht University or pharmacy technicians assisted in the selection and monitoring of the patients. They were adequately trained to measure patients' BP and a help desk was available throughout the research period.

Study population

In each participating pharmacy patients with a DDI alert for a newly initiated NSAID and a RAS inhibitor (ACE inhibitor or angiotensin-II receptor blocker), beta-blocker or diuretic (loop or thiazide) were contacted. Only adult patients enlisted in the participating pharmacy, with a newly initiated NSAID (no NSAID used in the preceding week) and concomitant use of one of the aforementioned antihypertensives prescribed for hypertension for at least three months, and with no change in their antihypertensive regimen during the preceding month, were enrolled.

Patients' BP was measured at inclusion (T0, baseline BP). Patients with a baseline SBP over 180 mmHg were excluded and referred to their physician.[12]

BP measurements

BP was measured according to a pretested protocol[22] at inclusion (T0), one week after inclusion (T1) and two weeks after inclusion (T2) by means of the automated and validated Omron M6 Comfort monitor.[23]

During measurement, patients were in the sitting position. After a minimum of 5 min rest two consecutive measurements with 2 min in between were recorded. Mean SBP and mean diastolic BP (DBP) over both measurements were calculated.

When patients' SBP at T1 was $\geq$180 mmHg the pharmacist informed the patients' physician, based on European guidelines of cardiovascular disease prevention.[12]

Additional data collection

At T0, T1 and T2 the following data were recorded using a pretested, structured questionnaire form[22] (requiring 10 min per patient): patients' age, sex, height and weight, dose and regimen of the NSAID and antihypertensive(s) in use, comorbidities with a potential effect on BP (diabetes, cardiovascular diseases and renal dysfunction), personal habits (smoking, alcohol use, low salt diet). Defined daily doses of the NSAIDs and antihypertensive(s) in use were calculated using the World Health Organization ATC/defined daily dose methodology.[24]

Data analysis

Changes in SBP from T0 (inclusion) were determined at T1 (6–10 days after inclusion) and T2 (13–21 days after inclusion). We applied these intervals because guidelines recommend that BP should be regularly monitored, particularly during the initiation of NSAID therapy[1–5,20] and the fact that in daily clinical practice NSAIDs are often used intermittently or for a limited period of time.

We calculated the number of patients in whom the SBP exceeded a predefined limit of change (PLoC). PLoC was defined as a SBP measurement at T1 or T2 of $\geq$140 mmHg[12] plus a change in SBP of $\geq$10 mmHg[8,25] measured as the difference between T0 and T1, or T0 and T2.

In a nested case-control design, cases were defined as patients exceeding PLoC at T1 and/or T2 while using an NSAID. Controls were patients not exceeding PLoC at either T1 or T2 while using an NSAID.

Differences in potential risk factors (e.g. age, BMI, gender, comorbidities) between cases and controls were analysed using chi-square tests and univariate logistic regression. Given the small number of cases we only explored the relationship between the several determinants by including potential risk factors with $p < 0.1$ in the univariate model as covariates in a multivariable logistic regression model.

Data were analysed using SPSS (version 19.0) and statistical software R (version 2.6.1).

Ethical approval and patient confidentiality

The study was submitted to the medical ethics committee of the region Arnhem-Nijmegen, The Netherlands (reference CMO-nr 2010/317), but did not require medical ethical approval according to current Dutch legislations. The work was conducted in compliance with the requirements of the UPPER institutional review board. All patient data were anonymized in the patients' community pharmacy.

