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**Time-trends in gastroprotection with NSAIDs**

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# 1 **Time-trends in gastroprotection with NSAIDs**

2

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5

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13

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3 **1 Abstract**  
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5 *2 Background:* Preventive strategies are advocated in patients at risk of upper gastrointestinal  
6 (UGI) complications associated with non-steroidal anti-inflammatory drugs (NSAIDs).  
7

8 *3 Aim:* We examined time trends in preventive strategies.  
9

10 *4 Methods:* In a study population comprising of 50,126 NSAID users  $\geq 50$  yrs from the  
11 Integrated Primary Care Information database, we considered two preventive strategies: co-  
12 prescription of gastroprotective agents and prescription of a cyclooxygenase-2-selective  
13 inhibitor. In patients with  $\geq 1$  risk factor (history of UGI bleeding/ulceration, age $>65$  yrs, use of  
14 anticoagulants, aspirin, or corticosteroids), *correct prescription* was defined as the presence of a  
15 preventive strategy, and *under-prescription* as the absence of one. In patients with no risk  
16 factors, *correct prescription* was defined as the lack of a preventive strategy, and *over-*  
17 *prescription* as the presence of one.  
18

19 *20 Results:* Correct prescription rose from 6.9% in 1996 to 39.4% in 2006 ( $p<0.01$ ) in high risk  
21 NSAID users. Under-prescription fell from 93.1% to 59.9% ( $p<0.01$ ). In the complete cohort,  
22 over-prescription rose from 2.9% to 12.3% ( $p<0.01$ ).  
23

24 *25 Conclusions:* Under-prescription of preventive strategies has steadily decreased between 1996  
26 and 2006, however 60% of NSAID users at increased risk of NSAID complication still does  
27 not receive adequate protection.  
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## 1 Introduction

2 Non-steroidal anti-inflammatory drugs (NSAIDs) are among the world's most  
3 frequently prescribed medications for arthritic and inflammatory conditions, but their use  
4 increases the risk of upper-gastrointestinal (UGI) toxicity. The effects range from mild UGI  
5 symptoms (e.g. dyspepsia) to severe complications, such as peptic ulcers and UGI  
6 haemorrhage, perforation or pyloric obstruction, which sometimes result in hospital admission  
7 and death. The incidence of these serious UGI adverse events is approximately 1.5% - 2.0%  
8 per year of therapy<sup>1-3</sup>, four times higher than in nonusers<sup>4,5</sup>.

9 Several evidenced-based guidelines have been proposed to reduce the burden of UGI  
10 events attributable to NSAID use<sup>6-10</sup>. Preventive strategies in particular include: 1)  
11 substituting COX (cyclooxygenase)-2-selective inhibitors (coxibs) for a non-selective  
12 (ns)NSAID; and 2) combining an NSAID with so-called gastroprotective agents (GPAs),  
13 including proton-pump inhibitors (PPIs), histamine-2 receptor antagonists (H<sub>2</sub>RAs), and  
14 misoprostol, a synthetic E1 prostaglandin analog<sup>6-13</sup>.

15 The first method involves prescribing a coxib instead of an nsNSAID. The  
16 gastrointestinal toxicity caused by nsNSAIDs is mainly due to inhibition of COX-1 isoform  
17<sup>14</sup>. Coxibs were developed to improve the UGI safety profile by preferentially inhibiting the  
18 inducible COX-2 isoform of the COX enzyme, which is involved in the desired anti-  
19 inflammatory effect. Although coxibs have been shown to be as effective as nsNSAIDs for  
20 relieving pain and do reduce the risk of UGI complications<sup>15-18</sup>, cardiovascular toxicity  
21 emerged unexpectedly during their post-marketing studies<sup>17, 19-21</sup>. This led to the voluntary  
22 withdrawal of two coxibs: rofecoxib in September 2004 and valdecoxib in April 2005<sup>22</sup>.

23 The second preventive method advocated in NSAID users is co-prescription of GPAs  
24 as they have been proven to reduce the incidence of NSAID-induced ulcer complications<sup>3, 12,</sup>  
25<sup>23</sup>.

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3 1 Only patients with high risk of NSAIDs-related UGI complications require  
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5 2 gastroprotective measures as a prophylactic intervention. Although different evidenced-based  
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7 3 guidelines provide slightly different definitions of such high-risk patients, all designate  
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9 4 advanced age, a medical history of UGI events, serious co-morbidity, and concurrent  
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11 5 administration of anticoagulants and corticosteroids as considerable risk factors<sup>6-9</sup>. The  
12  
13 6 guidelines are less consistent with regard to some other possible risk factors, such as high  
14  
15 7 doses or the use of multiple NSAIDs<sup>7-9</sup>, infection with *Helicobacter pylori*<sup>8,9</sup>, or concurrent  
16  
17 8 use of selective serotonin reuptake inhibitors (SSRIs)<sup>7,9</sup>.

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22 9 Though the need for preventive strategies is recognized, correct adherence to this  
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24 10 guidelines-supported advice remains low in daily clinical practice: a review showed that most  
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26 11 patients (76%) with one or more risk factors had not been assigned a recommended  
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28 12 preventive strategy<sup>24</sup>. This is presumed to be the major explanation for the observation that,  
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30 13 even though the prevalence of *H. pylori* is steadily decreasing in Western countries, the  
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32 14 incidence of peptic ulcer complications has not changed over the past 20 years<sup>25</sup>. Other  
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34 15 studies have reported a tendency of prescribing preventive strategies to patients at low risk  
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36 16 (up to 66%)<sup>26-29</sup>. Although extensive data are available on the use of preventive strategies in  
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38 17 NSAID users, little is known on how the prescription of these strategies was influenced by the  
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40 18 by time (calendar year) and the withdrawal of rofecoxib.

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45 19 The implementation of future guidelines would be improved by better insight into 1)  
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47 20 the adherence of general practitioners to the guidelines, and 2) how time and rofecoxib  
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49 21 withdrawal influenced the prescription behaviour of preventive strategies by general  
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51 22 practitioners. To examine time trends in and predictors of preventive strategies in day-to-day  
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53 23 practice among older NSAID users, we performed a population-based cohort-study, using  
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55 24 data from a Dutch general practitioner database between 1996 and 2006. We also studied the  
56  
57 25 possible influence of time and rofecoxib withdrawal on the observed trends.

## 1 **Patients and Methods**

### 3 **Study design**

4 A dynamic cohort study was conducted among incident NSAID users aged  $\geq 50$  years.

### 6 **Source of data**

7 The data used were contained in the Integrated Primary Care Information (IPCI)  
8 database, which is a dynamic general practitioner research database containing the  
9 longitudinal computer-based medical records of currently 1.2 million patients in the  
10 Netherlands. The IPCI database was set up in 1992, since when it has greatly expanded. The  
11 IPCI population has the same gender and age distribution as the Dutch general population<sup>30</sup>.

12 In the Dutch health care system, all citizens are registered at a GP practice, which acts  
13 as a gatekeeper in a two-way exchange of information with secondary care. The medical  
14 record of each individual patient can therefore be assumed to contain all relevant medical  
15 information. To further ensure completeness of the data, participating GPs are not allowed to  
16 use additional paper-based medical records.

17 Data held within the database comprise not only demographics, symptoms, and  
18 diagnoses (using the International Classification for Primary Care (ICPC<sup>31</sup>) and free text), but  
19 also referrals, clinical and laboratory findings, and hospitalizations. Information on drug  
20 prescriptions comprises their official label text, quantity, strength, ICPC coded indication,  
21 prescribed daily dose, and the Anatomical Therapeutic Chemical (ATC<sup>32</sup>) classification code.

22 The IPCI database complies with European Union guidelines on the use of medical  
23 data for medical research and has been proven valid for pharmaco-epidemiological research.  
24 Extensive details on the database have been reported elsewhere<sup>33</sup>. The Scientific and Ethical  
25 Advisory Board of the IPCI project approved the study design and use of the data.

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6 2**Study cohort**

7  
8 3 The source population consisted of all patients aged 50 years and over whose data had  
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10 4 been contributed to the IPCI database between January 1996 and December 2006, and who  
11  
12 5 had at least one year of valid database history before the date of study entry. This 12-month  
13  
14 6 period was required in order to allow assessment of baseline characteristics and inclusion and  
15  
16 7 exclusion criteria of all study subjects at the time of prescription.  
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20 8 Within the source population we identified all patients who newly started (no use in  
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22 9 the six months prior) on nsNSAIDs, coxibs, or high dose aspirin (>325 mg/day) during the  
23  
24 10 study period and had no history of a GI tract neoplasm, alcohol abuse, chronic liver disease,  
25  
26 11 inflammatory bowel disease, or a coagulopathy. Patients using only topical NSAIDs were  
27  
28 12 excluded, by virtue of the assumption that the UGI harm was limited. As the focus of this  
29  
30 13 study was to evaluate the use of prophylactic strategies in naive NSAID users, only the first  
31  
32 14 NSAID prescription of a patient was considered. The first day of NSAID prescription was  
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34 15 defined as the index date. To prevent overestimation of the number of patients receiving a  
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36 16 preventive strategy, we excluded patients who had been given PPI, misoprostol, or H<sub>2</sub>RA in  
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38 17 the six months prior to the index date.  
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**Identification of high-risk patients**

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48 20 On the basis of several international guidelines on the prevention of NSAID-related  
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50 21 UGI complications<sup>6-10</sup>, five risk factors were used to identify NSAID users at high risk of UGI  
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52 22 complications (risk set 1: 1) a history of GI bleeding/ulceration, 2) concurrent use of  
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54 23 anticoagulants, 3) concurrent use of antiplatelets (aspirin  $\leq$  325 mg/day), 4) concurrent use of  
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56 24 oral glucocorticoids (equipotent dose of  $\geq$ 5 mg prednisone), and 5) age  $\geq$  65 yrs). As several  
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58 25 additional risk factors can be of relevance in defining high-risk NSAID users, we extended  
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1 this first list of risks with four extra conditions, identified by the Dutch guideline<sup>9</sup>: 1) diabetes  
2 mellitus, 2) heart failure, 3) a high NSAID dose (> two times the defined daily dosage  
3 (DDD)<sup>32</sup>), and 4) concurrent use of SSRIs, effectively composing a second list (risk set 2). All  
4 risk factors were retrieved from the IPCI database by electronic searches in all data that was  
5 available before or at the index date. A previous medical history of UGI bleeding/ulceration  
6 was validated manually.

