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ORIGINAL ARTICLE

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Management of epistaxis associated with oral antithrombotic drugs in emergency department and impact on prescription thereafter

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Abstract

Objectives: To describe management, and to assess factors associated with antithrombotic prescription thereafter in patients who had epistaxis referred to emergency department (ED).

Design: Prospective cohort study. From EDs, clinical, biological and hospital data were collected. The clinical database was linked to the French Health Insurance Database where we retrieved antithrombotic drug deliveries in a 3-month period before and after referral.

Setting: Multicentric population-based cohort study within five well-defined areas.

Participants: We considered 306 patients referred for epistaxis with a stable oral antithrombotic regimen before referral.

Main Outcome Measures: We considered management, hospital outcome and case fatality. Antithrombotic prescription in a 3-month follow-up period was categorised into three classes: no change, class change, or discontinuation. During follow-up, hospitalisation for epistaxis or ischaemic events was searched.

Results: Among 306 adult individuals (mean age: 76 years), 166 took oral anticoagulant and 140 an antiplatelet drug. Blood transfusion was needed in 13.7% of patients and anterior packing alone in 61%. Half of the patients were hospitalised; 301 were discharged alive. Considering antithrombotic prescription thereafter we observed no change in 219 patients (72.8%), class changes in 47 patients (15.6%) and discontinuation in 35 patients (11.6%). We identified four independent predictors for antithrombotic prescription: hospitalisation (vs. returning home, $p = .05$), age ($p = .03$), haemoglobin level ($p = .03$) and oral anticoagulant (vs. antiplatelet agent, $p < .001$). During the 3 months following discharge, 2 thrombotic and 15 bleeding events were identified.

Karine Lacut who passed away in April 2021.

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Conclusions: Epistaxis referred to emergency department had an impact on subsequent antithrombotic prescription.

Clinical Trial Registration: Clinical Trials.gov identifier: NCT02886533.

KEYWORDS

antithrombotic drugs, emergency, epistaxis, management, medication decision

1 | INTRODUCTION

Epistaxis is common in a lifetime but fortunately only a few require medical attention and very few need an emergency department (ED) visit. Epistaxis mostly affect children and the elderly, the latter being more prone to have systemic illnesses that likely contributed to the epistaxis and/or to receive antithrombotic (AT) drugs. Indeed, epistaxis is common in patients taking oral anticoagulants or antiplatelet drug.

The increasing use of such medications, including new drugs, such as direct oral anticoagulant (DOAC, dabigatran, rivaroxaban or apixaban), or new regime, such as dual antiplatelet regime, is a key concern in terms of managing this epistaxis and decision for discontinuing such medications.

Some studies suggested that DOAC had an improved safety profile when considering severity (need for posterior tamponade or surgery or transfusion),[1–7] management (hospitalisation rate and duration)[3,4,6–9] or re-admission rate or recurrence[3,5,10] compared with vitamin K antagonist (VKA) or antiplatelet drugs. Other studies concluded the opposite as regards recurrence[2] or management.[1]

Data on the impact of epistaxis on AT prescription thereafter are scarce.[3,6,10] Whereas there was published guidance[11–13] for the acute phase, there is specifically no data to support the decision to definitely or temporarily withhold AT drug or to modify AT regimen after the acute phase.

1.1 | Objectives

Our objectives were to describe the management of patients referred to ED for epistaxis while receiving oral AT drugs (VKA, DOAC or antiplatelet agents), and to assess factors associated with AT prescription thereafter.

2 | MATERIALS AND METHODS

2.1 | Design

The SACHA study is a French prospective multicentric population-based cohort study on the incidence and outcome of major bleeding in patients treated with AT agents. From EDs, clinical, biological and hospital data were collected. The clinical database was linked to the French Health Insurance Database where we retrieved AT drug deliveries in a 3-month period before and after referral. The study design has been previously reported.[14]

Key points

- Epistaxis is common in patients receiving oral antithrombotic drugs but the impact on antithrombotic prescription thereafter is partly unknown.
- Among 306 patients who had epistaxis referred to emergency department (ED), blood transfusion was needed in 13.7% and anterior packing alone in 61% of patients.
- Considering antithrombotic prescription thereafter, there was no change in 72.8%, class changes in 15.6% and discontinuation in 11.6% of patients.
- Hospitalisation, age, haemoglobin level and oral anticoagulant are independent predictors for antithrombotic prescription.
- Epistaxis referred to ED has an impact on subsequent antithrombotic prescription.

