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Profiles and outcomes of patients treated with oral anticoagulants for atrial fibrillation who experience bleeding events requiring hospitalization in France

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ABSTRACT

Background: Patients with atrial fibrillation treated with oral anticoagulants are at risk of bleeding.
Aim: To describe oral anticoagulant-treated patients with atrial fibrillation who experience bleeding events requiring hospitalization, treatment patterns and outcomes following the bleeding event.
Methods: This was a retrospective cohort study using the French national health system claims database, analysing patients with atrial fibrillation newly treated with an oral anticoagulant, with at least one hospitalization for bleeding between 2014 and 2016, followed up to December 2019. Sites of bleeding, sociodemographic and clinical characteristics, treatment patterns before and after the first bleeding event, the number of bleeding events over follow-up, the time from index date to first bleed and the time from first bleed to death are described.
Results: Among 321,346 patients, 12,616 (3.9%) experienced at least one bleeding event (34.9% gastrointestinal). The median follow-up was 3.6 years from the index inclusion and 3.0 years from the first bleed. The mean age was 79.1 years, the mean Charlson Comorbidity Index score was 6.2 and 72% had modified HAS-BLED scores ≤ 3. Before the first bleed, 9.2% of patients had switched from the index oral anticoagulant to another oral anticoagulant, and 6.6% had stopped oral anticoagulant treatment. After the first bleed, 43.6% remained treated with the same oral anticoagulant, 5.2% switched to another oral anticoagulant and 31.7% received no oral anticoagulant. Most patients experienced only one bleeding event; the median time from first bleed to death was 9.3 months.
Conclusions: These "real-life" data show that patients with atrial fibrillation who experience a bleeding event have a high co-morbidity score, but often a low modified HAS-BLED score. The data document treatment patterns before and after bleeding, and show that in patients treated with oral anticoagulants, bleeding is associated with a high subsequent risk of death.

1. Abbreviations

AF	Atrial fibrillation
CI	Confidence interval
DOAC	Direct oral anticoagulant

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IBFB	Immediately before the first bleed
ICD-10	International Classification of Diseases, 10th revision
INR	International normalized ratio
LTD	Long-term disease
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulant
VKA	Vitamin K antagonist
SNDS	*Système National des Données de Santé*

2. Background

The main risks associated with atrial fibrillation (AF) are thromboembolic events, hospitalization and death [1]. Oral anticoagulants (OACs) are recommended for the prevention of stroke and systemic embolism in many (but not all) patients with AF [1]. OACs that are currently used are comprised mainly of vitamin K antagonists (VKAs), as the historical treatment, and direct OACs (DOACs), i.e., apixaban, dabigatran, edoxaban and rivaroxaban. DOACs have been shown to be non-inferior to VKAs in terms of prevention of thromboembolic events and risk of haemorrhagic events [2,3], require no coagulation monitoring and have limited food and drug interactions [4]. In France, in 2018, more than 220,000 patients with AF were newly treated with OACs [5], and this number is expected to grow as a result of the efficacy of treatment of cardiovascular diseases and increasing life expectancy.

In a previous analysis (the NAXOS study) [6], we observed fewer stroke/systemic thromboembolic events and lower death rates in patients treated with apixaban compared with patients treated with VKAs. In the same study, the major bleeding rates were similar in patients starting apixaban or dabigatran, and lower than in patients starting VKAs and rivaroxaban [6]. Although the risk of major bleeding is lower with DOACs compared with VKAs, particularly the risk of intracranial bleeding [7], DOACs are still associated with a residual risk of bleeding [8,9]. Recently, the FRAIL-AF trial drew further attention to the importance of bleeding events in frail patients treated with international normalized ratio (INR)-guided VKAs, showing that the rate of bleeding was higher in patients switching to DOACs compared with those continuing on VKAs [10]. However, little is known about the characteristics of patients who experience a bleeding event that requires hospitalization (i.e., a major bleeding event) or about the characteristics of the bleeding events, their management – in terms of anticoagulation – and subsequent outcomes.

This study used the French national health system claims database (*Système National des Données de Santé* [SNDS]) to characterize sociodemographic and clinical characteristics, and provide a detailed description of major bleeding events (i.e., sites and recurrences) in patients with AF without a history of rheumatic heart disease or previous valve replacement, who were treated with OACs and experienced at least one major bleeding event, i.e., a bleeding event severe enough to warrant hospitalization. We also describe OAC treatment patterns before and after the first bleeding event and deaths after the bleeding event, according to the bleeding site and the postbleeding treatment pattern.

3. Methods

3.1. Data source

We conducted a retrospective population-based cohort study using the SNDS, which contains anonymous individual information on sociodemographic characteristics, all non-hospital reimbursed healthcare expenditures (without corresponding medical diagnoses) and all hospital discharge summaries (based on International Classification of Diseases, 10th revision [ICD-10] codes). The SNDS does not provide direct information on behavioural or clinical baseline characteristics (tobacco smoking, body mass index, etc.), laboratory results, information on drugs dispensed during a hospital stay (except for specific costly medications) or cause of death. The SNDS currently covers more than 98% of the population of France, i.e., 66 million people [11].

3.2. Study population

Using the same inclusion/exclusion criteria as the preceding NAXOS study [6], we performed a new extraction from the SNDS data of all patients with AF (excluding those with rheumatic heart disease or previous valve replacement) aged ≥ 18 years and with at least one first reimbursement for an OAC, i.e., OAC-naïve patients treated with VKAs, apixaban, rivaroxaban or dabigatran (edoxaban was not available in France) between 01 January 2014 and 31 December 2016. This initial study population of OAC-naïve patients with AF was thus very close to the preceding NAXOS population (Fig. A.1), although small differences in numbers of patients occurred because of minor changes to the database between the two extractions.

