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Underutilization of preventive strategies in patients receiving NSAIDs

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Background. **Multiple treatment guidelines for non-steroidal anti-inflammatory drugs (NSAIDs) suggest that patients with one or more risk factors for NSAID-associated upper gastrointestinal (UGI) ulcer complications should be prescribed preventive strategies such as acid-suppressive drugs, misoprostol or cyclooxygenase (COX)-2-specific inhibitors to reduce their risk of serious ulcer complications. The purpose of the present study was to evaluate the extent to which new NSAID users receive recommended preventive strategies and to assess the association between risk factors and a prescription of acid suppressive drugs or misoprostol.**

Method. **A retrospective observational cohort study was conducted using the Integrated Primary Care Information (IPCI) database, a longitudinal database of electronic general practitioner patient records in The Netherlands. The study population comprised all new NSAID users, defined as users of non-specific NSAIDs, COX-2-preferential NSAIDs and COX-2-specific inhibitors, during the period from January 1996 to April 2002. Subjects were excluded if they had an H_2-receptor antagonist (H_2RA), proton pump inhibitor (PPI) or misoprostol prescription in the 3 months prior to the first NSAID prescription. Preventive use of acid-suppressive drugs or misoprostol was identified by the coprescription for these drugs on the same day (± 2 days) as the NSAID prescription. The drug use for each patient was validated as having a preventive indication by reviewing the physician-recorded symptoms and diagnoses. Risk factors for UGI ulcer events were defined as age > 65 yr, UGI history (gastroduodenal ulcer, UGI bleeding, dyspepsia) and concomitant medications (anticoagulants, aspirin, oral corticosteroids). The study population comprised 69 648 new NSAID users.**

Results. **Overall, 7.9% of NSAID users received a preventive strategy (6.6% received a gastroprotective agent and an additional 1.3% received COX-2-specific inhibitors). Patients using preventive drugs had higher odds of having one or more UGI risk factors than patients without preventive drugs [adjusted odds ratio (OR) 1.78, 95% confidence interval 1.66–1.92]. Despite the greater rate of preventive drug prescriptions in patients who may have been at higher risk, 86.6% of patients with one risk factor and 81.2% with two or more risk factors received no preventive strategies. In contrast to non-specific NSAIDs, patients who received a prescription for a COX-2-specific inhibitor had significantly lower adjusted odds (OR = 0.22) of having H_2RA/PPI or misoprostol coprescribed.**

Conclusions. **Although patients who are treated with preventive strategies have higher odds of having gastrointestinal risk factors than those not prescribed preventive therapies, the majority ($> 80\%$) of patients with one or more gastro-**

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intestinal risk factors do not receive the recommended NSAID treatment regimen of a COX-2-specific inhibitor or NSAID + H_2RA/PPI or misoprostol and are therefore undertreated.

KEY WORDS: NSAIDs, Preventive strategies, Drug utilization, Gastrointestinal events, Gastrointestinal risk.

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most widely prescribed classes of medications in the world [1–3]. While the efficacy of these agents is well documented across multiple indications, it is also well recognized that patients who use these agents are at increased risk of upper gastrointestinal (UGI) toxicity. This ranges from the development of dyspepsia and symptoms of drug intolerance to clinically important gastroduodenal ulcer complications, such as bleeding, obstruction and perforations. Individually and together, these drug-associated toxicities have a significant impact on medical outcomes, health-related quality of life and health-care expenditures [4–11]. Moreover, multiple studies have consistently identified important risk factors that, when present, heighten the rate of NSAID-associated UGI toxicity. These risk factors include older age, a history of gastroduodenal ulcers or UGI ulcer complications, dyspepsia, concomitant use of medications such as corticosteroids and anticoagulants, a high dose or the use of multiple NSAIDs, and the presence of other chronic comorbidities [12–14]. On the basis of this heightened risk and associated morbidity and mortality, several strategies and guidelines have been proposed to improve UGI outcomes/reduce the rate of adverse UGI events for patients using non-specific NSAIDs [14–19]. Some of these strategies, such as a reduction in the dose or switching to a less toxic (and sometimes less effective) drug, may be clinically untenable if they result in ineffective pain/anti-inflammatory relief. Alternatively, other clinically relevant options, such as the use of so-called gastroprotective agents (GPAs) or of cyclooxygenase (COX)-2-specific inhibitors, may be more appropriate. In fact, several society and national treatment guidelines specifically endorse these interventions to reduce UGI risk, especially in high-risk populations [15, 17, 20]. For example, the most recent American College of Rheumatology guidelines recommended that patients with at least one gastrointestinal risk factor receive either an NSAID plus a coprescribed protective agent or a COX-2-specific inhibitor [17], as does the National Institute of Clinical Excellence in the UK [21] and the Dutch general practitioner (GP) guidelines [19]. Despite these well-recognized recommendations, few data are available on the actual use of these preventive strategies in day-to-day practice, especially in Europe.