2.2 | Setting

Over a 3-year period (from 1 January 2013 to 31 December 2015), included patients were referred to EDs within five well-defined areas around five large French cities (Angers, Brest, Grenoble, Nantes and Rennes, covered slightly more than 3 million inhabitants) for epistaxis while receiving AT drugs.

2.3 | Participants

For this analysis, we considered only patients (i) referred for epistaxis without any other concurrent bleeding during the study period, retaining the first occurrence as index epistaxis, (ii) with a stable oral AT regimen before referral (i.e., without any change in therapeutic class of AT agents, within 3 months prior to epistaxis). Any other concurrent bleeding was excluded.

From EDs, demographic data, clinical data (co-morbid conditions, AT class with presumed indication and time since initiation, systolic blood pressure), as well as biological data (haemoglobin and creatinine level), therapeutic management such as red blood transfusion, platelet transfusion, plasma transfusion, vitamin K, protamin sulphate, prothrombin complex concentrate (PCC) and FEIBA® (anti-inhibitor coagulant complex), and hospital data (endoscopic or surgical procedures, ward type, intensive care unit (ICU) stay, length of stay [LOS] and case

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fatality) were collected. A modified Charlson index was calculated for each patient.[15] A modified CHA_2DS_2VaASc score (Table S1) was calculated for patient receiving oral anticoagulants.[16] In each ED, the local referent medical doctor validated the inclusion, and specifically, the bleeding severity defined as having at least one of the following criteria: unstable haemodynamic (systolic arterial pressure < 90 mmHg or mean arterial pressure < 65 mmHg) or haemorrhagic shock, need for transfusion or for emergency haemostatic procedure.

The clinical database was linked to the French Health Insurance Database (SNIIRAM) using common key variables (date of birth, gender, date of hospital entry and discharge, type of AT therapy, and care facility involved).[14] The SNIIRAM contains anonymous individual data on all reimbursements for health expenditure, including drugs (of note, the database does not provide the medical indication for each drug prescription), hospital discharge diagnoses (ICD-10 code) as well as details on medical acts.

2.4 | Main outcomes measures

We first considered hospital outcomes, focusing on ward type, ICU stay, LOS and case fatality.

Second, after hospital discharge, AT prescription in a 3-month follow-up period was categorised into three classes: no change, or class change when compared with the regimen before (drug delivery in a 3-month period before referral for epistaxis), or discontinuation (no AT drug delivery in the following 3 months).

During a 3-month follow-up period after hospital discharge, we retrieved SNIIRAM data on the occurrence of hospitalisation for epistaxis or ischaemic events as coded in main discharge diagnosis (ICD-10).

2.5 | Statistical analysis

Statistical analysis was performed from 1 January to 31 March 2022.

Clinical characteristics, management and outcomes were described according to the type of AT drugs (Antiplatelet monotherapy or dual therapy, VKA or DOAC, or combo, i.e., oral anticoagulant plus antiplatelet drug). Descriptive statistics were frequency (percentage) for categorical variables, mean ± standard deviation for continuous variables with a Gaussian distribution and median (first and third quartiles) otherwise. Comparisons of the type of AT drugs used chi-square test or Fisher exact test for categorical variables, analysis of variance for continuous variables with a Gaussian distribution and Kruskal–Wallis test otherwise.

To estimate the association between clinical predictors and AT prescription after hospital discharge (categorised as: no change, or class change when compared with the regimen before, or discontinuation, that is, no AT in the following 3 months), we ran a multivariable multinomial logistic regression model (generalised logit link) using "no change" as the reference category. Inclusion in the multivariable model was based on statistical significance (p-value < .15). A step-by-step backward selection was used. Interactions between selected variables and hospitalisation (vs. return home directly from ED) were tested. For continuous variables, a generalised additive model provided a plotting tool to ascertain the appropriate scale.

All statistical tests were two-tailed and p-values < 0.05 were considered significant. Statistical analyses were performed using SAS software 9.4 (SAS Institute, Cary, North Carolina).

