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SHORT COMMUNICATION

Prevalence and management of drug interactions between nonsteroidal anti-inflammatory drugs and antithrombotics in ambulatory care

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Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and antithrombotic agents is associated with increased risks of both bleeding and thromboembolism. In this prospective intervention study, community pharmacists screened for NSAID-antithrombotic interactions and contacted the prescribing physician to discuss interaction management. We included 782 interactions; these were found in an older, polymedicated patient population (mean age: 68 y, median of 5 other drugs). Ibuprofen (in 43.0% of cases) and low-dose aspirin (78.8%) were the most frequently involved NSAID and antithrombotic, respectively. Anticoagulants were involved in 16.1% of interaction cases. For 61% of cases, the interacting drugs were prescribed by the same physician. The pharmacist–physician discussion about how to manage the interaction mostly resulted in no change of pharmacotherapy (60.7%); the most frequent reason given by physicians was that the NSAID was for short-term use only. In 39.3% of cases the discussion resulted in a pharmacotherapy change; replacing the NSAID by paracetamol was the most common change.

KEYWORDS
antithrombotic therapy, drug–drug interactions, nonsteroidal anti-inflammatory drugs, safety

1 | INTRODUCTION

Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and antithrombotic agents is associated with increased risks of both bleeding and thromboembolism.[1–7] For example, in a large Danish cohort of patients with atrial fibrillation using oral anticoagulation therapy and/or antiplatelet therapy, there was an increased absolute risk for bleeding associated with 14 days of concomitant NSAID use.[2] The absolute increase in bleeding risk corresponded with a serious bleeding event in 1 of 400–500 patients exposed to an NSAID for 14 days. Concurrent NSAID–antithrombotic use was also associated with an increased absolute risk of thromboembolism.[2] These risks are of considerable public health concern, given the widespread use of NSAIDs.

It is thus essential for patient safety to identify and appropriately manage NSAID–antithrombotic interactions. In ambulatory care, community pharmacists can play a key role in this, as they are drug interaction experts and have view of patients' complete medication profile including over-the-counter (OTC) medication (of note, several NSAIDs are available OTC) and medication from different prescribers. This is in line with community pharmacists becoming more involved in patient care and contributing to medication reviews (including drug interaction screening). There is increasing evidence that such community pharmacist interventions have a positive impact on clinical and healthcare utilization outcomes.[8,9] However, studies on identifying and handling NSAID–antithrombotic interactions in this setting are currently lacking.

All authors confirm that the Principal Investigator for this paper is Koen Boussery.

In this study, community pharmacists screened for NSAID–antithrombotic interactions and contacted the prescribing physician to discuss management of the interaction. Aims were to determine prevalence and characteristics of NSAID–antithrombotic interactions, and to evaluate how a community pharmacist intervention can impact patients' pharmacotherapy.

2 | METHOD

A prospective intervention study was carried out between February and May 2016 in 195 community pharmacies in Belgium. On 10 random days, every patient purchasing a systemic NSAID (Anatomical Therapeutic Chemical (ATC) code, M01A excl. Glucosamine [ATC, M01AX5] and chondroitin sulfate [ATC, M01AX25]) or an antithrombotic drug (platelet aggregation inhibitors excluding Heparin [ATC, B01AC], vitamin K antagonists [ATC, B01AA] and direct oral anticoagulants [ATC, B01AE and B01AF]) was screened for presence of an NSAID–antithrombotic interaction. This was done by consulting their 6-month medication history in the pharmacy dispensing records and by directly asking patients about use of *painkillers* and *blood thinners*.

Pharmacists collected the following information during the 10 study days: number of NSAID–antithrombotic interactions, number of patient contacts, number of systemic NSAID dispensations and number of antithrombotic drug dispensations. This was used to calculate prevalence of NSAID–antithrombotic interactions on 3 different denominators (i.e. patient contacts, systemic NSAID dispensations and antithrombotic drug dispensations). Prevalence numbers were collected for all patients, but further intervention was only pursued if the patient provided written informed consent.

