Major bleeding with antithrombotic agents a 2012-2015 study using the French nationwide Health Insurance database linked to emergency department records within five areas - rationale and design of SACHA study

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Article type : Original Article

Major bleeding with antithrombotic agents: a 2012-2015 study using the French nationwide Health Insurance Database (SNIIRAM) linked to emergency departments records within five areas. Rationale and design of SACHA study

Running head*:* Emergency departments' bleedings and anti-thrombotic drugs

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ABSTRACT

Bleeding represents the most recognised and feared complications of antithrombotic drugs including oral anticoagulants. Previous studies showed inconsistent results on the safety profile. Among explanations, bleeding definition could vary and classification bias exist related to the lack of medical evaluation.

To quantify the risk of major haemorrhagic event and event-free survival associated with antithrombotic drugs (Vitamin K Antagonist [VKA], non-VKA anticoagulant [NOAC], antiplatelet agent, parenteral anticoagulant) in 2012-2015, we linked the French nationwide Health Insurance database (SNIIRAM) with a local "emergency database" (clinical and biological data collected in clinical records). In the VKA-NOAC comparison, a Cox regression analysis will be used to estimate the hazard ratio of major haemorrhagic event adjusted on gender, modified HAS-BLED score and comorbidities. A distinction on the type of major haemorrhagic event (intracranial, gastrointestinal and other haemorrhagic events) was made. We present here the study protocol and the databases linkage results.

Using six linkage keys, among 3,837,557 hospital visits identified in SNIIRAM, 5264 have been matched with a major haemorrhagic event identified in the "emergency database", thus clinically confirmed. The 1090 unmatched haemorrhagic events could be explained by the fact that patients were not extracted in the SNIIRAM database (patients living in accommodation establishment with internal use pharmacy, military people with specific insurance…).

We showed the value of SNIIRAM enrichment with a clinical database, a necessary step to categorise haemorrhagic events by a clinically relevant definition and medical validation; it will allow to estimate more accuracy each type of haemorrhagic event.

Keywords: antithrombotic, population-based study, emergency, linkage, bleeding.

INTRODUCTION

Antithrombotic drugs, i.e. oral anticoagulants as well as platelet aggregation inhibitors, have demonstrated significant benefits in preventing venous or arterial thrombotic events, especially in coronary disease, stroke, atrial fibrillation (AF), venous thromboembolism (VTE) and mechanical heart valves [1]. These drugs are commonly prescribed and their long-term use is increasing, particularly in elderly. Bleeding represents the most well-known and feared complications of antithrombotic drugs. Numerous studies on adverse events reported anticoagulants as the first drug class implicated in haemorrhage and specifically intracranial haemorrhage (ICH) which often results in substantial morbidity and mortality [2]. Using adverse events from a National Surveillance System database, Budnitz et al. demonstrated that warfarin and oral platelet aggregation inhibitors were respectively the first and the third drug classes leading to emergency department and hospitalization in adults 65 years of age or older [3]. Gastrointestinal bleeding and intracranial haemorrhage are expected as adverse effects of platelet aggregation inhibitors [4–6]. In a historical cohort, we reported that platelet aggregation inhibitors and oral anticoagulants were equally implicated in the incidence of major haemorrhage seen in an emergency department [7]. More recently, except for

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patients with mechanical heart valves, non-VKA oral anticoagulants (NOAC) were licensed for quite the same indications than vitamin K antagonists (VKA): prevention of stroke and systemic embolism in patients with non-valvular AF, curative and preventive treatment of VTE, thromboembolic prophylaxis before knee or hip replacement. International multicentre trials have shown non-inferiority to warfarin in patients with AF with lower risk of intracranial haemorrhage but a higher risk of gastrointestinal bleeding [8–10]. Several reports from registries and analysis of claims databases [11–48] have recently suggested, compared with VKA, a similar safety profile of NOAC in the community and in randomised trials. However, meta-analyses [49,50] highlighted inconsistency among those observational studies using different designs: Weeda et al. [49] showed a significant higher risk of gastrointestinal bleeding in studies that relied on claims without clinical identification of bleeding events, leading misclassification bias. Moreover, definitions of major bleeding were variable across studies. Differences between cohort and cross-sectional studies [50] such as heterogeneity of patient characteristics and use of propensity score analysis including various confounding factors held to various incidence rates of bleeding. Thus, the magnitude of bleeding risk associated with all these antithrombotic drugs remains unclear in the real-world clinical practice.

