Gastroenterology 2014;147:784–792

Risk of Upper Gastrointestinal Bleeding From Different Drug Combinations

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This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of these exercises, successful learners will be able to recognize, differentiate and apply the risk and excess risk of upper gastrointestinal bleeding associated with use of non-steroidal anti-inflammatory drugs and low-dose aspirin combined with other drugs.

Podcast interview: www.gastro.org/gastropodcast. Also available on iTunes. See Covering the Cover synopsis on page 721; see editorial on page 730.

BACKGROUND & AIMS: Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin increases the risk of upper gastrointestinal bleeding (UGIB). Guidelines suggest avoiding certain drug combinations, yet little is known about the magnitude of their interactions. We estimated the risk of UGIB during concomitant use of nonselective (ns) NSAIDs, cyclooxygenase -2 selective inhibitors (COX-2 inhibitors), and low-dose aspirin with other drugs. **METHODS:** We performed a case series analysis of data from 114,835 patients with UGIB (930,888 person-years of follow-up) identified from 7 population-based health care databases (approximately 20 million subjects). Each patient served as his or her own control. Drug exposure was determined based on prescriptions of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin, alone and in combination with other drugs that affect the risk of UGIB. We measured relative risk (incidence rate ratio [IRR] during drug exposure vs nonexposure) and excess risk due to concomitant drug exposure (relative excess risk due to interaction [RERI]). **RESULTS:** Monotherapy with nsNSAIDs increased the risk of diagnosis of UGIB (IRR, 4.3) to a greater extent than monotherapy with COX-2 inhibitors (IRR, 2.9) or low-dose aspirin (IRR, 3.1). Combination therapy generally increased the risk of UGIB; concomitant nsNSAID and corticosteroid therapies increased the IRR to the greatest extent (12.8) and also produced the greatest excess risk (RERI, 5.5). Concomitant use of nsNSAIDs and aldosterone antagonists produced an IRR for UGIB of 11.0 (RERI, 4.5). Excess risk from concomitant use of nsNSAIDs with selective serotonin reuptake inhibitors (SSRIs) was 1.6, whereas that from use of COX-2 inhibitors with SSRIs was 1.9 and that for use of low-dose aspirin with SSRIs was 0.5. Excess risk of concomitant use of nsNSAIDs with anticoagulants was 2.4, of COX-2 inhibitors with anticoagulants was 0.1, and of low-dose aspirin with anticoagulants was 1.9. **CONCLUSIONS:** Based on a case series analysis, concomitant use of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with SSRIs significantly increases the risk of UGIB. Concomitant use of nsNSAIDs or low-dose aspirin, but not COX-2 inhibitors, with corticosteroids, aldosterone antagonists, or anticoagulants produces significant excess risk of UGIB.

Keywords: Prostaglandin; Stomach; Side Effects; Treatment.

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Upper gastrointestinal bleeding (UGIB) has a major impact on patients' quality of life and public health care costs.[1] Although great improvements in prevention and treatment of UGIB have been achieved in recent decades, UGIB-related morbidity and mortality remain

Abbreviations used in this paper: **AP, proportion attributable to interaction; ATC, Anatomical Therapeutic Chemical; CI, confidence interval; COX-2 inhibitor, cyclooxygenase-2 selective inhibitor; EHR, electronic health record; GPA, gastroprotective agent; HSD, Health Search/CSD Longitudinal Patient Database; ICD, International Classification of Diseases; IPCI, Integrated Primary Care Information; IRR, incidence rate ratio; IRRp, pooled incidence rate ratio; NSAID, nonsteroidal anti-inflammatory drug; nsNSAID, nonselective nonsteroidal anti-inflammatory drug; PAR, population attributable risk; PPV, positive predictive value; RERI, relative excess risk due to interaction; S, synergy index; SCCS, self-controlled case series; SSRI, selective serotonin reuptake inhibitor; UGIB, upper gastrointestinal bleeding.**

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2014.06.007

substantial.[2] Most previous studies have focused on risks associated with use of nonsteroidal anti-inflammatory drugs (NSAIDs), which is one of the most common causes of UGIB. Clinical guidelines therefore recommend preventive strategies for at-risk patients treated with NSAIDs, including coprescription of proton pump inhibitors. Another preventive strategy is use of cyclooxygenase-2 selective inhibitors (COX-2 inhibitors), developed as a safer alternative to nonselective (ns)NSAIDs, especially among high-risk patients.[3]

Use of low-dose aspirin is considered the standard of care for cardiovascular prevention. However, low-dose aspirin is also known to increase the risk of UGIB.[4] The relative risk of UGIB associated with current use of low-dose aspirin compared with no use ranges from 1.6 to 4.0.[4–6] Thus, coprescription of gastroprotective agents (GPAs) is also recommended for at-risk patients treated with low-dose aspirin as a key strategy to minimize upper gastrointestinal events.[7] Adherence to preventive strategies in patients treated with low-dose aspirin is especially important given that an estimated 20% of these patients will also use NSAIDs and approximately 35% of the elderly population regularly uses low-dose aspirin.[7]

Clinical guidelines suggest avoiding use of certain drugs in combination with nsNSAIDs as well as COX-2 inhibitors; these drugs include corticosteroids, anticoagulants, selective serotonin reuptake inhibitors (SSRIs), and antiplatelets.[8] However, the concurrent use of NSAIDs and these other drugs has not been widely studied, and it remains unknown if, and to what extent, combinations of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with specific other drug groups exert synergistic effects on the risk of UGIB.

Understanding drug synergism is important in developing strategies to minimize the risk of UGIB, particularly in elderly patients who are at high risk for UGIB and are likely to use multiple drugs.[9,10] Therefore, we aimed to estimate the magnitude of interaction between nsNSAIDs, COX-2 inhibitors, or low-dose aspirin and specific drug groups reported to affect the risk of diagnosed UGIB.

Patients and Methods

Data Sources

Data were obtained from a network of 7 electronic health record (EHR) databases from 3 countries. The EU-ADR Project (Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge) has successfully established a platform that integrates data from various repositories of European EHRs for evaluation of drug safety.[11]

We analyzed data from 3 primary care databases (Integrated Primary Care Information [IPCI, The Netherlands]; Health Search/CSD Longitudinal Patient Database [HSD, Italy]; and Pedianet [Italy]) and 4 administrative/claims databases (Aarhus University Hospital Database [Aarhus, Denmark], PHARMO Institute [PHARMO, The Netherlands], and the regional databases of Lombardy [UNIMIB, Italy] and Tuscany [ARS, Italy]). The characteristics and study periods of the databases are shown in Table 1. All of these databases have been

Table 1. Database Characteristics and Number of Cases of UGIB per Database

Database (country)	No. of cases of UGIB	Total person-time of follow-up (*person-years*)	Type of database	Disease coding system	Drug coding system	Study period	Relative contribution of UGIB cases to data set pooled at patient level (%)	PPV of codes used to identify UGIB in database[a]
Aarhus (Denmark)	11,923	75,963	Administrative/claims	ICD-10	ATC	1999–2008	10.4	77% (95% CI, 69–83)
ARS (Italy)	11,519	49,417	Administrative/claims	ICD-9-CM	ATC	2002–2008	10.0	72% (95% CI, 65–78)
UNIMIB (Italy)	69,384	680,254	Administrative/claims	ICD-9-CM	ATC	2003–2006	60.4	72% (95% CI, 65–78)[b]
HSD (Italy)	5963	37,038	Primary care	ICD-9-CM + free text	ATC	2003–2009	5.2	78% (95% CI, 72–83)
Pedianet (Italy)	88	375	Primary care	ICD-9-CM	ATC	2003–2007	0.08	
IPCI (Netherlands)	9951	37,294	Primary care	ICPC + free text	ATC	1996–2011	8.7	21% (95% CI, 18–26)
PHARMO (The Netherlands)	6007	50,547	Hybrid (administrative with linkage to primary care)	ICD-9-CM	ATC	1998–2007	5.2	

ICPC, International Classification for Primary Care.
[a]PPVs were calculated in a validation study[17] showing that the PPV values did not affect the magnitude of risk estimates from drug-associated UGIB.
[b]The UNIMIB database is similar in setting and clinical characteristics to ARS, and the PPV of the ARS database may be extrapolated to the UNIMIB database.

extensively used in epidemiological studies.[11–14] Subjects can enter and may also leave the database at any time for several reasons (eg, death, moving out of the region, leave of practice). The primary care databases capture all prescriptions from general practitioners and some from secondary care (eg, repeat prescriptions). The study protocol was approved by the review board for all databases.

