

S06.3: focal brain injury
S06.4: epidural haemorrhage
S06.5: traumatic subdural haemorrhage
S06.6: traumatic subarachnoid haemorrhage
S27.1: traumatic haemothorax
S27.8: injury of other specified intrathoracic organs, haemomediastinum
S36.0: injury of spleen
S39.0: injury of muscle and tendon of abdomen, lower back and pelvis
T06.5: injury of intrathoracic organs with intraabdominal and pelvic organs
T45.5: poisoning: anticoagulants
T79.2: traumatic secondary and recurrent haemorrhage
T79.6: traumatic ischaemia of muscle
Y44.2: agents primarily affecting blood constituents: anticoagulants
Y44.4: agents primarily affecting blood constituents: antithrombotic drugs

Annex 5. Different types of major bleeding events

1. Intracranial bleeding: subdural haematoma, lobar (or intraparenchymal) haematoma, intraventricular haemorrhage, cerebellar haemorrhage, subarachnoid haemorrhage;
2. Gastrointestinal (GI) bleeding: upper GI tract (oesophagal, gastric, duodenal haemorrhage), lower GI tract (colonic, rectal haemorrhage), haematemesis, meloena;
3. Other bleeding events: muscular haematoma with details about location: lower limb, upper limb, face, thoracic or abdominal haematoma, intramuscular bleeding with compartment syndrome; subcutaneous haematoma with details about location; Haematuria; Haemarthrosis; Haemoptysis; Uterine and vaginal haemorrhage; Epistaxis, dental haemorrhage; Hemoperitoneum, haemopericardium, haemothorax; Scalp injury; Vascular injury.

Annex 6. Linkage details

In order to link the “emergency database” with the national healthcare database, two different sources were used in SNIIRAM (in DCIR and PMSI):

- (1) hospital visit with/out an administrative code for emergency room visit (codification error could have been done or some specific pathway care could exist, i.e., for patients coming from accommodation establishment for dependant people or rehabilitation service);
- (2) short visit in emergency room, identified through a package for emergency reception and treatment (“ATU” code [forfait Accueil et Traitement des Urgences]).

Annex 7. Modified HAS-BLED score

Letter	Original item	Modified item	New definition	ICD-10 code	Medical procedure	LTD	ATC	Score
H	Hypertension uncontrolled	Yes	Hospitalisation, LTD affiliation or treatment*	I10, I11, I15		12	C02, C03, C07-C09	1
A	Impaired renal and/or hepatic function	Yes	Hospitalisation, LTD affiliation	K70x, K713-5, K717, K721, K73, K74, Z49x, Z99x, I120, I131, N032, N033, N034, N035, N036, N037, N052, N053, N054, N055, N056, N057, N17x, N18x, N19, N250, Z490, Z492, Z940, Z992	JVJx	6, 19		1 or 2
S	Previous history of stroke	No		G45x, I63x, I693				1
B	Previous history of bleeding	No		I312, I60-I62, I982, J942, K226, K252, K262, K270, K272, K280, K282, K290, K625, K661, K920-K922, M250, N939, R040-R043, R31, R58, S064-S066				1
L	Labile INR	Not used [§]						1
E	Age > 65 years (Elderly)	No						NA
D	Drugs [£] /alcohol concomitantly	Yes	Hospitalisation related to alcohol abuse	E244x, F10x, G312x, G621x, G721x, I426x, K292x, K70x, K852x, K860x, O354x, R780x, Y90x, Z714x, Z721x, Z502x			B01AC, M01A [£]	1 or 2

The different criteria were assessed in the 12 months preceding inclusion date, i.e., the first observed antithrombotic delivery, except for AAP and NSAID where the criteria were assessed between the first observed antithrombotic delivery and censure date.

Labile INR initially used in the original HAS-BLED score was not considered; this item does not make sense in new users or even in prevalent users of NOAC

The modified HAS-BLED score varies from 0 to 8.