## 8 **Outcome**

9 We defined a preventive strategy as: 1) the use of a coxib, or 2) co-prescription of  
10 GPAs (H<sub>2</sub>RA, PPI, or misoprostol; either co-prescribed or the fixed combination with  
11 diclofenac) within two days of the index NSAID to proxy preventive use. This proxy has been  
12 shown to have a positive predictive value of approximately 85-90% in the IPCI database<sup>34</sup>.

13 The primary outcomes of interest were *correct prescription*, *over-prescription*, or  
14 *under-prescription* of preventive strategies at the index date. Correct prescription was defined  
15 as use of a preventive strategy in high-risk NSAID users and no use in low-risk patients.  
16 Under-prescription was defined as the absence of a preventive strategy in high-risk NSAID  
17 users. Over-prescription was defined as the presence of a preventive strategy in low-risk  
18 NSAID users. In line with evidence from randomized controlled trials, we considered co-  
19 prescription of a PPI with a coxib in high-risk users as correct prescription<sup>35, 36</sup>.

20 To avoid doubts about the need of preventive strategies in groups at the edge of the  
21 definitions we also performed a sub-group analysis using only patients at high or very high  
22 risk of NSAID-related UGI complications. Patients with at least one risk factor were defined  
23 as high-risk NSAID users, whereas NSAID users at very high risk comprised persons  $\geq 75$   
24 years *or* with a prior history of UGI complications. A further subgroup analysis was made in

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3 1 this cohort of very high risk persons by restricting to persons with a prior history of UGI  
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5 2 complications.

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8 3 To test whether the withdrawal of rofecoxib in 2004 was followed by an increase in  
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10 4 under-prescription of preventive strategies in patients at risk of NSAID related UGI  
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12 5 complications, under-prescription rates were measured in three successive study periods:  
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14 6 study period 1 (one year prior to the withdrawal of rofecoxib; 1 October 2003- 31 September  
15  
16 7 2004), study period 2 (one year after the withdrawal of rofecoxib; 1 October 2004 – 31  
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18 8 September 2005), and study period 3 (1 October 2005 – 31 September 2006).  
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## 25 10 **Analytic methods**

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27 11 Baseline characteristics were compared between high- and low-risk groups using a  $\chi^2$ -  
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29 12 test for dichotomous variables and independent t-test for age as a continuous variable. Within  
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31 13 high-risk users, uni- and multivariate analyses of potential predictors (such as gender, UGI  
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33 14 risk factors, number of UGI risk factors, year of index-prescription, number of co-  
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35 15 medications, and type of NSAID) of receiving a preventive strategy were conducted in order  
36  
37 16 to evaluate which risk factors are considered by general practitioners when deciding whether  
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39 17 or not to prescribe a gastroprotective strategy. Odds ratios (ORs) and their 95% confidence  
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41 18 intervals (CIs) were calculated by performing logistic regression analysis. Under-prescription  
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43 19 rates in the different study periods around rofecoxib withdrawal (2 vs 1 and 3 vs. 1) were  
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45 20 compared using a  $\chi^2$ -test. Linear regression was conducted to investigate the trend of correct,  
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47 21 over-, and under-prescription between 1996 and 2006. All analyses were performed using  
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49 22 SPSS version 16.  
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## 1 **Results**

### 2 **Study cohort**

3           Within the source population of 154,518 people aged 50 years and over, we identified  
4 55,962 incident NSAID users without any of the exclusion criteria. Of these, 5,836 used  
5 GPAs in the six months prior and were excluded. In total, 50,126 patients were included in  
6 the cohort. The median age of the study population was 63.1 (SD: 10.7) years; 56.9% was  
7 female. Baseline characteristics are described in table 1.

8 Twenty-six different types of NSAIDs were prescribed, diclofenac accounting for the highest  
9 number of prescriptions (38.8%), followed by ibuprofen (16.8 %) and naproxen (15.7%).

10

### 11 **Risk factors in NSAID users**

12           Table 1 shows that 28,441 patients (56.7% of the study population) had no NSAID-  
13 related UGI risk factor and were therefore defined as low-risk NSAID users. Individuals with  
14 at least one risk factor (43.3%) were defined as high-risk NSAID users; 81.6% of them had  
15 one risk factor and 18.4% had two or more risk factors. Age above 65 years was the most  
16 frequent (39.7%) of the NSAID-related UGI risk factors, followed by concomitant use of  
17 anticoagulants (8.6%), and diabetes mellitus as co-morbid condition (7.5%).

18           Diabetes mellitus and heart failure were more prevalent among high-risk users than  
19 among low-risk users (p-value<0.001). A high NSAID dose was rare, but significantly more  
20 prevalent among low-risk users than among high-risk users (2.4% vs 1.7%, p<0.001).

21

### 22 **Preventive strategies**

23           In total, 11.3% of all NSAID users received a preventive strategy in the form of a  
24 GPA. Excluding Arthrotec, PPIs were the most common co-prescribed GPAs (77.1%),

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1 followed by H<sub>2</sub>RA (22.1%) and misoprostol (0.7%). Only 4% of 327 users of prophylactic  
2 H<sub>2</sub>RAs were prescribed the recommended double dosages for UGI complication prophylaxis.

3 The use of coxibs and Arthrotec was more prevalent among high-risk users (coxibs:  
4 7.5% vs 4.0%, p-value<0.001; Arthrotec: 10.6% vs 6.7%, p-value<0.001), whereas low-risk  
5 users were more likely to receive an nsNSAID (88.2% versus 80.7%, p-value<0.001). Nearly  
6 17% of all NSAID users received a preventive strategy (GPA or coxib), which was  
7 significantly more prevalent in NSAID users at high risk than in low-risk NSAID users  
8 (21.9% vs 12.7%, p-value<0.001).

9 Of all high-risk patients, those with a history of UGI complications (OR 4.0; 95% CI  
10 2.9-5.4) or who concomitantly used systemic steroids (OR 3.7; 95% CI 2.5-5.6) had the  
11 highest chance of being prescribed a preventive strategy (Table 2A). Despite some guidelines  
12 identifying diabetes mellitus, heart failure, high NSAID dose, or the use of SSRI as a risk  
13 factor for NSAID-related UGI complications, these risk factors did not increase the odds of  
14 receiving preventive strategies. The odds of receiving a preventive strategy increased with the  
15 number of NSAID prescriptions on the same day (data not shown), and over calendar time  
16 (Table 2B). The likelihood of receiving a preventive strategy was highest for prescriptions of  
17 indometacin (OR 3.1; 95% CI 1.9-5.2) and ketoprofen (OR 2.5; 95% CI 1.2-5.5) and the  
18 lowest for carbasalate calcium (OR 0.3; 95% CI 0.1-0.8) (Table 2B).

## 20 **Correct, over- and under-prescription of preventive strategies in NSAID users**

### 21 *Risk set 1*

22 Figure 1 shows the time trend in prescription of preventive strategies in the 50,126  
23 NSAID users, when the definition of high-risk users was based on risk set 1 (history of UGI  
24 complication, concurrent use of anticoagulants, antiplatelets, or oral glucocorticoids, and age  
25  $\geq 65$  yrs). In the decade between 1996 and 2006, correct prescriptions of preventive strategies

1 rose by 10.6% from 52.7% to 63.3% ( $R^2=0.91$ , linear trend  $p<0.01$ ). Over the same period,  
2 under-prescription fell from 44.4% to 24.4% ( $R^2=0.94$ , linear trend  $p<0.01$ ). Over-  
3 prescription rose from 2.9% in 1996 to 12.3% in 2006 ( $R^2=0.92$ , linear trend  $p<0.01$ ).

#### 4 5 *Risk set 2*

6 When the broader criteria for NSAID-related UGI risk factors (risk set 2: adding  
7 diabetes mellitus, heart failure, high NSAID dose, and concomitant use of SSRIs to risk set 1)  
8 were used, more subjects were defined as high-risk users (48.4% versus 43.3%). This did not  
9 strongly influence the appropriateness of prescription strategies: correct prescription rose  
10 from 48.9% in 1996 to 60.7% in 2006 ( $R^2=0.93$ , linear trend  $p<0.01$ ), under-prescription fell  
11 from 48.5% to 28.5% ( $R^2=0.94$ , linear trend  $p<0.01$ ), and over-prescription rose from 2.6% to  
12 10.7% ( $R^2=0.91$ , linear trend  $p<0.01$ ) (data not shown).

#### 13 14 **Patients at high and very high risk of NSAID-related UGI complications**

15 We performed three sub-group analyses to investigate whether subjects at high or very  
16 high risk of developing NSAID-related UGI complications had received proper preventive  
17 strategies.