For the present analysis, the study population consisted of OAC-naïve patients with one hospital stay with a main diagnosis of major bleeding (ICD-10 codes used; Table A.1) during the inclusion period. The patients in this study were followed up to 31 December 2019 or until death or the last patient health record, whereas follow-up for the previous NAXOS analysis was terminated on 31 December 2016.

The date of the first dispensation of an OAC was defined as the index date. We excluded patients with any type of OAC treatment at the index date, those diagnosed with AF in the 24 months before their first OAC reimbursement and those possibly treated for an indication other than stroke prevention in the 6 weeks before the index date. We defined the date of the first bleed as the start date of the hospitalization for bleeding following the index date. We classified patients by site of bleeding: gastrointestinal, intracranial or other major bleeding. The "other major bleeding" category included acute posthaemorrhagic anaemia, intraocular bleeding, otorrhagia, pericardial bleeding, respiratory bleeding and haemoperitoneum, intra-articular, uterine and vaginal bleeding. In the case of bleedings identified at different sites on the same day, patients were classified as having "multiple bleedings".

3.3. Variables

We defined sex, age at first bleeding, co-morbidities, co-morbidity scores (age-adjusted Charlson Comorbidity Index) and modified HAS-BLED and CHA_2DS_2-VASc scores for the study population based on records of hospital stays identified within the 24 months before the date of the first bleed. Labile INRs were not taken into account in the calculation of the modified HAS-BLED score (no laboratory data available), and all co-morbidities impacting this score were identified through diagnoses for hospital stays or long-term disease status identified within the 24 months before the index date, and through drug markers or medical procedures whenever possible, thus allowing computation of a modified HAS-BLED score. We also described drugs dispensed within the 3 months preceding the date of the first bleed: heparins; platelet aggregation inhibitors; non-steroidal anti-inflammatory drugs; strong inhibitors of both CYP3A4 and P-glycoprotein; human immunodeficiency virus protease inhibitors; anticonvulsants that strongly induce hepatic enzymes; and proton pump inhibitors.

From the index date, we counted the number of bleeding events over the follow-up period, the time between the index date and the first bleed, the time between the first and second bleeding events and the time between the first bleed and death. The first line of treatment started at the index date. A line of treatment ended in

case of switch to another OAC, discontinuation (i.e., 30 days without any dispensation following the end of the coverage period of the last dispensation) or end of the follow-up period. We defined the OAC treatment immediately before the first bleed (IBFB) as the OAC treatment of the last treatment line started before the date of the first bleed, and not ending 3 months before the date of the first bleed; in the latter situation, the patient was considered as not treated. In patients who were treated with an IBFB OAC before the first bleeding event, the OAC treatment patterns over the first month after the first bleed were evaluated and compared with treatment patterns before the first bleed. Patients were defined as persistent if we identified at least one dispensation of the previously used IBFB treatment in the month after the bleeding; they were defined as discontinuing if they stopped being treated with any OAC after the bleeding; and they were defined as switchers if they started a new OAC line in the month following the bleeding. In patients who were not treated IBFB, we described those who remained untreated in the month following the bleeding. Treatment patterns of patients who discontinued their OAC within the 3 months before the first bleeding event, who started a new OAC line more than 1 month after the bleeding event or who died during the hospitalization for the first bleeding event were not evaluated.

3.4. Statistical analyses

We provide descriptive statistics for quantitative variables (mean, median, minimum, maximum, and quartiles) and/or qualitative variables (number of patients and relative percentages) to describe sociodemographic and clinical characteristics, stratified by the first bleeding site and postbleeding treatment patterns. We also describe those variables stratified by modified HAS-BLED score, i.e., separately in a subgroup of patients with modified HAS-BLED score ≤ 3 and in a subgroup with modified HAS-BLED score > 3. We describe the number of patients who switched between their index treatment and IBFB treatment. Using the Kaplan-Meier method, survival was described from the bleeding date, according to the bleeding site, in all patients, and from hospital discharge, according to the postbleeding treatment pattern, in patients who were alive at the end of the hospitalization for the first bleed. Corresponding death rates per 100 patient-years were also calculated. The median duration between the date of the first bleed and death was described in deceased patients. Finally, we compared the risk of death after hospital discharge, across postbleeding OAC treatment patterns, using a Cox model adjusted for confounding factors (i.e., age, sex, site of first bleed, co-morbidities and drugs dispensed [proton pump inhibitors, non-steroidal anti-inflammatory drugs and anti-platelet aggregators]), using persistent patients as a reference. We assessed the proportional hazards assumption for the treatment pattern effect by fitting the interaction with time; as this was not fulfilled, the hazard ratios presented represent the average effect of postbleeding OAC treatment patterns over the follow-up duration.

4. Results

4.1. Study population and distribution of bleeding events

We identified 321,346 OAC-naïve patients with AF, among whom 12,616 (3.9%) had at least one bleeding event over the inclusion period. The median (Q1–Q3) follow-up duration from the index date was 3.6 (1.6–4.9) years, and the main reason for the end of follow-up was death (52.6%) (Table 1).

At the index date, 14.6% of the study population were treated with apixaban, 5.3% with dabigatran, 26.2% with rivaroxaban and 54.0% with a VKA (Fig. 1). The distribution of the IBFB OAC treatment slightly differed from the distribution of the index treatment: 14.2% were treated with apixaban; 4.1% with dabigatran; 22.9% with rivaroxaban; 52.2% with a VKA; and 6.6% were not being treated with an OAC when the first bleed occurred.

Table 1
Bleeding sites and follow-up information of patients with non-valvular atrial fibrillation with at least one bleeding event ($n = 12,616$).