3 | RESULTS

3.1 | Characteristics of the study population

During the study period, a total of 306 adult individuals received a stable oral AT medication by the time they were referred for a first occurrence of severe epistaxis without concomitant other major bleeding. A flow chart is shown in Figure 1. Among the 306 adult individuals, 166 were prescribed oral anticoagulant and 140 an antiplatelet drug. Individuals prescribed oral anticoagulant received either fluindione ($n = 78$), warfarin ($n = 35$), acenocoumarol ($n = 8$), dabigatran ($n = 2$), or rivaroxaban ($n = 23$); individuals prescribed antiplatelet drug received either acetylsalicylic acid ($n = 88$), clopidogrel ($n = 34$) or dual regimen ($n = 18$); last, 20 individuals were prescribed combo (oral anticoagulant plus antiplatelet drug, mostly (17 out of 20) as VKA plus acid acetylsalicylic). Characteristics are displayed in Table 1. There were 215 (70%) males; mean age was 76 years. The most frequent comorbidity was arterial hypertension (61%). Charlson's comorbidity index was mostly low (index ≤2 for 76.8% of patients). The presumed indication was mostly atrial fibrillation for oral anticoagulant, with a CHA_2DS_2VASc score equal to 2 in more in 57%, and coronary artery disease for antiplatelet drug.

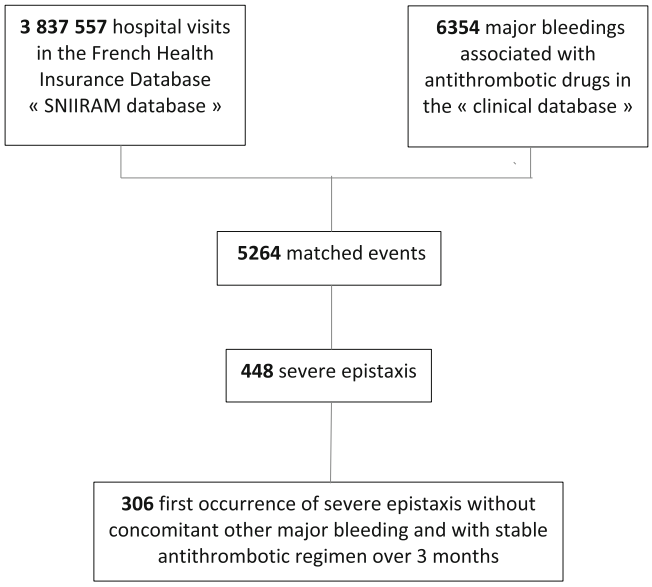

FIGURE 1 Flow chart.

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3.2 | Management

By design, all patients were referred to ED. The haemostatic management is reported in Table 2. Blood transfusion was needed in 13.7% of patients with a median number of two red cell packs. In patients receiving VKAs, vitamin K was prescribed for 24% of patients and PCC only in 8.3% of patients. Table 3, shows the specific management. Anterior packing alone was needed in 61% of patients. Forty-nine patients (16%) had a specific medical procedure (cauterization, $n = 41$; coagulation of sphenopalatine artery, by nasal endoscopy, $n = 4$; selective embolization, $n = 4$).

3.3 | Outcomes

Outcomes after ED are shown in Table 4. Half of the patients were hospitalised.

A total of 301 patients were discharged alive. Considering AT prescription thereafter we observed no change in 219 patients (72.8%), AT class changes in 47 patients (15.6%) and discontinuation in 35 patients (11.6%). Predictors of AT prescription are shown in Table S2. Using multivariable multinomial logistic regression, we identified four independent predictors for AT prescription: hospitalisation ($p = .05$), age ($p = .03$), haemoglobin level ($p = .03$) and AT class ($p < .001$; Table 5). When compared

TABLE 1 Clinical characteristics of the population.