18 For the 21,685 NSAID users with at least one UGI risk factor, under-prescription in  
19 this group decreased from 93.1% to 59.9% ( $R^2=0.94$ , linear trend  $p<0.01$ ) and correct  
20 prescription rose from 6.9% to 39.4% ( $R^2=0.93$ , linear trend  $p<0.01$ ) between 1996 and 2006)  
21 (Figure 2A).

22 When the cohort was restricted to 9,283 very high-risk NSAID users defined as being  
23 75 years or older or having a previous history of UGI complications (mean age:  $79.78\pm 6.84$ ;  
24 34.1% male) the patterns were slightly different. Between 1996 and 2006, under-prescription

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3 1 in this group decreased from 90.8% to 50.6% ( $R^2=0.94$ , linear trend  $p<0.01$ ) and correct  
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6 2 prescription rose from 9.2% to 49.4% ( $R^2=0.94$ , linear trend  $p<0.01$ ).

7  
8 3 As a history of UGI complications is widely assumed to be the risk factor most  
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10 4 associated with an increased risk of developing UGI complications related to NSAIDs, we  
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12 5 further restricted the cohort of very high risk patients to 661 subjects (1.32%) with a history  
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14 6 of UGI bleeding/complication (mean age:  $65.42\pm 10.7$ ; 54% male). During the study period,  
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16 7 under-prescription in this subgroup decreased from 72.7% in 1996 to 51.5% in 2006  
17  
18 8 ( $R^2=0.75$ , linear trend  $p<0.01$ ). Correct prescription rose simultaneously from 27.3% in 1996  
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20 9 to 48.5% in 2006 ( $R^2=0.77$ , linear trend  $p<0.01$ ) (Figure 2C).  
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### 27 **Influence of rofecoxib withdrawal on preventive strategies in high risk users**

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29 12 In our study population, the use of coxibs increased from the time of their introduction  
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31 13 in the Netherlands in 2000 to 17.5% of all first line NSAIDs in 2004. At that time, rofecoxib  
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33 14 accounted for 39.6% of this share of the coxib market, followed by etoricoxib (33.3%) and  
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35 15 celecoxib (26.3%). After the withdrawal of rofecoxib in September 2004, the overall coxib  
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37 16 prescription rate decreased dramatically, to 5.2% in 2006. In 2006, etoricoxib accounted for  
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39 17 76.9% of all coxibs prescribed and celecoxib for 21.8%.  
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43 18 To test whether the rapid decrease in coxib use after the withdrawal of rofecoxib had  
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45 19 been followed by an increase in under-prescription, we compared under-prescription in study  
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47 20 period 1 (1 year before withdrawal of rofecoxib) with study period 2 (1 year after withdrawal  
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49 21 of rofecoxib) and study period 3 (1 October 2005 – 31 September 2006). In the group of  
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51 22 patients at high risk (at least one risk factor), under-prescription increased significantly after  
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53 23 rofecoxib withdrawal (from 56.6% before to 60.1% after rofecoxib withdrawal,  $p=0.04$ ), but it  
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55 24 returned to period 1 levels quite rapidly again in period 3 (from 56.6% before to 58.0% two  
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57 25 year after rofecoxib withdrawal,  $p=0.56$ ). Correct prescription decreased (from 43.0% to  
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1 39.4%,  $p=0.03$ ). In the very high risk group, defined as being 75 years or older or having a  
2 previous history of UGI complications, under-prescription did not change after rofecoxib  
3 withdrawal (from 50.4% before to 50.1% after rofecoxib withdrawal,  $p=0.9$ ). This shows that  
4 the main effect was seen in patients at moderate risk (at least one risk factor but no UGI  
5 complication and  $\text{age}<75$ ). Indeed, under-prescription increased significantly in this subgroup  
6 from 61.1% in study period 1 to 66.6% in study period 2 ( $p=0.01$ ).

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## 1 Discussion

2 Preventive strategies (misoprostol, PPIs, H<sub>2</sub>RAs, or coxibs) have been proposed to  
3 circumvent the well-recognized UGI-complications attributable to non-specific NSAIDs,  
4 especially in people at high risk. We have demonstrated in the past that under-prescription of  
5 preventive strategies was considerable<sup>34</sup>. The current study shows that, under-prescription of  
6 preventive strategies by Dutch general practitioners decreased from 44% to 24% over a 10  
7 year period. Despite this drop in under-prescription, in 2006 still almost one-fourth of new  
8 NSAID users with at least one UGI risk factor and 52% of patients with a medical history of  
9 UGI events was not prescribed a proper preventive strategy. Over-prescription of preventive  
10 drugs was low, but rose from 3% in 1996 to 12% in 2006.

11 Our findings are in line with other Dutch studies reporting under-prescription of  
12 preventive strategies in patients who would benefit from appropriate protection at a range of  
13 43%-87%<sup>33, 36-40</sup>. Consistently low rates of prescription of preventive strategies have also  
14 been reported in studies from other countries<sup>28, 42-45</sup>. In a recent pooled analysis of 11 studies  
15 related to the appropriate use of gastroprotective strategies in NSAID users, 76% of patients  
16 at high risk did not receive a preventive strategy<sup>24</sup>. Our analysis extended these data in the  
17 sense that we demonstrated that that figure depends largely on the time of measurement,  
18 because we had data available of eleven subsequent calendar years.

19 Over-prescription of preventive strategies was low in our study-population: it has been  
20 reported in the range of 12-33%<sup>27, 28, 46, 47</sup>. However, other studies did not study over-  
21 prescription over time and in such a big study population.

22 As for our secondary aim, we showed that the withdrawal of rofecoxib may have had  
23 an effect on appropriate use of prophylactic strategies in moderate high-risk patients.  
24 Immediately after the withdrawal of rofecoxib we saw a significant increase in under-  
25 prescription in patients with a risk factor for NSAID related UGI complications, especially

1 when we excluded persons at very high risk. However, this effect disappeared quickly and no  
2 causality between the date of rofecoxib withdrawal and the small increase in under-  
3 prescription can be attributed. This finding however, is in line with another Dutch study  
4 describing the effects of rofecoxib withdrawal where the authors showed that 34% of patients  
5 who stopped coxib therapy were switched to an nsNSAID without a PPI, whereas only 21%  
6 were switched to an nsNSAID with a co-prescription of a PPI <sup>48</sup>.

7       Some methodological aspects of this study make that our results should be interpreted  
8 carefully. First, because we used prescription data instead of more reliable proxies for drug  
9 use, we were unable to study actual drug utilization. Secondly, although it has been clearly  
10 demonstrated that only high-dose H<sub>2</sub>RAs reduce the endoscopic ulcer rates associated with  
11 NSAIDs, we defined every H<sub>2</sub>RA prescription, irrespective of dose, as a preventive strategy.  
12 Thirdly, we did not have any information about over-the-counter-use of NSAIDs. Some  
13 H<sub>2</sub>RAs, such as ranitidine, were available over-the-counter as well. While these  
14 considerations are important, the aim of the study was to determine whether general  
15 practitioners' prescription of a preventive strategy to NSAID users reflected an intention to  
16 comply with (inter)national guidelines. Because we have considered single H<sub>2</sub>RA dose as a  
17 preventive strategy, we underestimated under-prescription of preventive strategies.

18       The strength of the present study is that, through ICPC-codes and free text, the IPCI-  
19 database contains complete information on all UGI risk factors and on drug prescriptions,  
20 including their quantity, strength, and prescribed daily dose. Because it contains a large  
21 number of eligible subjects and reflects the Dutch general population, the database also  
22 minimizes the potential for bias. Furthermore, we study the influence of calendar year on  
23 prescription of GPAs among NSAID users. We also address issues of over-prescription,  
24 which have not been studied before over time and in such a big study population.

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3 1 An additional finding of note is that physicians are not aware of the need for  
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5 2 gastroprotective strategies when prescribing carbasalate calcium or acetylsalicylic acid, as the  
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7 3 likelihood of receiving a preventive strategy was lowest in patients using this type of  
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9 4 medication.

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12 5 In conclusion, we observed that physicians increase correct prescriptions of  
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14 6 gastroprotection over a decade, which may be the result of guidelines, education, and  
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16 7 probably the availability of generic PPIs. Despite the improvement, prescription of  
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18 8 recommended strategies was still unacceptably low in 2006, especially in vulnerable  
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20 9 populations. Non-adherence to gastroprotective measures lead to increased risk of NSAID-  
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22 10 associated complications such as UGI-bleeds, as we have shown before <sup>49</sup>. The withdrawal of  
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24 11 rofecoxib may had have a temporarily negative effect on gastroprotection, especially in the  
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26 12 patients at risk but below age of 75 and without a history of UGI complications. This  
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28 13 indicates that appropriate measures were not taken to protect at-risk NSAID users at the time  
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30 14 of withdrawal. This is also important for regulators when risk minimization measures are  
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32 15 taken such as removal of a drug from the market.  
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1 Table 1:

2 Baseline characteristics and index NSAID prescription of the study population

	<b>Total</b>	<b>High-risk</b>	<b>Low-risk</b>	<b>p-value</b>
	<b>n(%)</b>	<b>patients</b>	<b>patients</b>	
		<b>n(%)</b>	<b>n(%)</b>	
<b>Number</b>	50,126 (100.0)	21,685 (43.3)	28,441 (56.7)	
<b>Age (mean±sd)</b>	63.14 (10.7)	72.99 (8.3)	55.62 (4.2)	p<0.001
<b>Gender (n(%) male)</b>	21,621 (43.1)	8666 (40.0)	12,955 (45.6)	p<0.001
<b>Type of index-prescription:</b>				
Coxib	2778 (5.5)	1632 (7.5)	1146 (4.0)	p<0.001
nsNSAID	42,584 (85.0)	17,509 (80.7)	25,075 (88.2)	p<0.001
Arthrotec	4214 (8.4)	2297 (10.6)	1917 (6.7)	p<0.001
Combinations	550 (1.1)	247 (1.1)	303 (1.1)	p=0.43
<b>Number of GI risk factors:</b>				
0	28,441 (56.7)	0 (0.0)	28,441 (100)	
1	17,705 (35.3)	17,705 (81.6)	0 (0.0)	
2	3807 (7.6)	3807 (17.6)	0 (0.0)	
3	171 (0.3)	171 (0.8)	0 (0.0)	
4	2 (0.0)	2 (0.0)	0 (0.0)	
<b>Individual GI risk factors:</b>				
Age > 65 year*	19,898 (39.7)	19,898 (91.8)	0 (0.0)	

