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Severe Gross Hematuria Associated with Antithrombotic Drugs: Management and Impact on Prescription Thereafter

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Abstract

Anfibatide is a synthetic antiplatelet thrombolysin derived from snake venom and is proposed to treat ischemic stroke and cerebral ischemia-reperfusion injury. Current standard treatments for ischemic stroke include the administration of rt-PA, a thrombolytic agent, or endovascular removal of thrombi. However, the post-treatments are often associated with the occlusion of vessels due to a lack of antiplatelet and unrecovered vessel injury. Anfibatide, as a GPIbα antagonist that interrupts the initiation of platelet aggregation caused by GPIbα-vWF binding, becomes a potential novel candidate for treating ischemic stroke due to its antiplatelet and antithrombosis effects. Key findings show that Anfibatide can significantly reduce microthrombus formation in cerebral vessels and reduce neuron apoptosis due to the release of pro-inflammatory mediators caused by ischemia or Ischemia-Reperfusion (I/R) injury. Significant improvement in neurological scores and reversal of brain structure alterations are observed in the Anfibatide-treated ischemic animal models. To facilitate the clinical development of Anfibatide, this paper aims to summarize the completed preclinical studies and the Phase I clinical trial results of anfibatide to evaluate the risks and therapeutic potentials of Anfibatide in ischemic patients.

Keywords: Anfibatide; Ischemic stroke; Cerebral ischemia-reperfusion injury; Antiplatelet; GPIbα-vWF binding; Antithrombosis

Abbreviation: rt-PA: Recombinant Tissue Plasminogen Activator; MT: Mechanical Thrombectomy; DALY: Disability-Adjusted Life Years; GP: Glycoprotein; NS: Normal Saline; FCA: Freund's Complete Adjuvant; ICH: Intracerebral Hemorrhage; β-TG: β-thromboglobulin; H&E staining: Hematoxylin and Eosin staining; SOD: Serum superoxide dismutase; GSH-Px: Serum Gutathione Peroxidase; MDA: Malonaldehyde; LDH: Lactate Dehydrogenase; NO: Nitrogen Oxides; I/R injury: Ischemia-Reperfusion Injury; EI: Edaravone-Injection; CRI: Constant Rate Infusion; PRP: Platelet-Rich Plasma; PT: Prothrombin Time; TT: Thrombin Time; aPTT: Activated Thromboplastin Time; INR: International Normalized Ratio

Introduction

Antithrombotic agents are the most commonly prescribed medications for older adults in the world. In this population, warfarin and antiplatelet agents represented respectively the first and the third medications leading to emergency hospitalizations for adverse effects [1]. Bleeding represent the most well-known and feared complication of antithrombotic agents. Most of clinical trials and observational studies have focused on Intracranial Hemorrhage (ICH) and Gastrointestinal (GI) bleeding associated with oral anticoagulants or antiplatelet agents [1-5]. Studies reporting on hematuria appear scarcer.

In a large cohort study, Wallis et al reported that use of antithrombotic agents was associated with a significant increased rate of hematuria-related complications compared to patients not exposed, with an incidence rate ratio of 10 [6]. Rate of gross hematuria among patients referred to emergency department while receiving any type of antithrombotic agent ranged from 3.9 to 5.7% [7,8]. This rate was higher in patients receiving oral anticoagulants, from 3% up to 24% depending on the methodology and the definition of bleeding severity used [3,9-13]. In patients prescribed with antiplatelet agents it appeared lower

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Table 1: Clinical characteristics of patients referred for severe gross hematuria (within 3 months) while receiving antiplatelet drugs or oral anticoagulants.

Variables	Value	Total N=300	Male N=260	Female N=40	P-value
Age	years	78.8 ± 10.1	78.6 ± 10.0	79.9 ± 10.5	0.46
Arterial hypertension		60.3(181)	59.2(154)	67.5(27)	0.32
Malignant disease		35.7(107)	37.7(98)	22.5(9)	0.06
Coronary artery disease		33.7(101)	34.6(90)	27.5(11)	0.37
Diabetes mellitus		25.3(76)	26.2(68)	20.0(8)	0.4
Stroke/Transient ischemic attack		21.3(64)	21.9(57)	17.5(7)	0.52
Chronic renal insufficiency		16.0(48)	16.2(42)	15.0(6)	0.85
Peripheral artery disease		15.0(45)	15.4(40)	12.5(5)	0.63
History of heart failure		11.7(35)	12.7(33)	5.0(2)	0.16
History of venous thromboembolism		10.0(30)	8.85(23)	17.5(7)	0.09
Smoking habit		8.3(25)	8.85(23)	5.0(2)	0.41
Alcoholism		6.0(18)	6.5(17)	2.5(1)	0.32
Valvular heart disease		5.0(15)	4.6(12)	7.5(3)	0.44
History of gastroduodenal ulcer		5.0(15)	5.8(15)	-	0.12
Liver cirrhosis		1.7(5)	1.9(5)	-	0.38
History of bleeding*		19.7(59)	20.0(52)	17.5(7)	0.71
Gastrointestinal		4.7(14)	4.6(12)	5.0(2)	
Cerebral		1.7(5)	1.15(3)	5.0(2)	
Other		13.3(40)	14.2(37)	7.5(3)	
Recent history of hematuria		12.0(36)	12.7(33)	7.5(3)	0.35
Charlson index	0	30.3(91)	30.8(80)	27.5(11)	0.43
	2-Jan	37.0(111)	35.4(92)	47.5(19)	
	4-Mar	19.3(58)	19.6(51)	17.5(7)	
	≥ 5	13.3(40)	14.2(37)	7.5(3)	

Values are percentage (frequency) or mean ± Standard Deviation. *history of bleeding within the last 6 months

Table 2: Urologic diseases identified through discharge diagnosis (ICD-10 codes) for the current or previous hospital stays among patients referred for severe gross hematuria while receiving an antithrombotic agent.

