

# Application of bleeding prophylactic criteria (NICE) in patients with acute gastrointestinal bleeding

## A Swiss prospective study

Martin Geyer<sup>a</sup>, Shajan Peter<sup>b</sup>, Hugo Bühler<sup>a</sup>, Philipp Bertschinger<sup>c</sup>

<sup>a</sup> Department of Internal Medicine, City Hospital Waid, Zürich, Switzerland

<sup>b</sup> Department of Gastroenterology, University Hospital of Basel, Switzerland

<sup>c</sup> Gastrozentrum Hirslanden, Zürich, Switzerland

## Summary

Multiple treatment guidelines for non-steroidal anti-inflammatory drugs (NSAIDs) suggest that patients with one or more risk factors for NSAID-related ulcer complications should be prescribed preventive strategies such as acid-suppressive drugs, misoprostol or COX-2-specific inhibitors to reduce their risk of serious ulcer complications. However data are lacking as to how many patients have been on preventive measures in accordance to the National Institute for Clinical Excellence (NICE) criteria in our population. We therefore evaluated the extent to which pa-

tients with acute gastrointestinal bleeding have been under ulcer-preventive strategies at the time of hospital entry. In a one-year-bleeding-study at the Waid city hospital, Zürich, ulcer preventive treatment was practiced in only 25% of 214 patients with acute gastrointestinal bleeding. We conclude that ulcer prevention in everyday medical practice is still being seldom applied.

*Key words: gastrointestinal bleeding; NICE criteria; ulcer prevention*

## Background

Non-steroidal anti-inflammatory drugs (NSAIDs) are currently among the most prescribed pharmaceuticals in general medical practice. Approximately 1–3% of older patients taking traditional NSAIDs regularly for 1 year develop serious gastrointestinal complications such as bleeding [1]. More than 70,000 hospitalisations and 10,000–20,000 deaths per year have been attributed to NSAIDs in the USA [2]. Multiple studies have consistently identified important risk factors that increase the rate of NSAIDs toxicity. These risk factors include older age, a history of peptic ulcer, gastrointestinal bleeding, concomitant use of anticoagulants or corticosteroids, higher doses of NSAIDs and chronic comorbidities [3–7]. Age over 65 years has been associated with an Odds-Ratio (OR) of 4.7; high dose of NSAIDs with an OR of 8, and corticosteroids in combination with NSAIDs an OR of 4.4. The OR for the combination of anticoagulation and NSAIDs was 12.7 [8].

In recent years, several strategies for the prevention of NSAID-associated complications have

been developed to reduce the toxicity associated with the use of NSAIDs. Apart from discontinuing all NSAIDs, these include alternatively giving Coxib or prescribing traditional NSAIDs along with gastroprotective agents such as E1 prostaglandin analogues, proton pump inhibitors (PPIs) and high-dose histamine-2 receptor antagonists (H2RAs). Misoprostol, an E1 Prostaglandin analogue leads to a 50% reduction in serious upper gastrointestinal complications associated with NSAIDs making it a potent drug in prevention of gastric and duodenal ulcers [3]. In large clinical trials, Rofecoxib and Celecoxib caused fewer gastrointestinal complications than traditional NSAIDs [4]. PPIs are effective in prevention of gastric and duodenal ulcers and this effect is more pronounced than the effect of misoprostol in duodenal ulcer prevention [9–11]. H2RAs are only useful in prevention of duodenal ulcers rather than gastric ulcers [12, 13].

Several guidelines have been proposed for the use of gastroprotective measures in patients at high-risk for haemorrhage or perforation from

NSAIDs or aspirin [8]. From the recent guidelines of the American College of Rheumatology, patients with at least one gastrointestinal risk factor were recommended to receive either an NSAID along with a co-prescribed protective agent or COX-2-specific inhibitor [14]. These recommendations are similar to those of the National Institute of Clinical Excellence in the UK [15] and the Dutch general practitioner guidelines [16]. However, the extent to which these guidelines have been implemented in clinical practice is not clearly known. One of the first population-based assessment of guidelines adherence showed that only 16% of NSAID users received gastroprotective therapy (10% NSAIDs along with antiulcer drugs, 6% coxibs). Among patients with more than 2 risk factors for ulcer complications (age over 75 years, peptic ulcer, bleeding in the past year, and concurrent use of oral anticoagulants or corticosteroids) 30% received such protective therapy [17]. In

another study, 86.6% of the patients with one risk factor (defined as age over 65 years, history of upper gastrointestinal bleeding, concomitant medications such as anticoagulants, aspirin, and oral steroids) and 81.2% of patients with two or more risk factors received no prevention [18]. These data show that usage of recommended strategies to decrease ulcer complications in vulnerable populations is relatively uncommon.