Study Design

The study population included all people registered in the database network with at least 1 year of valid and continuous data. A self-controlled case series (SCCS) analysis was performed on all identified cases of UGIB. The SCCS is a case-only study (ie, control subjects are not included) in which the relative incidence of UGIB is estimated for exposed and nonexposed time in each case.[15,16] Each case serves as its own control. The SCCS method assumes that all cases in the analysis should (1) have exposed and unexposed person-time, (2) experience an UGIB, and (3) contribute follow-up time before and after the UGIB. The primary advantage of the SCCS is that it automatically adjusts for confounding factors that are fixed within subjects (ie, genetic factors, sex, chronic disease, or other comorbidity).

Case Definition

From the study population, we identified all subjects who experienced an UGIB during follow-up by using pertinent disease codes from the different coding systems in each database.[11] UGIB was assessed by using hospital discharge codes (in claims databases) or general practitioner diagnosis/recordings (in primary care databases). We included all codes indicating gastroduodenal ulcers and hemorrhages, melena, and hematemesis. Codes for variceal bleeding specifically were not included. We only included codes corresponding to an acute UGIB, because for the SCCS the outcome should be an acute event with a clear disease onset. Supplementary Table 1 shows the corresponding codes for each coding system. A free-text search of clinical narratives was performed in IPCI and HSD. A validation study was conducted in 4 of the databases used in the current study[17] and showed a high concordance for International Classification of Diseases (ICD)-9 (positive predictive value [PPV] of 78% and 72%) and ICD-10 codes (PPV of 77%) that was not seen with the International Classification for Primary Care coding system (PPV of 21% for codes and free text only).

Definition of Exposure

We focused on concomitant use of nsNSAIDs, COX-2 inhibitors, and low-dose aspirin with other drugs reported to be associated with an increase or decrease in risk of UGIB. The drug groups of interest were as follows: (1) nsNSAIDs,[4] (2) COX-2 inhibitors,[18] (3) low-dose aspirin,[4,14] (4) high-dose aspirin,[19] (5) corticosteroids,[5,20–24] (6) SSRIs[25] (citalopram, fluoxetine, and paroxetine were assessed individually), (7) GPAs,[25,26] (8) aldosterone antagonists,[13,27] (9) calcium channel blockers,[28,29] (10) anticoagulants,[4,30] (11) antiplatelets,[4,30] and (12) nitrates.[4,26] Drugs of interest were categorized according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system.[31] Supplementary Table 2 shows the corresponding ATC codes. We created mutually exclusive exposure categories: no use of any drug of interest (reference group), use of only one drug of interest, or concurrent use of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with one other drug of interest (Supplementary Figure 1). All other combinations of drugs of interest and combinations of >2 drugs were combined in a separate category. Fixed drug combinations were included in the corresponding drug combination group. Duration of exposure was calculated by dividing the total number of prescribed/dispensed pills by the number of pills per day or defined daily dosages. We assumed that all dispensed drugs were consumed. All exposed and unexposed person-time was therefore included in the analysis. Drug dose and frequency were not taken into account because such information is not consistently recorded in all databases.

Main Statistical Analyses

To estimate the relative incidence of UGIB, incidence rate ratios (IRRs) with 95% confidence intervals (CIs) were obtained using conditional Poisson regression by comparing the incidence rate of UGIB during periods of drug exposure with the incidence rate during all other observed time periods. Age-adjusted IRRs were calculated within each database and by pooling all data together (IRRp). To account for heterogeneity between the databases, pooling of data was also performed by a random effects meta-analytic model on the database-specific risk estimates resulting in an overall IRR.

To estimate the magnitude of drug interaction (excess risk), the following measures were calculated: the relative excess risk due to interaction (RERI), the proportion attributable to interaction (AP), and the synergy index (S).[32] Interaction on an additive scale meant that the observed effect of the drug combination was larger than the sum of the effects of the drugs separately but less than multiplicative. If the IRR of the combination was more than the sum of the 2 drugs separately, interaction (at least on an additive scale) was present. Corresponding 95% CIs were also calculated for the RERI using the Hosmer–Lemeshow delta method.[33] The estimated measure of the RERI, AP, or S itself does not provide any information on risk and cannot be interpreted in isolation. However, based on the relative risk, it can be concluded that an excess risk is present when the RERI is larger than 0 and the CIs around it do not cross 0. Additionally, it may be concluded that there is more excess risk with a RERI of 1 than with a RERI of 2 (see Supplementary Table 3 for more details).

Population attributable risk (PAR) was calculated to estimate the proportion of UGIB in the general population that is attributable to concomitant use of drugs using the following formula: $\mathrm{PAR} = (p * [\mathrm{IRR} - 1])/(p * [\mathrm{IRR} - 1] + 1)$.[12] For this calculation, drug utilization data from the participating databases (data not shown) were used to derive the prevalence of exposure (p) to which the IRR pertained.

Sensitivity Analyses

Because increasing age confers additional risk of UGIB, analyses by stratifying on age (with a cutoff of 60 and 70 years) and sex were conducted to investigate effect modification by age or sex. To explore the possibility of confounding by contraindication, we performed a sensitivity analysis by truncating the drug exposure at the time of the event. A pooled analysis excluding the IPCI database was performed due to the low PPV in IPCI.

Results

Risk of UGIB With Drug Monotherapy

In total, 114,835 patients with UGIB (cases) with corresponding follow-up of 930,888 person-years were included in the analysis (Table 1). For all drugs of interest, monotherapy showed a significantly increased relative risk compared with no use of any of the drugs of interest. Monotherapy with nsNSAIDs was associated with an IRRp of 4.3 (95% CI, 4.1–4.4), which is higher than monotherapy with either COX-2 inhibitors (IRRp, 2.9; 95% CI, 2.7–3.2) or low-dose aspirin (IRRp, 3.1; 95% CI, 2.9–3.2) (Table 2). The risk of diagnosed UGIB for all other drugs ranged from 1.6 for calcium channel blockers to 4.1 for corticosteroids (Table 2). IRRs were also estimated for 3 individual SSRIs and yielded an IRRp of 2.0 (95% CI, 1.6–2.5) for fluoxetine, 2.3 (95% CI, 2.1–2.5) for citalopram, and 1.9 (95% CI, 1.7–2.2) for paroxetine, all similar to the IRRp for the overall SSRI class of 2.1 (95% CI, 1.9–2.2).

Supplementary Table 4 shows the total duration of exposure to each drug and drug combination, and Supplementary Table 5 shows the distribution of events across age groups and sex.

Risk of UGIB With Drug Combinations

Generally, concomitant use of nsNSAIDs with other drugs showed a higher risk of diagnosed UGIB compared with a combination with low-dose aspirin or COX-2 inhibitors (Table 2). To estimate the risk of diagnosed UGIB for drug combinations with nsNSAIDs, COX-2 inhibitors, or low-dose aspirin, estimates of the separate drugs of interest were pooled. Combinations of any of the drugs of interest with nsNSAIDs yielded the highest IRR (6.9; 95% CI, 5.3–9.1), followed by combinations with low-dose aspirin (4.6; 95% CI, 3.6–6.0) and with COX-2 inhibitors (4.2; 95% CI, 3.0–5.9).

Looking at separate drug classes, the highest risk of diagnosed UGIB was observed for the combination of nsNSAIDs and corticosteroids (IRRp, 12.8; 95% CI, 11.2–14.7), which was higher than the risk with use of low-dose aspirin and corticosteroids (IRRp, 8.4; 95% CI, 7.1–9.8) or COX-2 inhibitors and corticosteroids (IRRp, 6.0; 95% CI, 4.3–8.3). Use of aldosterone antagonists with nsNSAIDs resulted in an IRRp of 11.0 (95% CI, 8.6–14.0), which was also higher than the combined use of aldosterone antagonists and low-dose aspirin (IRRp, 5.0; 95% CI, 4.1–6.1) or that with COX-2 inhibitors (IRRp, 4.0; 95% CI, 2.1–7.8).

The combination of anticoagulants with nsNSAIDs showed an IRRp of 8.7 (95% CI, 7.3–10.4), which was higher than the combination of anticoagulants with low-dose aspirin (IRRp, 6.9; 95% CI, 5.9–8.2) or that with COX-2 inhibitors (IRRp, 5.0; 95% CI, 3.2–7.8). Combinations with SSRIs were associated with a 5-fold, 6-fold, and 7-fold increased risk for low-dose aspirin, COX-2 inhibitors, and nsNSAIDs, respectively. When using a meta-analytic approach by applying a random effects model, substantial heterogeneity across databases was observed for some drug combinations but generally resulted in minor attenuations of the effects (Supplementary Table 6).