Results

Patient population

The BP of 112 patients was measured at T0. Two patients with a baseline SBP above 180 mmHg were excluded and immediately referred to their physician. Finally, 110 patients were included in the analysis. Figure 1 presents the flow chart of our study population. The BP was measured at both T1 and T2 for 84

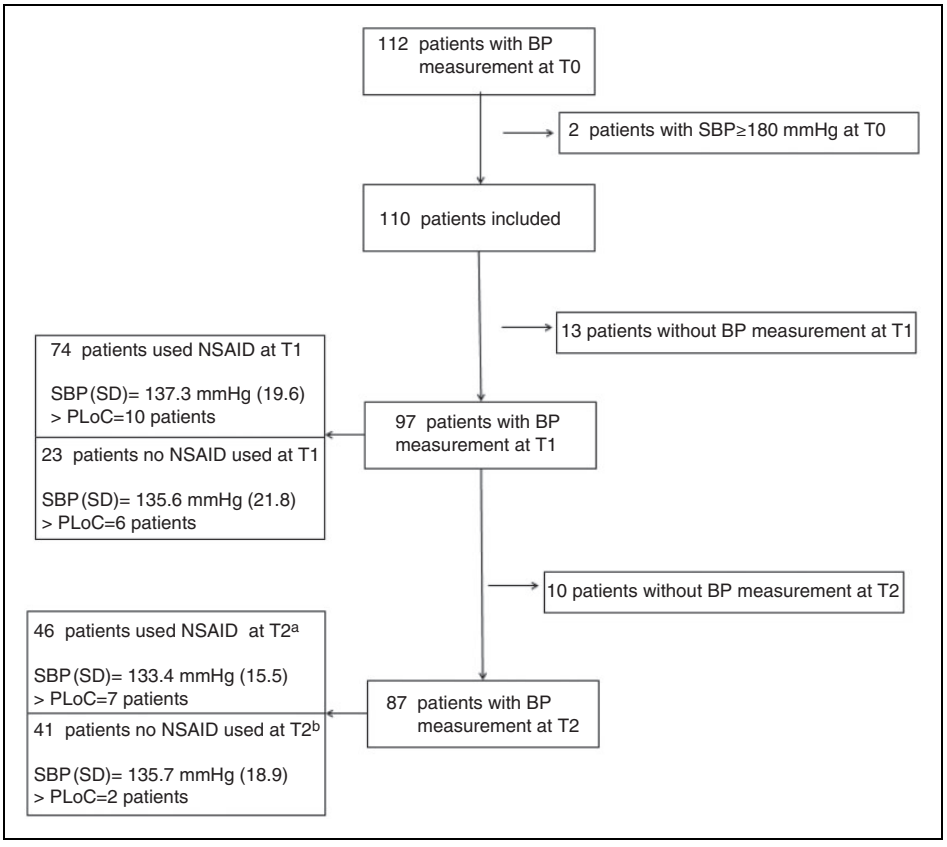

Figure 1. Flow chart of our study.
[a]Including one patient without NSAID use at T1 and one patient without BP measurement at T1.
[b]Including 25 patients without NSAIDs at T1 and two patients without BP measurement at T1.
NSAID: non-steroidal anti-inflammatory drug; BP: blood pressure; SBP (SD): mean systolic blood pressure (standard deviation); PLoC: predefined limit of change in SBP: $\geq$ 10mmHg to $\geq$140mmHg.

patients (76.4%). For three patients (2.7%) the BP was measured only at T2.

The NSAID most often used was diclofenac. The most common antihypertensive therapy was monotherapy with a RAS inhibitor (21.8%), followed by a combination of a RAS inhibitor and a diuretic (15.5%). Relatively few patients received monotherapy with a beta-blocker (8.2%) or diuretic (6.4%). In 47 patients (42.7%) the SBP at T0 was ≥140 mmHg (Table 1).

Short-term effect of a newly initiated NSAID on SBP in patients with an antihypertensive

According to our study protocol, the pharmacists informed the patients' physician about two patients (2.1%) with an SBP ≥180 mmHg at T1 and about 30 patients (34.5%) with an SBP ≥140 mmHg at T2.