For each interaction for which the patient provided informed consent, the pharmacist completed a case report form that collected patient's age and sex, interaction characteristics, and comedication. The pharmacist subsequently contacted the prescribing physician to discuss management of the interaction. The agreed action and reason(s) given by the physician for not wanting to act upon the interaction were also recorded on the case report form. In case of interactions with OTC NSAIDs intended for self-care, the pharmacist managed the interaction without contacting the physician.

Approval for the study was granted by the Ethics Committee of Ghent University Hospital.

3 | RESULTS

During the 10-day observation period, the 195 participating community pharmacies had 230 541 patient contacts and dispensed 15 788 times an NSAID and 7878 times an antithrombotic drug. A total of 1231 NSAID–antithrombotic interactions were found. This corresponds with a NSAID–antithrombotic interaction prevalence of 0.5% for all patient contacts, 7.8% for all dispensations of an NSAID and 15.7% for all dispensations of an antithrombotic drug.

What is already known about this subject

- Combined use of nonsteroidal anti-inflammatory drugs (NSAIDs) and antithrombotics is associated with increased risks of both bleeding and thromboembolism.
- This study aimed to detect and manage drug interactions between NSAIDs and antithrombotic agents in ambulatory care, because such real-life clinical practice studies are currently lacking.

What this study adds

- We found a high prevalence of NSAID–antithrombotic interactions; these interactions were mainly found in an older, polymedicated patient population.
- For almost half of interactions pharmacotherapy was changed (mostly switching the NSAID to paracetamol). The most common reason given by physicians for not changing pharmacotherapy was that the NSAID was intended for short-term use only.

For 449 of the 1231 observed NSAID–antithrombotic interactions (36.5%), the patient was not willing to provide informed consent resulting in a sample of 782 interaction cases available for further analysis.

The patients involved in the drug interaction cases ($n = 782$) had a mean age of 68 years (range 21–92 years) and about half were male (49.2%).

NSAIDs most frequently involved were ibuprofen (in 43.0% of cases) and diclofenac (in 20.3% of cases; Table 1). Most NSAIDs (83.0%) were prescribed and 17% were dispensed over-the-counter. In about half of cases, the patient used the NSAID on a daily basis. The antithrombotic agent(s) involved were antiplatelets in 89.1% of cases and anticoagulants in 16.1%; the antiplatelets were mainly aspirin (in 78.8% of cases) and clopidogrel (in 7.2% of cases).

In about 3/4 of cases, the concomitant NSAID–antithrombotic use was not new, meaning that patients had already been using the drug combination for some time (Table 1). For example, in 40% the patient had been using an NSAID and an antithrombotic concomitantly for 1 year or longer. The NSAID and the antithrombotic were not dispensed at the same moment (i.e. at different patient contacts) in 75% of cases. In most of these situations (88.8%), the pharmacist detected the interacting drug via the pharmacy dispensing records. However, in the remaining 11.2%, the interacting drug was not present in pharmacy dispensing records but was identified via patient questioning. For 61% of cases, both interacting drugs were prescribed by the same physician.

Patients used a median of 5 other medications (range, 0–20) in addition to the NSAID and antithrombotic. In 37.3% of cases, the

TABLE 1 Characteristics of the nonsteroidal anti-inflammatory drug (NSAID)–antithrombotic interaction cases ($n = 782$)

	n (% of interactions)
NSAID	
Type[a]	
Ibuprofen	336 (43.0)
Diclofenac	159 (20.3)
Meloxicam	68 (8.7)
Piroxicam	66 (8.4)
Aceclofenac	46 (5.9)
Nabumetone	44 (5.6)
Celecoxib	38 (4.9)
Etoricoxib	27 (3.5)
Other	40 (5.0)
By prescription[b,c]	649 (83.0)
OTC	135 (17.3)
Frequency of use	
Daily	378 (48.3)
Several times/wk	164 (21.0)
<1×/wk	233 (29.8)
Antithrombotic[d]	
Type	
Aspirin	616 (78.8)
Clopidogrel	56 (7.2)
Rivaroxaban	33 (4.2)
Warfarin	29 (3.7)
Apixaban	20 (2.6)
Fenprocoumon	19 (2.4)
Acenocoumarol	13 (1.7)
Dabigatran	12 (1.5)
Other	25 (3.2)
Duration of concomitant NSAID–antithrombotic use	
0 d[e]	205 (26.2)
1–15 d	75 (9.6)
16–30 d	39 (5.0)
2–6 mo	104 (13.3)
7–11 mo	39 (5.0)
1–2 y	127 (16.2)
3–5 y	108 (13.8)
>5 y	76 (9.7)
NSAID and antithrombotic dispensed…	
At the same time	194 (24.8)
At different times	588 (75.2)
NSAID and antithrombotic prescribed by same physician?	
Yes	480 (61.4)
No	128 (16.3)
Not applicable[f]	172 (22.0)

