

## Supplementary Online Material

**Table S1.** ICD-10 codes selected for the bleeding events.

<b>Overt gastrointestinal bleeding<sup>a</sup></b>	<b>K25.0, K26.0, K27.0, K28.0</b> Acute ulcer with hemorrhage <b>K25.2, K26.2, K27.2, K28.2</b> Acute ulcer with both hemorrhage and perforation <b>K25.4, K26.4, K27.4, K28.4</b> Chronic or unspecified ulcer with hemorrhage <b>K25.6, K26.6, K27.6, K28.6</b> Chronic or unspecified ulcer with both hemorrhage and perforation <b>K62.5</b> Hemorrhage of anus and rectum <b>K92.0</b> Hematemesis <b>K92.1</b> Melena <b>K92.2</b> Gastrointestinal hemorrhage, unspecified <b>K29.0</b> Acute hemorrhagic gastritis
<b>Occult gastrointestinal bleeding<sup>b</sup></b>	<b>D50.0</b> Iron deficiency anemia secondary to blood loss <b>D50.9</b> Iron deficiency anemia, unspecified
<b>Non-gastrointestinal bleeding</b>	<u>Intracranial bleeding:</u> <b>I60-</b> Nontraumatic subarachnoid hemorrhage <b>I61-</b> Nontraumatic intracerebral hemorrhage <b>I62-</b> Other and unspecified nontraumatic intracranial hemorrhage <u>Urinary bleeding:</u> <b>R31</b> Hematuria <u>Gynecological bleeding:</u> <b>N92.0</b> Excessive and frequent menstruation with regular cycle <b>N92.1</b> Excessive and frequent menstruation with irregular cycle <b>N93.8</b> Other specified abnormal uterine and vaginal bleeding <b>N93.9</b> Abnormal uterine and vaginal bleeding, unspecified <b>N95.0</b> Postmenopausal bleeding <u>Respiratory bleeding:</u> <b>J94.2</b> Hemothorax <b>R04.0</b> Epistaxis <b>R04.1</b> Hemorrhage from throat <b>R04.2</b> Hemoptysis <b>R04.8</b> Hemorrhage from other sites in respiratory passages

	<p><b>R04.9</b> Hemorrhage from respiratory passages, unspecified</p> <p><u>Anemia due to bleeding:</u></p> <p><b>D62</b> Acute posthemorrhagic anemia</p> <p><b>D500<sup>c</sup></b> Iron deficiency anemia secondary to blood loss</p> <p><b>D509<sup>c</sup></b> Iron deficiency anemia, unspecified</p> <p><u>Muscle hematoma:</u></p> <p><b>S35.9</b> Injury of unspecified blood vessel at abdomen, lower back and pelvis level</p> <p><b>T13.0</b> Superficial injury of lower limb, level unspecified</p> <p><u>Joint bleeding:</u></p> <p><b>M25.0</b> Hemarthrosis</p> <p><u>Post-procedure bleeding:</u></p> <p><b>T81.0</b> Hemorrhage and hematoma complicating a procedure, not elsewhere classified</p> <p><u>Abdominal bleeding:</u></p> <p><b>K66.1</b> Hemoperitoneum</p> <p><u>Others:</u></p> <p><b>R58</b> Hemorrhage, not elsewhere classified</p>
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ICD-10: International Classification of Diseases, Tenth Revision

<sup>a</sup> K25: stomach, K26: duodenum, K27: site unspecified, K28: gastro-jejunal

<sup>b</sup> Hospitalizations of men, regardless of age, and women over 50 years of age were selected. We did not include women of less than 50 years of age, in order to avoid anemia due to excessive menstrual bleeding in women of childbearing age.

<sup>c</sup> Hospitalizations of women under 50 years of age were selected.

**Table S2.** Anatomical Therapeutic and Chemical codes for the substances studied

Drug class	Substance	ATC Code level 5	ATC level 5
Antiplatelet agents	clopidogrel	B01AC04	clopidogrel
	prasugrel	B01AC22	prasugrel
	ticagrelor	B01AC24	ticagrelor
	ticlopidine	B01AC05	ticlopidine
	acetylsalicylic acid <sup>a</sup>	B01AC06	acetylsalicylic acid
	acetylsalicylic acid <sup>a</sup>	C10BX02	pravastatin and acetylsalicylic acid
Anticoagulants	acenocoumarol	B01AA07	acenocoumarol
	apixaban	B01AF02	apixaban
	dabigatran	B01AE07	dabigatran etexilate
	fluindione	B01AA12	fluindione
	rivaroxaban	B01AF01	rivaroxaban
	phenindione	B01AA02	phenindione
	warfarin	B01AA03	warfarin
Nonsteroidal anti-inflammatory drugs (excluding acetylsalicylic acid)	aceclofenac	M01AB16	aceclofenac
	alminoprofen	M01AE16	alminoprofen
	celecoxib	M01AH01	celecoxib
	dexketoprofen	M01AE17	dexketoprofen
	dexketoprofen	N02AJ14	tramadol and dexketoprofen
	diclofenac	M01AB05	diclofenac
	diclofenac	M01AB55	diclofenac, combinations
	etodolac	M01AB08	etodolac
	etoricoxib	M01AH05	etoricoxib
	fenoprofen	M01AE04	fenoprofen
	flurbiprofen	M01AE09	flurbiprofen
	flurbiprofen	R02AX01	flurbiprofen
	ibuprofen	M01AE01	ibuprofen
	ibuprofen	N02AJ08	codeine and ibuprofen
	indometacin	M01AB01	indometacin
	indometacin	M01AB51	indometacin, combinations
	ketoprofen	M01AE03	ketoprofen
	mefenamic acid	M01AG01	mefenamic acid
	meloxicam	M01AC06	meloxicam
	morniflumate	M01AX22	morniflumate
	nabumetone	M01AX01	nabumetone
	naproxen	M01AE02	naproxen
	niflumic acid	M01AX02	niflumic acid
nimesulide	M01AX17	nimesulide	
parecoxib	M01AH04	parecoxib	
piroxicam	M01AC01	piroxicam	

