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Risk of Bleeding Associated With Nonsteroidal Anti-inflammatory Drug Use in Patients Exposed to Antithrombotic Therapy: A Case-Crossover Study

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Abstract

Concomitant nonsteroidal anti-inflammatory drug (NSAIDs) and antithrombotic drug use is associated with an increased risk of bleeding, mainly gastrointestinal. The goal of this study was to quantify the transient increase in the risk of hospitalization for bleeding associated with NSAID use in patients treated with antiplatelet agents or anticoagulants. We performed a unidirectional case-crossover study using the EGB (Échantillon généraliste de bénéficiaires), a permanent random sample of the French nationwide health database. Patients receiving antithrombotic therapy and hospitalized for bleeding between 2009 and 2017 were included. We compared their NSAID exposure during a 15-day hazard window immediately before hospital admission to 3 earlier 15-day control windows. The risk of hospitalization for bleeding associated with the recent use of NSAIDs was estimated using conditional logistic regression to estimate odds ratios (ORs). During the study period, 33 patients treated with anticoagulants and 253 treated with antiplatelet agents received NSAIDs and were included in the case-crossover analysis. We found an increased risk of hospitalization for gastrointestinal bleeding after exposure to NSAIDs, with an adjusted OR of 3.59 (95%CI, 1.58-8.17) in patients receiving anticoagulant therapy and 1.44 (95%CI, 1.07-1.94) in patients receiving antiplatelet therapy. The risk of nongastrointestinal bleeding was also increased after exposure to NSAIDs with an adjusted OR of 2.72 (95%CI, 1.23-6.04) in patients exposed to anticoagulant therapy. The risk of gastrointestinal and nongastrointestinal bleeding increases after NSAID use in patients treated with anticoagulants, while the risk of gastrointestinal bleeding increases, but to a lesser extent in those treated with antiplatelets.

Keywords

adverse drug reactions, antithrombotic, drug interactions, drug safety, nonsteroidal anti-inflammatory drugs (NSAIDs), pharmacovigilance

Antiplatelet agents and anticoagulants are antithrombotic drugs that are frequently prescribed for the prevention and treatment of cardiovascular diseases. Nonsteroidal anti-inflammatory drugs (NSAIDs), which have analgesic, anti-inflammatory, and antipyretic properties, are often used to treat mild to moderate pain, in traumatology and rheumatology (osteoarthritis, rheumatism). Thus, elderly people are

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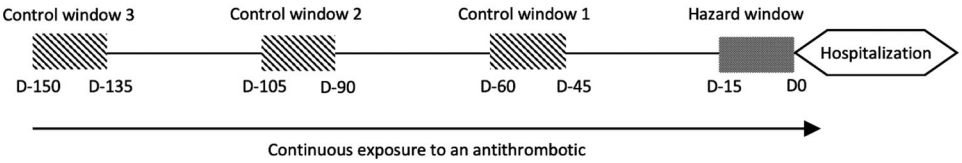

Figure 1. Case-crossover study design. Exposure to nonsteroidal anti-inflammatory drugs were compared during the hazard window and the 3 control windows.

very likely to take both treatments together, especially since several NSAIDs are available over the counter in pharmacies.

An estimated 5.3% to 69% of patients receiving antithrombotic treatment have concomitant exposure to NSAIDs,[1,2] while an antiplatelet agent was used by up to 22% of patients receiving NSAIDs for the treatment of osteoarthritis.[2,3] In France, 1.5% of the population received NSAIDs and antiplatelet drugs simultaneously and 0.24% NSAIDs and oral anticoagulants in 2016, a trend that has been increasing in both populations in the past decade.[4] The association of these 2 drug classes increases the risk of bleeding, mainly gastrointestinal.[5,6]

The goal of this study was to quantify the risk of hospitalization for severe bleeding (gastrointestinal and nongastrointestinal) in patients receiving antithrombotic therapy (antiplatelets or anticoagulants) and exposed to NSAIDs, based on pharmacy drug dispensing and hospital data from a French health insurance database.

Methods

Ethics

National Institute for Health and Medical Research agreement for the research protocol was given November 15, 2017. Neither ethics committee authorization nor request to national commissions for individual data protection is required according to French law to access this kind of anonymous and restricted access database. Access to EGB (Échantillon généraliste de bénéficiaires) is possible only through a secured connection to a specific server. Data are accessible online and are analyzed by the software SAS Enterprise Guide version 4.3 (SAS Institute Inc., Cary, North Carolina).