Variables	Overall ($N = 306$)	Antiplatelet drug ($N = 140$)	Oral anticoagulant ($N = 166$)	*p*-Value
Gender, male	215	67.8 (103)	60.9 (112)	.190
Age, years	76 ± 11	73 ± 11	78 ± 10	.001
Malignancy	31	10.7 (15)	9.6 (16)	.756
Arterial hypertension	187	65.0 (91)	57.8 (96)	.200
Diabetes mellitus	57	18.6 (26)	18.7 (31)	.982
Smoking habit	27	13.6 (19)	4.8 (8)	.007
Alcohol habit	23	9.3 (13)	6.0 (10)	.281
Heart failure	35	3.95 (6)	15.8 (29)	.001
Presumed indication				.001
AF	101	–	60.8 (101)	
CHA_2DS_2VASc score				
0			16.8 (17)	
1			25.7 (26)	
2			57.4 (58)	
PVD	27	17.9 (25)	1.20 (2)	
Stroke/TIA	20	14.3 (20)	–	
CAD	54	38.6 (54)	–	
Cardiac valvular disease	24	–	14.5 (24)	
VTE	16	–	9.6 (16)	
Other	64	29.3 (41)	13.9 (23)	
History of bleeding	70	25.7 (36)	20.5 (34)	.278
Gastrointestinal	14	4.3 (6)	4.8 (8)	.374
Intracranial	4	0.7 (1)	1.8 (3)	
Other location	52	20.7 (29)	13.9 (23)	
Liver cirrhosis	5	2.9 (4)	0.6 (1)	.121
Chronic renal insufficiency	26	6.4 (9)	10.2 (17)	.233
Charlson index				
0	133	42.1 (59)	44.6 (74)	.080
1–2	102	40.0 (56)	27.7 (46)	
3–4	55	13.6 (19)	21.7 (36)	
≥5	16	4.3 (6)	6.0 (10)	

Note: Values are percentage (frequency) or mean ± standard deviation.
Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

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TABLE 2 Haemostatic management of patients referred for severe epistaxis while receiving oral antithrombotic.

	Overall (*N* = 306)	VKA (*N* = 121)	DOAC (*N* = 25)	Combo (*N* = 20)	Antiplatelet monotherapy (*N* = 122)	Dual antiplatelet regimen (*N* = 18)
Reversal therapy						
INR		2.6 [2.1–3.3]				
INR ≥6		3.3 (4)				
Vitamin K		24.0 (29)				
PCC		8.3 (10)				
Transfusion						
Red cell pack	13.4 (41)	13.2 (16)	4.0 (1)	10.0 (2)	17.2 (21)	5.56 (1)
Red cell pack number	2 [2–3]	2 [2–3]	3	5 [4–6]	2 [2–3]	2
Platelet	0.65 (2)	1.7 (2)	—	—	0.8 (1)	—
Plasma	1.6 (5)		—	—	2.5 (3)	—

Abbreviations: DOAC, direct oral anticoagulant; PCC, prothrombin complex concentrate; VKA, vitamin K antagonist.

TABLE 3 Specific management of patients referred for severe epistaxis while receiving oral antithrombotic.

	Overall (*N* = 306)	VKA (*N* = 121)	DOAC (*N* = 25)	Combo (*N* = 20)	Antiplatelet monotherapy (*N* = 122)	Dual antiplatelet regimen (*N* = 18)
Medical procedure	16.0 (49)	16.5 (20)	12.0 (3)	10.0 (2)	17.2 (21)	16.7 (3)
Cauterization	13.4 (41)	12.4 (15)	12.0 (3)	10.0 (2)	14.7 (18)	16.7 (3)
Coagulation[a]	1.3 (4)	1.65 (2)	—	—	1.6 (2)	—
Selective embolization	1.3 (4)	2.5 (3)	—	—	0.8 (1)	—
Posterior tamponade	7.8 (24)	7.4 (9)	4.0 (1)	5.00 (1)	8.2 (10)	16.7 (3)
Anterior packing	61.4 (188)	59.5 (72)	76.0 (19)	65.0 (13)	60.7 (74)	55.6 (10)
Missing	14.7 (45)	16.5 (20)	8.0 (2)	20.0 (4)	13.9 (17)	11.1 (2)

Note: Values are percentage (frequency) or median [Q1–Q3].
Abbreviations: DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.
[a]Spheno-palatine artery, by nasal endoscopy.

TABLE 4 Outcomes after emergency department referral for epistaxis while receiving antiplatelet drugs or oral anticoagulant.

	Overall (*N* = 306)	VKA (*N* = 121)	DOAC (*N* = 25)	Combo (*N* = 20)	Antiplatelet monotherapy (*N* = 122)	Dual antiplatelet regimen (*N* = 18)
Died in ED	0.3 (1)	—	—	—	0.8 (1)	—
Hospitalisation	49.7 (152)	57.0 (69)	52.0 (13)	35.0 (7)	44.3 (54)	50.0 (9)
Medical ward	45.4 (69)	42.0 (29)	61.5 (8)	57.1 (4)	44.4 (24)	44.4 (4)
Surgical ward	35.5 (54)	39.1 (27)	15.4 (2)	28.6 (2)	33.3 (18)	55.6 (5)
ICU	2.0 (3)	2.9 (2)	—	—	1.85 (1)	—
Observational unit	17.1 (26)	15.9 (11)	23.1 (3)	14.3 (1)	20.4 (11)	—
Length of stay (days)[a]	3 [2–5]	4 [2–6]	3 [1–4]	2 [2–7]	3 [2–6]	2 [1–3]