Emergency departments represent a privileged place to observe and to report outpatient adverse drugs events [51], in particular bleeding associated with antithrombotic drugs. Amazingly, to our knowledge, no data based on prospective assessment of emergency department records of subjects referred for bleeding has been reported so far. We set up SACHA study (Survey of acute haemorrhage with antithrombotic drugs), a prospective multicentre study with a three-year inclusion (2012-2015) period and a 6-month follow-up.

Using a local “emergency database” linked with the French nationwide Health Insurance database, the primary objective was to quantify the risk of major bleeding associated with antithrombotic drugs; in a relevant comparison such as VKA-NOAC, we will compare the event-free survival. Secondary objectives were to describe the clinical and therapeutic management of these bleeding events and 1-month and 6-month prognosis (vital status, thrombotic events and/or bleeding recurrence). We herein report methods in details, following RECORD checklist [52], with a particular emphasis on efforts addressing sources of bias and linkage process between the nationwide and local databases.

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METHODS

Study design

Called the SACHA (survey of acute haemorrhage with antithrombotic drugs) project, we set up a prospective population-based study linking French Health Insurance Database (SNIIRAM) to data from all emergency departments located within five defined areas surrounding large cities (Angers, Brest, Grenoble, Nantes and Rennes) in France. The current study got regulatory approval (CNIL, DR-2013-488 with subsequent substantial modification DR-2016-489); ClinicalTrials.gov identifier: NCT02886533.

Funding: This study was supported by the National Clinical Research Hospital Program of the French Ministry of Health (PHRC-12-009-0243).

Data sources and variables

(i) SNIIRAM links anonymously and comprehensively a health reimbursement database (DCIR) to the French hospital discharge database (PMSI) [53]. DCIR contains basic data such as age, date of death, and data on drug prescription and delivery including all reimbursed deliveries with strength per unit, number of units per pack for each drug as well as the date of prescription and dispensing. PMSI contains diagnostic codes (International Classification of Disease, 10th revision, ICD-10), admission dates and medical acts (Common Classification of Medical Acts [CCMA] classification) for all hospitalizations either in public or private hospitals; PMSI does not contain information as regards drugs used during hospital visit.

(ii) From the emergency department, clinical and biological data collected in clinical records as regards major haemorrhagic events (ICD-10 codes listed in annex 1) related to antithrombotic drugs (*see section outcome and exposure*) were reported in an "emergency database": demographics (month and year of birth, sex), medical history, co-morbid conditions, drug class, indication and duration of antithrombotic agent, concomitant medical treatment, type of bleeding/outcome, vital signs at admission, contributory procedures that led to diagnostic of major bleeding (CT scan, endoscopy), biological data on admission, therapeutic haemorrhagic event management in the emergency room, time between admission and diagnosis, time between admission and reversal therapy, length of stay in hospital, and decision about antithrombotic treatment after the first major haemorrhagic event. All cases of major haemorrhagic event were clinically confirmed by clinician.

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Source population

Thanks to SNIIRAM, we included all adult (> 18 year) subjects, living within the five above mentioned areas, affiliated to French Health Insurance System (whatever the insurance plan), with at least one reimbursement for an antithrombotic drug (list in annex 2) in 2012-2015.

Exposure. Using SNIIRAM, we considered all antithrombotic drugs, alone or in combination, between 2012 and 2015, whatever the indication and dosage drug: oral anticoagulants defined by VKA (warfarin, fluindione, acenocoumarol), and NOAC (dabigatran, rivaroxaban, apixaban); antiplatelet agents (aspirin, clopidogrel, ticagrelor, prasugrel…); parenteral anticoagulants (unfractionned heparin (UFH), low molecular weight heparin (LMWH), fondaparinux, heparinoid). For analyses, a "dose" variable was defined as follows using packaging type delivered: low (dabigatran 110 mg, rivaroxaban 10 mg, apixaban 2.5 mg twice a day; calciparin 2500 or 5000 UI, enoxaparin 2000 or 4000 UI, nadroparin 2850 UI, reviparin 1432 UI, tinzaparin2500 or 3500 UI, fondaparinux 2.5 mg, UFH 5000 UI), and high (dabigatran 110 mg twice a day or 150 mg twice a day, rivaroxaban 15 or 20 mg, 15 mg twice a day; UFH > 5000 UI or other dosage for LMWH).