Therefore, the purpose of this study was to determine the prevalence of the use of preventive strategies in high-risk patients and to specifically identify the impact of the number of risk factors on the rate of preventive prescriptions for H_2-receptor antagonists (H_2RAs)/proton pump inhibitors (PPIs) and misoprostol.

Methods

Setting

A retrospective cohort study was conducted that used data from the Integrated Primary Care Information (IPCI) database in The Netherlands. The IPCI database is a longitudinal observational database consisting of data from computer-based patient records of a group of 150 GPs. In the Dutch health-care system the GP plays a pivotal role, acting as a gatekeeper for medical care and information. Details of the database have been described elsewhere [22, 23]. Briefly, the database contains the complete electronic medical record for approximately 500 000 patients. The electronic records contain coded and anonymous data regarding patient demographics, symptoms (in free text), diagnoses using the International Classification for Primary Care [24] and free text, clinical findings, referrals, laboratory findings and hospitalizations. Furthermore, there is a complete record of all drug prescriptions, their physician-linked indications and dosage regimen. To maximize completeness of the data, GPs participating in the IPCI project are not allowed to maintain a system of paper-based records separate from the electronic medical records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmacoepidemiological research [23]. The Scientific and Ethical Advisory Group of the IPCI project approved the study design and use of the data.

Study population

The study population comprised all patients $\geq$18 yr of age with at least 12 months of valid database history prior to the date of study entry, which was the date of the index NSAID prescription during the study period (January 1996 to April 2002). A valid database history was defined as one referring to a patient who had been registered with the GP for a minimum period of 12 months (which is independent of health status) and to which the GP had contributed data for at least 12 months. This 12-month period was required in order to allow assessment of inclusion and exclusion criteria as well as baseline characteristics of all study subjects, including the von Korff chronic disease score [25]. Prevalent (or continuing) NSAID users, defined as patients with any documented use of NSAIDs in the 6 months prior to the index NSAID prescription, were excluded from this analysis.

On the basis of the index anti-inflammatory agent, the study population was divided into four categories: users of COX-2-specific inhibitors (celecoxib and rofecoxib); users of COX-2-preferential agents (nimesulide, nabumetone and meloxicam); users of diclofenac plus misoprostol (Arthrotec®); and users of non-specific NSAIDs. Use of a preventive strategy

was identified as a coprescription of a PPI or H_2RA within 2 days (before or after) of the index NSAID or COX-2-specific inhibitor prescription, or the use of misoprostol (either coprescribed as misoprostol or in the fixed combination with diclofenac, i.e. Arthrotec). To confirm that the PPI or H_2RA prescription indication was truly for prevention of NSAID-associated gastrointestinal toxicity, a manual review of the database was conducted by evaluating the indication, symptoms, complaints and diagnoses of patients with a coprescription of PPI/H_2RA. By definition, the use of Arthrotec was considered preventive. The use of H_2RA or PPI was indicated for NSAID-related prevention if the GP coded the prescription as such, or if there were no other apparent clinical indications for their prescription. Prescriptions of an H_2RA or PPI were considered unrelated to prevention if there was another linked indication, or if the acid-suppressive prescription was linked to existing oesophageal, gastric, duodenal or abdominal complaints/diagnoses. NSAID users who received one or more prescriptions for H_2RAs or PPIs in the 3 months prior to the first NSAID prescription were excluded from the analysis to prevent the inclusion of subjects who were given these agents for reasons other than as a preventive strategy.

