JAANP

CE

Predictors of gastrointestinal bleeding in older persons taking nonsteroidal anti-inflammatory drugs: Results from the FDA adverse events reporting system

Deborah Dillon McDonald, PhD (Associate Professor)

ABSTRACT

Background and purpose: Older adults continue to take nonsteroidal anti-inflammatory drugs (NSAIDs) to manage chronic pain. The study's purpose was to identify predictors of gastrointestinal (GI) bleeding in older adults taking NSAIDs.

Methods: A secondary analysis of the 2016 Food and Drug Administration's Adverse Events Reporting System data was conducted with 1,347 cases aged 65 years and older with an NSAID as the primary suspect for an adverse drug event (ADE). Data included age, sex, NSAID, multiple NSAID use, rivaroxaban, warfarin, clopidogrel, cardiovascular drug (proxy for cardiovascular disease), diabetes drug (proxy for diabetes mellitus), and primary adverse drug response.

Conclusions: Aspirin was the primary suspect NSAID in 72.5% of cases. Rivaroxaban was taken in 67.9% of cases. Logistic regression was conducted to predict GI bleed versus other NSAID-related ADEs with age, sex, cardiovascular medication, diabetes medication, warfarin, clopidogrel, concurrent NSAID use, aspirin, and rivaroxaban as predictors. Aspirin, rivaroxaban, and concurrent NSAID were significant predictors of GI bleed. Gastrointestinal bleed risk versus other ADE risk increased by 39.77 times when taking aspirin, rivaroxaban, and another NSAIDs concurrently.

Implications for practice: Results support reduced NSAID use by older adults, especially aspirin, and avoidance of rivaroxaban in older persons taking NSAIDs.

Keywords: adverse drug event; nonsteroidal anti-inflammatory drugs; older adults.

Journal of the American Association of Nurse Practitioners 31 (2019) 206–213, © 2019 American Association of Nurse Practitioners

DOI# 10.1097/JXX.0000000000000130

Older adults aged 65 years and older comprised 58% of the adults hospitalized for upper gastrointestinal (GI) bleeding in the United States from 2002 to 2012 (Wuerth & Rockey, 2018). Adults of all ages made 2,691,658 medical visits because of GI bleeding in 2010 (Peery, Crockett, Barritt, & Dellon, 2015). Adults made 796,323 emergency department visits because of GI bleeding, resulting in 507,440 hospitalizations at an estimated cost of $4,853,663,600 in 2012. Death occurred in 11,065 (2.2%) of the cases (Peery et al.). Gastrointestinal bleeding remains a significant cause of morbidity and mortality. It is therefore important to identify and reduce GI bleeding risk for older adults.

The American Geriatrics Society (2009) Panel on the Pharmacological Management of Persistent Pain in Older Persons recommended nearly a decade ago to avoid nonsteroidal anti-inflammatory drug (NSAIDs) in older adults because of the risk of adverse drug events (ADE), such as GI bleeding. The recommendation included the caveat that a proton pump inhibitor (PPI) be coadministered for gastro-protection if an NSAID was used. However, PPIs do not protect from lower GI bleeding (Lue & Lanas, 2016). Although many older adults use acetaminophen to manage pain, a recent meta-analysis suggests that pain relief from acetaminophen may be ineffective for many (Machado et al., 2015). As a result and despite the increased risk of GI bleeding (Coxib and traditional NSAID Trialists' [CNT Collaboration] Coxib and Traditional NSAID, & Trailists' (CNT) Collaboration, 2013), cardiovascular adverse events (Arfe et al., 2016; Trelle et al., 2011), and kidney disease (Hsu, Wang, Hsu, Chuang, & Huang, 2015), many older adults continue to use oral nonsteroidal anti-inflammatory drugs (NSAIDs) to self-manage their pain (Enthoven et al., 2014). Supporting older adults to safely self-manage their pain, avoid ADEs, and maintain good quality of life requires discussion of risks with their

University of Connecticut, School of Nursing, Storrs, Connecticut

Correspondence: *Deborah Dillon McDonald, University of Connecticut, School of Nursing, 231 Glenbrook Road, Storrs, CT 06269-4026. Tel: 860-486-3714 Fax: 860-486-0001; E-mail: deborah.mcdonald@uconn.edu*

Received: *22 June 2018; accepted 10 August 2018*

practitioner to identify safe efficacious multimodal treatment regimens. More precise levels of risk associated with NSAIDs are needed to inform older adults and their practitioners and to guide pain management. The aim of this study was to identify predictors of GI bleeding in older adults when an NSAID was identified as the primary suspect for an ADE.