Table 1. Baseline characteristics of the study population ($n = 110$)

Characteristics	Number of patients	%
Male	49	44.5
Female	61	55.5
Age, mean	63.2 ± 11.1 years	
Body mass index, mean	29.3 ± 5.2	
Systolic blood pressure, mean	134.9 ± 19.0 mmHg	
Diastolic blood pressure, mean	83.0 ± 11.8 mmHg	
Diabetes mellitus	31	28.2
Ischaemic heart disease	17	15.4
Heart failure	8	7.3
Renal disease	3	2.7
Low-sodium diet	23	20.9
Smoking	19	17.3
Alcohol male >3 glasses/day or female >2 glasses/day	9	8.1
NSAIDs, average duration of use (days)	10.2 (0–21)	
Diclofenac	77	70
Ibuprofen	9	8.2
Naproxen	9	8.2
Meloxicam	7	6.4
Etoricoxib	6	5.5
Celecoxib	2	1.8
Antihypertensive drugs, mean use (range)	2.1 (1–5)	
Renin–angiotensin system (RAS) inhibitors	84	76.4
Diuretics	64	58.2
Beta-blockers	51	46.4
Calcium channel blockers	24	21.8

Analysis of cases. In Figure 2 the change from baseline SBP (T0) is provided for NSAID users at T1 ($n = 74$ patients) and T2 ($n = 46$ patients). At T1 PLoC was exceeded in 10 NSAID users (13.5%), seven of whom used diclofenac, two etoricoxib and one naproxen. At T2 PLoC was exceeded in seven NSAID users (15.2%), three of whom used diclofenac, three etoricoxib and one naproxen. In three patients PLoC was exceeded at both T1 and T2, one of whom used diclofenac, one etoricoxib and one naproxen.

Analysis for associations. In 17 of the 120 measurements (14.2%) the PLoC was exceeded (Table 2). The risk of exceeding the PLoC was significantly associated with male patients, with the use of etoricoxib and with >1 defined daily dose (DDD) of an NSAID used. The NSAIDs with a DDD>1 were diclofenac (>100 mg/day in six of 10 cases), naproxen (>500 mg/day in two of two cases) and etoricoxib (>60 mg/day in two of five cases). We did not find an association between type of antihypertensive used, comorbidity, patient's age, BMI or personal habits, and the risk of rise in SBP after initiating an NSAID. After correcting for the three risk factors found, male sex appeared not to be an independent risk factor.

Discussion

Our study shows that the mean changes in SBP after initiation of an NSAID in patients using a RAS inhibitor, beta-blocker or diuretic are negligible. However, more than 10% of patients had SBP increases within two weeks of treatment of ≥10 mmHg resulting in an SBP of ≥140 mmHg. Three patients developed an SBP above 180 mmHg after initiation of an NSAID. We found patients using etoricoxib and high NSAID doses (DDD>1) to be at increased risk for a relevant rise in SBP.

It is difficult to compare our findings directly with other studies because reported SBP changes could be related to variation in the NSAID used, doses used, duration of treatment, antihypertensive used and BP measurement method (e.g. sitting or standing, mean arterial pressure or SBP).[2,26–28] Moreover, we conducted our study in daily clinical practice instead of conducting a randomized controlled trial. The high percentage of patients who used an NSAID for less than two weeks in our study is quite different from the long-term NSAID use in trials and represents the frequent short-term or intermittent use of NSAIDs in daily practice.[29,30]

Our finding that in more than 10% of the patients in our study population the PLoC was exceeded within two weeks after initiating an NSAID suggests the BP should be regularly monitored, particularly during the initiation or intensification of NSAID therapy, as is

advised in the current drug interaction management guidelines.[4,5,20] But because of the risk of overriding the many alerts concerning the combination of NSAIDs and antihypertensives[11] there is a need to identify risk factors associated with increased SBP. This seems especially warranted, because patients with a strong increase in BP may be at increased risk for stroke and ischaemic heart disease events.[8,10,31] In this regard it should also be noted that antihypertensive treatment should be aimed not only at reducing the average BP value, but also at reducing short-term and longer-term variability in BP.[32,33]