The aims of this study were 1) to assess the frequency of ulcer prophylaxis in patients on NSAIDs who were hospitalised for acute gastrointestinal bleeding, 2) to apply the NICE criteria on this group of patients with respect to bleeding prophylaxis, and 3) to thereby give a perspective into the current knowledge and practices on this subject. This would then form the basis of a benchmark analysis into the development of further guidelines relevant to the concerned population. This is the first such study in a Swiss based population.

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## Methods

The study population was drawn from another prospective observational study conducted on gastrointestinal bleeding performed between 1.1.2003 and 31.12.2003 to assess the spectrum and outcome of acute symptomatic gastrointestinal bleeding at one of Zürich's large city hospitals (with 300 beds involving medical, surgical and geriatric departments) covering an area of 160,000 inhabitants. Inclusion criteria included all patients who presented with acute gastrointestinal bleed as evidenced by haemetemeis, melena or haematochezia. As part of quality control measures, we aimed to find out the frequency of established bleeding prevention strategies according to NICE-criteria [16] in patients on NSAIDs at hospital entry. NSAID consumption was verified by history and charts.

Outcomes noted were 1) prevalence of the use of prophylactic strategies (acid-suppressive agents (PPI or

H2RA, misoprostol or COX-2 inhibitors) by history in patients presenting with acute gastrointestinal bleeding who were on NSAIDs and 2) number of risk factors and associated frequency of the preventive strategy. The risk factors for upper gastrointestinal bleeding (UGIB) were defined according to NICE recommendations as age over 65 years, ulcer and UGIB history, concomitant medications of anticoagulants, aspirin, oral corticosteroids and comorbid conditions (cardiovascular, hypertension, diabetes, liver, kidney disease and diabetes) [16]. Additionally ASA (American Society of Anesthesiologists) classification was assessed. Diagnosis and location of gastrointestinal bleeding were done according to common standard protocols.

Statistics were done with SPSS Version 11.0. This being a descriptive study, descriptive analysis was used for variables.

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## Results

Between 1.1.03 and 31.12.03, out of 7,406 in-patients admitted in the hospital, 214 patients (224 treatments) who presented with acute gastrointestinal bleeding were included into the study. The mean age of this group was 72 (16) years. 80% of the patients with gastrointestinal bleeding were older than 65 years of age. 53 % were females and 47% males. The females were older than the males (77 (14) *vs* 66 (18) years). 65% of the 214 patients had relevant comorbidities of which cardiac and renal were most common (table 1). Only 20% were ASA-class II, while 73% were class III or more. Of the total number of patients who presented with gastrointestinal bleeding, 45% were diagnosed to have acute upper gastrointestinal bleeding, 34% had acute lower gastrointestinal bleeding, 1.4% had bleeding from both areas and in 20% of pa-

tients, the source was either unknown or was not fully investigated. 103 (48%) of all patients were under NSAIDs inclusive of aspirin (table 1). In the group of patients presenting with only upper gastrointestinal bleedings 49% were under NSAIDs and the numbers were not significantly different in comparison to 55% of the patients with lower gastrointestinal bleeding under NSAIDs treatment.

Of the 103 patients on NSAID therapy, 97 (95%) fulfilled the criteria for being on prophylaxis according to NICE criteria (table 2). 66% of these patients were found to have more than one risk factor at entry (figure 1).

Subanalysis of risk factors in those patients presenting with only upper gastrointestinal bleeding on NSAIDs (n = 46) revealed that 26% were found to have one, 54% two and 11% three risk

**Table 1**  
Baseline characteristics (n = 214).

Comorbidities	
Comorbidities over all	139 (65%)
Cardiac	74 (35%)
Renal	56 (26%)
Vascular (e.g. Hypertension)	24 (11%)
Diabetes	24 (11%)
Liver cirrhosis	19 (9%)
Previous history of GI bleeding	12 (10%)
Disease Severity	
ASA class	
I	15 (7%)
II	43 (20%)
≥III	156 (73%)
Demographics	
Males	101 (47%)
Females	113 (53%)
Mean age (SD)	72 (16)
Mean age females	77 (14)
Mean age males	66 (18)
Alcohol >20 g/d	35 (16%)
Cigarette use	49 (23%)
Medication	
Medication influencing bleed	127 (59%)
NSAIDs including ASS	103 (48%)
only ASS	27 (13%)
only NSAIDs	27 (13%)
Steroids	16 (8%)
Cumarines	21 (10%)
Heparin	6 (3%)
SSRI	7 (3%)
Site of bleeding	
Upper GI	96 (45%)
Upper GI with ulcers	49 (23%)
Lower GI	73 (34%)
Both upper & lower GI	3 (1.4%)
Unknown	43 (20%)