Prior UGI complication*	661 (1.3)	661 (3.0)	0 (0.0)	
Use of antiplatelets*	4301 (8.6)	4301 (19.8)	0 (0.0)	
Use of vitamin K antagonists*	678 (1.4)	678 (3.1)	0 (0.0)	
Use of systemic steroids*	302 (0.6)	302 (1.4)	0 (0.0)	
Diabetes mellitus	3744 (7.5)	2392 (11.0)	1352 (4.8)	p<0.001
Heart failure	1172 (2.3)	1061 (4.9)	111 (0.4)	p<0.001
High NSAID dose (> 2x DDD)	1051 (2.1)	365 (1.7)	686 (2.4)	p<0.001
Use of SSRI	915 (1.8)	386 (1.8)	529 (1.9)	p=0.51
<b>GPA</b>	5667 (11.3)	3170 (14.6)	2497 (8.8)	p<0.001
<b>Preventive strategy (GPA or Coxib)</b>	8370 (16.7)	4752 (21.9)	3618 (12.7)	p<0.001

1 \* Risk factors used to define high-risk NSAID users (risk set 1).

1 Table 2A: Predictors of prescription of preventive strategies in high-risk patients (risk factors)

	No Prev.	With Prev.	OR crude	OR adjusted*	P-value
	Strategy	Strategy	(95% CI)	(95% CI)	
	n (%)	n (%)			
<b>Total (%)</b>	16933 (78.1)	4752 (21.9)			
<b>Gender (% male)</b>	6867 (40.6)	1799 (37.9)	1.12 (1.05-1.20)	1.08 (0.92-1.26)	p=0.35
<b>Individual risk factor</b>					
Age >65	15511 (91.6)	4387 (92.3)	1.10 (0.98-1.24)	1.71 (1.30-2.23)	p<0.001
Prior UGI complication	443 (2.6)	218 (4.6)	1.79 (1.52-2.11)	3.98 (2.94-5.39)	p<0.001
Use of antiplatelets	3272 (19.3)	1029 (21.7)	1.15 (1.07-1.25)	1.35 (1.13-1.61)	p<0.001
Use of vitamin K	504 (3)	174 (3.7)	1.24 (1.04-1.48)	1.89 (1.35-2.64)	p<0.001
Antagonists					
Use of systemic	203 (1.2)	99 (2.1)	1.75 (1.38-2.24)	3.72 (2.46-5.64)	p<0.001
Steroids					
Diabetes mellitus	1821 (10.8)	571 (12)	1.13 (1.03-1.25)	0.86 (0.68-1.08)	p=0.20
Heart failure	770 (4.5)	291 (6.1)	1.37 (1.19-1.57)	1.0 (0.72-1.39)	p=0.98
High NSAID dose	196 (1.2)	26 (0.5)	0.47 (0.31-0.71)	0.57 (0.23-1.44)	p=0.24
Use of SSRI	281 (1.7)	105 (2.2)	1.34 (1.07-1.68)	1.38 (0.87-2.20)	p=0.17
<b>Number of GI risk factors</b>					
1	14059 (83)	3646 (76.7)	1.0 (ref)		
2	2749 (16.2)	1058 (22.3)	1.48 (1.37-1.61)		

3	124 (0.7)	47 (1)	1.46 (1.04-2.05)
4 or more	1 (0)	1 (0)	3.86 (0.24-61.66)

1 \* Adjusted for known UGI riskfactors (gender, age, prior UGI complication, use of antiplatelets, use of steroids, diabetes mellitus, heart failure, dose, use of SSRIs), year of cohort entry and type of nsNSAIDs.

For Peer Review

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3 1 Table 2B: Predictors of prescription of preventive strategies in high-risk patients (index-  
4  
5  
6 2 prescription).  
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	<b>No Prev.</b>	<b>With Prev.</b>	<b>OR crude</b>	<b>OR adjusted*</b>	<b>P-value</b>
	<b>Strategy</b>	<b>Strategy</b>	<b>(95% CI)</b>	<b>(95% CI)</b>	
	<b>n (%)</b>	<b>n (%)</b>			
<b>Index -prescription in</b>					
1996	1246 (7.4)	93 (2)	1.0 (ref)	1 (ref)	
1997	1994 (11.8)	164 (3.5)	1.10 (0.85-1.44)	1.23 (0.66-2.31)	p=0.52
1998	2308 (13.6)	254 (5.3)	1.47 (1.15-1.89)	2.15 (1.22-3.81)	p=0.01
1999	2881 (17)	322 (6.8)	1.50 (1.18-1.90)	2.16 (1.23-3.78)	p=0.01
2000	2460 (14.5)	581 (12.2)	3.16 (2.52-3.98)	2.56 (1.46-4.48)	p<0.001
2001	1516 (9)	584 (12.3)	5.16 (4.10-6.50)	2.83 (1.58-5.07)	p<0.001
2002	1233 (7.3)	543 (11.4)	5.90 (4.67-7.45)	3.30 (1.83-5.96)	p<0.001
2003	1167 (6.9)	651 (13.7)	7.47 (5.93-9.42)	5.40 (3.06-9.51)	p<0.001
2004	1132 (6.7)	849 (17.9)	10.05 (7.99-12.63)	8.03 (4.62-13.95)	p<0.001
2005	634 (3.7)	467 (9.8)	9.87 (7.75-12.57)	20.67 (11.95-35.76)	p<0.001
2006	362 (2.1)	244 (5.1)	9.03 (6.92-11.78)	23.92 (13.62-42.03)	p<0.001
<b>Type of index- prescription</b>					
Ibuprofen	3573 (21.1)	119 (2.5)	1.0 (ref)	1.0 (ref)	

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4	Diclofenac	7194 (42.5)	392 (8.2)	1.64 (1.33-2.02)	1.28 (1.03-1.59)	0.03
5						
6	Naproxen	2806 (16.6)	105 (2.2)	1.12 (0.86-1.47)	1.98 (0.75-1.29)	0.89
7						
8	Indometacin	249 (1.5)	20 (0.4)	2.41 (1.48- 3.94)	3.12 (1.87-5.18)	0.00
9						
10	Piroxicam	707 (4.2)	30 (0.6)	1.27 (0.85-1.92)	1.48 (0.97-2.26)	0.07
11						
12	Ketoprofen	115 (0.7)	8 (0.2)	2.09 (1.0-4.38)	2.54 (1.18-5.50)	0.02
13						
14	Nabumetone	485 (2.9)	12 (0.3)	0.74 (0.41-1.36)	1.10 (0.59-2.04)	0.76
15						
16	Carbasalate calcium	425 (2.5)	6 (0.1)	0.42 (0.19-0.97)	0.33 (0.14-0.77)	0.01
17						
18	Acetylsalicylic acid	86 (0.5)	1 (0)	0.35 (0.05-2.53)	0.34 (0.05-2.51)	0.29
19						
20	Combi					
21						
22	Meloxicam	748 (4.4)	49 (1)	1.97 (1.40-2.77)	1.10 (0.77-1.58)	0.61
23						
24	Other nsNSAIDs	367 (2.2)	12 (0.3)	0.98 (0.54-1.80)	0.95 (0.51-1.76)	0.86
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30 1 \* Adjusted for known UGI riskfactors (gender, age, prior UGI complication, use of

31 2 antiplatelets, use of steroids, diabetes mellitus, heart failure, dose, use of SSRIs), year of

32 3 cohort entry and type of nsNSAIDs.

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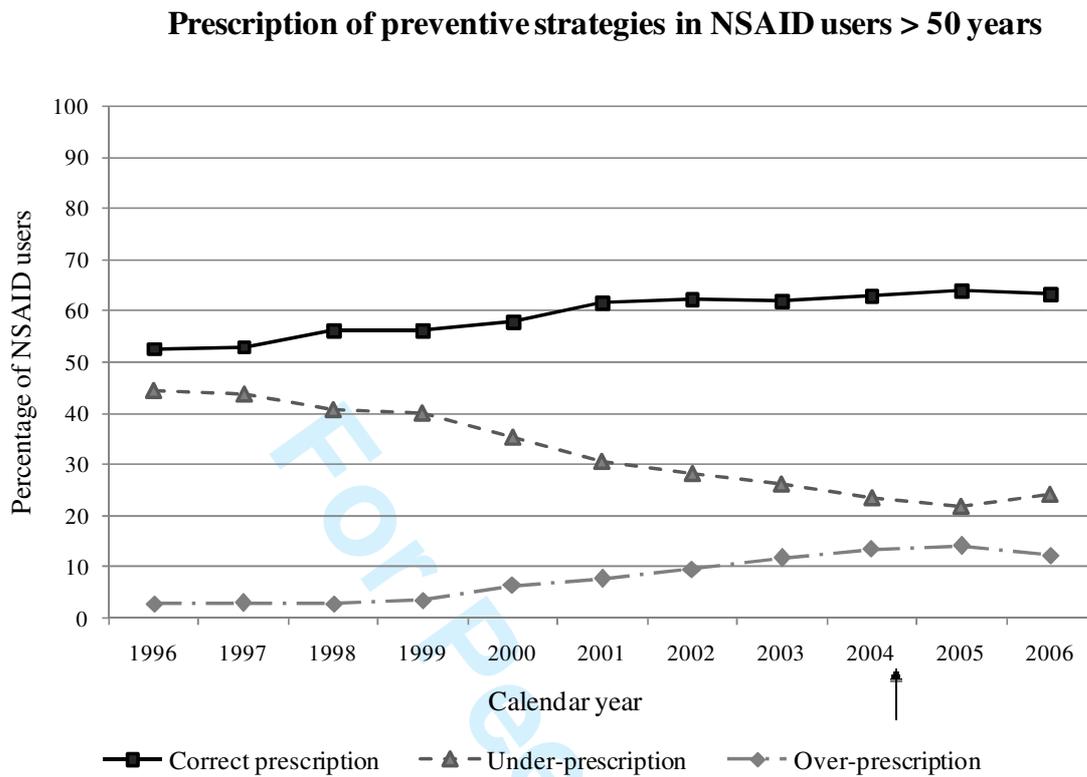
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1 Figure 1:



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3 Prescription of preventive strategies in NSAID users &gt; 50 years (n=50,126).