Follow-up duration (years)	3.6 (1.6–4.9)
First bleeding site	
Gastrointestinal	4399 (34.9)
Intracranial	2750 (21.8)
Multiple	142 (1.1)
Other	5325 (42.2)
Reason for end of follow-up	
Death	6630 (52.6)
End of study	5593 (44.3)
Last health record for patient	393 (3.1)

Data are expressed as median (Q1–Q3) or number (%).

The most common site of the first bleeding event was gastrointestinal ($n = 4399$; 34.9%, 95% confidence interval [CI] 34.0–35.7%), followed by intracranial ($n = 2750$; 21.8%, 95% CI 21.1–22.5) and multiple sites ($n = 142$; 1.1%, 95% CI 0.9–1.3). Other bleeds ($n = 5325$; 42.2%, 95% CI 41.3–43.1) occurred at various sites (Table 1). The distribution of the site of the first bleed by OAC index treatment is presented in Table A.2.

4.2. Patients' characteristics

Table 2 presents sociodemographic and clinical characteristics in the overall study population and by modified HAS-BLED score at the date of the first bleed, including OAC treatment before the first bleed and other treatments taken at the date of the first bleed. The mean age was 79.1 ± 10.0 years, and 56.6% of the population were male. The mean CHA_2DS_2-VASc score was 4.0, and the mean modified HAS-BLED score was 2.9; 71.5% ($n = 9016$) of the patients had a modified HAS-BLED score ≤ 3, i.e., were considered at low risk of bleeding. Half of the patients (50.2%) were treated with antiarrhythmic agents, and 53.0% were treated with proton pump inhibitors.

Patients' characteristics by bleeding site are presented in Table A.3. Among patients with gastrointestinal bleeding, 57.6% were treated with proton pump inhibitors, whereas 45.1% of patients with intracranial bleeding, 57.7% of patients with multiple bleedings and 53.2% of patients with other bleedings were receiving this treatment. One third (32.8%) of patients were treated with acetylsalicylic acid.

In the subgroup of patients with a modified HAS-BLED score > 3, almost two thirds of patients (65.0%) were treated with proton pump inhibitors and 42.6% were treated with acetylsalicylic acid; in the subgroup of patients with a modified HAS-BLED score ≤ 3, 48.2% were treated with proton pump inhibitors and 25.5% with acetylsalicylic acid (Table 2).

The mean Charlson Comorbidity Index score for the study population was 6.2 and, overall, the prevalence of co-morbidities was high (Table 3). The most common co-morbidity was hypertension (61.6%), followed by previous myocardial infarction, peripheral artery disease or aortic plaque (38.9%) and congestive heart failure (38.2%). A history of bleeding was present in < 20% (18.4%) of patients.

4.3. Occurrence of bleeding events and follow-up information

Most patients ($n = 10,171$; 80.6%) had a single major bleeding event over the entire follow-up, with a median number of bleeding events of 1 (minimum number = 1; maximum number = 18). The median (Q1–Q3) time from index date to first bleed was 6.8

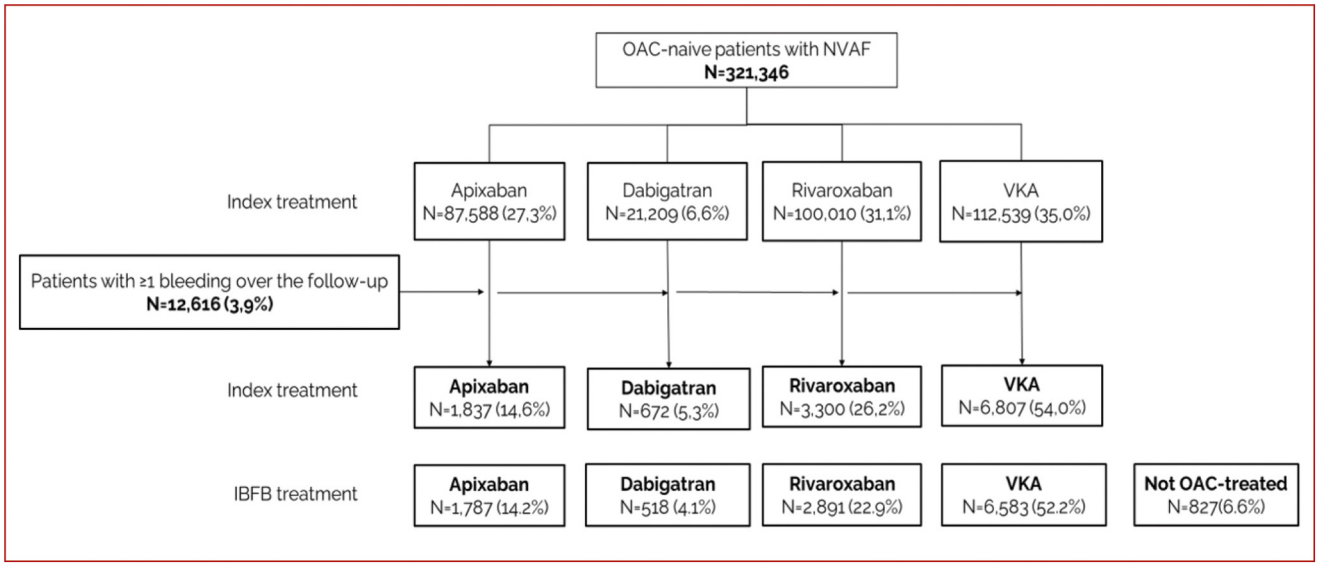


Fig. 1. Flowchart of the study population, by index treatment and by immediately before the first bleed (IBFB) treatment. NVAF: non-valvular atrial fibrillation; OAC: oral anticoagulant; VKA: vitamin K antagonist.

Table 2
Sociodemographic and clinical characteristics of patients with at least one bleeding event in the overall study population, and stratified by risk of bleeding according to modified HAS-BLED score.