American Society of Anaesthesiologists (ASA): physical status classification  
 ASS: Acetylsalicylic Acid  
 GI: Gastrointestinal tract  
 NSAIDs: Non Steroidal Anti-Inflammatory Drugs  
 SD: Standard deviation  
 SSRIs: Selective serotonin reuptake inhibitors

factors while only 24% had a bleeding prophylactic medication. This did not differ from the 25% (26/103) of all NSAID users in which PPI therapy

**Table 2**  
Prophylaxis criteria\* [16].

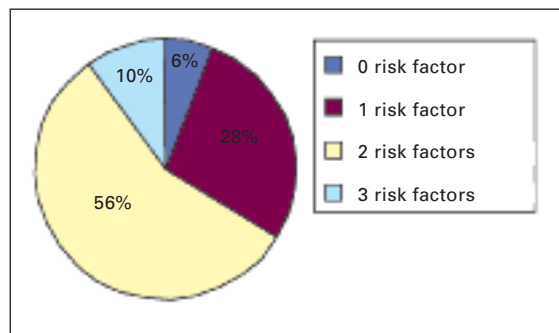
Age over 65 years
History of ulcer or gastrointestinal bleeding
Concomitant steroid therapy
Anticoagulation
Severe comorbidity (cardiovascular, kidney, liver disease, diabetes)

\* one or more of the following

**Table 3**  
PPI prophylaxis frequency and risk factors (n = 214).

1 Risk factor	18/77 (23%)
2 Risk factors	22/94 (23%)
3 Risk factors	12/96 (46%)

**Figure 1**  
Percentage of risk factors in NSAID users (n = 103).



had been established at admission and therefore indication for therapy were presumed to be noted as prophylactic agents. The use of either H2RAs or misoprostol was uncommon and there was no patient with NSAID therapy on either of these co-medications. COX-2-specific inhibitors were prescribed in 21 (10%), but 13 (62%) of them were additionally taking NSAIDs or ASS. From this descriptive analysis, it showed that the more risk factors were present, the more common was the PPI prophylaxis (table 3). Moreover one risk factor was enough to cause bleeding.

49 patients presented with upper gastrointestinal tract ulcer bleedings and 67% of them took either ASS or other NSAIDs. The use of NSAID or ASS was more prevalent in this group as compared to the overall study patients (42%). In contrast only 14% of them were on gastroprotective measures thereby receiving bleeding prophylaxis.

Overall mortality observed in the study was 3%.

## Discussion

Endoscopically noted ulcers secondary to NSAIDs are seen in up to 40% of patients who have been on long term exposure, however only 15% of these ulcers are symptomatic, with an annual incidence of 1.5% having serious complica-

tions [3]. Reports from the USA suggest that 5 to 10% of the population and at least 15% of older people take NSAIDs on a regular basis. Furthermore, one quarter of the upper gastrointestinal bleeds can be attributed to NSAIDs [1]. In our

study, a significantly high number of the patients (49%) with upper gastrointestinal bleeding were taking NSAIDs. As NSAIDs are so commonly consumed and frequently associated with complications, prophylaxis is an important issue. Gastro-protective agents (PPI, H2RA, and misoprostol) or COX-2-specific inhibitors are recommended to circumvent the well recognised ulcer complications associated with non-specific NSAIDs, especially in high-risk patients. In this patients requiring long-term NSAIDs, clinicians have the options to additionally prescribe ulcer prophylaxis such as misoprostol or a potent antisecretory agent, or to switch to a COX-2-specific inhibitor.

Recent studies have raised the concern of the prothrombotic effect of coxibs, thereby questioning the use of COX-2 specific inhibitors as a first line strategy in ulcer prevention [19]. In our experience, like in other European studies, coxibs are still not frequently prescribed due to their high cost. Only 10% of our patients were on medication with a COX-2-specific inhibitor. Surprisingly, 62% of these patients were prescribed the same inhibitor, in addition to ASS or NSAID. The beneficial gastroprotective effect of coxibs is lost when given along with ASS or other NSAIDs as shown in the CLASS and TARGET studies [4, 20]. Therefore the high percentage of patients on this combination in our study reflects poor medical practice.