Original items are those described by Pisters et al, Chest 2010; LTD denotes long-term disease;

* at least two deliveries in 2012 of a drug belonging to one of the following ATC classes: C02, C03, C07-C09;

[§] of note, this item is not relevant to new users of NOAC;

[£] antiplatelet agents (B01AC04-B01AC07, B01AC22-B01AC24, B01AC30 or B01AC56) or nonsteroidal anti-inflammatory drugs (M01A, including M01AX02 (niflumic acid) and M01AX17 (nimesulide) but none of the other drugs labelled M01AX; at least one delivery concomitant with any anticoagulant

Other comorbidities not included in modified HAS-BLED score (assessed in 12 months preceding inclusion date unless otherwise stated):

- History of hemorrhagic stroke (ICD-10 code I63, I64),
- Coronary heart disease (ICD-10 code I20-I25 (hospitalisation or long-term disease registration) or DDAF001, DDAF003 to DDAF010, DDMA003 to DDMA009, DDMA011, DDMA012, DDMA013, DDMA015 to DDMA038, DDQH006, DDQH009-DDQH015, DDAA002, DDFF001, DDFF002, DDPF002),
- Diabetes mellitus (ICD-10 code E10* or E11* for hospitalisation or long-term disease registration; delivery of specific drugs, ATC code A10A or A10B),
- Lipid-lowering drug use (ATC code C10AA*, C10AB*, C10AX* or C10B*),
- Obesity (ICD-10 code E66*),
- antiulcer agent (ATC code A2B),

Diseases of the blood and disorders involving the immune system (ICD-10 code D50-D89, hospitalisation or long-term disease registration).

Annex 8. Modified Charlson comorbidity index [55]

Factors	Weight	ICD-10 code	Medical act code	ATC code
Congestive heart failure	2	I110, I130, I132, I50x		
Peripheral vascular disease	1	I70x, I71x, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959	EEAFx, ECPFx, ECFAx, EBFAX,, EENFfx, EEPFfx, EEFAx, EECAX, ENNFfx, ENFAx, DGAFx, EDAX, DGFPx, EDPFfx, DGFAx, EDFAx, DGCAx, EDCAx, EDPFfx, EDJFfx, EDKAx, EDEAx, EDLfx, EDNFfx, EDPFfx, EDJFfx, EDMAx, EANF002, ECNF002, ECJF001, ECCA007, ECCA009, ECCA003, ECCA002, ECMA001, ECKA002, EBNF001, EDEA001, EDLF007, EEJF001, EDCA005, ENAF001, ENAF002, DGKA004, EDNF003, EDKA002	
Cerebrovascular disease	1	G45x, G46x, H340, I60x-I69x		
Dementia	2	F00x–F03x, F051, G30x, G311		N06D (at least 3 deliveries)
Chronic pulmonary disease	1	I278, I279, J40x–J47x, J60x–J67x, J684, J701, J703		R03 (at least 2 deliveries)
Mild liver disease	2	B18x, K700–K703, K709, K713–K715, K717, K73x, K74x, K760, K762–K764, K768, K769, Z944		
Moderate or severe liver disease	2	I850, I859, I864, I982, K704, K711, K721, K729, K765, K766, K767		
Hemiplegia	1	G041, G114, G801, G802, G81x, G82x, G830–G834, G839		
Moderate or severe renal disease	2	I120, I131, N032–N037, N052–N057, N18x, N19x, N250, Z490–Z492, Z940, Z992		
Any malignancy, including leukemia and lymphoma	3	C00x–C26x, C30x–C34x, C37x–C41x, C43x, C45x–C58x, C60x–C76x, C81x–C85x, C88x, C90x–C97x		
Metastatic solid tumour	11	C77x–C80x		
AIDS/HIV	1	B20x–B22x, B24x, Z21		

Assessed in 12 months preceding inclusion date (first observed antithrombotic delivery or January 1st 2013 for prevalent users).

Other comorbidities not included in modified Charlson comorbidity index (assessed in 12 months preceding inclusion date unless otherwise stated):

- History of haemorrhagic stroke (ICD-10 code I63, I64),
- Coronary heart disease (ICD-10 code I20-I25 (hospitalisation or long-term disease registration) or DDAF001, DDAF003 to DDAF010, DDMA003 to DDMA009, DDMA011, DDMA012, DDMA013, DDMA015 to DDMA038, DDQH006, DDQH009-DDQH015, DDAA002, DDF001, DDF002, DDPF002),
- Diabetes mellitus (ICD-10 code E10* or E11* for hospitalisation or long-term disease registration; delivery of specific drugs, ATC code A10A or A10B),
- Lipid-lowering drug use (ATC code C10AA*, C10AB*, C10AX* or C10B*),
- Obesity (ICD-10 code E66*),
- antiulcer agent (ATC code A2B),
- Diseases of the blood and disorders involving the immune system (ICD-10 code D50-D89, hospitalisation or long-term disease registration).