Outcomes

Outcomes were (i) prevalence of the use of prophylactic strategies (acid-suppressive agents, misoprostol or COX-2-specific inhibitors) and (ii) the association of gastrointestinal risk factors and other risk factors with the probability of receiving a preventive strategy. As previously established [14], UGI risk factors included increased age (≥65 yr), a history of gastrointestinal events (gastroduodenal ulcer, UGI bleeding), dyspepsia, the use of concomitant medications [anticoagulants, low-dose aspirin (80 mg) and corticosteroids] and the presence of comorbid conditions (cardiovascular or cerebrovascular disease).

Statistics

Standard descriptive statistics were used to describe the study cohort and their utilization of NSAIDs, PPIs and H_2RAs. The χ^2 test was used to compare distributions of categorical variables. Analysis of variance was used to compare the age distributions between preventive H_2RA/PPI or misoprostol users and NSAID users not using these preventive drugs. Software used for analysis was Statistical Product and Service Solutions, version 10 (SPSS, Chicago, IL, USA). Multivariate logistic regression analysis was performed to identify independent predictors of prophylactic H_2RA/PPI or misoprostol use.

Results

The entire IPCI population consisted of 381 996 patients over the age of 18 yr. Of these, 79 617 patients (18.2%) were users of NSAIDs, and 69 648 patients met the eligibility criteria based on the rules for inclusion and exclusion. Non-specific NSAIDs were the most frequently used anti-inflammatory drugs (approximately 20 prescriptions/100 persons per year, $n = 62\,969$ users), while prescription rates of COX-2-specific inhibitors (available from 1999 onwards), COX-2-preferential inhibitors and Arthrotec were much lower, with rates around 1–2/100 persons per year (Fig. 1).

Table 1 shows the baseline characteristics of the study population. Fifteen per cent of subjects were ≥65 yr of age, 56% were female, and the prevalences of individual risk factors were relatively low. In this population, 78% of subjects did not have a risk factor for UGI ulcer complications at the start of their NSAID, approximately 18% had one risk factor, and 4% of subjects had two or more risk factors.

The number of patients coprescribed an H_2RA or PPI concomitant with an NSAID is shown in Table 2, along with the positive predictive value (PPV) of the H_2RA or PPI coprescription based on our chart review. If the criteria for the H_2RA or PPI coprescription were the only measures considered, the overall PPV of approximately 85% indicates that about 15% of patients who were concurrently coprescribed H_2RA or PPIs at the time of NSAID prescription (±2 days) would be misclassified as prophylactic users. Therefore, on the basis of our chart review process we used the validated figures of documented H_2RA or PPI use (column 2, $n = 969$) in all subsequent calculations.

As shown in Table 2, among non-specific NSAID users, 1.2% of patients received preventive H_2RAs or PPIs. Among users of prophylactic H_2RAs, which accounted for 47.7% of the acid-suppression use, 85% of subjects used daily dosages that were below the recommended dose for effective UGI complication

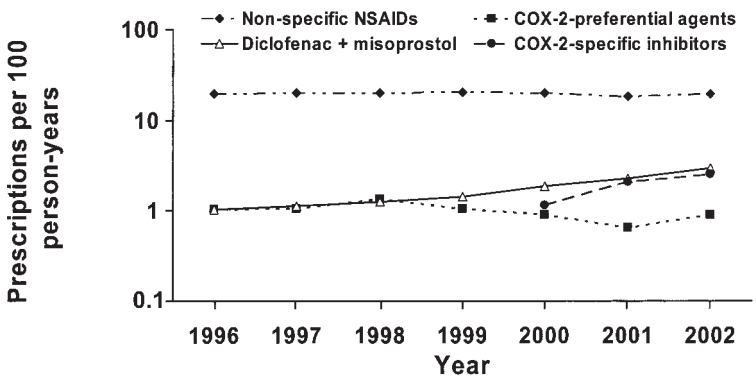

FIG. 1. Use of NSAIDs in the IPCI population during the study period 1996–2002 (logarithmic scale).

prophylaxis. Among PPI users, only 7% had dosages below the recommended daily dose [26]. It should be noted that 2.0% of patients who received diclofenac plus misoprostol as a fixed combination also received a PPI or H_2RA. H_2RAs and PPIs were also prescribed to 4.4% of COX-2-preferential NSAID users and 2.5% of COX-2-specific inhibitor users. The prevalence of prophylactic use was 6.6% in the entire cohort when prescriptions of H_2RAs, PPIs and misoprostol (alone or in combination) were considered. If the use of COX-2-specific inhibitors was also included as a preventive strategy, the overall prevalence of the use of protective strategies increased to 7.9% (Table 2). The overall prevalence of the use of protective strategies changed during the study period, increasing from 5.1% in 1996 to 15.9% in 2002.