	rofecoxib	M01AH02	rofecoxib
	sulindac	M01AB02	sulindac
	tenoxicam	M01AC02	tenoxicam
	tiaprofenic acid	M01AE11	tiaprofenic acid
	valdecoxib	M01AH03	valdecoxib

<sup>a</sup> Only the low-dose forms of acetylsalicylic acid (from 75 to 300 mg/day) used for its antithrombotic action

**Table S3.** Antithrombotic exposure of patients hospitalized for **serious bleeding**.

<b>Antithrombotic exposure No (%)</b>	<b>Gastrointestinal bleeding</b>	<b>Non-gastrointestinal bleeding</b>
<b>Anticoagulant analysis</b>	<b>33 (100%)</b>	<b>38 (100%)</b>
Vitamin K antagonists	22 (66.7%)	29 (76.3%)
fluindione	20	24
warfarine	1	4
acenocoumarol	1	1
Direct oral anticoagulants	8 (24.2%)	7 (18.4%)
rivaroxaban	6	3
apixaban	2	2
dabigatran	-	2
Dual therapy	3 (9.1%)	2 (5.3%)
dabigatran + fluindione	1	-
apixaban + fluindione	1	-
rivaroxaban + apixaban	1	-
warfarine + fluindione	-	1
fluindione + rivaroxaban	-	1
<b>Antiplatelet agent analysis</b>	<b>250 (100%)</b>	<b>288 (100%)</b>
Monotherapy	208 (83.2%)	238 (79.3%)
acetylsalicylic acid	168	197
clopidogrel	39	41
ticagrelor	1	-
Dual therapy	42 (16.8%)	50 (16.7%)
acetylsalicylic acid + clopidogrel	42	48
acetylsalicylic acid + prasugrel	-	1
acetylsalicylic acid + ticagrelor	-	1

**Table S4.** Characteristics, drugs exposure and type of NSAIDs dispensed during the hazard window, for patients hospitalized for **non-gastrointestinal bleeding** after being continuously exposed to antithrombotic and with a discordant NSAID exposure across hazard and control windows.

Characteristics No (%)	Non-gastrointestinal bleeding	
	Antithrombotic Group	
	Anticoagulant (N=38)	Antiplatelet agent (N=288)
Women	16 (42%)	115 (40%)
Age (years) median [IQR]	72 [64; 78.75]	76 [66; 83]
Duration of hospitalization, median [IQR]	4.5 [3; 9]	8 [4; 14]
Death in hospital	4 (11%)	14 (5%)
<b>At least one dispensation within one of the control and hazard windows</b>		
PPI/H2 antagonists	19 (50%)	182 (63.2%)
Systemic or inhaled corticosteroids	5 (13%)	53 (18.4%)
Anticoagulant	-	14 (4.9%)
Antiplatelet agent	7 (18.4%)	-
<b>Dispensation of NSAIDs during the hazard window</b>		
Non-selective NSAIDs	17 (85%)	95 (91%)
Coxib	3 (15%)	9 (9%)
Delay between NSAID dispensation and hospital admission, median [IQR]	7 [3; 10.75]	8 [5; 12]

NSAIDs: nonsteroidal anti-inflammatory drugs, IQR: interquartile range, PPI: proton pump inhibitor

**Table S5.** Hospitalizations for **non-gastrointestinal bleeding** in patients included in the case crossover study according to antithrombotic exposure.

<b>Events No (%)</b>	<b>Anticoagulant (N=38)</b>	<b>Antiplatelet agent (N=288)</b>
Post-procedure bleeding	13 (34.2%)	85 (29.5%)
Anemia caused by bleeding	8 (21%)	49 (17%)
Respiratory bleeding	4 (10.5%)	49 (17%)
Intracranial bleeding	4 (10.5%)	24 (8.3%)
Urinary bleeding	3 (8%)	53 (18.4%)
Genital bleeding	3 (8%)	8 (2.8%)
Abdominal bleeding	1 (2.6%)	2 (0.7%)
Muscular hematoma/haemorrhage	1 (2.6%)	2 (0.7%)
Post-procedure bleeding + localized bleeding <sup>a</sup>	1 (2.6%)	16 (5.6%)

<sup>a</sup> Articular, genital, respiratory, urinary, muscular and not elsewhere classified