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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.**

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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.