Excess Risk

Excess risk due to concomitant drug use, measured by additive interaction of nsNSAIDs/COX-2 inhibitors/low-dose aspirin use with other drugs, is shown in Figure 1 and

Table 2. Relative Risk of Diagnosed UGIB During Exposure to Specific Drug Groups (With Corresponding 95% CIs) in Monotherapy and in Combination With Other Drugs

	Monotherapy		Combination with					
			nsNSAIDs		COX-2 inhibitors		Low-dose aspirin	
Drug groups	n	IRR (95% CI)	n	IRR (95% CI)	n	IRR (95% CI)	n	IRR (95% CI)
No drug[a]	69,664	1.00 (reference)	NA		NA		NA	
nsNSAIDs	3327	4.27 (4.11–4.44)	NA		NA		416	6.77 (6.09–7.53)
COX-2 inhibitors	635	2.90 (2.67–3.15)	NA		NA		131	7.49 (6.22–9.02)
Low-dose aspirin	4733	3.05 (2.94–3.17)	416	6.77 (6.09–7.53)	131	7.49 (6.22–9.02)	NA	
Corticosteroids	1378	4.07 (3.83–4.32)	244	12.82 (11.17–14.72)	40	5.95 (4.25–8.33)	190	8.37 (7.14–9.81)
SSRIs	1793	2.06 (1.94–2.18)	210	6.95 (5.97–8.08)	65	5.82 (4.45–7.62)	401	4.60 (4.09–5.17)
GPAs	5279	1.61 (1.56–1.66)	678	3.90 (3.59–4.24)	95	2.37 (1.92–2.93)	607	2.54 (2.32–2.78)
Aldosterone antagonists	1211	3.27 (3.06–3.50)	76	11.00 (8.63–14.03)	10	4.02 (2.07–7.81)	131	5.01 (4.13–6.08)
Calcium channel blockers	3546	1.57 (1.51–1.63)	363	4.45 (3.98–4.98)	77	3.11 (2.46–3.93)	1123	3.07 (2.86–3.29)
Anticoagulants	1760	3.01 (2.85–3.19)	143	8.69 (7.30–10.35)	21	5.01 (3.21–7.82)	168	6.94 (5.86–8.22)
Antiplatelets (excluding low-dose aspirin)	994	1.74 (1.61–1.87)	87	6.50 (5.19–8.15)	9	1.73 (0.87–3.44)	246	5.49 (4.71–6.41)
Nitrates	2572	2.55 (2.43–2.68)	172	5.82 (4.97–6.82)	49	5.09 (3.79–6.82)	859	3.79 (3.51–4.10)

NOTE. n refers to the number of UGIB events during exposure to specific drug groups (the total number does not add up to 114,835 because of diagnoses of UGIB in "other drug category").
NA, not applicable.
[a]No use of the predefined drugs of interest.

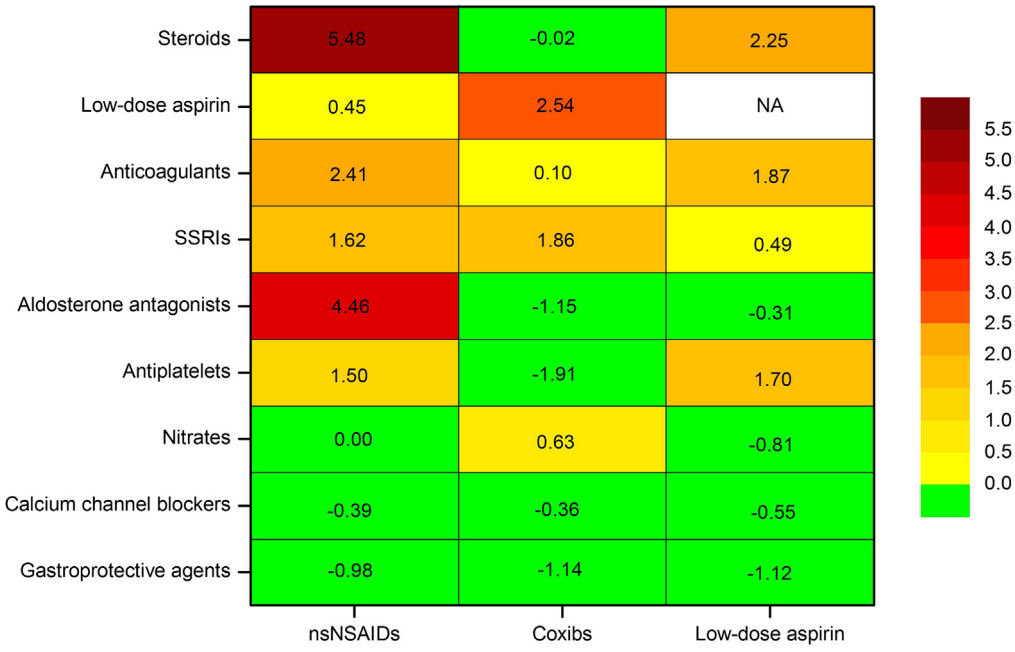

Figure 1. Heat map of interaction of nsNSAIDs, COX-2 inhibitors, and low-dose aspirin in combination with other drugs. The color intensity of the heat map is based on the RERI. *Green* represents no interaction, and from *yellow* toward *red* represents the presence and increasing strength of interaction. NA, not applicable.

Supplementary Table 3. The highest excess risk was observed for the combination of nsNSAIDs and corticosteroids (RERI, 5.5; 95% CI, 3.7–7.3). Corticosteroids had significant interaction with low-dose aspirin as well, but not with COX-2 inhibitors. Aldosterone antagonists showed significant interaction with nsNSAIDs (RERI, 4.5; 95% CI, 1.8–7.1) but not with low-dose aspirin or COX-2 inhibitors. Anticoagulants showed significant interaction with nsNSAIDs and with low-dose aspirin but not with COX-2 inhibitors. Combinations of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with GPAs or nitrates did not show excess NSAID-associated risk of UGIB.

PAR

Based on an estimated 0.04% prevalence of nsNSAID use, the proportion of cases of UGIB in the general population attributable to nsNSAID monotherapy was 11.8%. In other words, of 100 people experiencing UGIB while exposed to nsNSAID monotherapy, 11.8% of these cases were attributable to nsNSAID monotherapy. The corresponding proportion attributable to corticosteroid monotherapy was 10.4% (estimated prevalence of corticosteroid use of 0.04%), while the PAR for concurrent NSAID and corticosteroid use was 6.4%. The PAR for other drugs is shown in Supplementary Table 7.

Sensitivity Analyses

Age stratification showed that subjects who were 60 years of age or older had higher IRRs of diagnosed UGIB than younger subjects (younger than 60 years) except for the combination of nsNSAIDs and anticoagulants and of COX-2 inhibitors and corticosteroids. No significant difference in risk between male and female subjects was observed.

Sensitivity analyses with truncation of follow-up at the time of UGIB (to avoid confounding by contraindication) showed that the exposure pattern of the drugs (and in particular the nsNSAIDs) did not change after UGIB (Supplementary Figure 2). When adjusting for acute myocardial infarction and anaphylactic shock, the results were similar (Supplementary Figure 3). When excluding IPCI from the main analysis, the results were also similar (Supplementary Figure 4).

Discussion

We determined the magnitude of increased risk of diagnosed UGIB when nsNSAIDs, COX-2 inhibitors, and low-dose aspirin were combined with specific drug classes that may be independently associated with diagnosed UGIB. Although it may seem reasonable to assume synergistic effects with concurrent use of drugs that independently increase risk, these effects have rarely been investigated. To study the risk of diagnosed UGIB during use of specific drug combinations, it is essential to have a large number of data and an efficient study design. For this study, we used data from a huge network of European electronic health care databases, representing more than 20 million subjects. In addition, the SCCS is a suitable and efficient method to address the question of excess risk of UGIB with drug combinations while at the same time controlling for time-fixed confounding factors as well as confounding by indication. We observed that, overall, the risk of UGIB during concomitant use of drugs was significantly higher compared with what would have been expected based on the sum of the risk of the individual drugs. The magnitude of statistical additive interaction, which may be seen as a surrogate measure for biological synergism, was highest for the

combination of nsNSAIDs with corticosteroids and the combination of nsNSAIDs with aldosterone antagonists. In line with previous studies, we observed that the risk of nsNSAID monotherapy was higher than that of monotherapy with low-dose aspirin or COX-2 inhibitors.[4,24] The risk of UGIB was always higher for drug combinations with nsNSAIDs than that for low-dose aspirin or COX-2 inhibitors.