Data Sources

This study was performed using data from the EGB, a 1/97th random sample of the SNDS (Système National des Données de Santé), the French nationwide claims database, which covers around 99% of the French population. The EGB database includes more than 700 000 individuals[7] and is representative of the French population for age, sex, geographic location, and health care use. The EGB has provided anonymous sociodemographic and medical information since 2003, allowing longitudinal patient follow-up. It contains in-depth data on hospital admissions and medications dispensed in community pharmacies transmitted for reimbursement.

Pharmacy dispensations of NSAIDs and antithrombotic drugs were identified according to the Anatomical, Therapeutic, and Chemical drug classification system, and hospitalizations for bleeding were identified from the International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes.

Study Design and Study Population

We performed a unidirectional case-crossover analysis. In this self-controlled design, each patient acts as his or her own control[8]; thus, the potential effects of time-invariant confounding factors, such as sex, genetic or socioeconomic characteristics, chronic comorbidities, and long-term treatments, are controlled.[8,9]

We included patients over 18 years old who had been continuously exposed to antithrombotic treatment and were hospitalized for severe bleeding between January 1, 2009, and December 31, 2017. Exposure to NSAIDs in these patients was compared between a hazard window (0-15 days before hospital admission) and 3 control windows (45-60 days, 90-105 days, and 135-150 days before hospital admission) (Figure 1). We chose 15-day windows since the recommended duration for NSAID treatment is short. Each of these windows was separated by a 30-day washout period, minimizing any relationship between the windows. Thus, the study period for each patient extended from the beginning of the third control window to hospital admission, for a total of 150 days (Figure 1).

Hospitalizations for Severe Bleeding

Severe bleeding included gastrointestinal, intracranial, urinary, gynecological, respiratory, joint, muscle, abdominal and postprocedural bleeding, anemia due to bleeding, and other unclassified hemorrhages. Hospitalizations were identified using ICD-10 codes registered as primary, secondary, or related diagnosis. ICD-10 codes were selected from published studies and reviewed by an expert group (Table S1).[10–12] We selected the first hospitalization for severe bleeding during the study period for each patient.

Our main analysis evaluated the risk of gastrointestinal bleeding. The secondary analyses evaluated hospitalizations for overt gastrointestinal bleeding (ulcers and gastritis with hemorrhage, hematemesis, melena, anal and rectal hemorrhage, and unspecified gastrointestinal hemorrhage), and hospitalizations for occult gastrointestinal bleeding (ICD-10 code for iron deficiency anemia in men of all ages and women over 50 years of age). We also analyzed nongastrointestinal bleeding and all bleeding combined.

Exposure to Antithrombotic Therapy

The antithrombotic therapy could be an anticoagulant (vitamin K antagonist [VKA] or direct oral anticoagulant [DOAC]), or an antiplatelet agent (acetylsalicylic acid at low dose [75-300 mg/day],[13] clopidogrel, prasugrel, ticagrelor, or ticlopidine) (Table S2).

Patients included in the case-crossover analysis were continuously exposed to antiplatelet agents or anticoagulants during the 150 days before their hospital admission for severe bleeding (Figure 1). Continuous exposure was defined by 2 criteria. Persistence was defined as a delay between the dispensation of 2 antiplatelet or anticoagulant prescriptions that did not exceed the estimated treatment duration plus a grace period of 30 days. We chose 30 days on the basis of the packaging of antithrombotics in France and the median delay between 2 dispensations. Patients also met an adherence criterion so that the medication possession ratio (estimated as the total drug supply dispensed divided by the number of days of the period) had to be $\geq$0.8.[14] The treatment duration was estimated using the defined daily dose.[15]

Exposure to NSAIDs

Exposure to NSAIDs was investigated during the hazard and control windows. If NSAIDs were dispensed during one of the windows, the patient was considered to be exposed to NSAIDs.

Statistical Analysis

We first evaluated the absolute risk of hospitalization for gastrointestinal bleeding associated with the exposure to NSAIDs in patients already taking an antithrombotic treatment. For this absolute risk analysis, we took into account hospitalizations from the start of NSAID treatment to 15 days after its end.

We then evaluated the risk increase of hospitalization for gastrointestinal bleeding associated with NSAIDs in patients on long-term antithrombotic treatment. For this analysis, we used a case-crossover design. In this design, instead of using patients who were hospitalized for gastrointestinal bleeding as cases and matched subjects who were not hospitalized for gastrointestinal bleeding as controls, only patients hospitalized for gastrointestinal bleeding were included and exposure to NSAIDs was compared between a 15-day hazard window immediately preceding the hospitalization and 3 remote 15-day control windows (Figure 1). Moreover, only patients with discordant NSAID exposure between the hazard window and at least one control window were used to estimate the odds ratio with conditional logistic regression stratified on individuals. Separate analyses were performed for antiplatelet agents and anticoagulants.