Annex 9. Definition of presumed indication of oral anticoagulant, co-morbidities (according to International Classification of Diseases, 10th revision (ICD-10) or medical act classification) and co-medications (Anatomical Therapeutic Chemical (ATC) system).

Conditions	ICD-10 code	Medical act code	ATC code
AF, peripheral embolism, ischemic stroke	I490x, R002x, I470x, I48x, I481x, I482x, I480x, I489x, I500x, I501x, I743x, I471x, I495x, I509x, I742x, I110x, I498x, K550x, I499x, I479x, I745x, R000x, I744x, E059x, I740x, E058x, I748x, K551x, I132x, E055x, I130x, I741x, R008x, R4700x, I63x, G45x, I670x, I64x, I652x, I651x, I653x, I658x, I694x	DEMP001, DEMP002, YYYY490, DKRP004, DZQM002, DAQM003, DEQP001, EQR002, GLRP004, DZQJ001, DEQP002, DZQJ008, DZQJ011, DZQJ010, DZQJ009, DEQP004, DEQP003, DZQM006, DEQP007, DZQM005, DZQJ001, DEQP005, DERP003, DZQJ008, DZQJ006, EEFA004, EEFA002, ECFA002, DERP004, DEQP001, EEFA001, EBQM002, EBQM001, ACQH003, EBQM003, ACQJ002, ACQN001, ACQJ001, ACQN004, EAQM003	
Venous thromboembolism	I26x, I801x, I802x, I803x, I808x, I809x, I81x, I822x, I823x, I829x, I636x, I676x, I828x, G08x, I800x, I820x, O871x, I821x, K751x, O223x	DHQH003, DHQM002, ECQH010, ECQH011, EFQM001, EJQH003, EJQM003, EJQM004, EJQM004, EJQP001, EMQH001, EQBP001, GFQL002, GFQL006, ZBQH001	
Lower limb orthopaedic surgery	T840x, Y831x, Z470x, Z966x	BFKA001, DBKA006, LFCA001, LHCA002, LHQH001, MBCA005, MDCA011, MDCB003, MEQH001, MGDA002, MGQH001, MHDB001, MHEP002, MHQH001, MZJB001, MZMP013, MZMP015, MZQH001, NAFA002, NBKA001, NBKA004 to NBKA006, NBKA010, NBKA014, NBKA015, NBCB003, NBCB004, NBFA003, NBMA002, NBMA003, NBPA011, NBPA016, NCCA002, NCCA004, NCCA007, NCCA012, NCCA014, NCCA017, NCCA018, NCCB006, NCEP002, NCFA006, NCPA001 to NCPA003, NCPA008, NCPA013 to NCPA015, NDCA006,	

		NDEP001, NDFA002, NDGA003, NDPA002 to NDPA004, NDPA011, NDPA013, NDPA014, NEEP002, NEFA004, NEFC001, NEJA001, NEKA001 to NEKA0021, NELA003, NEMA018, NEMA020, NEMA021, NFCA002, NFCA003, NFCC002, NFEA002, NFEC002, NFFA002, NFFA004, NFFC001 to NFFC004, NFJA001, NFJA002, NFJC002, NFKA001, NFKA002, NFKA004 to NFKA009, NFMA002, NFMA004, NFMCO02, NFMCO03, NFMP001, NFMP002, NFPA002, NFPC001, NFQC001, NFQH001, NFQP001, NFRP001, NGCA001, NGDA002, NGDA004, NGJA001, NGMP001, NGMP002, NGQH001, NHDA003 to NHDA005, NHFA001, NHMA002, NHMA008, NJCA001, NJEA002, NJEA003, NJFA005, NJMA002, NJMA004, NJPA018, NJPA025, NJPA029, NZJB001, NZMP003, NZMP006, NZMP008, NZMP014, NZQH002, PAGA009 to PAGA011, PAGB004, PAPA003, ZEMP006,	
Valvular heart disease	I05x, I080x, I081x, I083x, I342x, Z952x, Z953x, Z954x, I350x, I340x, I351x, I352x, I330x, I361x, I060x, I341x, Q231x, I062x, I348x, I371x', I339x, I38x, I398x, I088x, I089x', I349x, I358x, I391x, Q224x, Q230x	YYYY108, YYYY118, DBMA011, DGKA025, DGKA011, DBKA011, DBQM001, DBKA006, YYYY062, DBMA002, DBMA003, DZQJ002, DBLF001, DBKA011, DBKA009	
Diabetes	E10x, E11x, E12x, E13x, E14x	BGNA001, BGNP001, BGNP004, BGNP006, BGNP007, BGNP008	A10A, A10B
Ischemic heart disease	I20 to I25	DDAF001, DDAF003 to DDAF010, DDMA003 to DDMA009, DDMA011, DDMA012, DDMA013, DDMA015 to DDMA038, DDQH006, DDQH009 to DDQH015, DDAA002, DDF001, DDF002, DDPF002	
Hematologic or immune diseases	D50 to D89		
Lipid-lowering drug			C10AA, C10AB, C10AC01, C10AC02, C10BA02, C10BA05, C10AX, C10BX03
Antiulcer agent			A2B
Anti-platelet inhibitors			B01AC