	All patients (n = 12,616)	Modified HAS-BLED score ≤ 3 (n = 9016)	Modified HAS-BLED score > 3 (n = 3600)
Male sex	7140 (56.6)	4939 (54.8)	2201 (61.1)
Age at date of first bleed (years)	79.1 ± 10.0	78.6 ± 10.5	80.4 ± 8.5
CHA_2DS_2-VASc score	4.0 ± 1.7	3.6 ± 1.5	5.2 ± 1.5
Modified HAS-BLED score	2.9 ± 1.2	2.3 ± 0.7	4.4 ± 0.6
Antiarrhythmic	6339 (50.2)	4749 (52.7)	1590 (44.2)
Proton pump inhibitor	6688 (53.0)	4348 (48.2)	2340 (65.0)
Acetylsalicylic acid	3833 (30.4)	2301 (25.5)	1532 (42.6)
Clopidogrel	1049 (8.3)	656 (7.3)	393 (10.9)
Co-prescription or co-dispensation of two platelet aggregation inhibitors	483 (3.8)	294 (3.3)	189 (5.3)
Enoxaparin	1340 (10.6)	960 (10.6)	380 (10.6)
Tinzaparin	632 (5.0)	472 (5.2)	160 (4.4)
NSAID	922 (7.3)	691 (7.7)	231 (6.4)
IBFB OAC treatment			
Apixaban	1787 (14.2)	1386 (15.4)	401 (11.1)
Dabigatran	518 (4.1)	428 (4.7)	90 (2.5)
Rivaroxaban	2891 (22.9)	2376 (26.4)	515 (14.3)
VKA	6593 (52.2)	4257 (47.2)	2336 (64.9)
Not treated	827 (6.6)	569 (6.3)	258 (7.2)

Table A.3 presents the same table by bleeding site for the overall population. IBFB: immediately before the first bleed; NSAID: non-steroidal anti-inflammatory drug; OAC: oral anticoagulant.

(2.3–14.0) months, whereas the median (Q1–Q3) time from start of IBFB treatment to first bleed was 4.2 (1.5–9.3) months (Table 4). Overall, 2445 patients (19.4%) experienced a second major bleeding event over the follow-up period. The median (Q1–Q3) time between the two bleeding events was 5.0 (0.7–18.6) months. More than two thirds of the second bleeding events occurred in the year following the first bleeding event (65.8%), and at the same site as that of the first bleed (69.0%) (Table 4).

The median (Q1–Q3) follow-up duration after the first bleeding event was 3.0 (0.6–3.9) years. The main reason for the end of follow-up after the first bleed differed according to the site of the first bleed: death was the main reason for the end of follow-up in two thirds of the patients with intracranial bleeding (66.8%) or multiple bleedings (64.8%), whereas it was the end of the study for half (50.3%) of the patients with other bleedings. The median follow-up duration also differed between bleeding sites, with 0.9 years after intracranial bleeding and 2.4 years after multiple bleedings, versus

Table 3
Co-morbidities of patients with non-valvular atrial fibrillation identified in the 24 months before the date of the first bleeding event (n = 12,616).

Charlson Comorbidity Index score	6.2 ± 2.9
Hypertension	61.6
Previous myocardial infarction, peripheral artery disease or aortic plaque	38.9
Congestive heart failure	38.2
Gastrointestinal disease	28.6
Diabetes mellitus	27.7
Cancer	25.6
Anaemia	23.5
Malnutrition	22.6
Bleeding history	18.4
Myocardial infarction	18.4
Peripheral vascular disease	16.6
Previous stroke, transient ischaemic attack or thromboembolic event	15.6
Coronary artery disease	14.9
Obesity	14.6

Data are expressed as mean ± standard deviation or %.

Table 4
Bleeding patterns of patients with atrial fibrillation who experienced at least one major bleeding event (n = 12,606).

Overall				
Number of bleeding events	1.0 (1.0–1.0)			
Minimum–maximum	1.0–18.0			
Time between index date and first bleed (days)	208.0 (69.0–427.0)			
Time between start of IBFB treatment and first bleed (days)	127.0 (45.0–282.0)			
Patients with at least two bleeding events	2445 (19.4)			
Time between first and second bleeding event (days)	152.0 (21.0–566.0)			
By bleeding site	**Gastrointestinal**	**Intracranial**	**Multiple**	**Others**
Follow-up duration after first bleeding event (years)	3.1 (0.9–4.0)	0.9 (0.0–3.4)	2.4 (0.7–3.7)	3.2 (1.2–4.1)
Reason for end of follow-up				
Death	2201 (50.0)	1836 (66.8)	92 (64.8)	2501 (47.0)
End of study	2071 (47.1)	803 (29.2)	43 (30.3)	2676 (50.3)
Last health record for patient	127 (2.9)	111 (4.0)	7 (4.9)	148 (2.8)

Data are expressed as median (Q1–Q3) or number (%). IBFB: immediately before first bleed; OAC: oral anticoagulant.

3.1 years and 3.2 years after gastrointestinal bleeding and other bleedings, respectively (Table 4).

4.4. Death after the first bleeding event

After the first bleeding event, 47.0% of the patients died, corresponding to a death rate of 20.9/100 patient-years (95% CI 20.4–21.4). Among patients who died, the median (Q1–Q3) time from first bleed to death was 9.3 (1.5–25.9) months: the median (Q1–Q3) time to death after the first bleed was 1 (0.2–13.0) month after intracranial bleeding, whereas it was 12.1 (3.1–28.7) months, 13.5 (3.4–30.1) months and 14.1 (4.3–28.7) months after gastrointestinal, multiple and other bleedings, respectively. The corresponding death rates were 38.7/100 patient-years (95% CI 36.9–40) following intracranial bleedings, and 18.9 (95% CI 18.1–19.7) patient-years, 28.1 (95% CI 22.9–34.5) patient-years and 16.7/100 (95% CI 16.1–17.4) patient-years following gastrointestinal, multiple and other bleedings, respectively. Kaplan-Meier curves showing survival probability overall and by bleeding site are presented in Fig. 2.