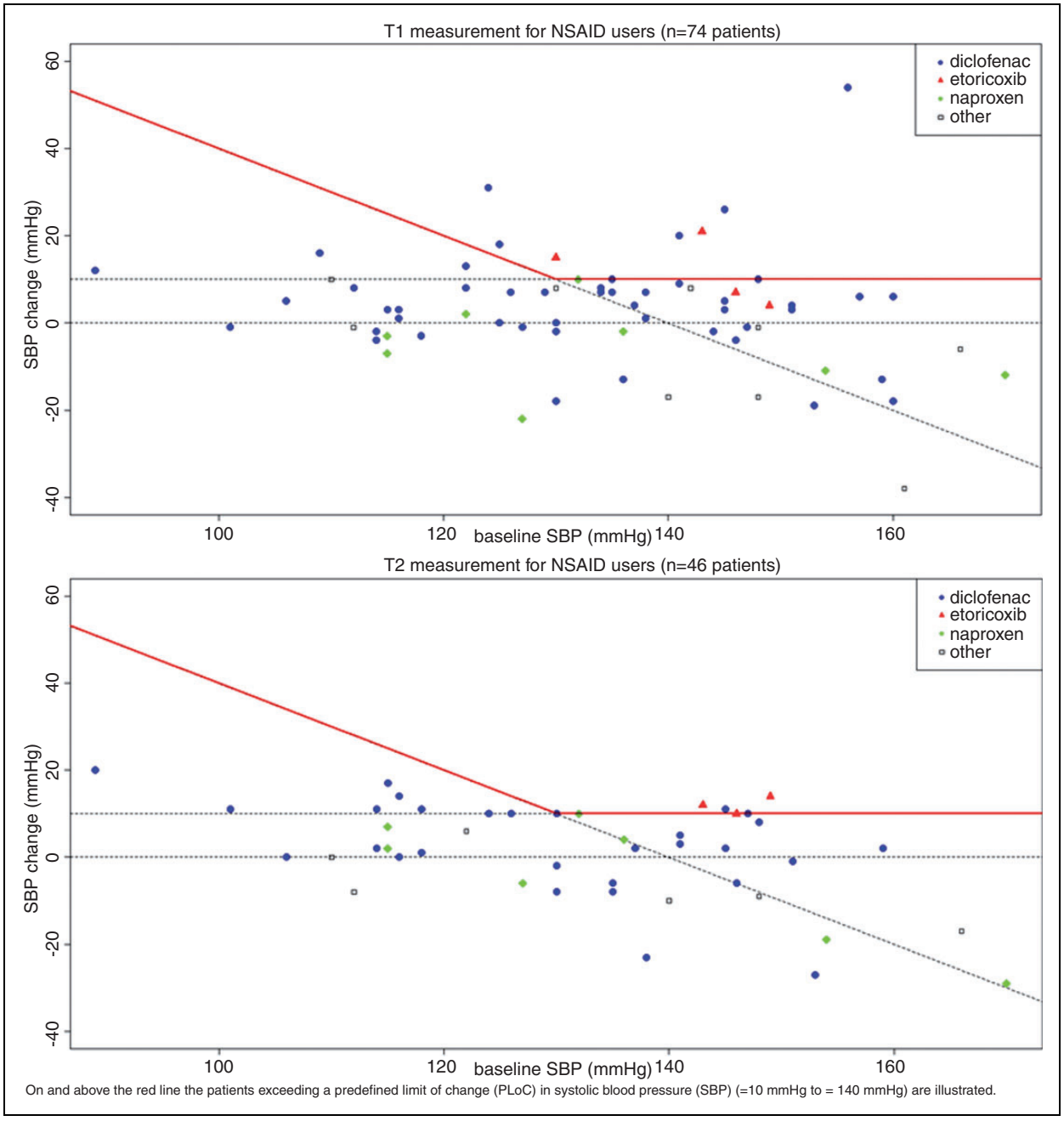

Figure 2. (a) T1 measurement for non-steroidal anti-inflammatory drug (NSAID) users ($n = 74$ patients). (b) T2 measurement for NSAID users ($n = 46$ patients). For (a) and (b): On and above the bold line, the patients exceeding PLoC (predefined limit of change in SBP of ≥ 10 mmHg to ≥ 140 mmHg) are illustrated.