TABLE 1 (Continued)

	n (% of interactions)
Relevant comedication	
Gastroprotection	
Proton pump inhibitor	292 (37.3%)
Medication that might further increase bleeding risk	
SSRI	46 (5.9%)
Systemic corticosteroids	31 (4.0%)

[a]Some patients used >1 NSAID.
[b]Subject to missing data.
[c]Medication with over-the counter (OTC) status that was prescribed by a physician was categorized as *by prescription*.
[d]Some patients used >1 antithrombotic.
[e]The concomitant NSAID–antithrombotic use was new for the patient (= the drug combination was dispensed for the first time).
[f]Because 1 of the interacting drugs was dispensed OTC.

patient also used a proton-pump inhibitor. In 9%, the patient also used comedication that can further increase bleeding risk (i.e. SSRI and/or systemic corticosteroids).

For 28.8% ($n = 225$) of cases, the pharmacist decided not to contact the physician to discuss interaction management (Figure 1). This was mainly because the interaction involved the nonprescription use of an NSAID for self-care. In about half of these cases (114/225; 50.7%), pharmacists handled these interactions by replacing the NSAID by a non-NSAID analgesic (mainly paracetamol). However, in a substantial proportion of cases (94/225; 41.8%), they dispensed both interacting drugs.

For the other 71.2% ($n = 557$) of cases, pharmacists contacted the prescribing physicians to discuss how to manage the interaction (Figure 1). Twenty-eight physicians refused to participate, resulting in 529 interactions that were discussed with the physician. This discussion most often resulted in no change in pharmacotherapy (321/529; 60.7%); most frequent reasons for this given by physicians were: NSAID is for short-term use only ($n = 63$); both interacting drugs deemed necessary for the patient ($n = 62$); and alternative for the NSAID proposed by the pharmacist was already tried in the past and considered insufficiently effective ($n = 50$). In 208 cases (208/529; 39.3%), the pharmacist–physician discussion resulted in a pharmacotherapy change; the top 3 changes were replacement of the NSAID by a non-NSAID analgesic (most often paracetamol; $n = 61$); initiation of a proton-pump inhibitor ($n = 50$); and replacement of the NSAID by another, safer NSAID ($n = 46$).

4 | DISCUSSION

The main findings are that prevalence of NSAID use among patients on antithrombotic therapy is high and that, for almost half of included interactions, the intervention resulted in a pharmacotherapy change.

For 16% of antithrombotic dispensations, an interaction with an NSAID was detected. This high prevalence is not surprising since pain is common and often co-exists with cardiovascular disease.[10] It certainly enforces the need for risk-reduction actions, such as vigilant drug interaction screening. Importantly, the interactions in our study were found in an older, polymedicated patient population (mean age of 68 years and median of 5 other drugs in addition to the interacting drugs). These patients are more vulnerable for the adverse effects of drug interactions, so extra caution and careful evaluation of benefits and risks are warranted. In this context, the D-PRESCRIBE intervention is interesting to note. This recent pragmatic randomized controlled trial highlighted the ability of community pharmacists to lead an educational intervention resulting in a reduction of inappropriate medication use including NSAIDs, in community-dwelling older adults.[11] Deprescribing NSAIDs also showed to be a cost-effective strategy, conferring greater health benefits at lower costs than usual care in older adults.[12] These findings plead for a greater participation of pharmacists in rational pharmacotherapy decision making.