4.5. Treatment patterns and deaths

Switches between the various OACs and no treatment before the first bleeding event are presented in Table 5. Some patients were treated differently before their first bleeding event than they were at the index date: 9.2% (n = 1155) received an IBFB treatment that differed from their index treatment, i.e., they switched at least once between their index treatment and their first bleeding event; 6.6% (n = 827) of the patients did not receive any OAC treatment before their first bleeding event. After the first bleeding event, treatment patterns and corresponding deaths were described in 10,092 patients who did not die during the hospitalization for the first bleeding event: most patients continued to be treated with the same OAC as immediately before the bleeding event (n = 5506; 54.6%); 6.4% (n = 650) switched to another OAC; 33.5% (n = 3382) remained without OAC treatment until the end of follow-up; and 5.5% (n = 554) were not treated before the first bleeding event, and remained untreated in the month following discharge. Sociodemographic and clinical characteristics of patients by postbleeding treatment pattern are presented in Table A.4.

Kaplan-Meir curves showing survival probability overall and by treatment pattern after the first bleeding event are presented in Fig. 3. Overall, in deceased patients (n = 5238), the median (Q1–Q3) time to death after the first bleed was 9.6 (2.0–25.7) months. After adjustment for confounders, the Cox model showed that, compared with persistent patients, those who discontinued and those who were not treated had a higher risk of death over the follow-up (respective hazard ratios: 2.48, 95% CI 2.32–2.64; and 2.06, 95% CI 1.83–2.31), whereas no significant difference was found for patients who switched (hazard ratio 0.93, 95% CI 0.82–1.07). The hazard ratios presented represent the average effect of postbleeding OAC treatment patterns over the follow-up duration, as the proportional hazard assumption was not satisfied. The detailed results of the model are presented in Table A.5.

5. Discussion

5.1. Key findings

Based on real-life data, this study presents a detailed overview of sociodemographic and clinical characteristics and treatment patterns of patients with AF who experienced bleeding events between 2014 and 2016 in France, while newly treated with OACs. First, we observed that 4% of the patients newly treated with OACs for AF experienced at least one bleeding event that required admission, the most common bleeding site being gastrointestinal. Second, these patients were old (mean age: 79 years) and had multiple co-morbidities (Charlson Comorbidity Index mean score: 6.2). However, a vast majority (81.6%) of these patients had no history of bleeding, and almost three quarters (71.4%) had a modified HAS-BLED score ≤ 3, i.e., an expected low risk of bleeding, which might explain why predicting bleeding events in this population is difficult. Thus, age and co-morbidities seem to reflect the risk of bleeding in patients with AF treated with OACs more than the modified HAS-BLED score does. For instance, one quarter of patients had cancer as a co-morbidity, which is identified as an increased risk of bleeding in patients treated with antithrombotics [12]. As already found in previous studies [13], our study confirms that major bleeding events in the population of patients with AF who are treated with an OAC are ominous: the median time from first bleed to death was only 9.3 months. In particular, intracranial bleeding had a dramatic impact on deaths, with a median survival time from first bleed to death of 1 month. Finally, almost one third (33.5%) of the patients stopped being treated with an OAC after their first bleeding event. Survival comparison analysis showed that patients discontinuing their OAC and patients not treated by an OAC during the first month following discharge from hospitalization for bleeding had lower survival than persistent patients, even after adjustment for confounders.

5.2. Comparison with the initial NAXOS study population

The preceding NAXOS study population included 321,501 patients with AF, newly initiating OAC treatment, meeting the same inclusion/exclusion criteria and over the same