Table 2. Analysis for associations for the measurements at T1 and T2 for NSAID use

	Cases[a] ($n=17$)		Controls ($n=103$)				
Variable	*N*	%	*N*	%	OR[b]	95% CI	p[b]
Male *vs.* female	12	70.6	41	39.8	3.6	1.2–11.1	0.02
Age $\geq$70 years *vs.* age <70 years	5	29.4	24	23.3	1.4	0.4–4.3	0.59
BMI $\geq$30 kg/m^2 *vs.* BMI <30 kg/m^2	3	17.6	42	40.8			
SBP at T0 $\geq$140 mmHg *vs.* SBP at T0 <140 mmHg	10	58.8	40	38.8	2.25	0.79–6.39	0.12
Diabetes mellitus yes *vs.* no	2	11.8	35	34.0			
Ischaemic heart diseases yes *vs.* no	2	11.8	21	20.4			
Heart failure yes *vs.* no	1	5.9	5	4.9			
Renal disease yes *vs.* no	2	11.8	3	2.9			
Low-sodium diet yes *vs.* no	5	29.4	23	22.3	1.9	0.6–6.3	0.28
Smoking yes *vs.* no	4	23.5	21	20.4	1.3	0.4–4.5	0.67
Alcohol male >3 or female >2 glasses/day *vs.* alcohol male $\leq$3 or female$\leq$2 glasses/day	2	11.8	10	9.7			
Diclofenac yes *vs.* no	10	58.8	73	70.9	0.6	0.2–1.7	0.32
Ibuprofen yes *vs.* no	0	0.0	5	4.9			
Naproxen yes *vs.* no	2	11.8	13	12.6			
Meloxicam yes *vs.* no	0	0.0	8	7.8			
Etoricoxib yes *vs.* no	5	29.4	2	1.9	21.0	3.7–120.6	0.00
Celecoxib yes *vs.* no	0	0.0	2	1.9			
DDD NSAID >1 DDD *vs.* $\leq$1 DDD	10	58.8	33	32.0	3.3	1.1–10.0	0.03
Renin–angiotensin system inhibitors	15	88.2	79	76.7	2.3	0.5–10.7	0.29
Diuretics	8	47.1	53	51.5	0.8	0.3–2.3	0.74
Beta-blockers	5	29.4	52	50.5	0.4	0.1–1.2	0.11
Calcium channel blockers	6	35.3	21	20.4	2.1	0.7–6.4	0.17
Combination therapy *vs.* monotherapy	10	58.8	59	57.3	1.1	0.38–3.02	0.91

[a]Cases are patients exceeding PLoC (predefined limit of change in SBP of $\geq$10 mmHg to $\geq$140 mmHg) at T1 and/or T2; [b]Analysis only for >3 cases; OR: odds ratio; CI: confidence interval; BMI: body mass index; SBP: systolic blood pressure; DDD: defined daily dose; NSAID: non-steroidal anti-inflammatory drug.

Despite the relatively small number of patients in our study we found that two risk factors were significantly associated with an SBP increase: etoricoxib and high NSAID dose. The finding in the univariate model that male sex was a risk factor has been reported by other researchers, but remains to be investigated.[2,20] More daily practice research, preferably with a control group (as pain itself may also influence the SBP), is needed to corroborate the risk factors found in our study and to define those patients who are at risk for a rise in SBP when using an NSAID and antihypertensive agent together. A recent observational study showed predictors for attaining BP control and predictors for failing to maintain BP goals, and found a higher number of NSAID prescriptions in patients who lost BP control compared with those who maintained BP control.[34]

The effect of etoricoxib on BP has been described earlier both in healthy elderly subjects[35] and in hypertensive patients.[20] The European summary of product characteristics (SPC) of etoricoxib and a 'Dear Doctor letter' alert physicians not to prescribe etoricoxib to patients with uncontrolled hypertension. Hypertension should be monitored before treatment with etoricoxib, within two weeks after initiation of treatment and periodically thereafter.[36,37] Nonetheless, three out of six patients who were prescribed etoricoxib already had an SBP above 140 mmHg at baseline (T0). Until the reasons for this finding have been investigated in more depth, one could best err on the safe side of caution by giving preference to another NSAID in hypertensive patients.