4 The vertical arrow indicates calendar year 2004, in which rofecoxib was withdrawn.

5 Index prescriptions within a given calendar year were pooled. The denominator is the  
6 number of prescriptions per calendar year.

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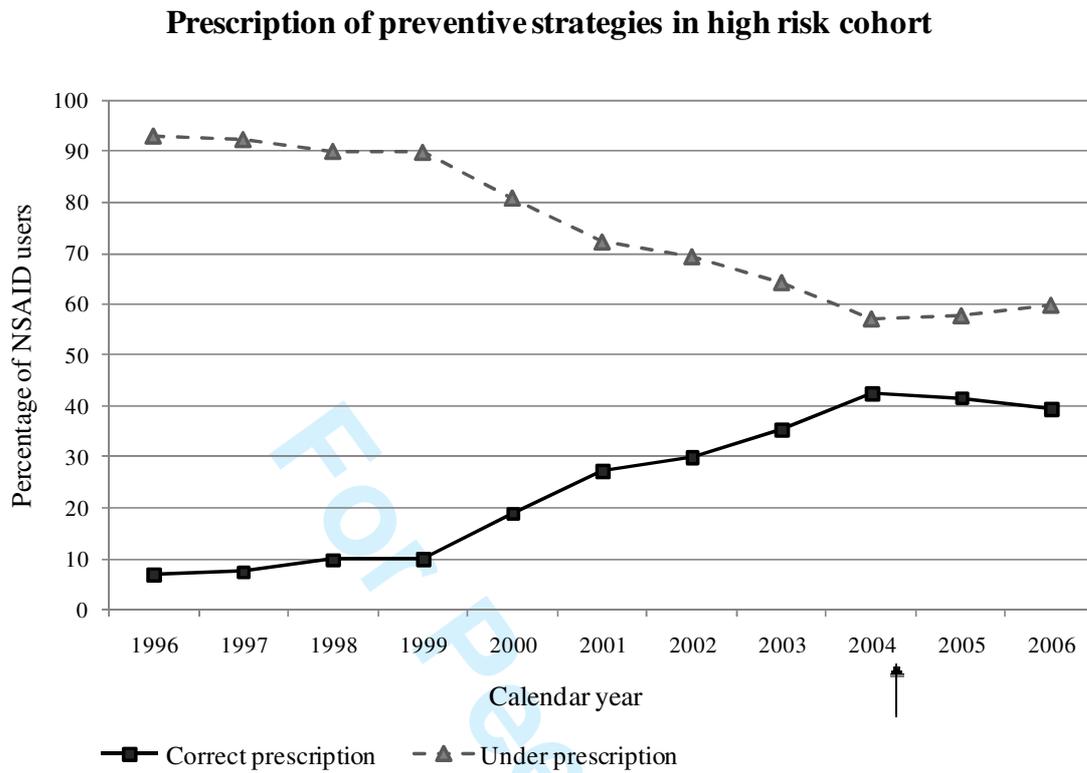
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1 Figure 2A:



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Prescription of preventive strategies in NSAID users with at least one risk factor

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(n=21,685). The vertical arrow indicates calendar year 2004, in which rofecoxib was

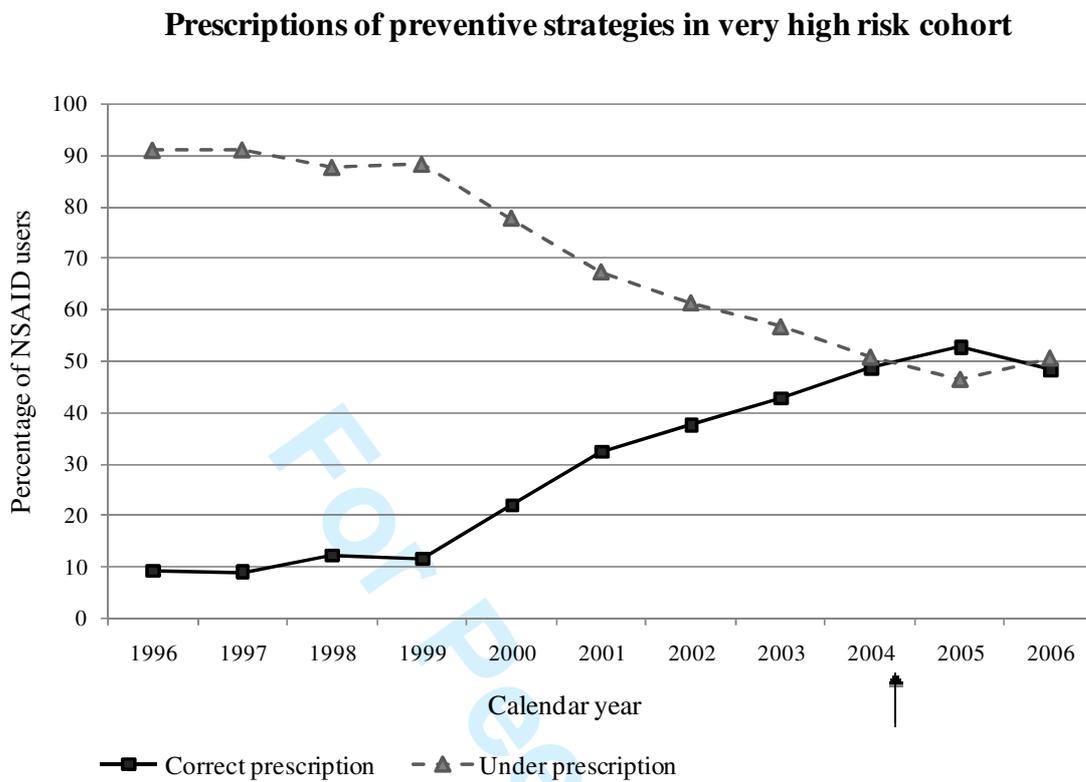
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withdrawn. Index prescriptions within a given calendar year were pooled. The

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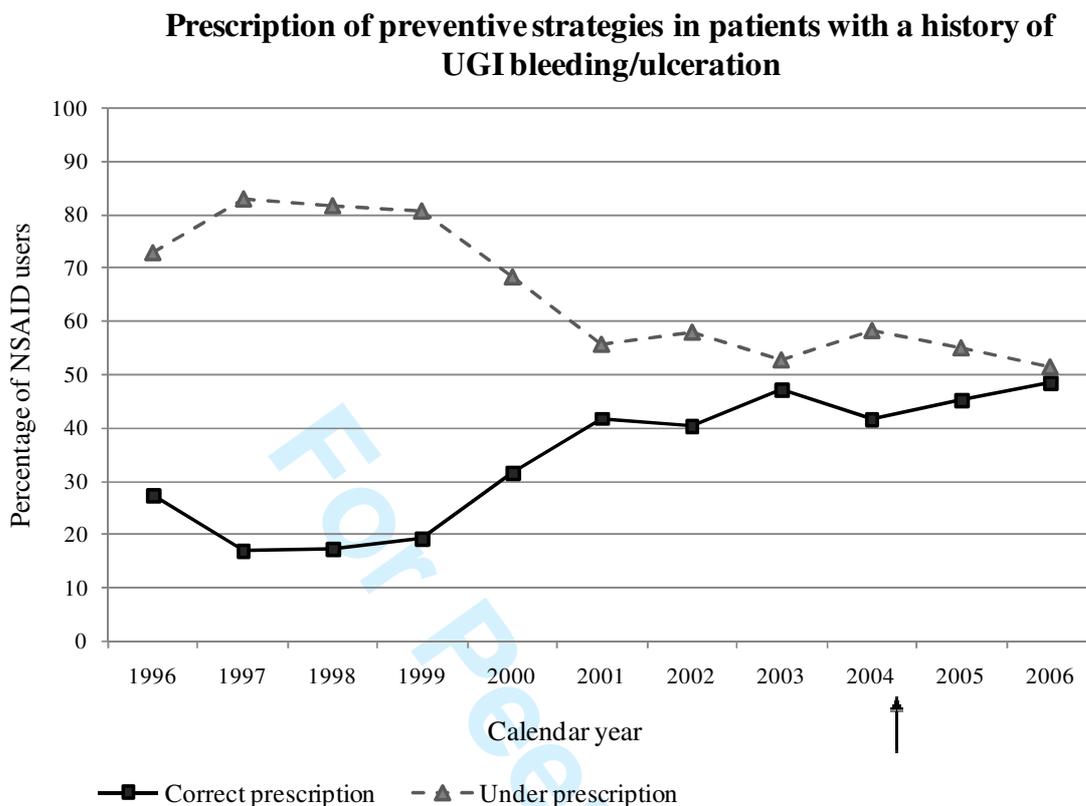
denominator is the number of prescriptions per calendar year.