We defined a new user, in each antithrombotic class (annex 2), as a patient who has no reimbursement for that class in his or her medication history.

Primary objectives' outcome. From the patients in the SNIIRAM database, between January 1, 2013 and December 31, 2015 we prospectively and consecutively identified all clinically confirmed case of major haemorrhagic events (annex 1) occurring in patients exposed to antithrombotic drug in the community and which motivated care in an emergency department (see list of participating centres in annex 3). Some events were not considered: major haemorrhagic event in patients during hospitalization whereas patient was referred for another reason to emergency room; patients exposed to an antithrombotic drug living outside of the defined areas; intentional overdose of antithrombotic drugs. No informed and signed consent was needed for the basic survey. In contrast, to obtain the 1-month and 6-month follow-up, each included patient received a non-opposition letter and in case of a declared opposition, no data were collected on follow-up.

All public and private care facilities emergency departments in the defined areas able to receive and take care of patients referred for bleeding event as well as pre-hospital emergency medical services participated in. Patients were firstly identified through haemorrhage at emergency admission: computerised requests based on several related-haemorrhagic diagnostic codes (list in annex 4) and specific emergency therapies (red blood transfusion, platelet transfusion, vitamin K, protamin sulfate, PCC (prothrombin complex concentrate) and FEIBA) were made on electronic health records.

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In each emergency department, the local referent medical doctor validated definitive inclusion of all screened records as regards bleeding severity (primary outcome, see below).

More specifically, major haemorrhagic event was defined by at least one of the following criteria: unstable hemodynamic (systolic arterial pressure < 90 mmHg or mean arterial pressure < 65 mm Hg) or haemorrhagic shock, uncontrollable bleeding, need for transfusions or haemostatic procedure (embolization, endoscopic procedure, surgery), a life-threatening location such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, thoracic, intra-articular, intramuscular haematoma with compartment syndrome, acute gastrointestinal bleeding. We also considered major haemorrhagic event in case of epistaxis with at least two procedures of nasal packing and in case of haematuria when bleeding remained during more than 12 hours despite bladder washing. We anticipated some differential association according to the type of major haemorrhagic event (see annex 5 for details) and defined 3 groups: intracranial haemorrhage, gastrointestinal bleeding and other bleeding events.

Secondary outcome concerned event-free survival.

Secondary objectives' outcomes. First, we focused on initial therapeutic haemorrhagic events management, especially the use of red blood transfusion, platelet transfusion, vitamin K, protamin sulfate, PCC or FEIBA. Secondly, at 1 month and at 6 months after the first major haemorrhagic event (primary outcome), we identified recurrence of major haemorrhagic event (as previously defined) or occurrence of ischemic event (ischemic stroke, transient ischemic attack, myocardial infarction or acute coronary syndrome, deep vein thrombosis or pulmonary embolism, or any peripheral arterial thrombosis) and vital status. We kept in mind the initial indication of antithrombotic agent and whether this agent was withdrawn or replaced by another one after the first major haemorrhagic events.

Linkage. The following key variables were available in SNIIRAM and "emergency" databases: date of birth (month, year), gender, date (day, month, year) of hospital entry +/- 3 days, type of antithrombotic drug, geographic area of the first antithrombotic drug delivery, care facilities (participating centres). Hits were defined as an emergency department stay identified in the SNIIRAM database which matched on key variables with an event selected in the "emergency database" (see annex 6 for linkage details). Duration stay consistency was also assessed to help choosing the most appropriate hit. Patients included in the "emergency database" who were not linked to the SNIIRAM database have been considered as not belonging to the SNIIRAM extraction.

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For note, modified HAS-BLED scoring and Charlson comorbidity index required SNIIRAM data for a fair assessment in all subjects exposed to an antithrombotic drug whether or not they experienced a major bleeding event for which they were referred to hospital.