Given that nsNSAIDs, COX-2 inhibitors, and low-dose aspirin are commonly used by elderly patients, with a self-reported prevalence of 35%,[7] the observed risks in the current study emphasize the substantial risk of use of nsNSAIDs, COX-2 inhibitors, and low-dose aspirin in the general population. This is especially true considering that elderly patients are inherently at higher risk due to physiological aging mechanisms.[10,34]

Corticosteroids

Interestingly, we observed that the risk of diagnosed UGIB with use of corticosteroid monotherapy was of the same magnitude as that with nsNSAID monotherapy. Previous studies have shown inconsistent results with respect to risk of UGIB with corticosteroids.[20,21,23] Because nsNSAIDs are known to pose a greater risk of inducing upper gastrointestinal ulcers compared with COX-2 inhibitors, interaction between corticosteroids and nsNSAIDs, but not with COX-2 inhibitors, was expected.[35] The suggested pathophysiological mechanism behind this increased risk for corticosteroids is inhibition of ulcer healing.[39] Previous studies estimated the magnitude of this risk to range from 9-fold to 12-fold,[21–24,35] although drug interaction between corticosteroids and nsNSAIDs was not consistently observed.[23] Aside from the small numbers of concomitant users of nsNSAIDs and corticosteroids in previous studies,[20–22,24] there were also differences in outcome definitions and reference categories used (varying from no drug use in the past 7 days[23] to 180 days[24]). According to guidelines, corticosteroids should be considered an independent risk factor for UGIB and gastroprotective measures should be prescribed to patients treated with corticosteroids.[8] To translate the observed risks to the general population, we estimated the PAR due to drug use. The PAR was 6.4% for concurrent use of nsNSAIDs and corticosteroids, 11.8% for nsNSAID monotherapy, and 10.4% for corticosteroid monotherapy. This implies that the proportion of UGIB in the general population attributable to the previously mentioned therapies was high, given the assumption that the association between drug use and occurrence of UGIB is causal. Although this can be reduced by correct use of gastroprotection, future studies should investigate the risk of a combination of corticosteroids and nsNSAIDs with GPAs compared with a combination of corticosteroids and COX-2 inhibitors.

SSRIs

SSRIs showed statistically significant interaction with nsNSAIDs and COX-2 inhibitors but not with low-dose aspirin. From a biological point of view, this interaction seems plausible because SSRIs decrease the serotonin level, resulting in impaired thrombocyte aggregation and an increased risk of bleeding in general, including UGIB. Based on this mechanism, NSAIDs, and low-dose aspirin to a lesser extent,[36,37] are suspected to produce synergism with SSRIs. Although previous studies report an increased risk between 2.6-fold and 16-fold for UGIB with use of SSRIs and NSAIDs when compared with drug monotherapy,[36–38] others could not show interaction.[25,38] However, these were not performed primarily on NSAID users,[37] did not control for important confounders,[36,37] and did not create mutually exclusive drug exposure groups.[36]

Aldosterone Antagonists

The risk of aldosterone antagonists concurrently used with nsNSAIDs was higher than when used with low-dose aspirin or COX-2 inhibitors. Earlier, case reports indicated a possible association between aldosterone antagonists and UGIB or UGI ulcers.[39] More recently, case-control studies confirmed this association.[13,27] The potential mechanism may be related to impaired healing of gastric and duodenal erosions due to inhibition of fibrous tissue formation.[13]

Anticoagulants and Antiplatelets

Use of anticoagulants is an acknowledged risk factor for UGIB, with previous studies showing risks from 5.3-fold to 6.5-fold for concomitant use of anticoagulants with low-dose aspirin,[18,30] 4.6-fold with COX-2 inhibitors,[18] and up to 19-fold with nsNSAIDs.[4] In the current study, anticoagulants showed a higher risk when combined with low-dose aspirin than with nsNSAIDs or COX-2 inhibitors. The difference between these findings and previous studies may rely on less stringent control for confounders in previous studies than in the current study; furthermore, with the SCCS, all within-person confounders that are fixed over time are immediately dealt with. In line with others, concomitant use of low-dose aspirin eliminates the presumed benefit of COX-2 inhibitors over nsNSAIDs on the risk of upper gastrointestinal adverse events.[4,40–42]

GPAs

The increased risk of diagnosed UGIB observed with the concomitant use of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with GPAs seems counterintuitive; however, no interaction was observed for any of these drug combinations. The increased risk is thus more likely explained by the phenomenon of "channeling," in which high-risk patients receive concurrent prescriptions for GPAs whereas low-risk patients do not. Another explanation is protopathic bias, because GPAs might be given as treatment for first symptoms of UGIB.[43]

Age-Related COX Enzyme Selectivity

As expected, the risk of diagnosed UGIB with use of the drugs of interest (monotherapy), except antiplatelets, was lower for subjects younger than 60 years of age than for subjects older than 60 years of age. Surprisingly, the difference in risk between younger and older subjects was larger for drug combinations with COX-2 inhibitors than for combinations with nsNSAIDs. Application of a cutoff level of

70 years of age did not yield different results. However, using an age cutoff of 70 years showed excess risk for the combination of COX-2 inhibitors and corticosteroids, whereas this was not present with an age cutoff of 60 years. In elderly subjects, prostaglandin levels decreased due to decreased conversion of arachidonic acid to prostaglandin, resulting in an increased risk of UGIB. This partially accounts for the recommendation to use gastroprotective measures in elderly patients.[8] We hypothesize that COX enzyme selectivity with aging might explain the difference in drug interaction between nsNSAIDs and COX-2 inhibitors. In animal studies, older rats expressed different COX enzyme mRNA levels than younger rats and an impaired response of prostaglandin synthesis to irritants with older age was shown.[9] In humans, higher basal acid output in the stomach among elderly patients[34] results in lower mucosal prostaglandin concentrations in the stomach and duodenum.[44] However, these observations were related to the COX-1 enzyme and do not explain our findings. Because the SCCS, by definition, controls for confounders fixed within person and the baseline risk, this also does not explain the difference between younger and older subjects for COX-2 inhibitor combinations in the current study. Future studies are needed to elucidate these findings.

Strengths and Limitations

A major strength of the current study is that while previous studies reported data from single centers[4] or single databases,[9,13,18,20–22,25,30,36–38] we performed a multidatabase study to increase the power for studying the risk of UGIB due to drug synergism of relatively uncommon drug combinations. Additionally, we specifically looked at drug combinations of low-dose aspirin, nsNSAIDs, and COX-2 inhibitors separately.[14]

However, we acknowledge the following limitations. A key assumption of the SCCS is that the exposure distribution within the observation period and the observation period itself must be independent of the time of the event. This assumption could have been violated, because the standard of care considers use of an nsNSAID without gastroprotection as relatively contraindicated after occurrence of UGIB. However, sensitivity analyses involving truncation of follow-up at the time of the event showed that drug exposure of nsNSAIDs did not change after the event (ie, results obtained were similar to those from the original analysis), meaning that confounding by contraindication was unlikely to explain the findings (Supplementary Figure 2). The health condition of a subject may vary over time at all phases of follow-up. Nevertheless, many chronic conditions, such as type 2 diabetes mellitus, hypertension, and peripheral vascular disease, are relatively stable diseases and vary little over time. We have no reason to believe that this will influence the estimates. The sensitivity analysis adjusting for acute myocardial infarction and anaphylactic shock did not yield different estimates as compared with the main analysis (Supplementary Figure 3). In addition, the age of a subject increases during follow-up, and given that older subjects are at higher risk than when at a younger age, we also adjusted for age in the analysis. Residual confounding due to an underlying clinical condition that led to a drug prescription, although unlikely, cannot be ruled out.

Misclassification of exposure time of NSAIDs could have occurred, because NSAIDs are often used intermittently rather than continuously, although this is probably true more for over-the-counter use of NSAIDs. Over-the-counter use of NSAIDs is not captured in EHR databases and could have led to a potential underestimation of use. However, the proportion of NSAIDs used over the counter is limited given that prescribed NSAIDs are reimbursed whereas over-the-counter drugs are not. Although information on drug use differed between dispensing and prescribing data, patterns of use of NSAID classes varied among different countries but were similar among different databases in the same country.[11] In addition, we defined nonexposure as no use of any of the drugs of interest instead of no use of any drug. We mitigated misclassification of nonexposure by restricting the analysis to drugs that have been reported to significantly increase or decrease the risk of UGIB. We used a rather broad definition of UGIB, including all gastroduodenal ulcers and hemorrhages, which may have led to less severe cases of UGIB in the primary care databases compared with administrative databases. A validation study was performed in 4 databases. For this purpose, a sample of UGIB cases was manually validated by medical chart review to characterize and document any outcome misclassification related to drug-associated UGIB. This showed that misclassification was uncommon and did not affect the magnitude of risk estimates.[17] Second, when excluding the data set with the lowest PPV for diagnosis of UGIB in the current study, the estimates were not different from the main analysis. In addition, incidence rates of UGIB in these databases did not differ substantially across European countries and are in accordance with the literature.[11] Variceal bleeding was not included as part of the definition of UGIB. However, we cannot rule out that variceal bleeding may have been wrongly coded as a code more specific for UGIB than variceal bleeding.