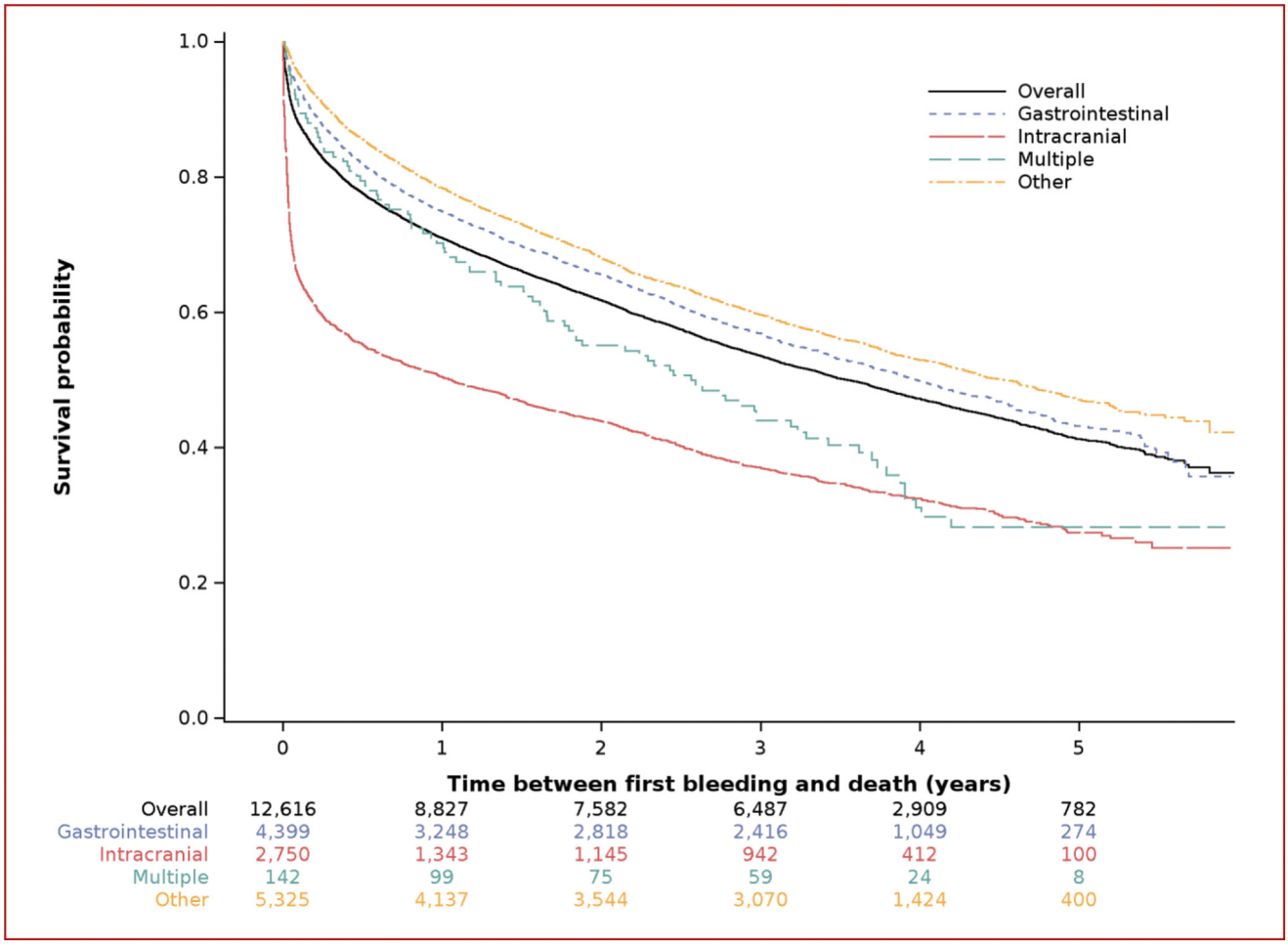


Fig. 2. Survival probability over 72 months of follow-up, according to the site of the first bleeding event (n = 12,616).

Table 5
Anticoagulant treatment patterns between the index date and the first bleeding event in patients who experienced at least one bleeding event.

Index treatment	IBFB treatment					
	No IBFB treatment	Apixaban	Dabigatran	Rivaroxaban	VKA	Total
Apixaban	109 (5.9)	1508 (82.1)	10 (0.5)	58 (3.2)	152 (8.3)	1837
Dabigatran	68 (10.1)	36 (5.4)	441 (65.6)	43 (6.4)	84 (12.5)	672
Rivaroxaban	252 (7.6)	104 (3.2)	26 (0.8)	2623 (79.5)	295 (8.9)	3300
VKA	398 (5.8)	139 (2.0)	41 (0.6)	167 (2.5)	6062 (89.1)	6807
Total	827 (6.6)	1787 (14.2)	518 (4.1)	2891 (22.9)	6593 (52.3)	12,616

Data are expressed as number (%) or total number. IBFB: immediately before first bleed; VKA: vitamin K antagonist.

period (between 2014 and 2016) [6] (see Fig. A.1). This previous cohort included patients who would experience bleeding events and patients who would not. The mean modified HAS-BLED score was lower than noted in the present study population (i.e., patients with AF with a bleeding event), but not considerably lower: 2.3 vs. 2.9, respectively. However, the prevalence of previous bleeding during the 24 months before the index date in the preceding NAXOS population was 5.8%, whereas 18.4% of the present study population of patients with bleeding had previous bleeding in the 24 months before the date of the first bleed. Overall, the prevalence of co-morbidities was much lower in the preceding NAXOS study population (data not shown) than in the patients who experienced bleeding events (mean Charlson Comorbidity Index score: 4.8 vs. 6.2 in the bleeding population), and the mean age was lower (75.1 vs. 79.1 years), again suggesting that patients experiencing bleeding are frailer than the overall population of patients with AF. Finally, only 6.6% of the patients who experienced bleeding had stopped their OAC treatment before bleeding, whereas one third of the overall population of patients with AF (33.2%) stopped their OAC over the follow-up, thus making their bleeding risk lower.

5.3. Comparison with other studies

A Swiss study recently described the occurrence of bleeding events (both major bleedings and clinically relevant non-major bleedings) in 3277 patients with AF treated with OACs [14]: 19.7% had bleeding over their follow-up; and 9.1% had major bleeding. The authors showed that patients who experienced bleeding were significantly older and had significantly more history of hypertension, stroke, percutaneous coronary intervention, heart failure, bleeding or chronic kidney disease, supporting the assumption that patients with bleedings are frail. The authors also showed that patients who experienced bleeding had a higher risk of stroke, myocardial infarction or death from any cause, confirming the seri-