To prevent confounding by indication, we restricted our sample to patients with constant exposure to antithrombotic from the beginning of the observation period to hospital admission.[16] This also ensures that included patients complied with their antithrombotic therapy. Because of the short observation period (150 days), age and comorbidities were considered to be the same for all periods (control and risk). Analyses were adjusted for exposure to different medications between the hazard and control windows for drugs that could interfere with the risk of bleeding: proton pump inhibitors (PPIs) or H2 antagonists, systemic or inhaled corticosteroids, anticoagulants in patients exposed to antiplatelet therapy, and antiplatelet therapy in patients exposed to anticoagulant therapy.

To determine whether the risk of bleeding was related to the use of NSAIDs or their indication, we also performed a case-crossover analysis using a negative control precipitating substance. We replaced NSAIDs with paracetamol, which has similar indications.

Moreover, sensitivity analyses were performed to assess the robustness of our estimates. We reduced the duration of the hazard and control windows from 15 days to 12, 10, and 7 days, and the length of the grace period for the persistence criterion from 30 days to 15 and 7 days.

All analyses were performed using the statistical software R version 3.6 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Risk of Gastrointestinal Bleeding

From 2009 to 2017, in the EGB database, 8272 individuals were exposed simultaneously to an anticoagulant and NSAIDs. Among them, 74 (0.89%) were hospitalized for gastrointestinal bleeding during or within 15 days after the end of the concomitant exposure. For antiplatelet agent and NSAIDs, 37 718 individuals were exposed to this association, and 296 (0.78%) were hospitalized for gastrointestinal bleeding