Methods

Design

The design was a secondary analysis of data extracted from the Food and Drug Administration Adverse Events Reporting System (FAERS) 2016 third-quarter data, which was the most current data available at the time. A brief description of the FAERS provides context for the design and sample. The FAERS is the FDA's surveillance system for all the marketed drugs and biologic products. The Food and Drug Administration Adverse Events Reporting System receives required reports of ADEs from manufacturers and voluntary reports of ADEs from health care providers and consumers. Reports are not medically verified, and duplicate reports for a consumer and health care provider are possible. Identification of a drug as a primary suspect does not guarantee that the drug caused the ADE or the outcome. Data cannot be used to determine prevalence. The International Conference on Harmonization's safety reporting guidelines are used to structure the data reported in the FAERS. Adverse events are coded using terms from the Medical Dictionary for Regulatory Activities.

Sample

A total of 1,347 cases were extracted for analysis. Cases met the following inclusion criteria: NSAID as the primary suspect for the ADE and age 65 years or older. Cases were excluded if the route of administration was documented as intravenous, the ADE was due to a medical administration error, or the ADE was identified as an ineffective pain relief.

Procedure

Institutional review board review was not required because the data analyzed in the research was publicly available and deidentified data. Data were imported and converted to an SPSS version 23 data file following the procedure documented for the FAERS data files. Four distinct data files were imported and converted to SPSS. The files included the demographic, drug, reaction, and outcome files. Cases with an NSAID as the primary suspect were sequentially extracted from the drug data file until 3,631 cases were extracted. Each case was matched via the case identification number to the same case in the demographic data file. Only cases with a documented age of 65 years or older were retained for a total of 1,389 cases. Age, sex, and weight in kilograms were abstracted for the cases.

The remaining cases were matched to the ADE file, and the ADE was added to the case data. When multiple ADEs were listed, the probable major precipitating ADE was identified. For example, when GI bleed and acute renal failure were colisted, GI bleed was entered as the major precipitating ADE because the GI bleed was more likely to have caused hypotension and acute renal failure than the reverse. For ADEs specific to GI bleed, cases were coded as upper GI bleed, lower GI bleed, or unspecified GI bleed. Cases were matched to the outcomes data file by case identification. The resulting outcome was added to each case and included the following six categories: hospitalization, other serious, death, life threatening, disability, and required intervention to prevent permanent damage.

Additional variables associated with either causing or preventing GI bleeding were also extracted. The variables included use of a concurrent NSAID in addition to the primary suspect NSAID, rivaroxaban, warfarin, clopidogrel, and PPI.

The 1,389 cases were hand-screened for duplicates, and duplicates were removed. For example, an ADE frequency analysis was conducted for all cases of women age 65 years. Each ADE with more than one case (e.g. two nonspecific GI bleed) was examined for the date of ADE occurrence. If the ADE date was the same for both cases, the cases were considered suspected duplicates, and one case was removed. Additional data were also used to determine case duplication when date of the ADE was not documented. Weight was examined when documented. When the weight was the same, the cases were considered suspected duplicates, and one case was removed. Source of the ADE report was also examined, and if the

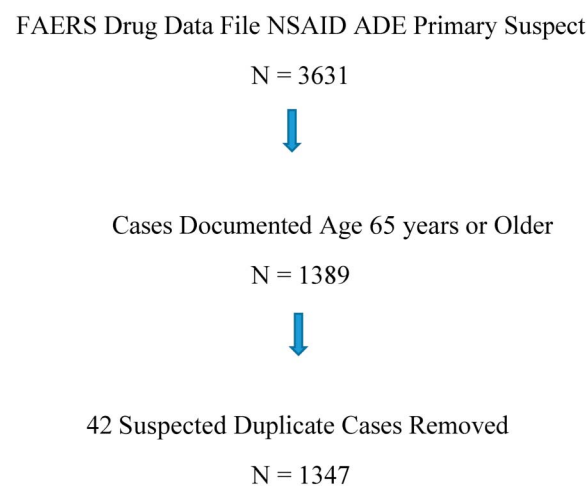

Figure 1. FAERS case selection for older adults with NSAID as ADE primary suspect. ADE = adverse drug event; FAERS = Food and Drug Administration Adverse Events Reporting System; NSAID = nonsteroidal anti-inflammatory drugs

sources were different (e.g. physician and consumer) and the country of origin was the same (e.g. Italy for both), the cases were considered suspected duplicates in which the same ADE was reported by two different sources, and one case was removed. A total of 42 suspected duplicate cases were identified and removed. The final sample consisted of N = 1,347 cases of adults age 65 years and older with an NSAID as the primary suspect of an ADE reported in the FAERS database during the third quarter of 2016. **Figure 1** illustrates the exclusion of cases leading to the final sample.

Most GI bleeds were listed as unspecified, preventing a clear distinction between upper and lower GI bleeds. GI bleed was therefore computed as an upper GI bleed, lower GI bleed, or unspecified GI bleed. Additional predictor variables of GI bleed were computed. Cases with cardiovascular medication (e.g. metoprolol) were computed for the variable cardiovascular medication. Cases with antidiabetic medication (e.g. metformin) were computed for the variable diabetes medication. The variables provided proxies for cardiovascular disease and diabetes, respectively. Use of PPIs was examined but not included in the correlations or regression analysis because of the inability to distinguish upper and lower GI bleeds and the lack of PPIs' efficacy in preventing lower GI bleeds.