Comorbidities. A modified HAS-BLED score derived from Pisters et al. [54] and already used by some authors [23,24] was calculated (see annex 7). Of note, SNIIRAM does not include laboratory results, thus we were not able to assess a labile international normalized ratio (INR) initially used in the original HAS-BLED score. In addition, this item does not make sense in new users or even in prevalent users of NOAC. At variance with the original score, items were calculated from data available within a year before antithrombotic first use. At the first antithrombotic reimbursement date, a high and low bleeding risk will be defined by, respectively, a modified HAS-BLED score > 2 or ≤ 2; of note the modified HAS-BLED maximal score is 8 points instead of 9 in the original one. All analyses were adjusted on these bleeding risks. We used the modified Charlson comorbidity index (see annex 8) to assess patients' overall comorbidity burden [55]. From the medical history available in the month preceding the first delivery of antithrombotic, we extrapolated the indication for antithrombotic. As regards the anticoagulation indications, we considered three main reasons: deep vein thrombosis or pulmonary embolism (VTE), short-term VTE preventive setting (for instance hip or knee replacement surgery), atrial arrhythmia with or without peripheral embolism (list of codes in annex 9); others were classified as unknown or miscellaneous.

Statistical methods and variables. Statistical analyses will focus on patients newly exposed to oral anticoagulant during the 2013-2015 period, without any reimbursement of oral anticoagulant in 2012, with the first delivery date identified through SNIIRAM database.

Focusing on the VKA - NOAC comparison, we will analyse patients with at least one reimbursement of VKA or NOAC with or without oral antiplatelet agents or parenteral anticoagulant without restriction on the indication of the anticoagulant used; the first type of oral anticoagulant will be used as the exposure category; VKA will be considered as the reference group. We will perform descriptive statistics: they will concern for categorical variables, frequency and percentage, and mean ± standard deviation or median (inter-quartile range) for continuous variables whether the distribution is normal or not. Description will focus on major haemorrhagic event characteristics and clinical parameters according to antithrombotic drug exposure. The main analysis will follow an on-treatment principle as we deal with a safety outcome. Exposed time will be censored at the earliest date of end of the study period, date of major haemorrhagic event, date of death, date of defined area leaving, date of anticoagulant switch (between VKA and NOAC) or, for the main analysis, date of

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NOAC dose change (low to high dose and vice versa). Crude incidence rates for major haemorrhagic event per 10 000 person-months will be calculated, within each HAS-BLED strata, and distinguishing duration of use (< 6 month, 6 to 12 months and > 1 year, as we anticipate that instantaneous bleeding risk was not constant over time), dose (low or high) and type of major haemorrhagic event (intracranial haemorrhage, gastrointestinal bleeding and other bleeding events). For further comparison within each analysis, Cox proportional hazard regression analysis will be used to estimate the hazard ratio of major haemorrhagic event adjusted on gender, modified HAS-BLED score and comorbidities; a similar analysis will be done for the event-free survival outcome. As a sensitivity analysis, for each indication, we will estimate a propensity score and use stabilized inverse probability of treatment weighting (SIPTW) regression modelling.
Subsequent analyses (descriptive analyses and incidence rates estimation) for the new users of parenteral anticoagulants users group and the new users of the antiplatelet agent users group will follow the same principles.

Study size. Our main analysis and comparison will concern the NOAC and VKA new users: the power calculation took into account NOAC major haemorrhagic events, considering that NOAC were recently commercialized and less prescribed than VKA on the 2012-2015 period; under the assumption that the cumulative percentage of major bleeding at 12 months was 1.5 % in the VKA group (reference group), 120,000 patients overall were needed to detect a relative risk of 1.20 with 90 % power at a two-sided 5 % alpha-level, accounting that VKA dispensation is roughly 4-fold greater (ratio 4:1) than NOAC group. For the parenteral anticoagulant group, no comparison is planned. For antiplatelet agents, *a posteriori* power calculation is planned.

Data access and cleaning methods. On-site monitoring was performed to specifically check the validity of the primary outcome and eligibility criteria. Queries were edited to minimize errors identified as outliers or missing values.

Bias. We think that major bleeding always led to hospital admission. Being doubtful as regards accuracy of PMSI database (hospital discharge diagnoses) to adequately categorize patients as being referred for major haemorrhagic event, we comprehensively and prospectively collected data from all emergency departments within selected areas. Those areas were defined as catchment region surrounding each main city hospitals in order to avoid missing any major bleeding being cared elsewhere. Medical validation of primary outcome ensured minimization of classification bias; on the other hand, drug exposure was based on SNIIRAM database (reimbursement claims). Most importantly, the main analysis focused on first users, thus avoiding immortal bias. In addition,

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selection bias is minimized as SNIIRAM database is quasi exhaustive within selected areas. Lastly, to consider indication bias, analyses will be stratified on a modified HAS-BLED score [54] with further adjustment on a modified Charlson comorbidity index [55]. Those scores and index are measured through SNIIRAM database in all analysed subjects thus minimising classification bias.