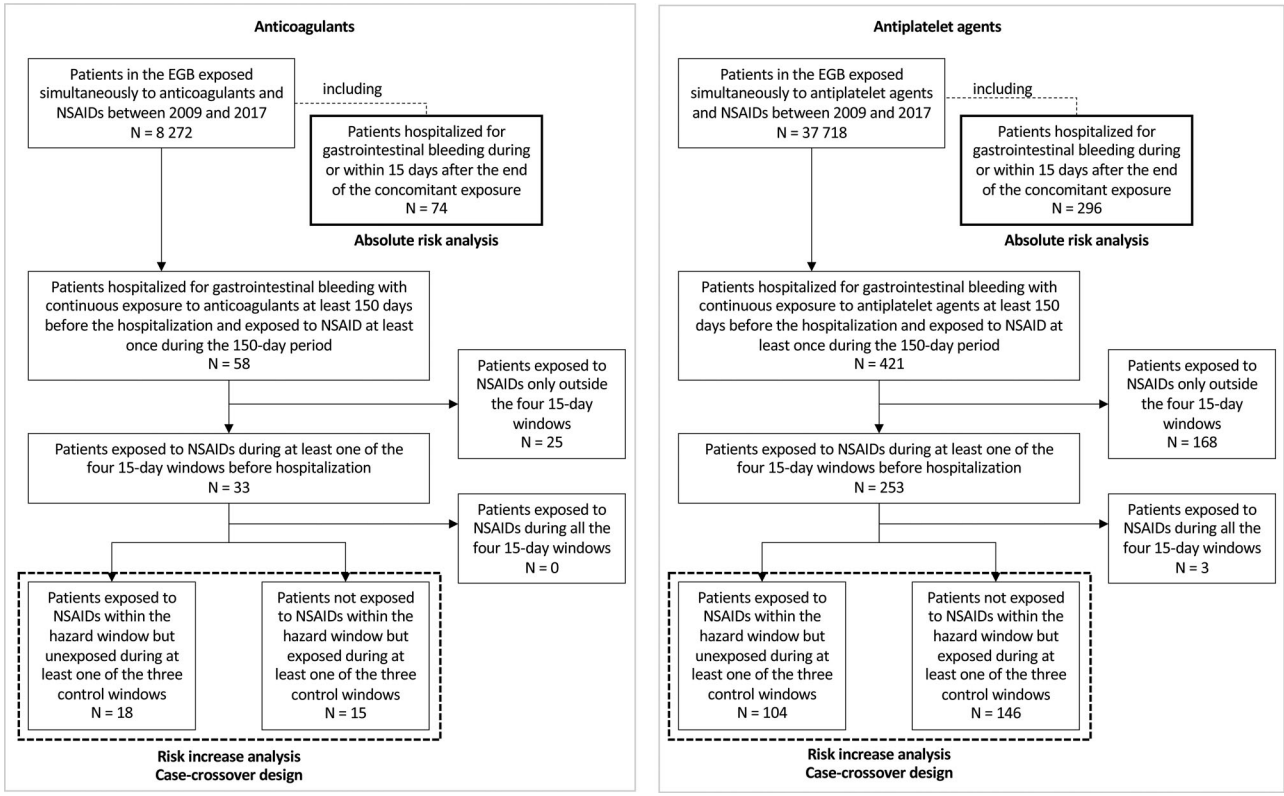

Figure 2. Patient selection for the absolute risk analysis and for the case-crossover analysis. EGB, Échantillon généraliste de bénéficiaires; NSAIDs, nonsteroidal anti-inflammatory drugs.

during or within 15 days after the end of the concomitant exposure (Figure 2). Thirty-three patients with constant exposure to anticoagulants and 253 patients with constant exposure to antiplatelet were exposed to NSAIDs for at least one of the four 15-day windows preceding the hospitalization. The patients included in the case-crossover analysis had "discordant" exposure to NSAIDs between the hazard and control windows, corresponding to 33 patients in the anticoagulant group and 250 patients in the antiplatelet group (Figure 2).

The main characteristics of the study population are described in Table 1. There were mostly men in both antithrombotic groups, and the median age was 74 (interquartile range [IQR], 69-79) in patients exposed to anticoagulant therapy and 78 (IQR, 68-84) in patients exposed to antiplatelet therapy. Two-thirds of the patients exposed to anticoagulant therapy were dispensed at least 1 prescription of PPIs or H2 antagonists (n = 22), as well as 71.2% of patients exposed to antiplatelet therapy (n = 178).

A total of 66.7% of the 33 patients exposed to anticoagulant therapy were exposed to VKAs (n = 22), mainly fluindione (n = 20), 24.2% to DOACs (n = 8), mainly rivaroxaban (n = 6), and 9.1% to dual anticoagulant therapy, to either 1 DOAC and 1 VKA (n = 2) or 2 DOACs (n = 1) (Table S3). More than 80% of the patients exposed to antiplatelet agents were receiving monotherapy (n = 208), mainly acetylsalicylic acid (n = 168) or clopidogrel (n = 39), and 16.8% were receiving dual therapy with acetylsalicylic acid and clopidogrel (n = 42).

The median hospital stay in both antithrombotic groups was 7 days, and <5% of patients died during hospitalization (Table 1). Overt gastrointestinal bleeding represented 73% of hospitalizations in the anticoagulant group (n = 24) and 59% in the antiplatelet group (n = 148) (Table 2). In the anticoagulant group, these 73% were divided between 61% of hospitalizations for melena, hematemesis, anal/rectal hemorrhage, or unspecified gastrointestinal hemorrhage (n = 20); 9% of hospitalizations for hemorrhagic gastrointestinal lesion (ulcer or gastritis type, n = 3); and 3% of hospitalizations had 2 ICD-10 codes of overt gastrointestinal bleeding (n = 1). In the antiplatelet group, this distribution of overt gastrointestinal bleeding was 48% (n = 120), 8% (n = 21), and 3% (n = 7), respectively. Occult gastrointestinal bleeding represented 27% of hospitalizations in the anticoagulant group (n = 9) and 41% of hospitalizations in the antiplatelet group (n = 102).

Table 1. Characteristics, Drug Exposure, and Type of NSAIDs Dispensed During the Hazard Window in Patients Hospitalized for Gastrointestinal Bleeding After Being Continuously Exposed to Antithrombotics and With Discordant NSAID Exposure Across the Hazard and Control Windows

	Overt or Occult Gastrointestinal Bleeding	
	Antithrombotic Group	
Characteristics	Anticoagulant (N = 33)	Antiplatelet Agent (N = 250)
Women, n (%)	14 (42)	119 (48)
Age, y, median (IQR)	74 (69-79)	78 (68-84)
Duration of hospitalization, days, median (IQR)	7 (3-10)	7 (4-13)
Death at hospital, n (%)	1 (3)	9 (3.6)
At least 1 dispensation within 1 of the control and hazard windows, n (%)		
PPI or H2 antagonists	22 (66.7)	178 (71.2)
Systemic or inhaled corticosteroids	7 (21.2)	30 (12)
Anticoagulant	…	8 (3.2)
Antiplatelet agent	9 (27.3)	…
Dispensation of NSAIDs during the hazard window, n (%)	18 (55)	104 (42)
Nonselective NSAIDs	17 (94)	96 (92.3)
Coxib	1 (6)	8 (7.7)
Delay between NSAID dispensation and hospital admission, days, median (IQR)	6.5 (2.5-11.8)	8 (4-11)

IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pomp inhibitor.