Nevertheless, nondifferential misclassification cannot be ruled out and may have resulted in an underestimation of the true estimates. Finally, we did not take any carryover effect or dose of drug exposure into account, which potentially limits the generalizability concerning causality of the associations.

The SCCS assumes that observation periods should be independent of event times, which may be violated if subjects die quickly after the event. By applying an alternative method[45] in one database, taking this assumption into account by weighting the post-event periods, the estimates remained within the 95% confidence limits of the original analysis.

When estimating the magnitude of interaction, the presence and direction depend on the scale used: either additive or multiplicative interaction. In the current study, multiplicative interaction was only observed for the combination of low-dose aspirin and antiplatelets. However, statistical interaction does not directly imply biological interaction.[32]

In conclusion, concomitant use of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with SSRIs is associated with a

significantly increased risk of diagnosed UGIB. Concomitant use of nsNSAIDs or low-dose aspirin, but not COX-2 inhibitors, with corticosteroids, aldosterone antagonists, or anticoagulants was associated with an increased and excess risk of UGIB. These findings may help clinicians in tailoring therapy to minimize UGIB adverse events and are especially valuable in elderly patients who are likely to use multiple drugs concurrently.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at http://dx.doi.org/10.1053/j.gastro.2014.06.007.

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Received September 2, 2013. Accepted June 11, 2014.

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Conflicts of interest
The authors disclose the following: V.E.V., as an employee of Erasmus University Medical Center, has conducted research for AstraZeneca. M.J.S. has accepted a full-time position at Janssen R&D since completion of this research. R.H. is scientific director of PHARMO Institute, which performs studies for various pharmaceutical companies. G.M. has started working for the European Medicines Agency since completion of this research. M.C.J.M.S is coordinating a research group that has unconditional research grants from Pfizer, Novartis, and Lilly, none of which are related to this research. The remaining authors disclose no conflicts.

Funding
EU-ADR is a research and development project funded by the European Commission Seventh Framework Programme (FP7/2007–2013) under grant no. 215847–The EU-ADR Project. The funding agency had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Supplementary Table 1. Definition of Codes for UGIB Among Different Coding Systems

ICD-9-CM (ARS, HSD, Pedianet, PHARMO, UNIMIB)		ICD-10 (Aarhus)		International classification for primary care (IPCI)	
531.00/531.01	Gastric ulcer, acute with hemorrhage	K25.0	Gastric ulcer, acute with hemorrhage		
531.10	Gastric ulcer, acute with perforation	K25.1	Gastric ulcer, acute with perforation		
531.20/531.21	Gastric ulcer, acute with hemorrhage and perforation	K25.2	Gastric ulcer, acute with both hemorrhage and perforation		
532.00/532.01	Duodenal ulcer, acute with hemorrhage	K26.0	Duodenal ulcer, acute with hemorrhage	D85	Duodenal ulcer
532.10	Duodenal ulcer, acute with perforation	K26.1	Duodenal ulcer, acute with perforation		
532.20	Duodenal ulcer, acute with hemorrhage and perforation	K26.2	Duodenal ulcer, acute with both hemorrhage and perforation		
533.00	Peptic ulcer, site unspecified, acute with hemorrhage	K27.0	Peptic ulcer, site unspecified, acute with hemorrhage	D86	Peptic ulcer, other
533.10	Peptic ulcer, site unspecified, acute with perforation	K27.1	Peptic ulcer, site unspecified, acute with perforation		
533.20	Peptic ulcer, site unspecified, acute with hemorrhage and perforation	K27.2	Peptic ulcer, site unspecified, acute with both hemorrhage and perforation		
534.00/534.01	Gastrojejunal ulcer, acute with hemorrhage	K28.0	Gastrojejunal ulcer, acute with hemorrhage		
534.10	Gastrojejunal ulcer, acute with perforation	K28.1	Gastrojejunal ulcer, acute with perforation		
534.20/534.21	Gastrojejunal ulcer, acute with hemorrhage and perforation	K28.2	Gastrojejunal ulcer, acute with both hemorrhage and perforation		
535.01	Acute gastritis, with hemorrhage	K29.0	Acute hemorrhagic gastritis		
535.11	Atrophic gastritis, with hemorrhage				
535.41	Other specified gastritis, with hemorrhage				
535.51	Unspecified gastritis and gastroduodenitis, with hemorrhage				
578.0	Hematemesis, vomiting of blood	K92.0	Hematemesis	D15	Hematemesis
578.1	Blood in stool, melena	K92.1	Melena	D14	Melena
578.9	Hemorrhage of gastrointestinal tract, unspecified	K92.2	Gastrointestinal hemorrhage, unspecified		

Supplementary Table 2. Corresponding ATC Codes for Drug Groups of Interest[31]

Drug group	ATC codes[a]
nsNSAIDs	M01AB, M01AC, M01AE, M01AG, M01AX
COX-2 inhibitors	M01AH
Low-dose aspirin	B01AC06
High-dose aspirin	N02BA01, N02BA15
Corticosteroids	H02AB
SSRIs	N06AB
GPAs	A02BC, A02BA, A02BB01
Aldosterone antagonists	C03DA01, C03DA02, C03DA03, C03DA04
Calcium channel blockers	C08CA, C08CX01, C08DA01, C08DA02, C08DB01, C08EA01, C08EA02, C08EX01, C08EX02
Anticoagulants	B01AA, B01AB
Antiplatelets	B01AC, excluding B01AC06
Nitrates	C01DA02, C01DA04, C01DA05, C01DA07, C01DA08, C01DA09, C01DA13, C01DA14

[a]Includes all ATC codes for the drug group.

Supplementary Table 3. Additive Interaction Measures for Drug Combinations of nsNSAIDs, Low-Dose Aspirin, and COX-2 Inhibitors With Other Drugs

	RERI (95% CI)[a]	AP[a]	Synergy index[b]
nsNSAIDs + LDA	0.45 (−0.27 to 1.18)	0.07	1.09
nsNSAIDs + corticosteroids	**5.48 (3.71 to 7.26)**	**0.43**	**1.87**
nsNSAIDs + SSRIs	**1.62 (0.58 to 2.66)**	**0.23**	**1.38**
nsNSAIDs + gastroprotective agents	−0.98 (−1.33 to −0.62)	−0.25	0.75
nsNSAIDs + aldosterone antagonists	**4.46 (1.79 to 7.13)**	**0.41**	**1.81**
nsNSAIDs + calcium channel blockers	−0.39 (−0.90 to 0.13)	−0.09	0.90
nsNSAIDs + anticoagulants	**2.41 (0.89 to 3.94)**	**0.28**	**1.46**
nsNSAIDs + antiplatelets[c]	**1.50 (0.03 to 2.97)**	**0.23**	**1.37**
nsNSAIDs + nitrates	0.00 (−0.93 to 0.93)	0.00	0.10
COX-2 inhibitors + LDA	**2.54 (1.13 to 3.94)**	**0.34**	**1.64**
COX-2 inhibitors + corticosteroids	−0.02 (−2.03 to 1.99)	0.00	0.10
COX-2 inhibitors + SSRIs	**1.86 (0.28 to 3.44)**	**0.32**	**1.63**
COX-2 inhibitors + gastroprotective agents	−1.14 (−1.69 to −0.59)	−0.48	0.55
COX-2 inhibitors + aldosterone antagonists	−1.15 (−3.84 to 1.53)	−0.29	0.72
COX-2 inhibitors + calcium channel blockers	−0.36 (−1.12 to 0.41)	−0.11	0.86
COX-2 inhibitors + anticoagulants	0.10 (−2.15 to 2.34)	0.02	1.03
COX-2 inhibitors + antiplatelets[c]	−1.91 (−3.13 to −0.69)	−1.10	0.28
COX-2 inhibitors + nitrates	0.63 (−0.87 to 2.14)	0.12	1.18
LDA + corticosteroids	**2.25 (0.91 to 3.59)**	**0.26**	**1.44**
LDA + SSRIs	0.49 (−0.05 to 1.03)	0.10	1.16
LDA + gastroprotective agents	−1.12 (−1.37 to −0.88)	−0.44	0.58
LDA + aldosterone antagonists	−0.31 (−1.30 to 0.67)	−0.06	0.93
LDA + calcium channel blockers	−0.55 (−0.79 to −0.32)	−0.18	0.79
LDA + anticoagulants	**1.87 (0.70 to 3.05)**	**0.27**	**1.46**
LDA + antiplatelets[c]	**1.70 (0.85 to 2.56)**	**0.31**	**1.61**
LDA + nitrates	−0.81 (−1.13 to −0.50)	−0.21	0.77

NOTE. Values in bold are drug combinations in which the additive interaction is significant based on 95% CIs of RERI not crossing 0.
LDA, low-dose aspirin.
[a]RERI = RR11 − RR10 − RR01 + 1; AP = RERI/RR11. RERI or AP of 0 indicates no interaction, RERI or AP <0 indicates a negative interaction or less than additive interaction, and a RERI or AP >0 indicates a positive interaction or more than additive interaction. R01 and R10 represent the relative risk of UGIB for each drug separately, and RR11 represents the relative risk of UGIB during combination therapy. The 95% CIs of RERI are calculated based on the variance and covariance of the separate estimates and the combined drug estimate.
[b]Synergy index = (RR11 − 1)/([RR10 – 1] + [RR01 – 1]). Synergy index of 1 indicates no interaction, synergy index <1 indicates negative interaction or less than additive interaction, and synergy index >1 indicates positive interaction or more than additive interaction.
[c]Antiplatelets excluding low-dose aspirin.