Table 1. Characteristics of the study population

Characteristics	Stratum total (*n*)	% of total (*n* = 69 648)
Demographic		
Age > 65 yr	10 548	15.1
Females	39 138	56.2
Private insurance	21 518	30.9
Concurrent drug use		
Corticosteroids	4567	6.6
Anticoagulants/antiplatelets	1881	2.7
Acetylsalicylic acid	1434	2.1
Prior GPA use[a]	1336	1.9
Comorbidity		
Osteoarthritis	5982	8.6
Rheumatoid arthritis	1629	2.3
Ulcer history	603	0.9
GI bleeding history	195	0.3
Dyspepsia	2746	3.9
Cardiocerebrovascular disease	9316	13.4
GI risk factors		
0	54 344	78.0
1	12 493	17.9
2+	2 811	4.0
Chronic disease score[b]		
0	47 185	67.7
1–3	14 554	20.9
4+	7 909	11.4

[a]Use of GPA during the 3- to 12-month period prior to start of NSAID.
[b]Von Korff chronic disease score [25].

Table 3 presents the risk factor-specific prevalence of the use of prophylactic therapies and the association between the individual risk factors and the probability of receiving such a therapy. It is worth noting that the prevalence of preventive strategy use is well below what is recommended across all risk factors evaluated. For example, of the patients > 65 yr of age, only 11.8% received any protective strategy.

The adjusted odds ratios (ORs) presented in Table 3 show that the strongest independent risk factors for prophylactic GPA use were a history of ulcers [OR 1.91, 95% confidence interval (CI) 1.55–2.37], a history of UGI bleeding (OR 1.79, 95% CI 1.22–2.61) and an H_2RA or PPI prescription in the 3- to 12-month period prior to the start of the new NSAID (OR 3.60, 95% CI 3.23–4.02). Moreover, it is clinically important to recognize that patients with one risk factor had 1.73-fold higher odds of receiving a concomitant PPI or H_2RA (OR 1.73, 95% CI 1.61–1.87), and patients with two or more UGI risk factors had more than 2-fold higher odds of being prescribed a PPI or H_2RA (OR 2.15, 95% CI 1.88–2.45).

As shown in Table 3 and Figs 2 and 3, among patients with at least one risk factor only 10.9% received an H_2RA, misoprostol or a PPI at the time of the index NSAID prescription, and among persons with two or more risk factors only 14.8% received such therapies. When the use of COX-2-specific inhibitors is considered as a protective strategy, 86.6% of patients with one risk factor did not receive protection, and 81.2% of patients with two or more risk factors did not receive appropriate protection. However, the rate of underutilization of gastroprotective strategies improved considerably over the study period. Among patients with one risk factor, 92.5% received no protective strategy in 1996, but in 2002 this proportion was reduced to 72.1%. Similarly, among patients with two or more risk factors, 91.6% did not receive any gastroprotective strategy in 1996, whereas in 2002 this percentage had diminished to 63.9%.

Table 3 also demonstrates that the initial prescription of a COX-2-specific inhibitor was associated with significantly reduced odds of being prescribed an H_2RA, misoprostol or PPI for prophylaxis (OR 0.22, 95% CI 0.14–0.33) compared with non-specific NSAIDs. Since the use of these agents was almost exclusively driven by the use of the fixed combination of misoprostol

Table 2. Positive predictive value (PPV) and prevalence of coprescriptions for preventive strategies by the type of index NSAID

	Calculation of PPV				Prevalence of use of preventive strategies		
	H_2RA/PPI coprescription (*n*)	H_2RA/PPI for prophylactic use (*n*)	PPV (%)	Use of NSAIDs (*n*)	H_2RA/PPI (%)	GPAs H_2RA/PPI/ misoprostol (%)	H_2RA/PPI/ misoprostol/COX-2 (%)
COX-2-specific inhibitors	25	23	92.0	936	2.5	2.5	100
COX-2-preferential NSAIDs	99	91	91.9	2084	4.4	4.4	4.4
Diclofenac + misoprostol (Arthrotec)	88	71	80.7	3659	2.0	100	100
Non-specific NSAIDs	930	784	84.3	62 969	1.2	1.2	1.2
Total	1142	969	84.9	69 648	1.4	6.6	7.9