RESULTS

Between 2013 and 2015, 3,837,557 hospital visits were identified in the SNIIRAM database, and 6,354 events in the "emergency database". Using the different keys, we identified 18,654 hits (*see method section for hit definition)* in the SNIIRAM database for 6,195 events in the "emergency database". We checked the consistency between the "emergency" and the SNIIRAM databases on two points: i) geographic area considering that patients identified in the SNIIRAM database could come from specific French region but outside of the defined area (see Annex 3); ii) anti-thrombotic drug considering that a potential inconsistency could exist between the drug class exposure at the haemorrhagic event date in the "emergency database" and the SNIIRAM database. Inconsistent hits were then excluded.

Finally, among those 3,837,557 hospital visits, 5264 have been matched with a major haemorrhagic event identified in the "emergency database", thus clinically confirmed (figure 1). More in depth, 4,751 events matched with only one hospital visit in the SNIIRAM database, and 513 events matching with 2, 3 or 4 hospital visits in the SNIIRAM database. For these 513 events, a selection on the most similar date of emergency department entrance and hospital discharge, and on the patient concomitant reimbursed drugs was made to select the right event. The remaining 1090 events found in the "emergency database" are thought to be related to patients out of the SNIIRAM extraction (*see discussion section*).

As regards the at-risk cohort of subjects exposed to antithrombotic drugs in 2013-2015 living in the defined area, identified through SNIIRAM, 102,560 subjects had been categorised as oral anticoagulant (VKA or NOAC, +/- antiplatelet agents) users.

DISCUSSION

The originality of our methodology lies on the linkage of Health Insurance Data to data from all emergency departments within a well-defined area. Dealing with the challenge of linking two databases allowed us: firstly, to enrich the SNIIRAM database, an anonymous medico-administrative database, with a clinical database; secondly, to complete specific missing data (date of antithrombotic initiation) in the clinical database thanks to SNIIRAM; thirdly, to have a clinically confirmed diagnosis. Such a methodology has been previously used for another safety issue [56].

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Strengths and limitations.

Based on information collected in medical records ("emergency database"), each major haemorrhagic event was categorised by a clinically relevant definition, without restriction to a validated indication, and was medically validated and carefully checked thereafter. Such an approach authorises a more accurate estimate of haemorrhagic risk. A recent study [57] showed that the manual medical records review was a necessary step especially for gastro-intestinal and urogenital bleeds, improving the true estimated incidence rates; in comparison, the codes used alone in database overestimated the incidence rates. Furthermore, such a medical review overcomes the classification bias related to retrospective analysis of data based on hospital discharge diagnosis (ICD-10 codes) without medical validation [49]. We had some suspicion about the accuracy of hospital discharge diagnoses in PMSI database to adequately categorize patients as being referred for major bleeding.

To define bleeding as a major haemorrhagic event, we used criteria of major bleeding recommended by the French National Authority for Health (HAS) [58] rather than criteria of the International Society of Thrombosis and Haemostasis (ISTH) [59]. These criteria were anyway close to each other and we considered that a fall in haemoglobin level of 20 g/l or more was a tricky criterion to estimate when recruiting in emergency rooms as the baseline haemoglobin level was not often available. These same criteria were used in other observational studies [31,32,47]. Otherwise, considering indication bias when comparing VKA to NOAC, we plan a sensitivity analysis on "common" indications. For note, NOAC have no indication in valvular heart diseases (cardiac prothesis); the VKA - NOAC comparison was thus not realised on this indication and this sub-group analysis was not performed.

Secondly, exhaustiveness of case identification is a main issue: all emergency departments of the defined catchment region surrounding each main city hospitals participated in our study.

Thirdly, to ensure that subjects referred for major haemorrhagic event were truly cases arising from the at-risk cohort (subjects exposed to antithrombotic agents living in the area), careful check of data on residency as well as linkage processing were conducted and monitored. Patients living in the area with a major haemorrhagic event occurring outside of the defined area (for instance, on vacation) were also captured through SNIIRAM but not in the "emergency database"; they are supposed to be marginal; if not, even they had not been clinically confirmed, we plan to include them in a sensitivity analysis to estimate the hazard ratio of major haemorrhagic event.