Supplementary Table 4. Number of UGIB Events and Total of Exposure Time (in Person-Years) to Specific Drug Groups (Monotherapy and Combinations of Drugs)

Drug groups	Monotherapy		Combinations with					
			nsNSAIDs		COX-2 inhibitors		Low-dose aspirin	
	n	Person-years	n	Person-years	n	Person-years	n	Person-years
No drug[a]	69,664	706,123	NA		NA		NA	
nsNSAIDs	3327	10,198	NA		NA		416	1040
COX-2 inhibitors	635	2825	NA		NA		131	295
Low-dose aspirin	4733	22,219	416	1040	131	295	NA	
Corticosteroids	1378	4078	244	312	40	98	190	383
SSRIs	1793	10,248	210	497	65	168	401	1441
GPAs	5279	33,385	678	2239	95	503	607	3332
Aldosterone antagonists	1211	4479	76	104	10	36	131	427
Calcium channel blockers	3546	28,260	363	1251	77	369	1123	5754
Anticoagulants	1760	7244	143	241	21	62	168	422
Antiplatelets (excluding low-dose aspirin)	994	6718	87	204	9	72	246	820
Nitrates	2572	15,665	172	503	49	161	859	3959

NOTE. n refes to the number of UGIB events during exposure to a specific drug group, and person-years refers to the total exposure time in person-years to a specific drug group.
NA, not applicable.
[a]No use of the predefined drugs of interest.

Supplementary Table 5. Distribution of UGIB by Sex Across All Age Categories

Age range (*y*)	No. of cases of UGIB	
	Female	Male
Total	51,440	63,395
0–4	813	1085
5–9	329	408
10–14	237	327
15–19	410	425
20–24	593	705
25–29	687	893
30–34	781	1339
35–39	1037	1835
40–44	1288	2392
45–49	1512	2830
50–54	1892	3876
55–59	2349	4755
60–64	3042	5978
65–69	4071	7366
70–74	5551	8380
75–79	7723	8556
80–84	8267	6643
85+	10,858	5602

Supplementary Table 6. IRRm of Diagnosed UGIB During Exposure to Specific Drug Groups (With Corresponding 95% Confidence Intervals) in Monotherapy and in Combination by Applying a Meta-analysis Random Effects Model

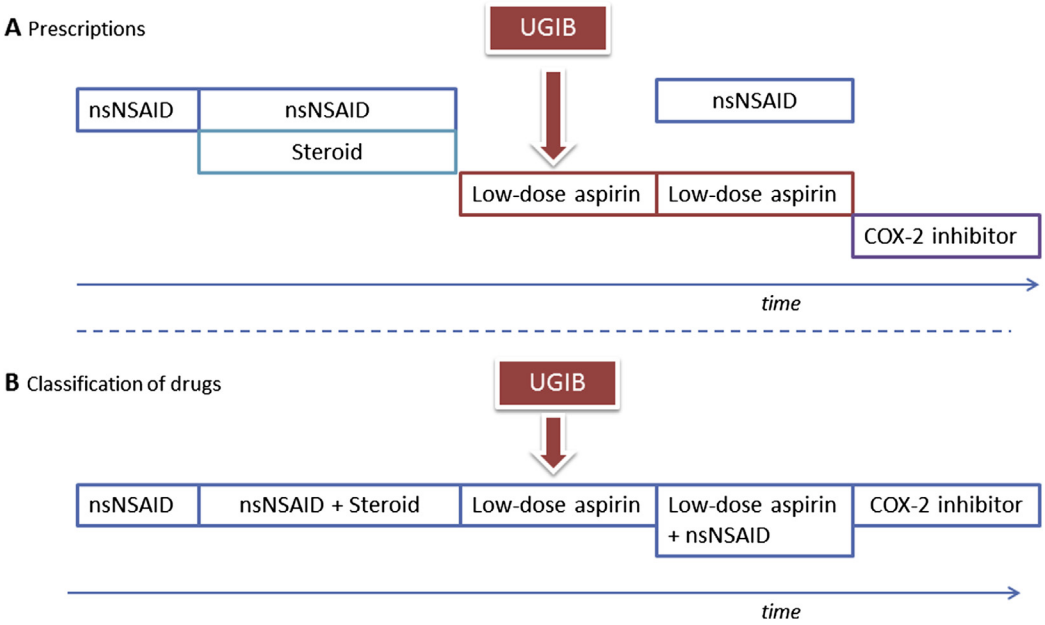
	Monotherapy			Combination with								
				nsNSAIDs			COX-2 inhibitors			Low-dose aspirin		
Drug groups	IRRm (95% CI)	*P* value Q statistic	I^2 (%)	IRRm (95% CI)	*P* value Q statistic	I^2 (%)	IRRm (95% CI)	*P* value Q statistic	I^2 (%)	IRRm (95% CI)	*P* value Q statistic	I^2 (%)
No drug[a]	1.00 (ref)	NA	NA				NA			NA		
nsNSAIDs	3.11 (2.15–4.51)	.00	98.0	NA			NA			5.05 (2.86–8.90)	<.001	94.9
COX-2 inhibitors	2.20 (1.58–3.05)	<.001	86.3	NA			NA			7.34 (4.74–11.36)	<.001	70.8
Low-dose aspirin	2.34 (1.87–2.92)	.00	96.0	5.05 (2.86–8.90)	<.001	94.9	7.34 (4.74–11.36)	<.001	70.8	NA		
Corticosteroids	2.37 (1.33–4.22)	.00	98.0	7.84 (4.61–13.36)	<.001	89.4	6.40 (4.55–9.01)	.90	0.00	6.97 (4.92–9.88)	.01	67.0
SSRIs	1.59 (1.20–2.12)	.00	94.9	4.58 (2.73–7.69)	<.001	87.2	6.30 (4.63–8.58)	.36	8.3	3.86 (2.75–5.42)	<.001	82.7
GPAs	1.31 (0.97–1.77)	.00	98.2	2.95 (1.88–4.62)	<.001	95.9	2.02 (1.34–3.05)	.02	62.9	1.87 (1.30–2.69)	<.001	93.1
Aldosterone antagonists	2.10 (1.31–3.38)	.00	95.3	9.98 (6.29–15.82)	.07	50.2	6.59 (3.17–13.69)	.43	0.00	3.96 (2.60–6.05)	.01	68.5
Calcium channel blockers	1.22 (0.95–1.57)	.00	95.3	3.35 (2.01–5.59)	<.001	91.8	3.16 (2.11–4.73)	.16	37.1	2.37 (1.86–3.02)	<.001	87.5
Anticoagulants	2.24 (1.60–3.13)	.00	95.7	6.97 (4.50–10.82)	<.001	76.6	5.52 (3.52–8.66)	.75	0.00	6.03 (4.48–8.12)	.04	57.2
Antiplatelets (excluding low-dose aspirin)	1.56 (1.27–1.91)	.00	83.0	6.30 (3.58–11.07)	<.001	79.2	1.79 (0.90–3.55)	.94	0.00	4.43 (2.83–6.93)	<.001	86.7
Nitrates	1.89 (1.34–2.66)	.00	94.9	4.94 (3.19–7.63)	.01	65.7	5.00 (2.37–10.52)	.04	56.7	3.14 (2.53–3.90)	<.001	75.5

IRRm, incidence rate ratio pooled on a random effect meta-analytic model; NA, not applicable.
[a]No use of the predefined drugs of interest.