1 Figure 2B:



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Prescription of preventive strategies in NSAID users > 75 years or with a history of UGI bleeding/ulceration (n=9,283). The vertical arrow indicates calendar year 2004, in which rofecoxib was withdrawn. Index prescriptions within a given calendar year were pooled. The denominator is the number of prescriptions per calendar year.

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Prescription of preventive strategies in NSAID users with a history of UGI bleeding/ulceration (n=661). The vertical arrow indicates calendar year 2004, in which rofecoxib was withdrawn. Index prescriptions within a given calendar year were pooled. The denominator is the number of prescriptions per calendar year.

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3 Rotterdam, Febr. 10<sup>th</sup> 2010  
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7 Dear Editor,  
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10  
11 Thank you for your time in carefully assessing our study and for giving us the chance to  
12 revise our article.  
13  
14

15  
16 We would also like to thank the reviewers for their welcome advice and useful comments. We  
17 hope our reply and adjustments as specified below in a point by point fashion are satisfactory.  
18 The comments are in **bold** and our answers are in *italic*. Where appropriate, we incorporated  
19 reviewers' suggestions in our manuscript.  
20  
21  
22

#### 23 24 **Editor's comments for the Author** 25

- 26 **1. The title should be altered to reflect the key message of the paper please.**  
27

28 *Answer: We appreciate this comment. To better reflect the key message of the article, we have*  
29 *changed the title accordingly.*  
30  
31

#### 32 33 **Reviewer 1 Comments for the Author.** 34

- 35 **1. None.**  
36

37 *Answer: We appreciate that the reviewer apparently appreciated our manuscript.*  
38  
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#### 41 42 **Reviewer 2 Comments for the Author.** 43

- 44 **1. I assume the data from all index prescriptions within a given calendar year were**  
45 **pooled, and that these pooled data are analyzed and depicted in Figures 1 and 2.**  
46 **This should be stated explicitly.**  
47

48 *Answer: This is a correct assumption. We have added the information to the methods section*  
49 *and in figure legend.*  
50  
51

- 52 **2. Figures 1 and 2. Placement of arrows suggests that rofecoxib was withdrawn in**  
53 **middle of 2004 when in fact it was withdrawn in September 2004.**  
54

55 *Answer: That is correct. We have repositioned the arrows in Figures 1 and 2 to the last*  
56 *quarter of 2004 instead of the middle of calendar year 2004.*  
57  
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59 **Also in these figures: Are the numbers of incident NSAID users in each year**  
60 **similar (what is the range)? If not, it would be informative to depict the number**  
**of subjects analyzed during each.**

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*Answer: Because the population is dynamic the numbers of incident NSAID users are not similar during each calendar year, but ranged between 362 and 2460. We have added this information to Table 2. We had originally removed this information from our manuscript because it made Table 2 very large. To overcome this problem, we propose to split Table 2 into 2A and 2B, respectively containing information on demographics plus risk factors, and index prescription data.*

**3. Figure 2 should be labeled “very-high risk cohort” rather than “high-risk cohort.”**

*Answer: we have adjusted this in the title of Figure 2.*

**I assume that the data in the high-risk cohort are comparable. This should be analyzed and stated.**

*Answer: Indeed, the data in the high risk NSAID users (defined as users with at least one UGI risk factor, n= 21,685) were very similar regarding correct, over-, and under prescription of gastroprotective agents as compared to Figure 2, in which we focus on very high risk users (defined as users with age > 75 years and prior history of UGI event).*

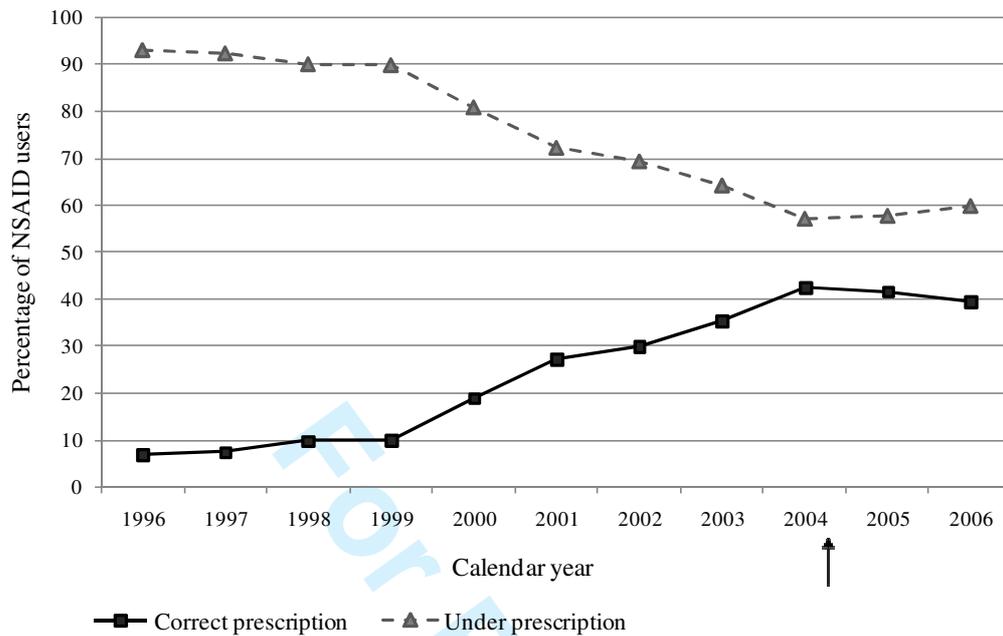
*Regarding very high patients: Between 1996 and 2006, under-prescription in this group decreased from 90.8% to 50.6% ( $R^2=0.94$ , linear trend  $p<0.01$ ) and correct prescription rose from 9.2% to 49.4% ( $R^2=0.94$ , linear trend  $p<0.01$ ).*

*For high risk patients: with at least one UGI risk factor the results were as follows. Between 1996 and 2006, under-prescription in this group decreased from 93.1% to 59.9% ( $R^2=0.94$ , linear trend  $p<0.01$ ) and correct prescription rose from 6.9% to 39.4% ( $R^2=0.93$ , linear trend  $p<0.01$ ). This is illustrated by the following three figures;*

- 1) prescription of preventive strategies in high risk cohort (at least one UGI risk factor)*
- 2) prescription of preventive strategies in very high risk cohort (age>75 yrs or UGI bleeding/ulceration), similar to Figure 2 in the manuscript, and*
- 3) prescription of preventive strategies in subset of very high risk cohort namely only the persons with UGI bleeding/ulceration.*

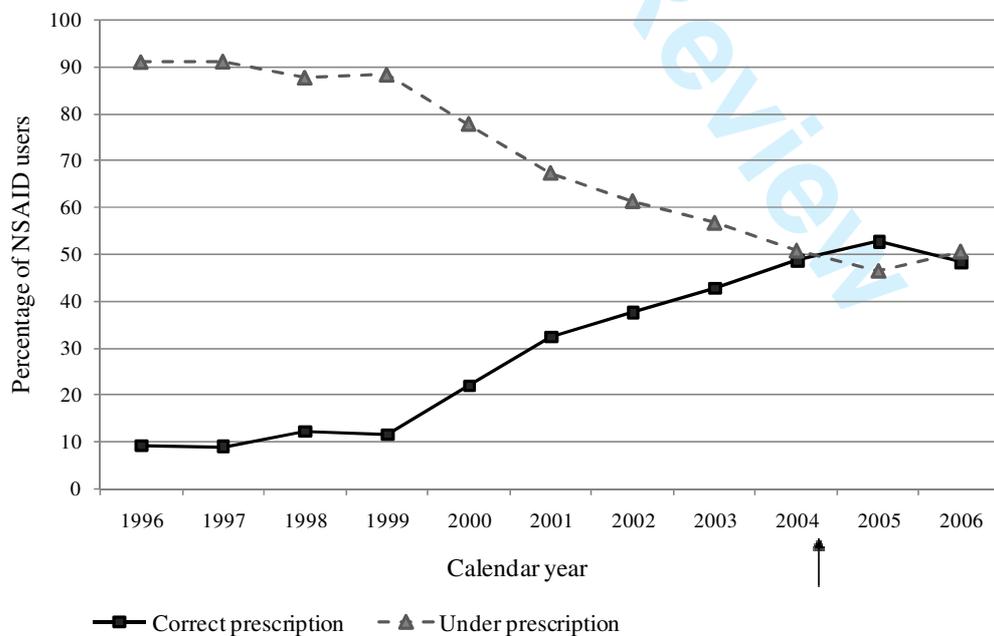
*1) Prescription of preventive strategies in high risk cohort (at least one UGI risk factor),*