Statistical analysis

Preliminary analysis included frequencies and correlations. A total of 72.5% of cases listed aspirin as the primary suspect. The remaining primary suspect NSAIDs constituted from 5.9% to 7.7% of the cases. As a result, aspirin as the primary suspect versus other NSAID as the primary suspect was computed as a predictor variable.

Assumptions for logistic regression were met with the exception that age did not have a linear relationship with GI bleed. Approximately 50% of cases were aged 75 years or older. To meet logistic regression assumptions, age was dichotomized as 0 = age 65 years through 74 years and 1 = age 75 years and older. Logistic regression was conducted with sex (men = 0, women = 1) and age (65 years through 74 years = 0, 75 years and older = 1) as step 1; use of cardiovascular medication or antidiabetes medication (nonuse = 0, use = 1) entered as step 2; and aspirin versus other NSAID as the primary suspect (other NSAID = 0, aspirin = 1), use of concurrent NSAID, rivaroxaban, warfarin, and clopidogrel (nonuse = 0, use = 1) entered as step 3.

Results

The mean age for the 1,347 cases included in the analyses was 76.0 years (SD = 7.28), range 65–100 years. NSAID ADEs affected a similar proportion of male (51%) and female (49%) cases. Aspirin was the primary ADE suspect NSAID in n = 977 (72.5%) of cases. Additional primary suspect NSAIDs were naproxen 7.6%, ibuprofen 6.8%, diclofenac 6.1%, celecoxib 5.9%, and other NSAIDs 1.1%. Aspirin dose (low versus normal dose) was documented for 643 cases. The majority were low-dose aspirin, n = 513 (79.8%). Proton pump inhibitors were documented in 183 cases (13.6%). Table 1 contains frequencies for the common NSAIDS, concurrent NSAID, rivaroxaban, warfarin, and clopidogrel.

Most ADEs were GI bleeds n = 692 (51.4%), with 156 (11.6%) upper GI, 162 (12.0%) lower GI, and 374 (27.8%) unspecified GI bleeds. Additional common ADEs included hemorrhagic stroke 70 (5.2%), acute renal injury or chronic renal failure in 44 cases (3.3%), hypersensitivity in 45 cases (3.3%), unspecified hemorrhage in 34 cases (2.5%), and skin reaction in 20 cases (1.5%). Heart failure was identified in only 8 (0.6%) cases.

Most cases (957) resulted in an outcome of hospitalization (79.0%). Death resulted for 58 (4.8%). Life-threatening outcomes occurred for 16 (1.3%), disability for 5 (0.4%), and 2 (0.2%) required intervention to prevent permanent damage. Other serious outcomes were documented for 173 (14.3%).

Logistic regression with age, sex, use of cardiovascular medication, use of diabetes medication, use of aspirin, a concurrent NSAID, rivaroxaban, warfarin, and clopidogrel supported rivaroxaban, aspirin, and concurrent NSAID as significant predictors of GI bleed versus other ADE, Cox and Snell R2 28%, and Nagelkerke R2 37%. Table 2 contains the logistic regression results. GI bleed risk versus other ADE risk increased 39.77 times when taking aspirin, rivaroxaban, and other NSAIDs concurrently.

Table 1. NSAIDs, rivaroxaban, warfarin, and clopidogrel frequencies (N = 1,347)

Medication	n	%
NSAIDs		
Aspirin	977	72.5
Naproxen	102	7.6
Ibuprofen	91	6.8
Diclofenac	82	6.1
Celecoxib	79	5.9
Other NSAIDs	16	1.1
Concurrent NSAID	157	11.7
Rivaroxaban	915	67.9
Clopidogrel	155	11.5
Warfarin	48	3.6

Note: NSAID = nonsteroidal anti-inflammatory drugs.

Table 2. Predictors of GI bleeding

Predictors	Standardized Beta	Confidence Interval	Significance
Age	1.22	0.94–1.58	.14
Sex	1.22	0.94–1.58	.14
Cardiovascular medication	0.85	0.60–1.20	.36
Diabetes medication	0.61	0.34–1.10	.10
Warfarin	0.81	0.41–1.62	.56
Clopidogrel	1.37	0.92–2.03	.13
Concurrent NSAID	1.69	1.02–2.80	.04
Aspirin	4.31	2.43–7.64	.000
Rivaroxaban	5.47	3.39–8.81	.000

Note: GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drugs.