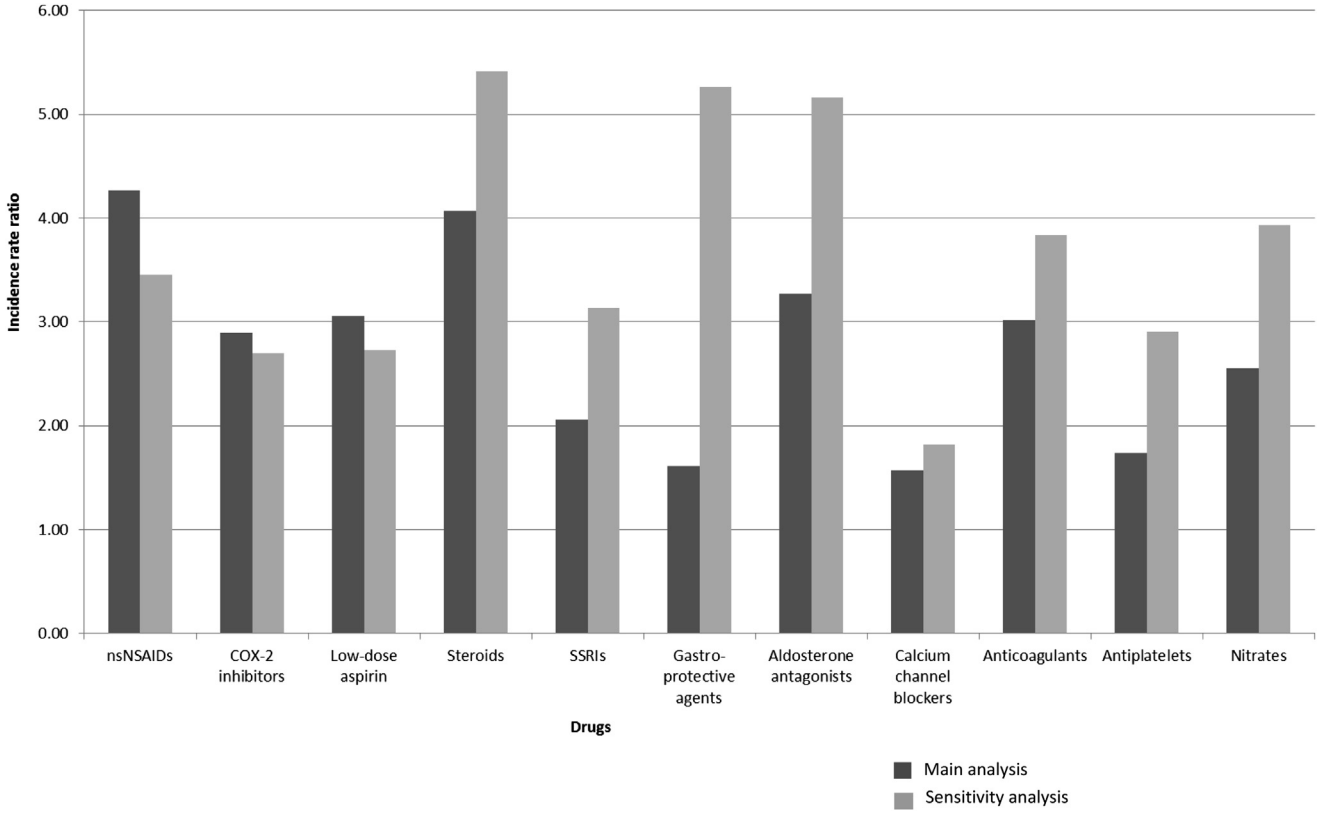
Supplementary Table 7. PAR of UGIB for Monotherapy

Drug groups	Monotherapy			Combinations with								
				nsNSAIDs			COX-2 inhibitors			Low-dose aspirin		
	Exposure prevalence (%)	IRR	PAR (%)	Exposure prevalence (%)	IRR	PAR (%)	Exposure prevalence (%)	IRR	PAR (%)	Exposure prevalence (%)	IRR	PAR (%)
nsNSAIDs	4.1	4.27	11.8							16.7	6.77	8.8
COX-2 inhibitors	1.7	2.90	2.0							3.5	7.49	2.2
Low-dose aspirin	6.5	3.05	11.7	16.7	6.77	8.8	3.5	7.49	2.2			
Corticosteroids	3.8	4.07	10.4	5.5	12.82	6.4	1.6	5.95	0.8	8.1	8.37	5.6
SSRIs	2.8	2.06	2.8	6.5	6.95	3.7	1.7	5.82	0.8	9.4	4.60	3.3
GPAs	7.4	1.61	4.3	24.4	3.90	6.6	4.4	2.37	0.6	28.3	2.54	4.2
Aldosterone antagonists	1.3	3.27	2.9	1.7	11.00	1.7	0.4	4.02	0.1	5.2	5.01	2.0
Calcium channel blockers	4.0	1.57	2.2	11.8	4.45	3.9	3.0	3.11	0.6	19.5	3.07	3.9
Anticoagulants	4.2	3.01	7.8	7.3	8.69	5.3	1.3	5.01	0.5	9.8	6.94	5.5
Antiplatelets (excluding low-dose aspirin)	2.4	1.74	1.8	3.5	6.50	1.9	0.7	1.73	0.1	13.6	5.49	5.8
Nitrates	3.0	2.55	4.4	6.5	5.82	3.0	1.6	5.09	0.7	20.8	3.79	5.5

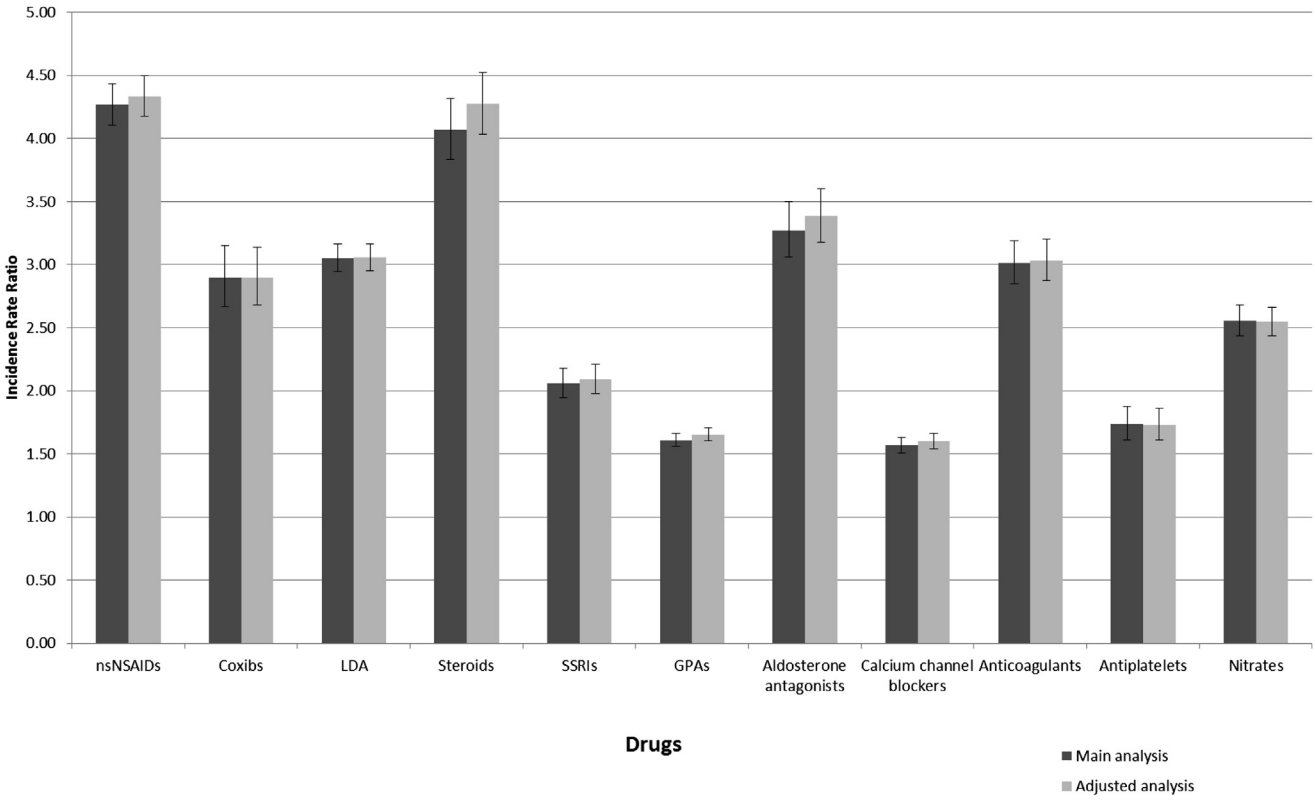
NOTE. The PAR is an estimate that reflects the absolute risk in the general population. The PAR is calculated using the relative risk and the exposure prevalence in the general population to which the relative risk pertains. However, the PAR does not reflect the absolute risk for a specific person but rather the proportion of UGIB in the general population due to drug use. For example, consider the PAR of nsNSAID monotherapy; of 100 people experiencing UGIB while exposed to nsNSAID monotherapy, 11.8% of these UGIBs are attributable to nsNSAID monotherapy. Exposure prevalence refers to drugs in the general population. The IRRs were used as calculated in this study (see Table 2).