Annex 10. Characteristics of recent real-world observational studies on the bleeding risk of direct oral anticoagulants (meta-analyses excluded)

Study author (year) ^{ref}	Country	Design	Drugs (N)	Setting	Bleeding definition	Follow-up	Comments
Graham (2015) ¹¹	US Medicare > 65	Rs (claims)	D (67207) W (67207)	AF	ISTH Code hospitalisation	18205 py 19382 py	New users
Lauffenburger (2015) ¹²	US HMO/medicare	Rs (claims)	D (21070) W (43865)	AF	Composite score Code ICD-9 hospitalisation	Mean 358 days	New users
Beyer-Westendorf (2015) ¹³	Germany (Dresden)	Ps (clinical)	D (341)	AF	ISTH	3 months	No comparator
Nishtala (2015) ¹⁴	New Zealand > 65	Rs (claims)	D (4835) W (4835)	AF	Any hospitalisation bleeding	Not defined	New users
Hernandez (2015) ¹⁵	US Medicare > 65	Rs (claims)	D (1302) W (8102)	AF	Anatomical site ICD-9	Mean 177 days Mean 228 days	New users
Yavuz (2016) ¹⁶	Turkey	Ps (clinical)	D (381) W (174)	AF	Any bleeding	6 months	
Tamayo (2015) ¹⁷	US	Rs (claims)	D (27467)	AF	ISTH	-	No comparator
Laliberte (2014) ¹⁸	US HMO	Rs (claims)	R (3654) W (14616)	AF	ISTH	6 months	Naïve and non-naïve VKA users
Hecker (2016) ¹⁹	Germany (Dresden)	Ps (clinical)	R (1204)	AF	ISTH	3 months	No comparator
Camm (2015) ²⁰	multicenter	Ps (clinical)	R (6784)	AF	ISTH	1 year	No comparator
Agno (2015) ²¹	multicenter	Ps (clinical)	R (2619) W (2149)	VTE	ISTH	1 year	
Chang (2015) ²²	US	Rs (claims) HMO	D (4907) R (1649) W (39607)	Any indication	Any GI bleeding ICD-9 hospitalisation	-	New users
Maura (2015) ²³	France	Rs (claims)	D (8443) R (4651) W (19713)	AF	Bleeding requiring hospitalisation	3 months	New users
Abraham (2015) ²⁴	US HMO / Medicare	Rs (claims)	D (8578) R (16253) W (67985)	Any indication AF/ non AF	GI bleeding	-	New users
Larsen	Denmark	Rs	A (6349)	AF	Any bleeding	Mean 2 years	New users