### Prescription of preventive strategies in high risk cohort

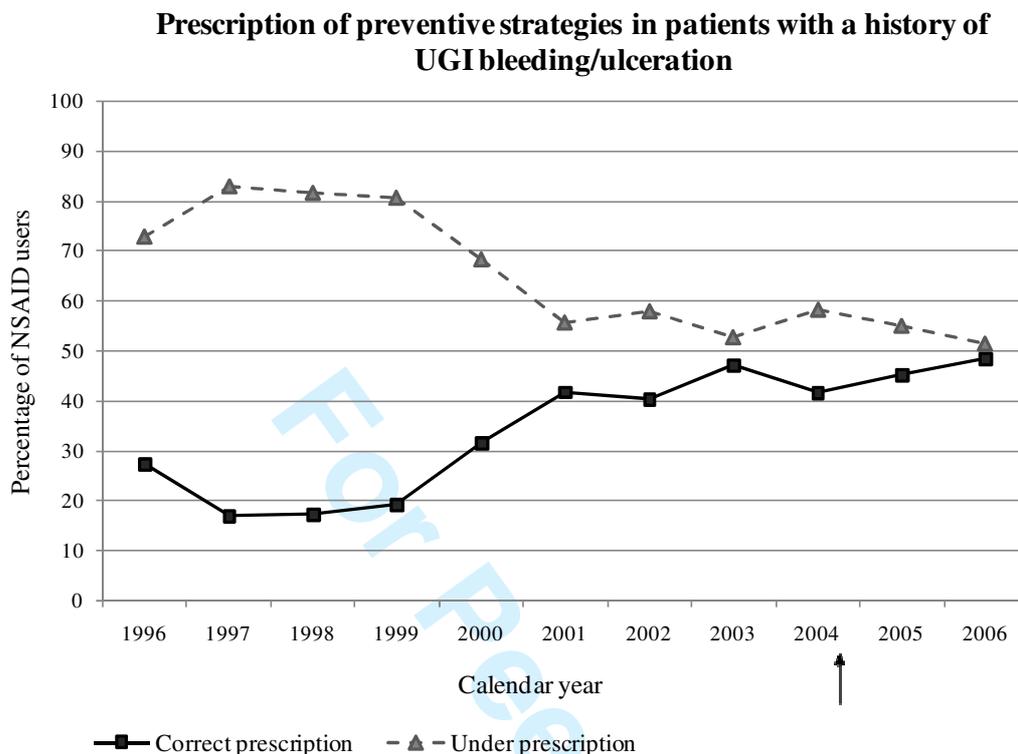


2) Prescription of preventive strategies in very high risk cohort (age > 75 yrs or UGI bleeding/ulceration), similar to Figure 2 in the manuscript

### Prescriptions of preventive strategies in very high risk cohort



3) Prescription of preventive strategies in subset of very high risk cohort (UGI bleeding/ulceration).



These figures have now been added to the manuscript as extension of Figure 2. Should the editor consider that the paper has become too long, we would of course be willing to either drop these additional figures, or add them as supplemental files through the journal's website.

4. Page 13, line 17 states that data for over-prescription is depicted in the figure when it is not.

Answer: We apologize and have adjusted this comment.

5. Page 14, sentence 19 ("no annual increase") is confusing. Figure 1 appears to show an up-tick of about 5% in under-prescription. Also years depicted are calendar years rather than years post rofe withdrawal.

Answer: We have deleted this sentence as it was indeed confusing.

6. Page 14, sentences 20-23. Was under-prescription pre-defined in the study protocol as under-prescription in the ENTIRE population or under-prescription in the HIGH RISK population? The ENTIRE population is used as the denominator for figures 1 and 2, and the HIGH RISK population is used as the denominator in the analysis of the impact of rofecoxib withdrawal. Was analysis of the impact of rofecoxib withdrawal in the HIGH RISK population a post hoc analysis? This is important because the differences between period 1 and period 2 are small and the p values are not that strong.

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3 *Answer: We analyzed under-prescription both for the entire cohort, as well as for individual*  
4 *risk groups and this risk group stratified analysis by calendar year (to look at effect of*  
5 *withdrawal of rofecoxib) was specified a-priori.*  
6

7  
8 *The denominator for Figure 1 is the number of prescriptions per calendar year. within the*  
9 *entire population (n=50,126), and the denominator for Figure 2 is the number of*  
10 *prescriptions per calendar year. within the very high risk cohort (n=9,283). This has been*  
11 *made explicit in the legend.*  
12

13 *As for the sentence to which the reviewer refers; we used as denominator the number of*  
14 *prescriptions per calendar year. within the high risk cohort (n=21,685). We have now*  
15 *ensured that we at all points clearly state the denominator for individual statements.*  
16

17  
18 **7. What are the rates of under-prescription (period 1 versus period 2) among VERY**  
19 **high risk patients?**  
20

21 *The study included a total of 1,468 very high risk patients, defined as patients > 75 years or a*  
22 *history of UGI complication, 857 started NSAIDs in study period 1(prior to rofecoxib*  
23 *withdrawal), 611 persons started NSAIDs in period 2. The rates of under-prescription among*  
24 *these patients were respectively 50.4% in period 1 and 50.1% in period 2 (p=0.9). Thus in this*  
25 *very high risk sub group there was no effect from rofecoxib withdrawal. The high risk group*  
26 *(comprising the very high risk group) did show a significant increase in under-prescription*  
27 *(as shown in the manuscript). This means that the high risk minus the very high risk group*  
28 *determined the difference (see below). We have added this difference to the text, and made*  
29 *more explicit that this differences shows that the effect of rofecoxib withdrawal was most*  
30 *apparent in those at risk but not at very high risk.*  
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33 *High risk group, excluding very high risk:*

34 *Under-prescription:*

	<i>Studyperiod 1</i>	<i>Studyperiod 2</i>	<i>Chi-square t-test</i>
<i>Under-prescription</i>	<i>721 (61.1%)</i>	<i>579 (66.6%)</i>	<i>p-value 2 vs. 1=0.01</i>
<i>Total</i>	<i>1180</i>	<i>870</i>	<i>2050</i>

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47 **8. What statistical test was performed to compare periods 1 and period 2?**  
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49 *Answer: A  $\chi^2$ -test was performed. We have added this information in the methods section*  
50 *under analytic methods.*  
51

52  
53 **9. Page 14. The difference in correct GPS utilization between pre- and post-**  
54 **rofecoxib withdrawal appears relatively small and only reflects one year of**  
55 **analysis. In fact, this may only be a blip in a favorable trend line. Your database**  
56 **extends through the end of 2006. What are the GPS under-prescription rates in a**  
57 **post-hoc analysis of a “period 3” (10/05-9/06)? This would help define whether**  
58 **the putative impact of rofecoxib withdrawal on GPS usage was a blip or had a**  
59 **lasting impact.**  
60

*Answer: We did perform the analyses as suggested by the reviewer.*

The results for:

Entire population:

	<i>Studyperiod 1</i>	<i>Studyperiod 2</i>	<i>Studyperiod 3</i>	<i>Chi-square t-test</i>
<i>Under-prescription</i>	1106 (23.3%)	858 (23.8%)	364 (22.1%)	<i>p-value overall=0.40</i> <i>p-value 2 vs 1=0.56</i> <i>p-value 3 vs 1=0.33</i>
<i>Total</i>	4748	3600	1645	

High risk population: we restricted to patients with at least one risk factor for NSAID related UGI problems;

	<i>Studyperiod 1</i>	<i>Studyperiod 2</i>	<i>Studyperiod 3</i>	<i>Chi-square t-test</i>
<i>Under-prescription</i>	1106 (56.6%)	858 (60.1%)	364 (58.0%)	<i>P-value overall=0.13</i> <i>p-value 2 vs. 1=0.04</i> <i>p-value 3 vs 1=0.56</i>
<i>Total</i>	1953	1428	628	

Very high risk population: For this purpose, we restricted to patients => 75 years or history of UGI complication;

	<i>Studyperiod 1</i>	<i>Studyperiod 2</i>	<i>Studyperiod 3</i>	<i>Chi-square t-test</i>
<i>Under-prescription</i>	432 (50.4%)	306 (50.1%)	141 (51.1%)	<i>P-value overall=0.96</i> <i>p-value 2 vs. 1=0.90</i> <i>p-value 3 vs 1=0.85</i>
<i>Total</i>	857	611	276	

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3 *These analyses show again that there is no effect of rofecoxib withdrawal in the very high risk*  
4 *patients. In the high risk patients the effect of rofecoxib withdrawal was short, in period 3 it*  
5 *has disappeared. We have added this to the text.*  
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10 **10. Page 15, lines 21-23. This “significant increase” only pertains to the high-risk**  
11 **subset.**

12  
13 *Answer: The reviewer is correct, we have clarified this in the discussion*  
14

15 **11. It should be stressed that the any differences can be associated with the date of**  
16 **rofecoxib withdrawal, but that causality cannot be attributed.**  
17

18 *Answer: We agree and have added this statement about non-causality in the discussion.*  
19

20 **12. Given the concerns above, the data regarding the impact of rofecoxib withdrawal**  
21 **should be de-emphasized in the abstract, title and in the conclusion.**  
22

23 *Answer: We have de-emphasized the data regarding the impact of rofecoxib withdrawal. To*  
24 *better reflect the key message of the article and to de-emphasize the impact of rofecoxib*  
25 *withdrawal, we have changed the title. The Conclusion and Abstract were adjusted*  
26 *accordingly.*  
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### Reviewer 3 Comments for the Author.