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Fourthly, drug exposure was assessed through clinical records (collected in emergency rooms or by contact with the general practitioner of the patient in case of missing data in the emergency clinical record) as well as on claim database, the two data sources being linked allowing cross-checking; recent and last drug exposure is anticipated to be reliably assessed through clinical records and we know otherwise that some drug exposure could not be traced by SNIIRAM (prescription and delivery within hospital or retirement homes with a dedicated pharmacy); on the other hand, SNIIRAM was more reliable to reconstruct the history of drug exposure (including initiation, switch, stop) than the patient interview (data supplied in emergency clinical records), especially when patient is exposed since a long time. Recent drug exposure consistency was considered when linking events between SNIIRAM and "emergency database" and SNIIRAM was the reference to classify first use anticoagulant type.

Fifthly and most importantly, the main analysis focused on first antithrombotic users (new users), thus avoiding immortal bias.

Sixthly, to consider indication bias, analyses will be stratified on modified HAS-BLED score and used further adjustment on components of modified Charlson comorbidity index. As regards the on-treatment principle, we planned to censor exposure time at the oral anticoagulant switch.

On the other hand, we acknowledge that there was no centralized event adjudication. All deaths, specifically those occurring outside the hospital will be identified but cause remained unknown.

Last but not least, as regards the 1090 events found in the "emergency database" but not in the SNIIRAM database, some explanations could be considered: a part concerned patients living in accommodation establishment for dependent people with internal use pharmacy (especially since the exposed population is rather old); the drug dispensation in such an establishment is not available in the SNIIRAM database and patients have not been extracted in the source population then. Another explanation concerned patients living in the Brest area which includes an over-representation of military people whose specific insurance is not include in the SNIIRAM and who are supposed to be also not extracted in the source population. Finally, as regards patients with parenteral anticoagulant identified through the "emergency database", they are supposed to be hospitalised in care facilities and then not extracted in SNIIRAM database; note that we are not interested in these patients, considering an analysis focused on bleeding from the community. Additionally, we also could not rule out some misclassification as regards antithrombotic drug exposure when clinically assessed.

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Discussion about methodologies used in real-world studies

Since 2014, several real-world observational studies investigated the bleeding risk of NOAC in many countries [11–48]. Annex 10 reports some characteristics of these post-approval published studies and shows heterogeneity for many aspects: most of them used retrospectively data from nationwide administrative or insurance databases with limited clinical information - no access for patient's mortality [22]. Few studies were prospective [13,16,19–21,30,34,37,38,47,48]. Medical validation of patient's bleeding events was scarce [16,30,34,37,38,47]. The follow-up of included patients were very different (from 1 month to 2 years). Most studies included only patients with atrial fibrillation [11–20,23,25–29,31–35,38,40,42–45], others only patients with venous thromboembolism diseases(21,36,37,46), few studies focused on a type of haemorrhagic event, gastrointestinal bleeding [22,24,33,39], or intracerebral bleeding [28,33,37,43]. The numbers of patients exposed to VKAs and to the different DOACs were very various, from few hundreds to many tens of thousands. The bleeding criteria are also quite different. Some studies included patients with prior warfarin exposure because all pivotal trials and routine clinical practice, the majority of patients initiating NOAC have previously used VKA. In Maura et al. study [23], patients with contraindications to treatment (history of valvular heart disease, ongoing cancer treatment, dialysis for end-stage renal disease, hematologic disease or certain immune system disorders considered to be at higher risk of major bleeding (LTD or ICD-codes D50-D89), hepatic cirrhosis or fibrosis or liver failure, acute bleeding peptic ulcer) were excluded. These different designs led to various and sometimes contradictory results, about incidence of the haemorrhagic risk of the different antithrombotic drugs and especially the anticoagulant agents. For note, study chronology faced to the time of drug approval may influence results in terms of safety: Laliberté et al. [18] reported a higher intracranial bleeding risk with rivaroxaban than other similar studies because of less experience of the prescribers.

With our SACHA current study, using French nationwide database enriched with an "emergency database", we will estimate the risk of clinical confirmed major haemorrhagic event in patients using antithrombotic drugs, regardless the antithrombotic indication, in real-world clinical practice, taking into account comorbidities, co-medications and medical history on a 3-years period. Contrary to the most previous studies where haemorrhagic risk estimation was based on the antithrombotic indication [22,24,41,47], we will consider patients baseline profile using comorbidities and the modified HAS-BLED score and the antithrombotic dose and duration. In our opinion, they appear as more relevant haemorrhagic risk factors, which will provide a better haemorrhagic risk estimation associated with determinate therapeutic classes.