Note: Values are percentage (frequency) or median [Q1–Q3].
Abbreviation: ICU, intensive care unit.
[a]1 missing value.

with unchanged prescription, class-changed prescription was 2.7 times as often among patients hospitalised than among those who returned home. For every 10 years increase, discontinued prescription was 1.4 times as often than unchanged prescription. For every decrease of 2 g/dL in haemoglobin level, discontinued prescription was 1.5 times as often than unchanged prescription. When compared with unchanged prescription, class changed prescription was eight-fold as often among patients previously receiving an oral anticoagulant than among those receiving an antiplatelet agent.

During the 3 months following discharge, whatever the AT prescription thereafter, 2 thrombotic and 15 bleeding events were identified (Table 6).

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TABLE 5 Independent factors associated with antithrombotic prescription thereafter among 263 patients referred for severe epistaxis while oral antithrombotic, and discharged alive.

Effect	Outcome	Unit	Odds ratio estimate (95% CI)	Type 3 test *p*-value
Hospitalisation[a]	Discontinuation vs. no change		1.19 (0.55–2.60)	.05
	Class change vs. no change		2.67 (1.22–5.84)	
Age	Discontinuation vs. no change	10	1.47 (0.99–2.17)	.03
	Class change vs. no change	10	0.78 (0.56–1.08)	
Haemoglobin	Discontinuation vs. no change	−2	1.51 (1.08–2.11)	.05
	Class change vs. no change	−2	1.09 (0.79–1.52)	
OAC vs. APA	Discontinuation vs. no change		0.92 (0.42–2.02)	.001
	Class change vs. no change		8.30 (2.95–23.3)	

Note: Estimates based on multivariable multinomial logistic regression model with a generalised logit link (no change, $n = 188$, as the reference category, discontinuation, $n = 34$ and class change, $n = 41$; 38 observations were deleted due to missing values for the response or explanatory variables).
Abbreviations: APA, antiplatelet agent; OAC, oral anticoagulant.
[a]Versus return home.

TABLE 6 Recurrences of epistaxis requiring emergency department referral and thrombotic events within 3 months according to antithrombotic prescription thereafter index epistaxis.

Variables	Overall ($N = 301$)	No change ($N = 219$)	Stop ($N = 35$)	Class change ($N = 47$)
Recurrence of epistaxis	4.98 (15)	5.02 (11)	5.71 (2)	4.26 (2)
Ischaemic heart disease	0.66 (2)	–	2.86 (1)	2.13 (1)

Note: Values are percentage (frequency).

4 | DISCUSSION

Based on a prospective multicentric population-based cohort study, this report described 306 individuals referred to ED for epistaxis without any other concurrent bleeding between 1 January 2013 and 31 December 2015, while receiving a stable (over the past 3 months) oral AT regimen.

Firstly, our results were consistent with current knowledge as regards clinical characteristics (age, male, hypertension), and management complied with usual practice.[12,13,17] Some studies suggested that DOAC had a lower hospitalisation rate and duration[3,4,6–9] compared with VKA or antiplatelet drugs. Another study concluded the opposite.[1]

Secondly, regarding AT prescription at discharge, we observed that (i) patients in whom there was a decision to change of such medication were more frequently hospitalised, but 20% (31 out of 151) of those who returned home had also stopped or changed their AT regimen; indeed, hospitalisation is a proxy of severe epistaxis; we could not definitely state that modifying or withholding AT regimen was a decision of the emergency physician in charge; we observed no delivery in the following 3 months, and we did not collect data on medical visit (general practitioner, or cardiologist) in the following 3 months; (ii) increasing age and decreasing haemoglobin level were associated with withholding AT treatment (at least for 3 months); and (iii) class changed prescription was eight-fold as often among patients previously receiving an oral anticoagulant than among those receiving an antiplatelet agent. Presumed indications were very largely lifelong and clearly correlated as expected with AT type (oral anticoagulant or antiplatelet agent). This may be the reason why indication was not strongly associated with AT decision at discharge. Systematic reviews[11,18] and guidelines[12,13] noticed a lack of evidence for the management of AT agents in epistaxis with only observational studies.