TABLE 3. Prevalence of prophylactic H_2RA/PPI or misoprostol use by risk factor, and the association between use of these drugs and risk factors

	Prophylactic use of misoprostol/ H_2RA/PPI (*n*)	Prevalence of prophylactic use within stratum (%)	No gastroprotection[a] (*n*)	Odds ratio	Adjusted odds ratio[b]	95% CI
Demographics						
Age >65 yr	1241	11.8	9307	2.24	1.74	1.60, 1.89
Females	2554	6.5	36 584	0.99	0.94	0.88, 0.99
Private insurance	1460	6.8	20 058	1.01	1.07	1.00, 1.15
Concurrent drug use						
Corticosteroids	134	2.9	4433	1.88	1.41	1.16, 1.71
Anticoagulants/antiplatelets	219	11.6	1662	1.92	1.08	0.92, 1.27
Acetylsalicylic acid	151	10.5	1283	1.70	1.08	0.90, 1.39
Prior GPA use[c]	375	28.1	961	4.91	3.60	3.23, 4.02
Comorbidity						
Osteoarthritis	653	10.9	5329	1.87	1.34	1.22, 1.47
Rheumatoid arthritis	179	11.0	1450	1.79	1.43	1.21, 1.68
Ulcer history	133	22.1	470	4.12	1.91	1.55, 2.37
GI bleeding history	40	20.5	155	3.70	1.79	1.22, 2.61
Dyspepsia	379	13.8	2367	2.40	1.43	1.27, 1.63
Cardiocerebrovascular disease	979	10.5	8337	1.86	1.24	1.13, 1.36
GI risk factors						
0	2789	5.1	51 555	Referent	Referent	
1	1361	10.9	11 132	2.26	1.73	1.61, 1.87
2+	417	14.8	2394	3.22	2.15	1.88, 2.45
Chronic disease score[d]						
0	2,390	5.1	44 795	Referent	Referent	
1–3	1,290	8.9	13 264	1.82	1.15	1.06, 1.25
4+	887	11.2	7022	2.37	1.19	1.06, 1.33
Type of NSAID						
Non-specific NSAID	4,452	6.7	62 176	Referent	Referent	
COX-2-specific inhibitor	23	2.5	913	0.35	0.22	0.14, 0.33
COX-2-preferential	92	4.4	1992	0.65	0.41	0.33, 0.51
Total	4567	6.6	65 081			

[a]Gastroprotection includes concurrent use of an H_2RA, PPI or misoprostol, but does not include prescription of COX-2-specific inhibitor.
[b]Odds ratios adjusted for all factors that were demonstrated by univariate analysis to be associated with H_2RA/PPI/misoprostol use (all except insurance). For estimation of the number of risk factors the individual risk factors were not included in the model, and vice versa.
[c]Use of H_2RA/PPI/misoprostol during the 3- to 12-month period prior to start of NSAID.
[d]Von Korff chronic disease score [25].
GI, gastrointestinal.

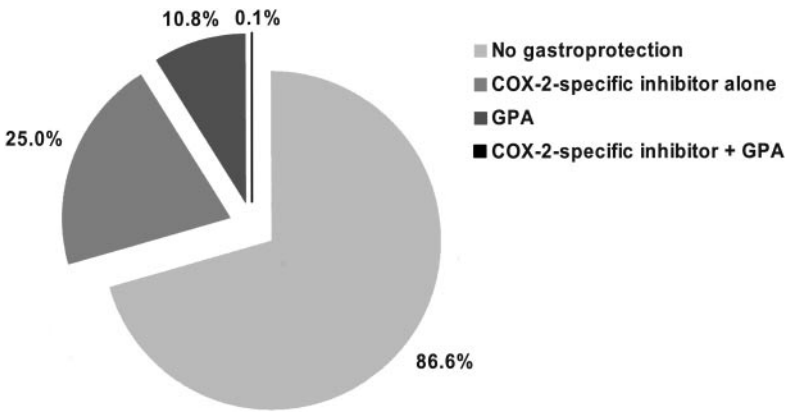

FIG. 2. Utilization of preventive strategies in patients with one risk factor for UGI ulcer complications. Percentages total more than 100% because of rounding.