Table 2. Hospitalizations for Gastrointestinal Bleeding in Patients Included in the Main Analysis

	Events, no (%)	Anticoagulant (N = 33)	Antiplatelet Agent (N = 250)
Overt gastrointestinal bleeding	Anal/rectal hemorrhage, melena, hematemesis, or unspecified gastrointestinal hemorrhage	20 (61)	120 (48)
	Hemorrhagic ulcer or gastritis	3 (9)	21 (8)
	Anal/rectal hemorrhage, melena, hematemesis, or unspecified gastrointestinal hemorrhage + hemorrhagic ulcer or gastritis	1 (3)	7 (3)
Occult gastrointestinal bleeding	Iron deficiency anemia in men of all ages and women over 50 years of age	9 (27)	102 (41)

A total of 55% (n = 18) of the patients exposed to anticoagulant therapy in the study were dispensed NSAIDs during the hazard window and 42% (n = 104) of patients exposed to antiplatelet therapy (Table 1). More than 90% of the dispensations were nonselective NSAIDs in both antithrombotic group, while selective cyclooxygenase (COX)-2 inhibitors (celecoxib or etoricoxib) were prescribed in <10% of patients (Table 1). The median time from NSAID dispensation to hospitalization in patients exposed to this drug during the hazard window was 6.5 days (IQR, 2.5-11.8) in patients exposed to anticoagulant therapy, and 8.0 days (IQR, 4-11) in patients exposed to antiplatelet therapy.

Compared to NSAID use during the control windows, NSAID use during the hazard window was associated with an increased risk of overt or occult gastrointestinal bleeding in patients exposed to anticoagulant therapy (adjusted odds ratio [aOR], 3.59; 95%CI, 1.58-8.17) as well as to antiplatelet therapy (aOR, 1.44; 95%CI, 1.07-1.94) (Table 3).

Risk of Overt Gastrointestinal, Occult Gastrointestinal, and Nongastrointestinal Bleeding

The risk of being hospitalized for overt gastrointestinal bleeding was increased after recent exposure to NSAIDs in both patients treated with anticoagulant therapy (aOR, 6.27; 95%CI, 2.24-17.53) and in those treated with antiplatelet therapy (aOR, 1.81; 95%CI, 1.21-2.72), compared to NSAID exposure during the control windows (Table 3). However, we did not observe an increased risk in hospitalizations for occult gastrointestinal bleeding.

The risk of nongastrointestinal bleeding was increased in case of coexposure to anticoagulants and NSAIDs during the hazard window (aOR, 2.72; 95%CI, 1.23-6.04) compared to coexposure during the control windows. The characteristics of patients

Table 3. Risk of Hospitalization for Severe Bleeding After NSAID Exposure in Patients Exposed to Continuous Antithrombotic Treatment in Case-Crossover Study

			NSAID Dispensation, n (%)[a]				Risk of bleeding	
Type of Bleeding	Antithrombotic	Patients With Discordant Exposure, n	Hazard Window, n (%)	Control Window 1, n (%)	Control Window 2, n (%)	Control Window 3, n (%)	cOR (95%CI)	aOR[b] (95%CI)
Main analysis								
Gastrointestinal bleeding	Anticoagulant	33	18 (55)	9 (27)	8 (24)	5 (15)	2.98 (1.47-6.03)	3.59 (1.58-8.17)
	Antiplatelet agent	250	104 (42)	76 (30)	75 (30)	79 (32)	1.48 (1.13-1.92)	1.44 (1.07-1.94)
Secondary analyses								
Overt gastrointestinal bleeding	Anticoagulant	24	15 (63)	5 (21)	4 (17)	2 (8)	4.63 (2.02-10.66)	6.27 (2.24-17.53)
	Antiplatelet agent	148	66 (45)	40 (27)	44 (30)	45 (30)	1.73 (1.23-2.42)	1.81 (1.21-2.72)
Occult gastrointestinal bleeding	Anticoagulant	9	3 (33)	4 (44)	4 (44)	3 (33)	0.74 (0.16-3.46)	0.48 (0.06-3.62)
	Antiplatelet agent	102	38 (37)	36 (35)	31 (30)	34 (33)	1.17 (0.76-1.78)	1.08 (0.69-1.72)
Nongastrointestinal bleeding	Anticoagulant	38	20 (53)	9 (24)	7 (18)	9 (24)	2.79 (1.46-5.36)	2.72 (1.23-6.04)
	Antiplatelet agent	288	104 (36)	85 (30)	89 (31)	87 (30)	1.24 (0.96-1.59)	1.19 (0.90-1.58)
Global bleeding	Anticoagulant	63	33 (52)	16 (25)	15 (24)	13 (21)	2.68 (1.61-4.45)	2.53 (1.38-4.63)
	Antiplatelet agent	504	198 (39)	152 (30)	154 (31)	153 (30)	1.31 (1.06-1.62)	1.30 (1.06-1.60)

aOR, adjusted odds ratio; cOR, crude odds ratio; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

[a] Frequency of exposure to NSAIDs in the patients included in the analysis because of discordant NSAID exposure.