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ANNEXES

Annex 1. ICD-10 codes used in SNIIRAM to detect bleeding events

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

Annex 1. ICD-10 codes used in SNIIRAM to detect bleeding events

Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism

D62 Acute post-haemorrhagic anaemia

D683 Haemorrhagic disorder due to circulating anticoagulants

Diseases of the eye and adnexa

H11.3 Conjunctival haemorrhage

H35.6 Retinal haemorrhage

H43.1 Vitreous haemorrhage

H45.0 Vitreous haemorrhage in diseases classified elsewhere

Diseases of the ear and mastoid process

H92.2 Otorrhagia

Diseases of the circulatory system

I31.2 Haemopericardium

I60.x Subarachnoid haemorrhage

I61.x Intra-cerebral haemorrhage

I62.0 Subdural haemorrhage (acute) (non traumatic)

I62.1 Non-traumatic extradural haemorrhage

I62.9 Intracranial haemorrhage (non-traumatic), unspecified

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I64 Stroke, not specified as haemorrhage or infarction
I77.2 Rupture of artery
I85.0 Oesophageal varices with bleeding
I98.3 Oesophageal varices with bleeding in diseases classified elsewhere
Diseases of the respiratory system
J94.2 Haemothorax
Diseases of the digestive system
K22.6 Gastro-oesophageal laceration-haemorrhage syndrome
K25 Gastric ulcer
K26 Duodenal ulcer
K27 Peptic ulcer, site unspecified
K280
subdivisions for use with categories K25-K28:
.0 Acute with haemorrhage
.2 Acute with both haemorrhage and perforation
.4 Chronic or unspecified with haemorrhage
.6 Chronic or unspecified with both haemorrhage and perforation
K29.0 Acute haemorrhagic gastritis
K51.8 Other ulcerative colitis
K51.9 Ulcerative colitis, unspecified
K62.5 Haemorrhage of anus and rectum
K66.1 Haemoperitoneum
K92.0 Haematemesis
K92.1 Melaena
K92.2 Gastrointestinal haemorrhage, unspecified
Diseases of the musculoskeletal system and connective tissue
M25.0 Haemarthrosis
Diseases of the genitourinary system
N02 Recurrent and persistent haematuria
N92 Excessive, frequent and irregular menstruation
N93.8 Other specified abnormal uterine and vaginal bleeding
N93.9 Abnormal uterine and vaginal bleeding, unspecified
N95.0 Postmenopausal bleeding
Symptoms, signs and abnormal clinical and laboratory finding
R04.0 Epistaxis
R04.1 Haemorrhage from throat
R04.2 Haemoptysis
R04.8 Haemorrhage from other sites in respiratory passages
R04.9 Haemorrhage from respiratory passages, unspecified
R31 Unspecified haematuria
R58 Haemorrhage, not elsewhere classified
Injury, poisoning and certain other consequences of external causes
S00.8 Superficial injury of other parts of head
S01.0 Open wound of scalp
S06.0 Concussion
S06.2 Diffuse brain injury
S06.3 Focal brain injury
S06.4 Epidural haemorrhage
S06.5 Traumatic subdural haemorrhage
S06.6 Traumatic subarachnoid haemorrhage
S27.1 Traumatic haemothorax

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S27.2 Traumatic haemopneumothorax
S36.0 Injury of spleen
S51.7 Multiple open wounds of forearm
S81.8 Open wound of other parts of lower leg
S81.9 Open wound of lower leg, part unspecified

Factors influencing health status and contact with health services
Z51.3 Blood transfusion (without reported diagnosis)