Most interactions involved antiplatelets (mainly low-dose aspirin) as antithrombotic, and not anticoagulants. The risk of serious gastrointestinal (GI) bleeding in older people on low-dose prophylactic aspirin might be larger than previously thought. The recent ASPREE trial, a large randomized placebo-controlled study, showed that low-dose aspirin increased overall baseline GI bleeding risk by approximately 60% in older patients (87% for upper and 36% for lower GI bleedings). This risk further increased in presence of other risk factors such as advanced age and NSAID use.[13] These findings highlight the importance of a careful evaluation of the indication for aspirin and to target modifiable risk factors (such as unnecessary NSAID use). In addition to the increased risk of bleeding, nonselective NSAIDs also have the potential to inhibit the antiplatelet effects of aspirin. This interaction is best documented for ibuprofen, with the majority of studies demonstrating that ibuprofen impedes aspirin's cardioprotective effects.[14] This is an additional argument to avoid the combination if possible, in order to reduce avoidable morbidity.

For most interactions (60%), both the NSAID and the antithrombotic agent were prescribed by the same physician. High rates of coprescription of interacting drugs have also been reported in Italy (71% of drug–drug interactions),[15] France (up to 58%)[16] and Poland (77%).[17] Coprescription can be a conscious act, driven by the absence of therapeutic alternatives, but may also indicate a lack of alertness or