(2016) ²⁵	Nationwide	(claims)	D (12701) R (7192) W (35436)		Hospitalisation		
Lip (2016) ²⁶	US HMO / Medicare	Rs (claims)	A (7438) D (4661) R (17801) W (15461)	AF	Bleeding requiring hospitalisation (pooling analysis on all major bleeding)	Mean 160 days	New users
Yao (2016) ²⁷	US HMO / Medicare	Rs (claims)	A (15390) D (28614) R (32350) W (76354)	AF	Any bleeding	Not defined	Naïve and non-naïve VKA users
Staerk (2016) ²⁸	Denmark Nationwide	Rs (claims)	A (6899) D (12613) R (5693) W (18094)	AF	Intracranial bleeding hospitalisation	median 204 d median 386 d median 208 d median 252 d	New users
Chan (2016) ²⁹	Taiwan	Rs (claims)	D (5921) R (3916) W (5251)	AF	Bleeding requiring hospitalisation	End of study date	
Becattini (2016) ³⁰	Italy and Germany	P (clinical) Case-only	DOAC (191) W (615)	Any indica tion	ISTH	1 month	
Graham (2016) ³¹	US Medicare > 65	R (claims)	D (52250) R (66651)	AF	ISTH except for - 2g/dl Hb + transfusion	15524 py 20199 py	New users
Halvorsen (2017) ³²	Norway	R (claims) Nationwi de	W (11427) D (7925) R (6817) A (6506)	AF	ISTH except for - 2g/dl Hb Hospital codes	Median 6 months	New users
Lai (2017) ³³	Taiwan	Rs (claims)	D (10625) R (4606)	AF	ICH, transfusion for GI bleeding	1 year	No comparator
Xu (2017) ³⁴	Canada	Ps (clinical) Case only Hospital- based	D (245) R (245) A (35) W (1542)	AF	ISTH	1 month	>66 years
Li (2017) ³⁵	US HMO / medicare	Rs (claims)	A (38470) W (38470)	AF	ISTH	1 year	New users
Sindet- Pedersen (2017) ³⁶	Denmark Nationwide	Rs (claims)	R (5411) W (6907)	VTE	ISTH	6 months	
Larsen (2017) ³⁷	Denmark	Ps (clinical)	R (1734) W (2945)	VTE	ICH, GI clinical relevant bleeding	6 months	New users
Helmert (2017) ³⁸	Germany, Dresden	Ps (clinical)	A (514)	AF	ISTH	3 months	
Abraham	US	Rs	D (17425)	Any indica	Any GI bleeding	Not defined	Head to head comparison

(2017) ³⁹		(claims)	R (19301) A (6576)	tion			
Amin (2017) ⁴⁰	US Medicare > 65	Rs (claims)	W (95390) A (20853) R (53146) D (16743)	AF	ISTH Claim based algorithm	mean 199 d mean 171 d mean 204 d mean 196 d	New users
Cangemi (2017) ⁴¹	US VA center	Rs (claims) Case only	DOAC (803) W(6263)	Any indication	ISTH Medical chart review	3 months	All users
Kohsaka (2017) ⁴²	Japan	Rs (claims)	A(5977) D(5090) R(6726) W(17793)	AF	Bleeding requiring hospitalisation	Date of bleeding	New users
Cha (2017) ⁴³	Korea nationwide	Rs (claims)	A(2189) D(3741) R(5681) W(23222)	AF	ICH Code ICD-10 hospitalisation	Mean 0.4 y Mean 1.5 y	New users
Denas (2017) ⁴⁴	Italy regional	Rs (claims)	DOAC (6923) VKA (33488)	AF	Any bleeding	6178 y 10611 py	New users
Hohnloser (2017) ⁴⁵	Germany	Rs (claims)	VKA (16179) A (3633) D (3138) R (12063)	AF	Bleeding requiring hospitalisation	Date of bleeding	New users
Coleman (2017) ⁴⁶	Canada	Rs (claims)	W (32244) R (13604)	VTE	Bleeding requiring hospitalisation	1 year	New users
Green (2018) ⁴⁷	UK	Ps (clinical) Hospital-based	W (1771) DOAC (418)	Any indication	ISTH + specific therapy	1 month	3-year prospective Medical validation
Vinogradova (2018) ⁴⁸	UK	Ps (claims)	W (132231) D(7744) R(37863) A(18223)	Subgroups AF and no AF	Major bleeding leading to death Hospital diagnoses	Median 5 to 12 months	New users
Our study	France	Ps (clinical) Population-based	DOAC (27331) VKA (20275)	Any indication	ISTH except for -2g/dl Hb	1 month and 6 months	3-year prospective Medical validation New users

Rs: retrospective; Ps: prospective; D: dabigatran; R: rivaroxaban; A: apixaban; W: warfarin; AF: atrial fibrillation; VTE: venous thromboembolism; ISTH: International Society of Thrombosis and Haemostasis; GI: gastrointestinal; ICH: intracerebral haemorrhage; VKA: vitamin K antagonist; DOAC: direct oral anticoagulant; Hb: hemoglobin; py: person-year.

Figure 1. Flow-chart