Annex 2. ATC codes for antithrombotic agents

ATC-7 codes	INN	Antithrombotic class
B01AA02	PHENINDIONE	VKA
B01AA03	WARFARINE	VKA
B01AA07	ACENOCOUMAROL	VKA
B01AA12	FLUINDIONE	VKA
B01AC04	CLOPIDOGREL	Antiplatelet inhibitor
B01AC05	TICLOPIDINE	Antiplatelet inhibitor
B01AC06	ACETYLSALICYLIQUE ACIDE	Antiplatelet inhibitor
B01AC07	DIPYRIDAMOLE	Antiplatelet inhibitor
B01AC22	PRASUGREL	Antiplatelet inhibitor
B01AC22	PRASUGREL	Antiplatelet inhibitor
B01AC24	TICAGRELOR	Antiplatelet inhibitor
B01AC30	DIPYRIDAMOLE & ACIDE ACETYLSALICYLIQUE	Antiplatelet inhibitor
B01AC30	CLOPIDOGREL & ACIDE ACETYLSALICYLIQUE	Antiplatelet inhibitor
C10BX02	PRAVASTATINE & ACIDE ACETYLSALICYLIQUE	NOAC
B01AE07	DABIGATRAN	NOAC
B01AF01	RIVAROXABAN	NOAC
B01AF02	APIXABAN	parenteral anticoagulant
B01AB01	HEPARINE	parenteral anticoagulant
B01AB04	DALTEPARINE	parenteral anticoagulant
B01AB05	ENOXAPARINE	parenteral anticoagulant
B01AB06	NADROPARINE	parenteral anticoagulant
B01AB08	REVIPARINE	parenteral anticoagulant
B01AB10	TINZAPARINE	parenteral anticoagulant
B01AX05	FONDAPARINUX	parenteral anticoagulant

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Annex 3. Participating emergency departments and pre-hospital emergency medical services

Area 1. Clinique de l'Anjou, Angers, France, 49000; CHU d'Angers, Angers, France, 49033

Area 2. Hôpital Inter-Armées, Brest, France, 29 240; CHU de Brest, Brest, France, 29 609

Area 3. Hôpital Privé Sévigné, Cesson Sévigné, France, 35576; Centre Hospitalier Privé, Saint Grégoire, France, 35768; CHU de Rennes, Rennes, France, 35033

Area 4. Clinique des Cèdres, Echirolles, France, 38432; Groupe Hospitalier Mutualiste, Grenoble, France, 38028; CHU de Grenoble, Grenoble, France, 38043

Area 5. Nouvelles Cliniques Nantaises, Nantes, France, 44277; CHU de Nantes, Nantes, France, 44093

Annex 4. Computerised requests made on electronic health records in every participating centre

D50.9: iron deficiency anaemia, unspecified
D51.9: vitamin B12 deficiency anaemia, unspecified
D52.9: folate deficiency anaemia, unspecified
D62: acute post-haemorrhagic anaemia
D64.6: anaemia, unspecified

I31.2: haemopericardium
I60: subarachnoid haemorrhage
I61: intracerebral haemorrhage
I62: other non-traumatic intracranial haemorrhage
I98.2: oesophageal varices with bleeding

J94.2: haemothorax

K22.6: gastro-oesophageal laceration-haemorrhage syndrome
K25.0: gastric ulcer
K26.0: duodenal ulcer
K62.5: haemorrhage of anus and rectum
K66.1: haemoperitoneum
K92.0: haematemesis
K92.1: meloena
K92.2 gastrointestinal haemorrhage, unspecified

M25.0: haemarthrosis

N93.9: abnormal uterine and vaginal bleeding, unspecified

R04.0: epistaxis
R04.1: haemorrhage from throat
R04.2: haemoptysis
R31: unspecified haematuria
R57.1: hypovolaemic shock
R58: haemorrhage, not elsewhere classified

S01.0: open wound of scalp
S06.0: concussion
S06.2: diffuse brain injury

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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]).

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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).

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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,, EENFx, EEPFx, EEFAx, EECAx, ENNFx, ENFAx, DGAFx, EDAFx, DGFPx, EDPFx, DGFAx, EDFAx, DGCAx, EDCAx, EDPFx, EDJFx, EDKAx, EDEAx, EDLFx, EDNFx, EDPFx, EDJFx, 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).

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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, 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 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, EQRP002, 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, NBCA001, NBCA004 to NBCA006, NBCA010, NBCA014, NBCA015, NBCB003, NBCB004, NBFA003, NBMA002, NBMA003, NBPA011, NBPA016, NCCA002, NCCA004, NCCA007, NCCA012, NCCA014, NCCA017, NCCA018, NCCB006, NCEP002, NCFA006, NCPA001 to NCPA003, NCPA008, NCPA013 to NCPA0015, NDCA006,	

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		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, NFMC002, NFMC003, 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, DDFF001, DDFF002, 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

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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
Ageno (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 / Medicaire	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

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(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

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(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 indica tion	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) Populatio n-based	DOAC (27331) VKA (20275)	Any indica tion	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.

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Figure 1. Flow-chart