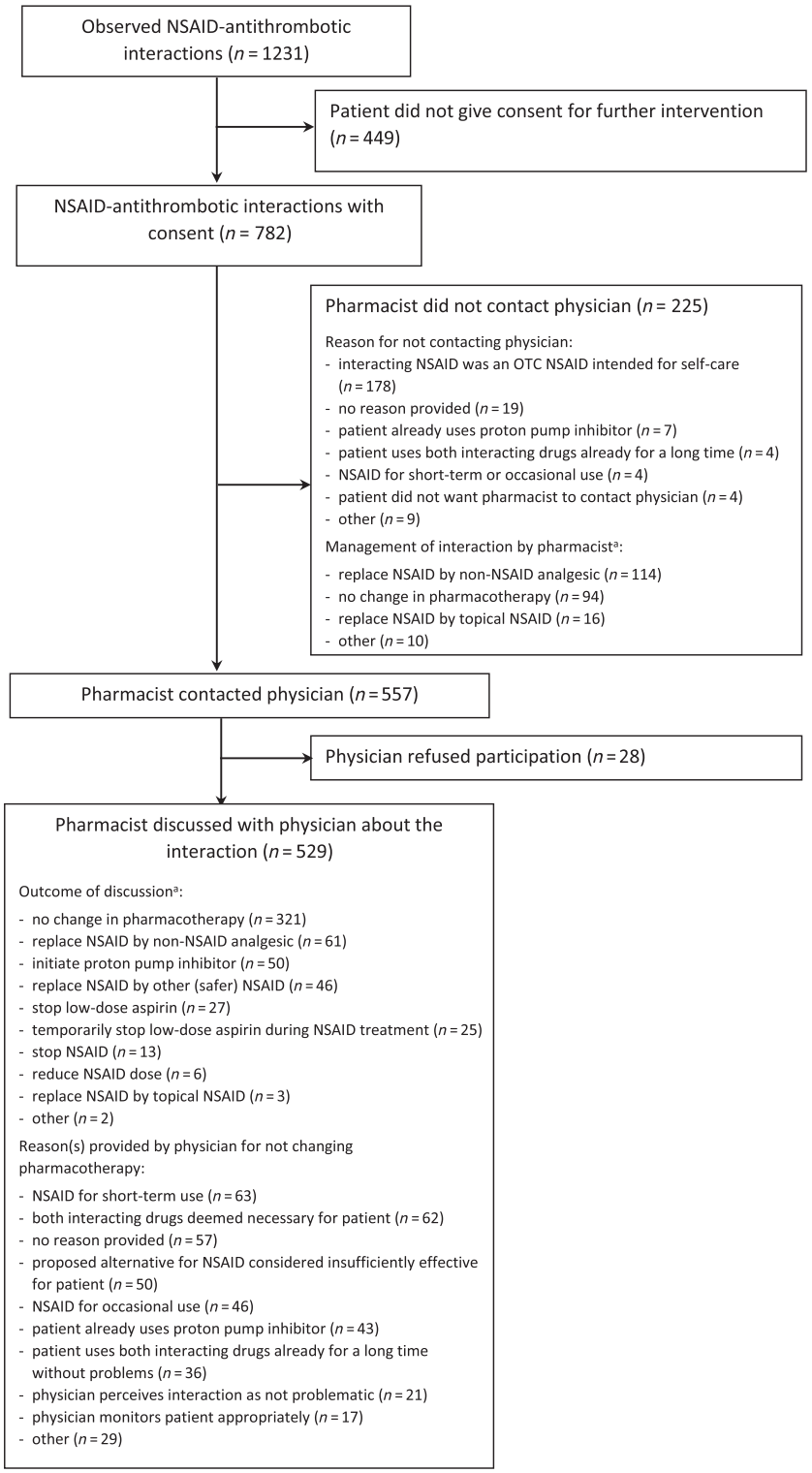

FIGURE 1 Inclusion and management of the nonsteroidal anti-inflammatory drug (NSAID)–antithrombotic interaction cases. [a] Sum exceeds total number of interactions, since some interactions were handled by >1 management strategy

knowledge on interactions of the physician. We can only speculate whether the coprescribers in our study were well aware of the interaction and its associated risks when prescribing. If so, they might perhaps have underestimated the bleeding risk of low-dose aspirin (most interactions involved aspirin as antithrombotic agent) and therefore considered the interaction as not clinically relevant.

Regarding management of the detected interactions, we found that for almost half of interactions pharmacotherapy was changed thus improving medication safety. This change mostly comprised switching the NSAID to paracetamol, which can often be a safe and effective alternative. The most common reason given by physicians for not changing pharmacotherapy was that the NSAID was intended

for short-term use only. Clinicians might think that short-term use of NSAID is safe; however, previous cohort studies suggested that even a few days of use is associated with increased risks of both bleeding and cardiovascular events.[2,3]

During a 10-day period, we observed 1231 NSAID–antithrombotic interactions in 195 pharmacies, which would correspond with around 750 000 interactions in the whole of Belgium (4797 pharmacies) over a 1-year period (pharmacies are open for about 250 d/y). With a number needed to harm for serious bleeding of 400–500,[2] this suggests about 1680 serious bleeding events in NSAID–antithrombotic users in Belgium per year. Thus, a community pharmacist intervention with the potential of reducing the risk of harm by implementing safer therapeutic options in almost half of cases seems a useful intervention. This supports the broader implementation of such interventions.

Limitations of this study include the high number of patients that refused to provide informed consent. Although the study did not involve active patient participation our local ethical committee required written informed consent from the patient for their anonymized medication data to be analysed in the context of this study. Another limitation is that we do not have full clinical data, for example to objectively assess a patient's bleeding or thromboembolic risk or the indication for low-dose aspirin. This was chosen deliberately, to reflect real-life clinical practice as much as possible. We also do not know whether replacing the NSAID by an alternative showed to be effective in pain relief for the patient, and whether patients were aware of the risks associated with the drug combination.

In conclusion, we have observed a high rate of concurrent NSAID use among patients on antithrombotic agents. Importantly, these NSAID–antithrombotic interactions were mainly present in a population vulnerable to the adverse effects of drug interactions (i.e. older, polymedicated patients). We recommend that health professionals are vigilant for interactions between NSAID and antithrombic agents. Community pharmacists should take a leading role in this; in strong collaborative relationships with physicians they may contribute to reducing avoidable patient harm from drug interactions.

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COMPETING INTERESTS

The authors declare that they have no conflicts of interest.

CONTRIBUTORS

E.M., T.D.B., F.D.K., T.C., I.V.T. and K.B. contributed to the concept and design of the study. E.M. performed the data analysis, interpretation and writing under the supervision of K.B. All authors revised the manuscript critically and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Please contact corresponding author for data requests.

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