Thirdly, we observed a low recurrence rate of either thrombotic events or epistaxis (5%) (requiring ED referral) in the following 3 months. Glikson et al.[10] observed during a 1 year follow-up a lower re-admission rate in the DOACs (4%–9%) compared with the antiplatelet and warfarin group (16%). Of note, withholding (may be only temporarily) was higher in the rivaroxaban group (25%) compared with other groups (9% and even only 3% in the antiplatelet group). Yaniv et al.[6] did not find significantly different recurrence rates during an average follow-up time of more than 2 years between VKA (13%), antiplatelets (15%) and DOAC (14%), as well as in a control group (15%) of patients not prescribed with AT drug. There was no clear statement as regard resuming or withholding AT drug.

4.1 | Clinical implications

AT therapy is an important aggravating factor for bleeding. In the context of severe epistaxis associated with ATs, very few studies reported the therapeutic decision thereafter.[11–13,18] We think that reassessment of AT therapy should be included in the management of severe epistaxis before discharge. In this context, we found four factors that led to treatment changes: need to hospitalisation, age, haemoglobin level and oral anticoagulant. These factors allowed change

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or discontinuation in a quarter of cases with a significant decrease of recurrences of epistaxis during the 3-month follow-up. In patients referred to ED for severe epistaxis, especially when a therapeutic modification was decided, a close monitoring is required over the following months. Withholding (at least temporarily) or modifying AT regimen after the acute phase of a severe epistaxis is a rather complex decision and requires close multidisciplinary management to refine the individual risk/benefit balance. Decision-making is a difficult process in which several key elements are involved: indication of AT treatment, comorbidities and factors associated with AT prescription thereafter. It should be shared between clinicians, general practitioner, otolaryngologist, careers, patients and their family.

4.2 | Strengths and limitations

The study has some strengths. All nosebleed events were medically validated, drug exposure and medical history were assessed through clinical records as well as on Health Insurance Database (SNIIRAM), the two data sources being linked allowing cross-checking. Health Insurance Database (SNIIRAM) allowed to identify patients with stable AT therapy for 3 months before epistaxis, and then epistaxis recurrence (referred to ED) without attrition bias.

The study has also some limitations mostly stemming from our inability to comprehensively measure some dimension of individual risk assessment such as presence of a third party at home to help with the preparation and taking of medication, disability and cognitive status, social context and life habits. There was also a risk of misclassification related to coding errors at the time of hospital admissions. We do acknowledge we observed a limited number of patients receiving DOAC and, a limited number of recurrences, which led to lack of power. Whether AT drug was continued or temporarily withheld in hospitalised patients was not reliably recorded. Conversely, claims for any drugs, including AT drug, after discharge were exhaustively collected within 3 months of follow-up. Although all bleeding events were medically validated, specifically in terms of severity, we were not able to retrieve for all patients all criteria (such as posterior tamponade, need for transfusion or for emergency surgery) which could have definitely supported enrolment. For example, symptoms related to blood loss (dizziness, tachycardia, lightheadedness, weakness or syncope) were not collected excepted blood pressure on admission. Half of our population returned home and severity should be challenged in those patients. We had no data on the process leading to emergency referral. In France, patients are authorised to visit ED as a self-decision, that is, without visiting before a general practitioner. Last, regarding the specific management reported in Table 3, our results have to be interpreted with caution due to missing data.

5 | CONCLUSION

This prospective multicentric population-based cohort study found that epistaxis referred to ED was associated with subsequent AT prescription in the following 3 months with a class-changing rate of 15.6% and a discontinuation rate of 11.6%. Predictive factors for AT modification are valuable but further studies are required before firm conclusion being drawn. Regardless of the modification, patients need regular therapeutic assessment from all patient health care providers.

AUTHOR CONTRIBUTIONS

Jacques Bouget conceived, designed, performed, supervised the study and drafted the article. Frédéric Balusson provided technical and material support and analysed the data. Pierre-Marie Roy, Damien Viglino and Karine Lacut performed the study. Emmanuel Oger conceived, designed, analysed the study and drafted the article. All authors revised and approved the final version of the article.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/coa.14040.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author. Under French law and regulations, patient-level data from SNIIRAM cannot be made available.

ETHICS STATEMENT

No informed signed consent was required for this study. The study received regulatory approval (Commission Nationale de l'Informatique et des Libertés 'NIL', no. DR – 2013-488 with subsequent substantial changes no. DR-2016-489).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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