A significant association between the NSAID dose and the SBP has not been reported before,[18,20,38] but dose-related increases in cardiac events have been found.[39] Whereas most studies calculated the assumed NSAID dose used, the patients in our study reported the daily dose actually taken, which was lower than the prescribed daily dose in more than half of the patients. This makes it worthwhile to explore this dose-relationship in daily practice in future studies.

Of note, it is of concern that more than 40% of the patients with an SBP above 140 mmHg at T0 were prescribed an NSAID while using an antihypertensive. In two cases, patients with a DDI alert had to be excluded from our study because of an initial SBP above 180 mmHg at T0. For both patients we could not find risk factors explaining the high SBP.

Limitations

There are several limitations to our study. First, it was an observational study without a control group. The indication for the NSAID may have increased stress and may therefore have been partly responsible for changes in SBP. This could have overestimated the effects found in this study. Secondly, the monitoring of BP in the pharmacy may have had the unintended effect of increased compliance with antihypertensives and restrained use of NSAIDs, especially in patients with high baseline SBP. This might have caused an underestimation of the number of patients with an SBP increase of $\geq$10 mmHg to an SBP $\geq$140 mmHg. Thus, without appropriate monitoring the risk for increased levels of SBP might be higher in daily practice.

Thirdly, the relatively small sample size limits the power to prove possible differences between the different NSAIDs and different antihypertensives used and the risk factors associated with an increased SBP. The large number of diclofenac users, which resembles real practice, complicates the finding of associations with the other NSAIDs. However, the SBP differences were large enough to have an adequate power for detection of a significant association for etoricoxib and NSAID dose >1 DDD.

Fourthly, changes in SBP were measured within 2–3 weeks after initiation of an NSAID. It is uncertain whether the SBP had reached steady state in all patients by then. More patients with an SBP increase of $\geq$10 mmHg to an SBP $\geq$140 mmHg could have been found when measuring for a longer period. Nonetheless, only in three patients the PLoC was exceeded at both T1 and T2, partly caused by the fact that patients with an exceeded PLoC at T1 stopped using the NSAID between T1 and T2.

Lastly, although the resistance to measure BP in the participating community pharmacies was low among patients, students and technicians encountered difficulties with identifying patients. Some patients were missed because of the high workload in the pharmacy resulting in the unnoticed overriding of the DDI alert. More importantly, many patients had (intermittently) used NSAIDs in the preceding week, often without prescription and not documented in the pharmacy information system. This emphasizes the need to know which patients are at risk for a rise in SBP in order to provide patients with appropriate monitoring and treatment. Finally some patients could not be monitored as NSAIDs were not supplied in the pharmacy, but delivered to the patients' homes.

In conclusion, concomitant use of a newly initiated NSAID plus a RAS inhibitor, beta-blocker or diuretic had a small effect on the mean changes in SBP (measured at one and two weeks after initiation of the NSAID). Patients using etoricoxib and high NSAID doses (>1 DDD) were at risk for an SBP increase within two weeks of use. As long as risk factors for a SBP rise by NSAID–antihypertensive interactions are not fully explored, NSAIDs should be used with caution in patients with antihypertensives, in the lowest dose possible, and with appropriate monitoring before treatment and during the initiation or intensification of NSAID therapy. Although the prescribing physician should be the first to monitor the BP, the pharmacist should accept his responsibility when a DDI alert for a newly initiated NSAID and antihypertensive occurs.

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Conflict of interest

The authors declare that there is no conflict of interest.

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