As with antisecretory drugs, there are two options of prophylaxis – normal dosage or double dosage. At normal dosage, H2RAs are protective against duodenal ulcers. However, they are not useful for prevention of gastric ulcers. At double dosage H2RA are effective in reducing both gastric and duodenal ulcers similar to PPIs [21]. However, these strategies have not been compared with each other. With regard to prostaglandin analogues, misoprostol is reported to have a 40% risk reduction for ulcer complications [3].

As mentioned previously, there are several cited guidelines for use of gastro-protection in patients at risk for haemorrhage or perforation from NSAIDs or aspirin [8]. The most recent American College of Rheumatology guidelines recommend that patients with at least one gastrointestinal risk factor should receive either an NSAID plus a co-prescribed protective agent, or a COX-2-specific inhibitor with the above mentioned restriction [14]. In our study we could clearly show that the presence of one or more risk factors according to the NICE criteria was enough to cause bleeding and therefore required bleeding prophylaxis. Despite these recommendations, our study demonstrated that very few of the patients presenting with gastrointestinal bleeding have received these drugs.

There have been a few limitations in our study. First, this study has been conducted primarily as a local epidemiological and outcome study of gastrointestinal bleeding. Therefore the data can only reflect a collective of bleeding patients coming to

our hospital, rather than the entire general population at risk. Nevertheless, it reflects the prophylaxis frequency in this group of patients. Second, we cannot discriminate between the true prophylactic and other indications of these medications. Thereby in 25% of NSAIDs consumers with gastroprotective measures, we may have overestimated the true prevalence of use of ulcer prophylaxis. Third, as the number of events was low for the number of predictors, a subgroup analysis using multiple logistic regressions could not be performed which would have given us a more appropriate correlation between individual risk factors. Nevertheless the descriptive analysis showed a trend. This we used to tentatively draw conclusions regarding individual subgroups.

It should be outlined that according to other data, the low incidence of gastroprotective therapy in our study sample likely reflects low prescription frequency in general, and can be extrapolated to the population without bleeding events. It should alert us that 75% of very high-risk patients did not receive any protective measure, despite of the fact that 66% of them had more than one risk factor. Sturkenboom et al. found that approximately 80% of high-risk patients using non-specific NSAIDs did not receive protective therapy [18]. This was even higher in a Dutch study, where 86% of elderly patients taking NSAIDs were not prescribed prophylactically H2RA, PPI or misoprostol [22]. For countries such as the UK, USA, Canada, Israel and France, where data are available, the general range of gastro-protection in NSAIDs users ranged from 20–50% [22–31]. The problem of non-utilisation of prophylaxis seems not to be unique. Protective strategies are still greatly under-prescribed and NSAID users in general seldom receive protective drugs. This under-treatment occurs even in patients at highest risk of NSAID-related ulcers and ulcer complications, as shown in our data. It could be argued, that the patients of our study simply reflect the ones that have not been treated according to prevention guidelines and therefore developed bleeding complications. The above cited data from other countries speak against that theory. Hence, the low rates of protection measures in gastrointestinal bleeding patients in our population should alarm us considering the fact that gastrointestinal bleeding has a significant relevant mortality and morbidity.

Gastro-protection would be cost-effective in high-risk patients. In patients with just a bleeding ulcer history, it has been shown that all protective strategies (PPI and COX 2-inhibitors) were cost-effective. With the other risk factors, all strategies are cost-effective too, but prevention of events is twice as expensive in patients below 75 years of age. Neither of the strategies shows superiority over the other, unless the cheapest generics are prescribed for PPIs [32]. Generally, it can be said, that PPIs are much more tolerated. There is some evidence that prescription practices have been improving in recent years [18]. From our results

and the review of the literature to date, we would like to raise attention to the problem of ulcer prophylaxis in risk patients as a whole.

### Conclusions

Considering the frequent use of NSAIDs in older patients, special attention should be paid to bleeding prevention in these patients. Therefore patients over 65 years of age, who take NSAIDs along with concomitant anticoagulation, steroid therapy, history of ulcer bleeding or severe comorbidities would benefit from receiving a gastroprotective agent. Further larger prospective studies

should focus on the development of gastroprotective measures, predicting risk factors necessitating prophylaxis and also taking into account the existing physician's knowledge of prevention strategies including patient compliance.

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#### Correspondence:

Dr. Martin Geyer

Gastroenterologie-Wettingen

Rosengartenstrasse 2

CH-5430 Wettingen

E-Mail: [geyer@gastroenterologie-wettingen.ch](mailto:geyer@gastroenterologie-wettingen.ch)

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