[b] Adjusted for the concomitant use of PPI/H2 antagonists, systemic or inhaled corticosteroids, anticoagulant in patients exposed to antiplatelet therapy, and antiplatelet therapy in patients exposed to anticoagulant therapy.

hospitalized for nongastrointestinal bleeding and their exposure to antithrombotic drugs were similar to those hospitalized for gastrointestinal bleeding (Tables S3 and S4, respectively). They were mainly men >70 years old. More than half of the patients in the anticoagulant group (55.2%) were hospitalized for postprocedural bleeding or anemia caused by bleeding (Table S5). The main reasons for hospitalization in the antiplatelet group were postprocedural bleeding (29.5%), urinary bleeding (18.4%), anemia caused by bleeding (17%), and respiratory bleeding (17%) (Table S5). The median hospital stay was 4.5 days (IQR, 3-9) in the anticoagulant group and 8 days (IQR, 4-14) in the antiplatelet group. Up to 11% of patients died during hospitalization in the anticoagulant group (n = 4) and 5% in the antiplatelet group (n = 14). The median time from NSAID dispensation to hospitalization in patients exposed to this drug during the hazard window was 7 days (IQR, 3-10.75) in patients exposed to anticoagulant therapy, and 8 days (IQR, 5-12) in patients exposed to antiplatelet therapy (Table S4).

Regardless of location, the association between severe bleeding and coexposure to NSAIDs and anticoagulants (aOR, 2.53; 95%CI, 1.38-4.63), or antiplatelet agents (aOR, 1.30; 95%CI, 1.06-1.60) during the hazard window was still significant compared to that during the control windows (Table 3).

Sensitivity Analyses

When the duration of the hazard and control windows was reduced, only patients exposed to antiplatelet agents had a significant increased risk of bleeding with 12- and 7-days windows (Table 4). The risk of gastrointestinal bleeding was still significant and higher when the persistence criterion (continuous exposure to antithrombotics) was reduced to 15 and 7 days.

Negative Control Using Paracetamol Exposure

The risk of gastrointestinal bleeding after exposure to paracetamol was not significant in patients exposed to anticoagulants (aOR, 1.04; 95%CI, 0.82-1.32) but was slightly increased in patients exposed to antiplatelets (aOR, 1.14; 95%CI, 1.01-1.29) (Table 5). The risk of nongastrointestinal bleeding increased significantly in patients with anticoagulants and paracetamol coexposure (aOR, 1.25; 95%CI, 1.02-1.54), but less so than with NSAID coexposure (aOR, 2.72; 95%CI, 1.23-6.04; Tables 3 and 5). The risk of nongastrointestinal bleeding increased significantly in patients with antiplatelets and paracetamol coexposure (aOR, 1.42; 95%CI, 1.26-1.59; Table 5).

Discussion

The concomitant use of antithrombotics and NSAIDs is not recommended because the interaction of these drugs could have significant clinical consequences. In this study, an increased risk of gastrointestinal bleeding after exposure to NSAIDs was observed in patients receiving antithrombotic therapy. This risk seemed to be higher in patients exposed to anticoagulants than in those receiving antiplatelet agents. An increased risk was also observed in nongastrointestinal bleeding following NSAID use in patients exposed to anticoag-

Table 4. Sensitivity Analyses: Risk of Hospitalization for Gastrointestinal Bleeding After Exposure to NSAIDs in Patients Exposed to Continuous Antithrombotic Treatment in a Case-Crossover Study With Different Window Durations and Persistence Criterion

		Anticoagulant		Antiplatelet Agent	
Gastrointestinal Bleeding Parameter	Number of Days	N	aOR[a] (95%CI)	N	aOR[a] (95%CI)
Duration of hazard and control windows, days	12	31	2.22 (0.99-4.98)	219	1.39 (1.01-1.91)
	10	28	1.45 (0.59-3.56)	200	1.29 (0.92-1.80)
	7	22	1.66 (0.57-4.85)	142	1.50 (1.06-2.13)
Duration of grace period used in persistence criterion, days	15	25	4.28 (1.58-11.59)	189	1.68 (1.20-2.37)
	7	17	3.75 (1.09-12.88)	109	1.69 (1.09-2.61)

aOR, adjusted odds ratio; PPI, proton pump inhibitor.
[a] Adjusted for the concomitant use of PPI/H2 antagonists, systemic or inhaled corticosteroids, anticoagulants in patients exposed to antiplatelet therapy and antiplatelet therapy in patients exposed to anticoagulant therapy.