Discussion

Aspirin was the NSAID most frequently associated with GI bleeds, occurring more than 9.5 times more frequently than any other NSAID. Aspirin dose was documented in 65.8% of the cases, most of which were low dose. The low dose suggests that aspirin was taken for antiplatelet cardio-protective rather than analgesic purposes and provides a plausible explanation for why aspirin was the predominate NSAID. Meta-analysis of nine randomized placebo controlled trials with more than 100,000 combined participants supported a 70% increased risk of bleeding of any kind and a 31% increased risk of nontrivial bleeding from aspirin. Bleeding was not specific to GI bleeding, however. Aspirin dose (less than 100 milligrams or greater than 100 milligrams) did not differ significantly for cases of nontrivial bleeding (Seshasai et al., 2012), similar to findings in the current study. Research that examined risk specific to GI bleed from aspirin revealed a 50% increased risk (Hansen, Sorensen, Clausen, Fog-Petersen, & Raunso, 2010), 19% greater risk than the findings of Seshasai and colleagues for risk of unspecified bleeding from aspirin. Similarly, the ROCKET AF study found a 42% increase in GI bleeding from aspirin. All ROCKET AF participants were on low-dose aspirin (Goodman & Wojdyla, 2014). Close monitoring of participants in the ROCKET AF study might have reduced GI bleeds. Aspirin remains a major factor associated with GI bleeding.

Findings from the current study supported a 4.31 greater risk of GI bleeding associated with aspirin compared with another ADE from an NSAID. It remains unclear from the current study whether other NSAIDs are associated with reduced risk of GI bleed compared with aspirin or if other NSAIDs are simply used less frequently than aspirin. Prevalence cannot be determined because of the methods used to report data to the FAERS. Meta-analysis results support greater risk from nonaspirin NSAIDs than aspirin for diverticular bleeding, 2.87 (CI 1.62–5.07) and 1.73 (CI 1.31–2.30), respectively (Yuhara et al., 2014), contradicting the current findings. However, the sample size for the meta-analysis was 313, much smaller than the current study sample of 1,347 cases, and all but one of the studies included in the meta-analysis were specific to Japan. The current study was also not specific to diverticular bleeding. Although not specific to aspirin, risk of death was increased by 76% with a nonselective NSAID compared with 39% with celecoxib in a post hoc study of Australian veterans when compared against new users of glaucoma/thyroid medication (Kerr et al., 2011). The current sample was composed of cases with a reported ADE from an NSAID, which might explain the increased GI bleed risk. Within the context of reported ADEs from NSAIDs, the strength of association in the current study between aspirin and GI bleeds remains noteworthy.

Knowledge of NSAID-associated risk is crucial for safe use of prescribed and over–the-counter NSAIDs. A survey of Australian adults found that, although awareness of true potential risk from NSAIDs increased by 11% (20% in 2001–31% in 2009), 30.9% took NSAIDs when a warning, contraindication, and/or potential interaction was possible. Only 22% were aware that a history of GI events increased the risk of an NSAID-related ADE (Stosic, Dunagan, Palmer, Fowler, & Adams, 2011). Results suggest the need for older adults to discuss NSAID risk with their pharmacist or primary care practitioner and to include discussion of nonserious ADEs to prevent them from becoming serious ADEs (Koffeman, Van Buul, Valkhoff, Jong, & Bindels, 2015). Meta-analysis of interventions to reduce ADEs in older adults supported a 36% reduction of

serious ADEs for older adults in the intervention groups compared with older adults in the control groups. All ADEs were reduced by 21% for older adults in the intervention groups. Pharmacist-led interventions reduced overall ADEs even more, by 35% (Gray et al., 2018). Multipronged public health education efforts that include pharmacists, primary care practitioners, state public health departments, and organizations such as the American Association of Retired People might raise even greater awareness about the safe use of NSAIDs and significantly reduce NSAID-related ADEs. Additional self-management measures might be needed for high-risk older adults such as self-monitoring for occult blood in the stool to identify GI bleeding earlier and reduce morbidity and mortality.

Rivaroxaban was associated with the greatest risk of a GI bleed, adding further evidence to the controversy regarding rivaroxaban and bleeding risk. The ROCKET AF study directly compared rivaroxaban against warfarin and supported similar frequency of GI bleeding between rivaroxaban and warfarin, 5.5% versus 4.1%, respectively (Goodman & Wojdyla, 2014). However, the risk of GI bleed increased to 2.33 with rivaroxaban compared with warfarin for participants with a history of previous GI bleed (Goodman & Wojdyla, 2014). Recent COMPASS study data indicate that GI major bleeds increased by 40% with rivaroxaban versus aspirin and that combination of aspirin and rivaroxaban increased the risk of GI bleeding by 2.15 (Eikelboom, Quinlan, Hirsh, Connolly, & Weitz, 2017). Results from the current study indicate a much greater risk of GI bleeding from rivaroxaban. Rivaroxaban increased risk by 5.47, whereas warfarin was not associated with any significant risk of GI bleed. Participants in the ROCKET AF study with a previous history of bleeding had an 88% increased risk of bleeding from rivaroxaban but not with warfarin (Goodman et al.), agreeing with the need for more cautious use of rivaroxaban.