with diclofenac (and therefore not a likely combination with COX-2-specific inhibitors), we also compared the use of acid-suppressive drugs in combination with non-specific NSAIDs, COX-2-specific inhibitors and COX-2-preferential agents. COX-2-specific inhibitor users appeared to have almost 2-fold higher odds of receiving a prophylactic H_2RA/PPI (unadjusted OR 1.93, 95% CI 1.27–2.94) when compared with non-specific NSAID users. However, this apparent increase in odds disappeared completely after adjustment

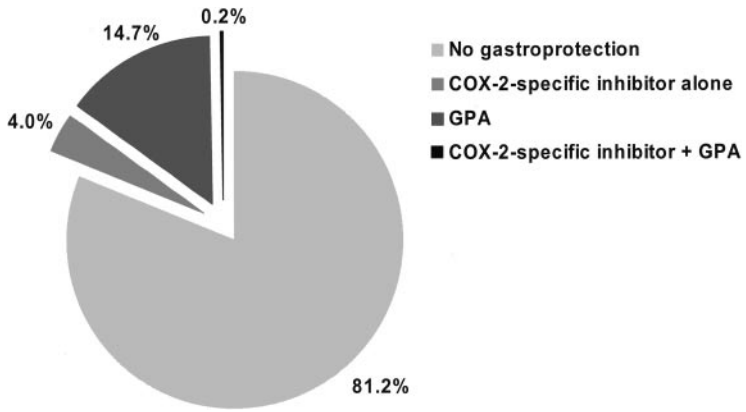

FIG. 3. Utilization of preventive strategies in patients with two or more risk factors for UGI ulcer complications. Percentages total more than 100% because of rounding.

for demographic characteristics, history of drug use, calendar year and gastrointestinal risk factors (adjusted OR 0.98, 95% CI 0.62–1.54).

Discussion

So-called GPAs (misoprostol, PPIs and H_2RAs) or COX-2-specific inhibitors are recommended to circumvent the well recognized UGI symptoms and ulcer complications associated with non-specific NSAIDs, especially in high-risk patients. Despite these recommendations, this study clearly demonstrates that very few new NSAID users receive these drugs as protective strategies. Although our results demonstrate that the rate of prescriptions for protective strategies is higher in patients who have risk factors for UGI ulcer complications and has been improving in recent years, it remains a serious concern that, as we have shown, protective strategies are still greatly underprescribed. This undertreatment occurs even in patients at highest risk of NSAID-related ulcers and ulcer complications (i.e. those with two or more UGI risk factors).

In fact, our findings demonstrate that, on average, approximately 80% of high-risk patients using non-specific NSAIDs receive no protective therapy. These results are consistent with another Dutch study that reported that only 14% of elderly patients taking NSAIDs were prophylactically prescribed an H_2RA, PPI or misoprostol [27]. Taken together, these results indicate that the majority of Dutch patients who would benefit from receiving protective therapies are not being appropriately treated.

This problem of underutilization, especially among patients at risk, is not unique to The Netherlands. The proportion of non-specific NSAID users using GPAs has been reported to be consistently low in several other countries; most studies report the use of GPAs in the general range of approximately 20–50% for countries where data are available (UK, USA, Canada, Israel and France) [28–36].

While these well-conducted studies reinforce our findings, they also have limitations in their design that lead to both under- and overestimation of the problem. For example, while two studies have evaluated the prevalence of protective strategies on the basis of the number of risk factors (one factor and two or more factors), with results that are relatively consistent with our current study [26, 37], other studies reported an overall prevalence of the use of protective strategies without stratification for risk. Consequently, these latter studies possibly underestimate the prevalence of the use of protective strategies in the targeted high-risk patients.