**This paper uses a clinical database in the Netherlands to determine the rate of appropriate use of gastroprotective therapy in patients taking NSAIDs for the first time. They compare this rate over time and before and after the withdrawal of rofecoxib from the market.**

- 1. The authors need to provide a more compelling case for why their study is novel and provides new information. Numerous publications have addressed the issue of appropriate uses of preventive strategies for patients taking NSAIDs and how often these strategies are implemented in practice, but few of these are referenced.**

*Answer: We appreciate this comment, and in fact already in the original version of the manuscript referred to other papers demonstrating low adherence to GPAs in daily clinical practice. This was done in the Introduction with a reference to an overview paper<sup>1</sup>. In the Discussion, we extended this with a reference to several original research papers, both from the Netherlands (ref 33, 36-40)<sup>2-7</sup> and international (ref 27, 41-45)<sup>8-12</sup>.*

**The authors should be able to tell us why this study is different than these other studies, including multiple prior papers on this subject from the Netherlands (examples: van Dijk et al. Pharm World Sci. 2002;24:100-3, Vonkeman et al. Int J Clin Pharmacol Ther. 2007;45:281-8).**

*Answer: Our paper differs from those other papers in several important aspects:*

#### *1) Time range.*

*Because we were able to include data over a 11-year time range (1996 -2006), we are able to demonstrate that adherence to GPAs among NSAID users shows major variation over time. This is the main result of our study, which other studies did not elaborate on. Other studies defined adherence to GPA among NSAIDs cross-sectionally using a smaller time range, mostly up to one or two years. One study<sup>4</sup> had data available of subsequent years ( 2000 and 2004), but aggravated all data in one pooled analysis and did not report on time trends. Our time trend data show that the results and conclusions of previous studies were strongly influenced by the calendar year in which the study was conducted. In our study, both in Figure 1 and 2, we demonstrate this time effect. To better explain this time trend we revised the manuscript and added calendar year as a predictor in Table 2. Table 2 shows that calendar year is a major predictor of prescription of preventive strategies in high-risk patients.*

#### *2) Determination of over-prescription in low-risk users*

*Most studies only focused on under-prescription in high-risk patients<sup>5-8, 10</sup>. Because we also included low-risk NSAID users in our population, we are able to focus not only on correct and under-prescription, but also on over-prescription. Over-prescription has been studied before<sup>9, 13-15</sup>, but only in small study cohorts over short time-spans. Data on over-prescription are clinically relevant, indicating that general practitioners are prescribing gastroprotection to NSAID users, regardless of identified UGI risk factors. As is shown in Figure 1, over-prescriptions did increase over time.*

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3 An additional finding of note is that trends regarding the over- and under-prescription of  
4 gastroprotective strategies have converged over the past decade. Although under-prescription  
5 was more prevalent than over-prescription (24% vs 12% in 2006), our data show that  
6 gastroprotective agents are often prescribed regardless of UGI risk factors, thereby  
7 increasing over-prescription. It is likely that when the prescription of preventive strategies  
8 increases, over-prescription will become equally prevalent as under-prescription. This would  
9 in particular lead to considerable increases in health care expenditure, and in addition would  
10 expose low-risk NSAID users, who do not need a preventive strategy, to adverse reactions of  
11 GPAs, albeit uncommon.  
12

### 13 3) Effect of rofecoxib withdrawal

14  
15 Our third and last argument why this study is adding new information, is that we additionally  
16 study the trend of GPA prescription around September 2004. Although, we cannot imply  
17 causality between the withdrawal of rofecoxib and the significant increase of under-  
18 prescription or decrease of correct prescription in high-risk users, the differences in correct  
19 and under-prescription between study period 1 and study period 2 may be associated with the  
20 date of rofecoxib withdrawal (especially in high risk and not at very high risk). One other  
21 Dutch study studying the effects of rofecoxib withdrawal showed that 34% of patients who  
22 stopped coxib therapy were switched to an nsNSAID without a PPI, whereas only 21% were  
23 switched to an nsNSAID with a co-prescription of a PPI<sup>16</sup>. Other studies investigating the  
24 effect of rofecoxib withdrawal did not study the effect on adherence to the guidelines, but  
25 rather studied the effect on switches to other analgetics such as paracetamol  
26 (acetaminophen)<sup>16-18</sup> or to evaluate changes in patients characteristics<sup>19</sup>.  
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32 We have elaborated on the strengths of our study in the Discussion section on page 16,  
33 paragraph 3 and paragraph 5.  
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35 **The comparison of the rate before and after the withdrawal of rofecoxib from the**  
36 **market is only marginally statistically significant and has little or no clinical**  
37 **relevance. The authors need to demonstrate this finding is important and how it**  
38 **affects clinical decisions.**  
39

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41 Answer: We agree that the focus on rofecoxib withdrawal could be toned down, and we have  
42 done so in the paper. The lessons to be learned however is that patients at moderately  
43 increased risk were undertreated for a short period of time. Alternative treatments/measures  
44 should be better communicated when a drug is withdrawn.  
45

46 **The results of this study may not be generalizable because the data were obtained**  
47 **from a single integrated healthcare system that may have unique practice**  
48 **patterns.**  
49

50 Answer: We believe that the data are generalizable for the following reasons:  
51

- 52 1) The IPCI population is large and has the same gender and age distribution as the  
53 Dutch general population, as explained in the Methods section (ref. 29).<sup>20</sup>  
54
- 55 2) Because there is homogeneity (e.g. similar findings/results) across databases, both  
56 across the Netherlands and across countries, we do believe that our findings are  
57 representative for a larger population and not only applicable to the patients in our  
58 database.  
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Discussion section: 'Our findings are in line with other Dutch studies reporting under-prescription of preventive strategies in patients who would benefit from appropriate protection at a range of 43%-87% (ref 33, 36-40)<sup>2-7</sup>. Consistently low rates of prescription of preventive strategies have also been reported in studies from other countries (ref 27, 41-45)<sup>8-12</sup>.'

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2. While the statistical analysis is adequate the authors need to provide a better rationale for how they defined high risk set 2. For example, why include SSRI use and not chronic renal disease when both have been shown to increase the risk of GI bleeding? The selection of heart failure and diabetes, but not respiratory disease or neurologic diseases is not explained. Most studies have had a broader definition of comorbid disease to capture a broad range of diseases. Similarly, we are not given the justification for the definition of "very high risk" patients being either extreme age or a prior history of a UGI complication. Why was this definition chosen instead of combining multiple other risk factors?

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Answer: We appreciate this comment. In fact, different evidenced-based guidelines provide slightly different definitions of high-risk patients. This is discussed in the Introduction section. We primarily adopted the Dutch guideline<sup>21</sup>, which besides the definite risk factors, also include the following aspects as additional risk factor; a high NSAID dose (OR 1.45), use of SSRIs (RR; 2.8-4.6), co-morbidity (specifically heart failure (OR 5.9) and diabetes mellitus (OR:3.1)). The guidelines of the American college of Rheumatology<sup>22</sup> identify serious co-morbidity as a risk factor, but they do not specify what is meant with co-morbidity. The guideline of the American College of Gastroenterology, originating from 1998<sup>23</sup>, does not identify co-morbidity as a risk factor. Apart from other evidence-based guidelines, we consulted this (obsolete) guideline while developing the risk sets. In February 2009, Lanza et al. updated the guidelines of the American College of Gastroenterology<sup>24</sup>. In this recent version of the guidelines, they identify 'chronic debilitating disorders' as a risk factor, especially cardiovascular disease. Also the National Health Service (NHS) Clinical Knowledge Summaries and NHS National Institute for Clinical Excellence (NICE)<sup>25, 26</sup> state that serious co-morbidity is a risk factor for developing UGI ulcer/complication during NSAID therapy. Also this guideline was published in 2009, while this research was already ongoing. The NICE guidance specifies serious cormorbidity as follows: cardiovascular disease, hepatic or renal impairment (including dehydration), diabetes, or hypertension.

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We chose to include diabetes and cardiovascular disease in risk set 2, as those were explicitly stated in the Dutch guidelines.

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Furthermore, we reasoned that most of the patients with co-morbidity would probably be older than 65 years of age. Age is therefore a good proxy for co-morbidity. We were strengthened in this reasoning, when we saw that the findings between risk set 1 and risk set 2 were very similar.

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We have referred to the Dutch guideline in the Methods section in the paragraph 'Identification of high-risk patients'.

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3 **3. It is also puzzling why the authors allowed low-dose H2RA use to be considered**  
4 **adequate protective therapy. They acknowledge this as a limitation. Would it not**  
5 **be possible to redefine appropriate use to adjust for this?**  
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8 *Answer: While this consideration is indeed important, the aim of the study was to determine*  
9 *whether general practitioners' prescription of a preventive strategy to NSAID users reflected*  
10 *an intention to comply with (inter)national guidelines, and not whether the correct dosage*  
11 *was prescribed. We are not measuring the effectiveness of the preventive measures in this*  
12 *paper. We have taken a conservative approach in assessing under-prescription by not*  
13 *classifying these patients as being under-prescribed. Overall the effect is small due to the*  
14 *relative small contribution of H2RA to the GPA use.*  
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17 **4. The statement on page 5 that "Only misoprostol...has been studied using primary**  
18 **clinical endpoints..." is incorrect. Several studies have used hospitalization for**  
19 **complications as the outcome measured for gastroprotective therapy (example:**  
20 **Ray et al. Gastroenterology. 2007;133:790-8).**  
21

22 *Answer: We have adopted this suggestion and refer to the suggested reference in the*  
23 *introduction section.<sup>27</sup>*  
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26 **5. When reviewing figure 1 the withdrawal of rofecoxib does not appear to**  
27 **substantially change the shape of the curve of appropriate therapy. While the**  
28 **difference between 56.6% and 60.1% may be barely statistically significant**  
29 **(p=0.04) there is no indication that it is clinically significant. The authors stretch**  
30 **the results into concluding that rofecoxib withdrawal "...may have resulted in**  
31 **some UGI events...". There are no data in the paper to support this speculation.**  
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33 *Answer: We have further analyzed the effect of rofecoxib withdrawal and have refined and*  
34 *toned down the conclusions (see reviewer 2).*  
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