The U.S. Food and Drug Administration recently approved a drug, coagulation factor Xa (recombinant) inactivated, to reverse life-threatening bleeding from Xa inhibitors such as rivaroxaban (U.S. Food and Drug Administration, 2018). However, safety data for the reversal drug was collected mostly from healthy volunteers. The increased risk of thrombus and emboli from coagulation factor Xa (recombinant) inactivated remains unclear, but is anticipated to be greater in people receiving rivaroxaban for the purpose of antithrombus therapy. Furthermore, outcomes from prolonged reversal of bleeding remain unknown (Faulcon, 2016). Cautious use of rivaroxaban therefore remains important.

GI bleeding risk increased to 23.57 times in the current study with combined use of rivaroxaban and aspirin, which can initiate bleeding through local GI epithelial and microvascular damage and increased mucosal vulnerability from prostaglandin depletion (Cryer & Mahaffey, 2014). Goodman and colleagues (2014) suggest that increased GI bleeding from rivaroxaban might be the result of increased surface bleeding because of the prevalence of an active anticoagulant in the intestines. Aspirin increased the risk of nonspecific bleeding and all-cause deaths in the ROCKET AF study, but increased risk with concurrent use of rivaroxaban versus warfarin was not supported (Shah, Hellkamp, Lokhnygina, Becker, & Berkowitz, 2016). The conflicting results might be due to closer symptom monitoring and treatment during the ROCKET AF study. Increased risk from rivaroxaban in the current study might be due to reduced coagulation monitoring compared with routine monitoring for patients taking warfarin (Eikelboom et al., 2017). The National Action Plan for ADE Prevention calls for further research on bleeding risk associated with new oral anticoagulant use in older adults (U.S. Department of Health and Human Services Office of Disease Prevention and Health Promotion, 2014). The Spanish Consensus Guideline panel recommended against combining NSAIDs and anticoagulants. The panel recommended a tailored baseline assessment of GI bleed risk (Lanas, Benito, Alonso, Hernandez-Cruz, & Baron-Esquivias, 2014). Results from the current study provide further evidence that aspirin and rivaroxaban should not be used concurrently in older adults.

Concurrent use of a second NSAID increased GI bleeding risk by 69%. Although the risk was much smaller in magnitude than the risk from aspirin or rivaroxaban, the additional risk remains significant. A total of 7.5% of Australia's regular NSAID users reported concurrent use of a second NSAID (Stosic et al., 2011). In the current study, use of aspirin, rivaroxaban, and a second NSAID increased risk of a GI bleed by 39.84. Results suggest that older adults taking a combination of aspirin, rivaroxaban, and an additional NSAID are at high risk of a GI bleed. Meta-analyses of NSAIDs and upper GI complications not specific to bleeding supported increased the risk of GI complications from celecoxib, ibuprofen, diclofenac, and naproxen (Castellsague et al., 2012; Coxib and Traditional NSAID Trailists' [CNT] Collaboration, 2013). Aspirin was not included in either meta-analysis, and results were nonspecific for GI bleeds, but support the need for cautious use of other NSAIDs. In a study specific to lower GI bleeding, 77% of patients who failed to discontinue their NSAID after hospital discharge for lower GI bleeding had a recurrent lower GI bleed within 12 months after discharge compared with 7.1% of patients who discontinued their NSAID after hospital discharge. None of the patients who discontinued their NSAID experienced a cardiovascular ADE (Nagata, Nikura, Aoki, Shimbo, & Sekine, 2015). Results from the current study indicate that concurrent use of two NSAIDs (e.g. low-dose aspirin for cardioprotection and ibuprofen for arthritis pain) increases the risk of GI bleeding.

The protective effect of PPIs was not included as a factor in the current study because of the large number of unspecified GI bleeds. A significant portion of the site-specified GI bleeds in the current study were lower GI, for which PPIs would not have been protective. It remains unclear whether GI bleed site was undetermined or known but imprecisely reported to the FAERS. The International NSAID Consensus Group recommends low-dose celecoxib and a PPI when an NSAID is required for people at high risk of GI bleed (Scarpignato et al., 2015). Meta-analysis of 28 studies of NSAIDs that included celecoxib, ibuprofen, diclofenac and naproxen, and risk for GI complications supported celecoxib provided 39% lower risk than ibuprofen, the next lowest risk NSAID examined (Castellsague et al., 2012). NSAID use for even a short duration (median 15 days) was associated with a 4.86 increased risk of upper GI bleeding, perhaps because PPIs were used by only 16.6% (Sostres, Carrera-Lasfuentes, & Lanas, 2017). People taking NSAIDs for arthritis used PPIs significantly more than people taking NSAIDs for acute musculoskeletal pain (Sostres et al.). Use of gastro-protective medications (H2 blockers at twice the dose or PPIs) indicated that gastro-protective medications were used by only 31.8% of high-risk individuals taking low-dose aspirin compared with 48.0% of high-risk individuals taking a regular dose of NSAIDs (Warle-van Herwaarden et al., 2015). Continued low rates of PPI use by NSAIDs users indicates a need to educate people about NSAID safety and use of PPIs even when taking NSAIDs for a short duration or taking low-dose aspirin. Lack of efficacy for preventing lower GI bleeding is important for patients to understand so that risks and benefits can be carefully weighed.