Additionally, prior studies were likely to classify subjects as prophylactically treated if they were given acid suppression that was not specifically prescribed for prevention of NSAID-associated ulcer complications. Consequently, these studies overestimate the use of preventive strategies, since they erroneously attribute the use of an acid-suppressive agent to ulcer prevention. To avoid this limitation, we specifically used chart review to avoid misclassification of prophylactic use. Lastly, older estimates have usually provided prevalence rates in a mixed group of NSAID users (chronic and new), whereas the estimate in this study is based on incident preventive strategy use in new NSAID users. On the basis of our more stringent inclusion/exclusion criteria as well as our risk stratification analysis, our study extends the findings of others, and we believe that our results more directly and accurately address and quantify the problem.

One limitation in the present study is that we assumed that all coprescriptions of protective agents and COX-2-specific inhibitors were equally efficacious across all ranges of risk. This is probably not the case, since we included all prophylactic H_2RA users and equated these patients with those receiving PPIs or misoprostol plus a non-specific NSAID. Several studies have clearly demonstrated that so-called low-dose H_2RAs are ineffective in NSAID prophylaxis and that only 'high-dose' H_2RAs reduce endoscopic ulcer rates associated with NSAID use [38]. However, we included these

patients in our study because our chart review documented that the ordering physician specifically prescribed the H_2RA as a protective agent. Consequently, our results may have overestimated the use of truly effective protective strategies, since approximately 85% of the prescriptions for H_2RAs were below the double dose/high dose. These results are not dissimilar from those of Smalley *et al*. [26], in which 40% of patients received so-called low-dose H_2RAs. If we consider that 85% of H_2RA users in this study were not protected on the basis of 'underdosing', the overall prevalence of preventive strategy use (GPA + COX-2-specific inhibitors) would actually be 7.4%.

There are three additional important considerations regarding the present study. The first is that our analysis was based on prescription records, which may not be a reliable indicator of actual drug utilization. While this is an important consideration, it should be noted that the purpose of this study was to describe prescription patterns of physicians. If patient compliance with gastroprotective drugs is less than 100%, effective so-called gastroprotection in day-to-day use will be even lower than our study suggests.

The second consideration concerns the definition of 'new NSAID user' that we used in this study. While we excluded patients who had an NSAID prescription within the previous 6 months, many of the patients might have used these drugs in the past. Consequently, a proportion of these patients may have already been aware of their own individual need for protective strategies. Although it is difficult to quantify this problem, one could argue that, if this was the case, the results reported here are likely to overestimate the actual prevalence of prophylactic prescriptions for protection.

The third consideration is our inability to evaluate the reason(s) that protective strategies may not have been prescribed despite their apparent clinical indication(s). As a consequence, our results may potentially overestimate the extent of underutilization; there may be medically sound reasons why cotherapies were not prescribed. It is recognized that, among the patients at risk who seemingly had an indication for a protective strategy, the use of different approaches, including the COX-2-specific inhibitors, may differentially affect outcomes such as patient quality of life as well as clinical and economic outcomes [39–41].

While the data in Figs 2 and 3 would suggest inadequate protection rates of 86.6 and 81.2% in patients with one risk factor and two or more risk factors respectively, the last interesting observation in the present study is the reported lower odds of prophylactic prescriptions in patients who start the use of COX-2-specific inhibitors. Although this is not a uniform finding in all studies, there are data from both retrospective and prospective studies that show a reduction in coprescriptions of acid-suppressive agents at the time of initial COX-2-specific inhibitor prescription as well as during subsequent use of COX-2-specific inhibitors [42–45]. In the largest of these studies, involving more than 70 000 patients taking COX-2-specific inhibitors, NSAIDs or paracetamol (acetaminophen), the adjusted OR (0.53, 95% CI 0.48–0.58) showed that the use of COX-2-specific inhibitors was associated with a decrease in coprescription of GPAs [45].

Conclusions

This study demonstrates that, while patients at higher risk of NSAID-associated ulcer complications have higher odds of receiving preventive strategies, the absolute rate of utilization of these therapies in high-risk populations is unacceptably low, even in recent years. Consequently, this study demonstrates that practice patterns are inconsistent with suggested nationally and globally recognized standards of care. Since prescribed medications in The Netherlands are covered by the national health plan, the low rate of utilization is unlikely to be driven by a patient's economic concerns. Instead, it suggests that there is an opportunity to better educate physicians and patients about the risks associated with the use of non-specific NSAIDs and develop better educational programmes to disseminate the appropriate guidelines toward the goal of reducing unnecessary NSAID-associated ulcer complications.

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