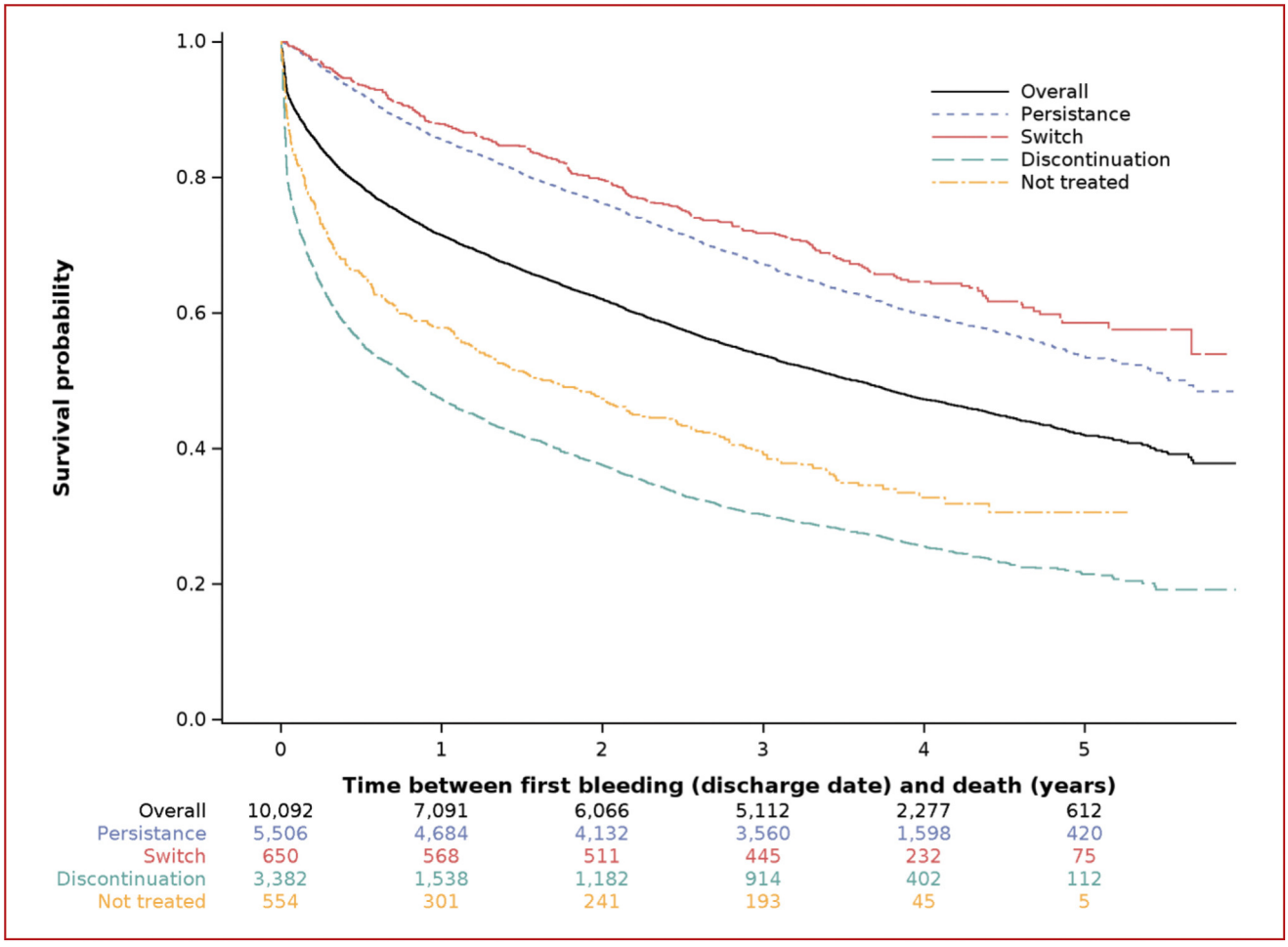


Fig. 3. Survival probability from discharge date over 72 months, according to postbleeding treatment patterns ($n = 10,092$).

ousness of bleeding events in the future outcomes of patients with AF. The same study also showed that 21.2% of the patients discontinued their OAC therapy after a major bleeding event, and that 17.5% switched to another OAC therapy, whereas we found 33.5% of the patients remained without any OAC treatment until the end of the follow-up after their first bleeding event, and 6.4% switched to another OAC. Finally, the observed death rate in the Swiss study was 9.72/100 patient-years, whereas we had a death rate of 20.9/100 patient-years. However, our study was based on an exhaustive medicoadministrative database, whereas the Swiss study was based on field data collected through standardized case report forms. It was thus to be expected that we would find more events, as our study is highly exhaustive compared with the Swiss study. In another French study, results showed that patients with AF who experienced major bleeding events were predominantly older female patients with a high burden of cardiovascular comorbidities [15].

In the FRAIL-AF randomized controlled trial, patients with AF initially treated with VKAs, and either remaining treated with VKAs or switching to DOACs, were followed up to identify major bleeding events or clinically relevant bleeding events [10]. The occurrence of major bleeding events was slightly lower than in our study, with 2.4% and 3.6% of patients identified with a major bleeding event in patients treated continuously with VKAs and in patients who switched to DOACs, respectively. However, patients were older (mean age: 83 years) than in our study, but were followed with strict INR management. For instance, two thirds (between 65.3% and 74.0%) of the patients in the FRAIL-AF trial had a stable INR, which may reflect randomized trial conditions more than real-life conditions of patients treated with VKAs, as observed in our study.

5.4. Strengths

Based on the French national health system claims database, which is representative of the French population, we can assume that this study included almost all patients with AF who initiated OAC treatment and experienced major bleeding events in France between 2014 and 2016, with an extended follow-up until the year 2019. This allowed us to provide a highly robust and detailed description of this specific patient population, their treatment patterns and their outcomes following the bleeding event, in terms of deaths and other bleeding events. This is crucial information for clinicians to identify and manage patients with AF who are most at risk of bleeding events.