Sex differences for GI bleed risk were not supported. Analysis of gender risk in the ROCKET AF rivaroxaban group supported no sex difference as well. Risk was for major unspecified bleeding rather than GI-specific bleeding, however (Goodman & Wojdyla, 2014). Shimomura, Nagata, Shimbo, Sakurai, and Moriyasu (2018) also did not find sex as a significant predictor of GI bleeding.

Increased age was not supported as a risk factor for GI bleeding. Age was dichotomized as a result of lack of normality. Lack of normality might have resulted from inclusion of only cases aged 65 years and older. Shimomura et al. (2018) also did not find age older than 70 years as a significant predictor of GI bleeding, perhaps because of the restricted age range. Results from the ROCKET AF study indicate that age increases the risk of nonspecific bleeding for people taking either rivaroxaban or warfarin (Goodman & Wojdyla, 2014). Factors associated with increased age rather than age alone might be more important contributors specific to increased GI bleeding risk. Replication and extension of the current study with adults aged 18 years and older would assist to clarify why age was not significant in the current study.

Study limitations suggest cautious interpretation of the findings. The FAERS is a voluntary reporting system. As a result, selection effects might exist for the types of ADEs reported, persons reporting ADEs, persons for whom ADEs are reported, and data included in the reports. For example, practitioners and patients reporting ADEs might not include all of the concurrent medications. Most cases included multiple concurrent medications, however. Data quality might differ between data reported by practitioners and consumers. Patients identified undocumented adverse events, some of which were ADEs sustained during hospitalization that had not been documented in the medical record (Weissman et al., 2008), supporting the importance of consumer ADE data contributions. Missing data for age curtailed the number of cases available for analysis, however, 1,347 cases were included. Variables collected in the FAERS include minimal variables. Age, sex and weight are included, but other variables such as race, ethnicity, education, income/socioeconomic status, and supplemental health insurance are not included and might contribute more nuanced prediction for GI bleeds. Variables more specific to GI bleeding such as a history of gastritis, previous GI bleeds, and alcohol intake (Nojkov & Cappell, 2016) were unavailable and might further assist prediction within the context of reported ADEs. Shimomura et al. (2018) found chronic renal disease, chronic obstructive pulmonary disease, history of peptic ulcer disease, and liver cirrhosis as significant predictors of GI bleeding. Cases reported to the FAERS include some cases reported from other countries. Health care practices and self-management behaviors might differ from the United States. Duplicate case reports are a concern in the FAERS, which could inflate findings. Screening was conducted to remove duplicates, with 42 (3%) suspected duplicates removed, thus reducing the threat from duplicates.

NSAIDs are frequently used by older adults and can result in serious GI bleeding and deaths in some cases. The current study analyzed FAERS data, a large national/international database that contains concurrent medications and some demographic data, to examine the risk factors for GI bleeding. Results from the current study provide practitioners and patients with risk levels associated with aspirin, concurrent NSAID use, and rivaroxaban to include when discussing risks and benefits within the context of individual clinical situations. Results support that avoidance of aspirin and rivaroxaban would significantly reduce the risk of GI bleeding.

Competing interests: *The author reports no conflicts of interest.*

References

U.S. Department of Health and Human Services Office of Disease Prevention and Health Promotion (2014). *National action plan for adverse event prevention*. Washington, DC.

U.S. Food and Drug Administration. (2018). 2018 biological license application approvals. Retrieved from https://www.fda.gov/biologicsbloodvaccines/developmentapprovalprocess/biologicalapprovalsbyyear/ucm596371.htm.

American Geriatrics Society. (2009). Pharmacological management of persistent pain in older persons. American Geriatrics Society panel on the pharmacological management of persistent pain in older persons. *Journal of the American Geriatrics Society*, 57, 1331–1346.

Arfe, A., Scotti, L., Varas-Lorenzo, C., Nicotra, F., Zambon, A., Kollhorst, B.,... Corrao, G. (2016). Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: Nested case-control study. *BMJ: British Medical Journal*, 354, i4857.