Table 5. Risk of Hospitalization for Severe Bleeding After Paracetamol Exposure in Patients Exposed to Continuous Antithrombotic Treatment in Case-Crossover Study

			Paracetamol Dispensation, n (%)[a]				Risk of Bleeding	
Type of Bleeding	Antithrombotic	Patients With Discordant Exposure, n	Hazard Window, n (%)	Control Window 1, n (%)	Control Window 2, n (%)	Control Window 3, n (%)	cOR (95%CI)	aOR[b] (95%CI)
Main analysis								
Gastrointestinal bleeding	Anticoagulant	406	178 (44)	165 (41)	164 (40)	163 (40)	1.13 (0.92-1.40)	1.04 (0.82-1.32)
	Antiplatelet agent	1394	605 (43)	534 (38)	553 (40)	515 (37)	1.20 (1.07-1.34)	1.14 (1.01-1.29)
Secondary analyses								
Overt gastrointestinal bleeding	Anticoagulant	207	97 (47)	78 (38)	84 (41)	79 (38)	1.33 (0.99-1.79)	1.19 (0.85-1.67)
	Antiplatelet agent	771	341 (44)	281 (36)	296 (38)	274 (36)	1.30 (1.12-1.51)	1.19 (1.00-1.40)
Occult gastrointestinal bleeding	Anticoagulant	199	81 (41)	87 (44)	80 (40)	84 (42)	0.95 (0.71-1.29)	0.90 (0.64-1.27)
	Antiplatelet agent	623	264 (42)	253 (41)	257 (41)	241 (39)	1.08 (0.91-1.28)	1.09 (0.90-1.32)
Non-gastrointestinal bleeding	Anticoagulant	495	215 (43)	193 (39)	184 (37)	170 (34)	1.26 (1.05-1.53)	1.25 (1.02-1.54)
	Antiplatelet agent	1550	719 (46)	586 (38)	561 (36)	561 (36)	1.40 (1.26-1.56)	1.42 (1.26-1.59)
Global bleeding	Anticoagulant	792	349 (44)	311 (39)	304 (38)	297 (38)	1.22 (1.05-1.42)	1.16 (0.98-1.37)
	Antiplatelet agent	2643	1190 (45)	1005 (38)	1009 (38)	968 (37)	1.30 (1.20-1.41)	1.27 (1.16-1.39)

aOR, adjusted odds ratio; cOR, crude odds ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.
[a] Frequency of exposure to paracetamol in the patients included in the analysis because of discordant paracetamol exposure.
[b] Adjusted for concomitant use of NSAIDs, PPI/H2 antagonists, systemic or inhaled corticosteroids, anticoagulant therapy in patients exposed to antiplatelet therapy, and antiplatelet therapy in patients exposed to anticoagulant therapy.

ulants. The median age was >65 years regardless of the type of bleeding.

Simultaneous exposure to NSAIDs and antithrombotic drugs is common. Indeed, 1.5% of the French population had simultaneous exposure to NSAIDs and antiplatelet drugs and 0.24% to NSAIDs and oral anticoagulants in 2016.[4] Thus, physicians should take this into consideration when prescribing these combinations. Previous studies have reported an increased risk of bleeding in patients in the same age group exposed to NSAIDs during antithrombotic therapy.[10,11,17–19] Although none of them used a case-crossover design (most were case-control studies), they report an increased risk of gastrointestinal bleeding consistent with our findings: from 1.81 (95%CI, 1.35-2.43) to 4.60 (95%CI, 2.77-7.64) for coexposure to anticoagulant therapy and NSAIDs,[11,17,18] and a 3.6 increase in the risk of hemorrhagic ulcers (95%CI, 1.19-10.81) in case of coexposure to aspirin at antiplatelet doses and NSAIDs.[19]

In our study, more than two-thirds of the patients had dispensation of at least 1 gastric protector (PPI or H2 antagonist) during the study period (66.7% in patients exposed to anticoagulants and 71.2% in those exposed to antiplatelet agents). This use of gastric protectors probably reduced the risk of ulcers and gastrointestinal bleeding.[20]

We also assessed the association between NSAID use and occult gastrointestinal bleeding, which has not been evaluated in previous studies. Because the main causes of iron deficiency anemia are occult gastrointestinal bleeding and heavy menstruation, we analyzed iron deficiency anemia in men of all ages and women over the age of 50. No increased

risk of occult gastrointestinal bleeding was identified probably because we only evaluated acute NSAID use 15 days before hospitalization, which would correspond more to acute bleeding than to chronic bleeding episodes such as occult gastrointestinal bleeding.