5.5. Limitations

As the SNDS does not contain any clinical or biological information (no results of laboratory tests, no diagnoses except those associated with hospital stays), we developed an algorithm to identify patients with AF. However, this algorithm was already used in the previously published efficacy and safety study [6], and corresponding results were used by the French Health Authorities to evaluate apixaban [16]. In the same way, we also modified the usual scores currently described in patients with AF, e.g., we modified the HAS-BLED score, which mainly contains clinician-reported

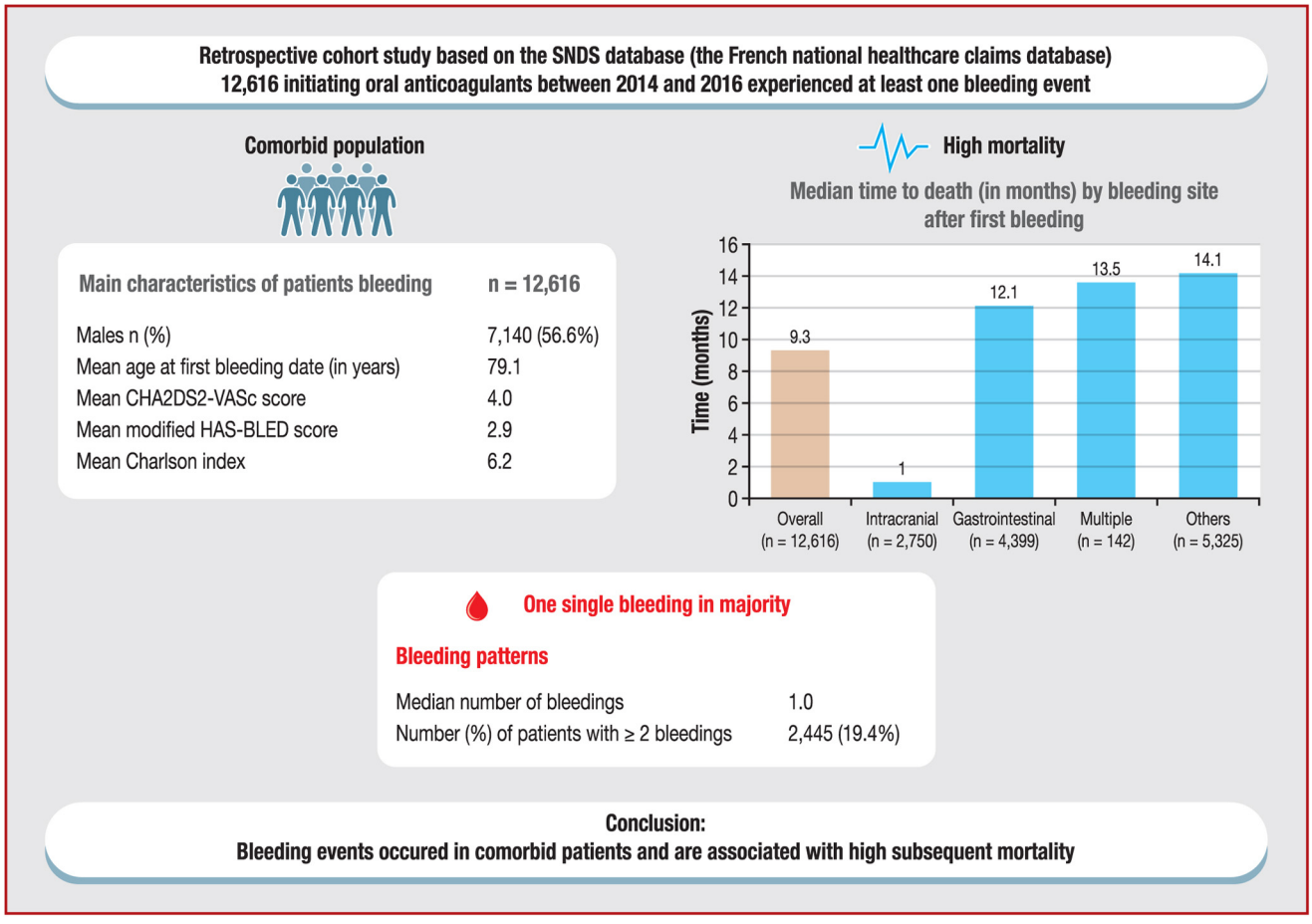
information, using previous diagnoses and drug reimbursements to account for the presence or absence of co-morbidities. For instance, the modified HAS-BLED score used in our study did not take INR into account (the item was deleted from the score); moreover, co-morbidities were assessed based on diagnoses associated with hospital stays and/or long-term disease status. Thus, it is reasonable to assume that the score we obtained with the modified version was underestimated compared with what would be obtained with the initial version of the questionnaire. This should be taken into account when interpreting the distribution of the modified HAS-BLED score; as it should predict the risk of bleeding, we would have expected higher values in the population of patients with AF who experienced bleeding.

The absence of clinical information in the database, other than that related to hospital stays, also prevented us from including patients with non-major bleedings, e.g. with clinically relevant bleedings not requiring hospitalization, but which could also impact patients' outcomes. Consequently, the number of patients in our study population is lower than the real number of patients with AF experiencing bleeding events. However, patients experiencing non-major bleedings and their treatment patterns may differ from patients experiencing major bleedings.

Finally, the results of the survival analysis across OAC treatment patterns should be interpreted with caution, as postbleeding treatment patterns were defined based on the month following discharge after bleeding, whereas survival was assessed over the whole follow-up duration. Patients may have changed treatment patterns after the first month following discharge, e.g. a patient classified as discontinuing during the first month may have started an OAC again subsequently. However, from a clinician's perspective, the immediate choice about OAC treatment management after a major bleeding event in patients treated with an OAC (i.e., should the treatment be maintained, stopped or switched) is a key decision.

6. Conclusion

This detailed description of patients with AF who experienced major bleeding events based on real-life data showed that these patients are old and frail, i.e., with a high number of co-morbid conditions, and have a high risk of death after the first bleeding event. As the modified HAS-BLED score fails to identify a majority of patients with bleeding, further studies are needed to improve bleeding risk prediction in this population (Central Illustration).



Central Illustration. Profile and outcome of patients on oral anticoagulants experiencing bleeding.

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Disclosure of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2025.04.058.

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