Castellsague, J., Riera-Guardia, N., Calingaert, B., Varas-Lorenzo, C., Fourrier-Reglat, A., Nicotra, F.,... Perez-Gutthann, S. (2012). Individual NSAIDs and upper gastrointestinal complications a systematic review and meta-analysis of observational studies (the SOS Project). *Drug Safety*, 35, 1127–1146.

Coxib and Traditional NSAIDTrailists' (CNT) Collaboration. (2013). Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomized trials. *Lancet*, 382, 769–779.

Cryer, B., & Mahaffey, K. (2014). Gastrointestinal ulcers, role of aspirin, and clinical outcomes: Pathobiology, diagnosis, and treatment. *Journal of Multidisciplinary Healthcare*, 7, 137–146.

Eikelboom, J., Quinlan, D., Hirsh, J., Connolly, S., & Weitz, J. (2017). Laboratory monitoring of non-vitamin K antagonist oral anticoagulant use in patients with atrial fibrillation: A review. *Journal of the American Medical Association Cardiology*, 2, 566–574.

Enthoven, W., Scheele, J., Bierma-Zeinstra, S. Bueving, H., Bohnen, A., Peul, W.,... Luijsterburg, P. (2014). Analgesic use in older adults with back pain: The BACE study. *Pain Medicine*, 15, 1704–1714.

Faulcon, L. (2016). Clinical review memo – ANDEXXA. Retrieved from https://www.fda.gov/downloads/biologicsbloodvaccines/cellulargenetherapyproducts/approvedproducts/ucm610008.pdf.

Goodman, S., Wojdyla, D., Piccini, J., White, H., Paolini, J., Nessel, C.... Califf, R. (2014). Factors associated with major bleeding events insight from the ROCKET AF Trial (Rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *Journal of the American College of Cardiology*, 63, 891–900.

Gray, S., Hart, L., Perera, S., Semla, T., Schmader, K., & Hanlon, J. (2018). Meta-analysis of interventions to reduce adverse drug reactions in older adults. *Journal of the American Geriatrics Society*, 66, 282–288.

Hansen, M., Sorensen, R., Clausen, M., Fog-Petersen, M., Raunso, J., Gadsboll, N.... Torp- pedersen, C. (2010). Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Archives of Internal Medicine*, 170, 1433–1441.

Hsu, C., Wang, H., Hsu, Y., Chuang, S., Huang, Y., Chang, Y.... Tsai, H. (2015). Use of nonsteroidal anti-inflammatory drugs and risk of chronic kidney disease in subjects with hypertension: nationwide longitudinal cohort study. *Hypertension*, 66, 524–533.

Kerr, S., Rowett, D., Sayer, G., Whicker, S., Saltman, D., & Mant, A. (2011). All-cause mortality of elderly Australian veterans using COX-2 selective NSAIDs: A longitudinal study. *British Journal of Clinical Pharmacology*, 71, 936–942.

Koffeman, A., Van Buul, A., Valkhoff, V., Jong, G., Bindels, P., Sturkenboom, M.... Bierma- Zeinstra, S. (2015). Adverse drug reactions in a primary care population prescribed non-steroidal anti-inflammatory drugs. *Scandinavian Journal of Primary Health Care*, 33, 163–169.

Lanas, A., Benito, P., Alonso, J. Hernandez-Cruz, B., Baron-Esquivias, G., Perez-aisa, A.... Gonzalez-juanatey, J. (2014). Safe prescription recommendations for non- steroidal anti-inflammatory drugs: Consensus document elaborated by nominated experts of three scientific associations (SER-SEC-AEG). *Rheumatology Clinics*, 10, 68–84.

Lue, A. & Lanas, A. (2016). Proton pump inhibitor treatment and lower gastrointestinal bleeding: Balancing risks and benefits. *World Journal of Gastroenterology: WJG*, 22, 10477–10481.

Machado, G., Maher, C., Ferreira, P., Pinheiro, M., Lin, C., ODay, R.... Ferreira, M. (2015). Efficacy and safety of paracetamol for spinal pain and osteoarthritis: Systematic review and meta-analysis of randomized placebo controlled trials. *BMJ: British Medical Journal*, 350, h1225.

Nagata, N., Nikura, R., Aoki, T., Shimbo, T., Sekine, K., Okubo, H.... Uemura, N. (2015). Impact of discontinuing non-steroidal anti-inflammatory drugs on long-term recurrence in colonic diverticular bleeding. *World Journal of Gastroenterology: WJG*, 21, 1292–1298.

Nojkov, B., & Cappell, M. (2016). Distinctive aspects of peptic ulcer disease, Dieulafoy's lesion, and Mallory-Weiss syndrome in patients with advanced alcoholic liver disease or cirrhosis. *World Journal of Gastroenterology: WJG*, 22, 446–466.

Peery, A., Crockett, S., Barritt, A., Dellon, E., Swathi, E., Gangarosa, L.... Sandler, R. (2015). Burden of gastrointestinal, liver, and pancreatic diseases in the United States. *Gastroenterology*, 149, 1731–1741.