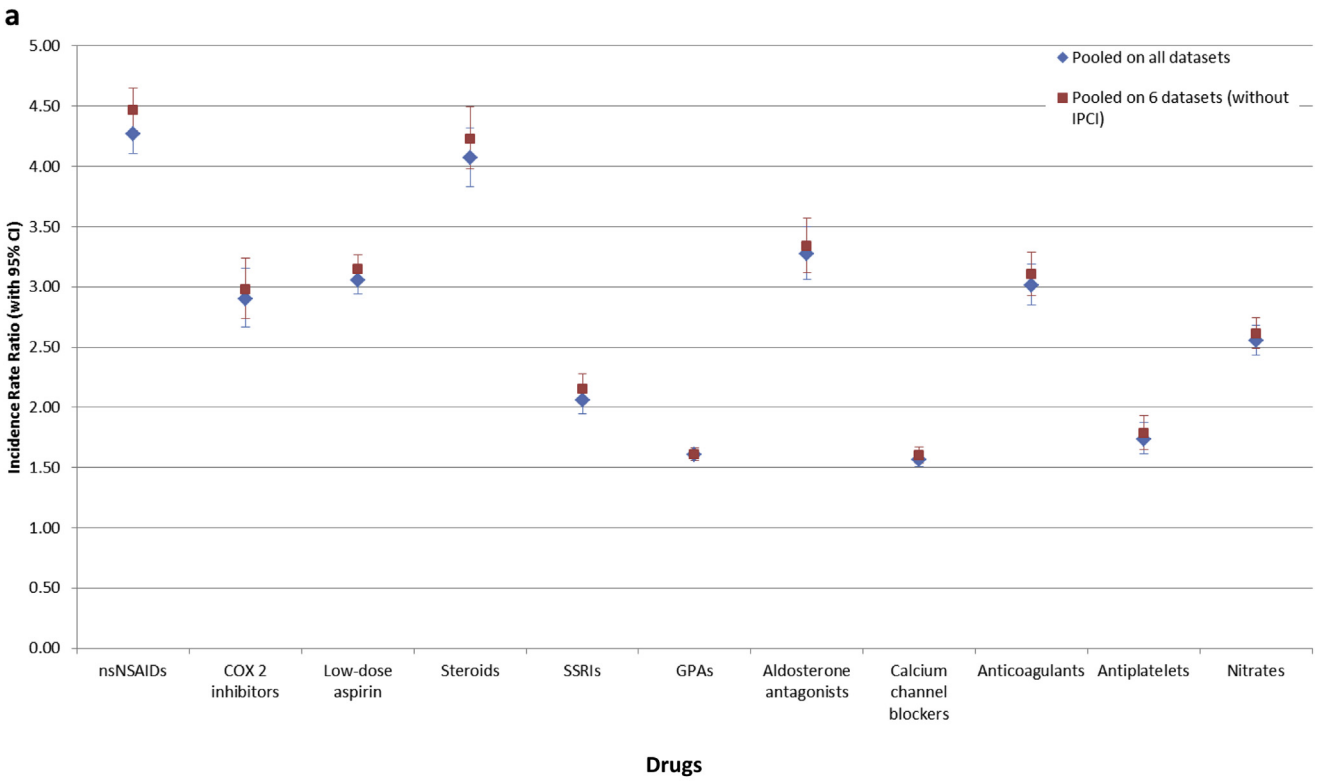
Supplementary Figure 1. Classification of (*A*) prescriptions and (*B*) drug categories.

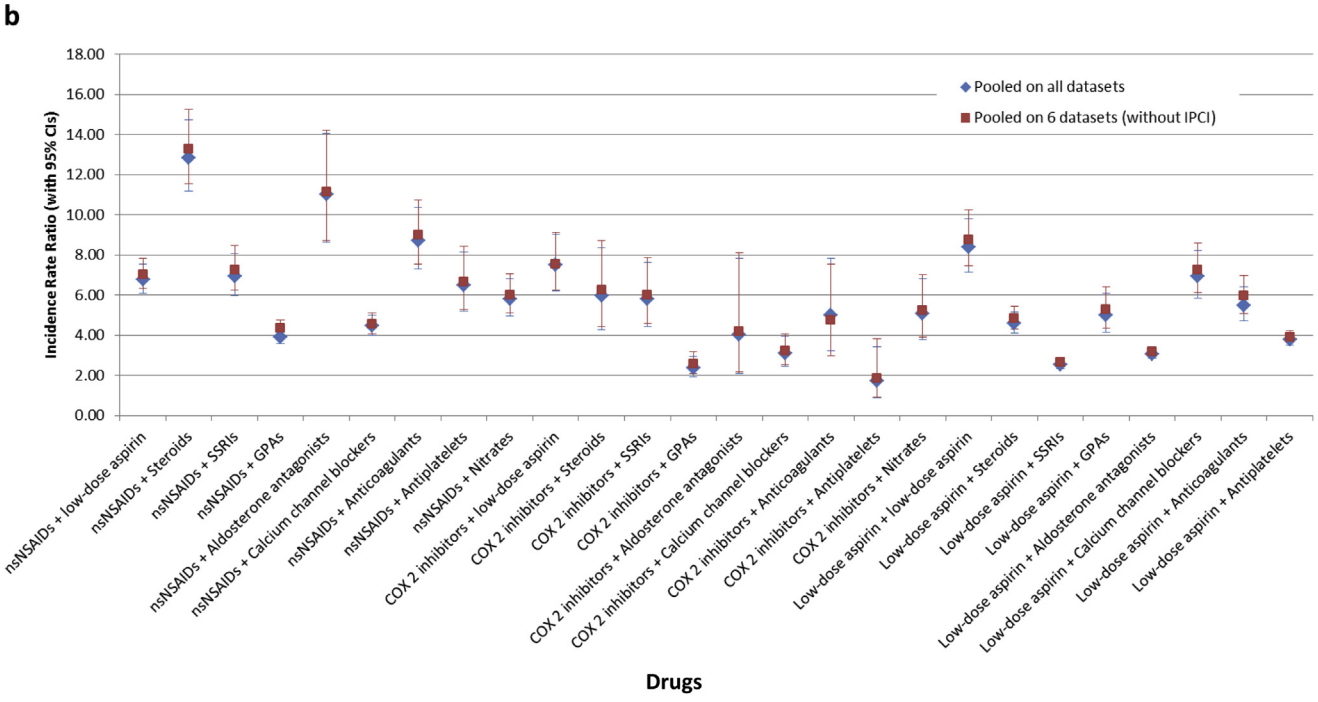


Supplementary Figure 2. Explanation of sensitivity analysis with observation time truncated at the time of the event. Observed IRRs of drug monotherapy for the main analysis in SCCS and sensitivity analysis. A key assumption of the SCCS is that the exposure distribution within the observation period and the observation period itself must be independent of prior event times. This could have been violated for some subjects, because use of an nsNSAID without gastroprotection is relatively contraindicated after UGIB. By truncating follow-up at the time of UGIB, we observed that the IRRs changed in magnitude for some drugs. We used a change of 10% of the initial estimate as an arbitrary cutoff to quantify the magnitude of the change. The estimates were higher for monotherapy of corticosteroids, SSRIs, GPAs, aldosterone antagonists, antiplatelets, and nitrates and lower for nsNSAIDs and low-dose aspirin in the analysis with truncation of follow-up time at the event. The estimates did not change by more than 10% of the initial estimate only for COX-2 inhibitor monotherapy. These analyses indicate that the exposure of, for instance, nsNSAIDs did not change significantly after the event but show the relative contraindication of nsNSAIDs after UGIB, because the IRR in the initial analysis was higher than that in sensitivity analyses (Supplementary Figure 1). However, these analyses show that confounding by contraindication is unlikely.



Supplementary Figure 3. Observed IRRs of drug monotherapy for main analysis and sensitivity analyses adjusted for acute myocardial infarction and anaphylactic shock.





Supplementary Figure 4. Observed IRRs (with 95% CIs) of drug monotherapy for main analysis and sensitivity analyses excluding IPCI.