The biological mechanisms underlying these interactions are different depending on the antithrombotic agent. The pharmacological properties of NSAIDs are related to the inhibition of COX enzymes COX-1 and COX-2, which normally promote the conversion of arachidonic acid to prostaglandins or thromboxanes.[21,22] The risk of a pharmacokinetic interaction following coexposure to NSAIDs and anticoagulants is known, resulting in an increase in international normalized ratio[23–25] or bleeding time.[26] The ulcerogenic risk and the antiplatelet effect of NSAIDs is a result of the inhibition of the COX-1 enzyme. Low-dose aspirin has antiplatelet aggregation properties through irreversible inhibition of the COX-1 enzyme, resulting in a potential pharmacodynamic interaction with NSAIDs. The other antiplatelet agents studied inhibit the adenosine diphosphate receptor, and further studies are needed to clarify the mechanisms related to the potential interactions with NSAIDs.[27] We could not study coxibs and nonselective NSAIDs separately because the number of patients was too limited. However, numerous studies have already shown an increased risk of bleeding following coexposure to coxibs and antithrombotics.[10,21,28]

Paracetamol was used as a negative control because its indications are similar to those of NSAIDs. Our mainly nonsignificant results are consistent with the debate about the risk of bleeding following coexposure to antithrombotics and paracetamol.[29–31] Thus, although an NSAID-related indication bias cannot be completely excluded, our results suggest that paracetamol is safer than NSAIDs in patients exposed to antithrombotics.

The main strength of this study is the use of real-life data, with a representative nationwide database including about 1% of the French population. The case-crossover design could be used to assess the short-term change in the risk of an acute outcome associated with transient exposure with adjustment for time-invariant confounding factors.[8] We also used multiple control windows to increase the power of the study and the accuracy of CI estimates.[32] This methodology can be used for other drug-drug interactions in which one substance is used on a long-term basis and another one is administered for a short period. The ICD-10 codes related to severe bleeding were mainly selected from published studies and were reviewed by a group of experts.[10,11] Finally, sensitivity analyses were performed to confirm the robustness of the results. With a more restrictive definition of continuous exposure to antithrombotic drugs, the risks of gastrointestinal bleeding were similar to the estimates from the main analysis. When shorter exposure windows were used, the results were mainly nonsignificant, probably because of the lower number of patients included. However, the estimated aORs remained similar to those in the main analysis.

This study has several limitations, mainly related to the type of data. First, only dispensation of reimbursed drugs was available to assess drug consumption, excluding over-the-counter NSAIDs. Moreover, NSAIDs may have been purchased, but not used, by the patient. However, both of these biases would tend to lower the association between NSAIDs and the risk of bleeding and cannot explain our results. Duration of treatment was not considered when determining NSAID exposure. Only patients with a dispensing date within the hazard or control windows were defined as exposed. Thus, there is a risk of misclassifying exposure and, again, underestimating the odds ratio. The unidirectional case-crossover design requires the absence of time trend in the prevalence of drug exposure. Although the prevalence of exposure to this drug-drug interaction increased between 2006 and 2016,[4] the effect of this time trend bias may be negligible, as the study period for each patient was short. Continuous exposure to antithrombotic therapy was defined by repeated antithrombotic dispensation to determine persistence. A dose-response relationship could not be investigated, and we do not know whether the antithrombotic drugs were taken for preventive or curative purposes. In addition, in this observational study, we could not control NSAID-related indication bias. However, paracetamol was used as negative control to estimate the impact of this potential bias.

Conclusion

NSAID use increased the risk of gastrointestinal and nongastrointestinal bleeding in patients treated with anticoagulants, and to a lesser extent the risk of gastrointestinal bleeding in patients treated with antiplatelet agents. The prescription of NSAIDs should be avoided in patients taking antithrombotics. Since several NSAIDs are available without a prescription, patients exposed to antithrombotic therapy should also be educated about the risks associated with this drug-drug interaction.

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Conflicts of Interest

The authors declare no conflicts of interest.

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