Scarpignato, C., Lanas, A., Blandizzi, C., Lems, W., Hermann, M., & Hunt, R. (2015). Safe prescribing of non-steroidal anti-inflammatory drugs in patients with osteoarthritis—an expert consensus addressing benefits as well as gastrointestinal and cardiovascular risks. *BioMed Central Medicine*, 13, 1–22.

Seshasai, S., Wijesuriya, S., Sivakumaran, R., Nethercott, S., Ergou, S., Sattar, N., Ray, K.K. (2012). Effect of aspirin on vascular and nonvascular outcomes. *Archives of Internal Medicine*, 172, 209–216.

Shah, R., Hellkamp, A., Lokhnygina, Y., Becker, R., Berkowitz, S., Breithardt, G.... Patel, M. (2016). Use of concomitant aspirin in patients with atrial fibrillation: Findings from the ROCKET AF trial. *American Heart Journal*, 179, 77–86.

Shimomura, A., Nagata, N., Shimbo, T., Sakurai, T., Moriyasu, S., Okubo, H.... Uemura, N. (2018). New predictive model for acute gastrointestinal bleeding in patients taking oral anticoagulants: A cohort study. *Journal of Gastroenterology and Hepatology*, 33, 164–171.

Sostres, C., Carrera-Lasfuentes, P., & Lanas, A. (2017). Non-steroidal anti-inflammatory drug related upper gastrointestinal bleeding: Types of drug use and patient profiles in real clinical practice. *Current Medical Research and Opinion*, 33, 1815–1820.

Stosic, R., Dunagan, F., Palmer, H. Fowler, T., & Adams, I. (2011). Responsible self-medication: Perceived risks and benefits of over-the-counter analgesic use. *International Journal of Pharmacy Practice*, 19, 236–245.

Trelle, S., Reichenbach, S., Wandel, S. Hildebrand, P., Tschannen, B., Villiger, P.... Juni, P. (2011). Cardiovascular safety of non-steroidal anti-inflammatory drugs: Network analysis. *Bmj: British Medical Journal*, 342, c7086.

Warle-van Herwaarden, M., Koffeman, A., Valkhoff, V., Jong, G., Kramers, C., Sturkboom, M., De Smet, P. A. (2015) Time-trends in the prescribing of gastroprotective agents to primary care patients initiating low-dose aspirin or non-steroidal anti-inflammatory drugs: A population-based cohort study. *British Journal of Clinical Pharmacology*, 80, 589–598.

Weissman, J., Schneider, E., Weingart, S., Epstein, A., David-Kasdan, J., Feibelmann, S.... Gatsonis, C. (2008). Comparing patient-reported hospital adverse events with medical record review: Do patients know something that hospitals do not? *Annals of Internal Medicine*, 149, 100–108.

Wuerth, B., & Rockey, D. (2018). Changing epidemiology of upper gastrointestinal hemorrhage in the last decade: A nationwide analysis. *Digestive Diseases and Sciences*, 63, 286–1293.

Yuhara, H., Corley, A., Nakahara, F., Nakajima, T., Koike, J., Igarashi, M.... Mine, T. (2014).Aspirin and non-aspirin NSAIDs increase risk of colonic diverticular bleeding: A systematic review and meta-analysis. *Journal of Gastroenterology*, 49, 992–1000.

Instructions:

- Read the article.
- The test for this CE activity can be taken online at www.NursingCenter.com/CE/JAANP. Find the test under the article title.
- You will need to create a username and password and login to your personal CE Planner account (It's free!) before taking online tests. Your planner will keep track of all your Lippincott Professional Development online CE activities for you.
- There is only one correct answer for each question. A passing score for this test is 13 correct answers. If you pass, you can print your certificate of earned contact hours and access the answer key. If you fail, you have the option of taking the test again at no additional cost.
- For questions, contact Lippincott Professional Development: 1-800-787-8985.

Registration Deadline: March 1, 2020.

Disclosure Statement:
The authors and planners have disclosed that they have no financial relationships related to this article.

Provider Accreditation:
This activity is approved for 1.25 contact hour(s) of continuing education (which includes 1.25 hours of pharmacology) by the American Association of Nurse Practitioners. Activity ID 19023573. This activity was planned in accordance with AANP CE Standards and Policies.
This activity is also provider approved by the California Board of Registered Nursing, Provider Number CEP 11749 for 1.25 contact hours. Lippincott Professional Development is also an approved provider of continuing nursing education by the District of Columbia Board of Nursing, Georgia Board of Nursing, and Florida Board of Nursing, CE Broker #50-1223.

Payment:

- The registration fee for this test is $12.95.
- AANP members are eligible for a 50% discount. Visit the member-benefit section on AANP website (https://aanp.org/membership/memberbenefits) to obtain the discount code. Use the code when asked for payment during checkout.