	Male N=260	Female N=40
Bladder cancer	12.7(33)	5.0(2)
Other bladder or urethra diseases	8.1(21)	2.5(1)
Prostatic diseases		
Benign prostatic hyperplasia	11.1(29)	
Acute prostatitis	3.85(10)	
Prostate cancer	3.1(8)	
Kidney cancer	1.15(3)	
Other kidney and ureter diseases	12.3(32)	10.0(4)
Cancer of other urinary organs	0.4(1)	
Not yet identified	47.3(123)	82.5(33)

Values are percentage (frequency)

than that in patients with oral anticoagulants [14,15]. Hematuria is considered less life-threatening bleeding than ICH or GI bleeding. Hematuria is common in Emergency Department (ED) and involves diagnostic evaluation and therapeutic management even if its etiology is not always found [16,17]. In addition, to our knowledge, decision about antithrombotic treatment after severe hematuria has never been reported. Our objectives were to describe the management of patients referred for severe gross hematuria while receiving oral antithrombotic agents, and to assess factors associated with antithrombotic prescription thereafter.

Methods

Design, Data Sources and Study Population

The SACHA (Surveillance des ACcidents Hémorragiques sous Antithrombotiques) study is a French prospective multicentric population-based cohort study on the incidence and outcome of major bleeding in patients treated with antithrombotic agents. The study design has been previously reported [18]. The SACHA study included a total of 6484 patients with major bleeding events during a 3-year period. For the current analysis, only patients treated with oral antithrombotic agents admitted to EDs for severe gross hematuria were studied.

From emergency departments within five well-defined areas around five large French cities (Angers, Brest, Grenoble, Nantes and Rennes), demographic data (age, gender), clinical data (comorbid conditions, antithrombotic drug class with presumed indication and time since initiation, systolic blood pressure), as well as biological data (hemoglobin and creatinine level), therapeutic management such as red blood transfusion, platelet transfusion, plasma transfusion, vitamin K, protamin sulfate, Prothrombin Complex Concentrate (PCC) and FEIBA® (anti-inhibitor coagulant complex), and hospital data (endoscopic or surgical procedures, ward type (medical or surgical), Intensive Care Unit (ICU) stay, Length Of Stay (LOS), and case fatality) were collected. A modified Charlson index was calculated for each patient [19]. The CHA2DS2VaASc score was calculated for patient receiving oral anticoagulants [20]. Modification of Diet in Renal Disease (MDRD) was also calculated [21]. In each emergency department, the local referent medical doctor validated the inclusion, and specifically the bleeding severity defined as having at least one of the following criteria [22]: unstable hemodynamics (systolic arterial pressure <90 mmHg or mean arterial pressure <65 mm Hg) or hemorrhagic shock, uncontrollable bleeding, need for transfusion or hemostatic procedure (embolization, surgery). This is slightly different from the International Society on Thrombosis and Haemostasis (ISTH) classification of major bleeding events, because no information was available on hemoglobin levels before emergency department referral [23]. Bleeding lasted more than 12 hours despite bladder washing was also defined as severe hematuria.

The clinical database was linked to the French Health Insurance Database (SNIIRAM) using common key variables (date of birth (month, year), gender, date of hospital entry and discharge, type of antithrombotic therapy, and care facility involved) [18]. 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. We identified pre-existing urologic diseases (before hematuria) and extracted the discharge diagnoses (main and secondary, focusing on urologic disease) as well as the medical procedures (endoscopy, surgery) coded for the hospitalization related to the index hematuria.

For this analysis, we considered only patients (i) referred for severe gross hematuria without any other concurrent bleeding between January 1, 2013 and December 31, 2015, retaining the first occurrence as index hematuria, (ii) with a stable oral antithrombotic regimen before referral (i.e., without any change in therapeutic class or posology of antithrombotic agents, within

Table 3 Part A: Management of patients referred for severe gross hematuria while receiving antiplatelet drugs or oral anticoagulant (antithrombotic management).

Variables	Total N=300	Antiplatelet monoherapy N=161	Antiplatelet dual therapy N=19	Vitamin K Antagonist N=105	Direct oral anticoagulant N=15	*P*-value
Urgent need for hemostatic procedure	74.3(223)	84.5(136)	68.4(13)	63.8(67)	46.7(7)	<.0001
INR†				2.7 [2.2-3.4]		
Vitamin K				28.6(30)		
Prothrombin complex concentrate				10.5(11)		
Blood transfusion	37.0(111)	33.5(54)	47.4(9)	36.2(38)	66.7(10)	0.06
Number of red cell pack	2.0[2.0-3.0]	2.0[2.0-3.0]	2.0[2.0-3.0]	2.0[2.0-3.0]	2.0[2.0-2.0]	
Plasma transfusion	0.7(2)	0.6(1)	-	-	6.7(1)	

Values are percentage (frequency) or median [Q1-Q3]. †10 missing values

Table 3 Part B: Management of patients referred for severe gross hematuria while receiving antiplatelet drugs or oral anticoagulant (urological management).

Variables	Total N=300	Antiplatelet monotherapy N=161	Antiplatelet dual therapy N=19	Vitamin K Antagonist N=105	Direct oral anticoagulant N=15	P-value
Endoscopy	46.6(140)	51.5(83)	31.6(6)	43.8(46)	33.3(5)	0.13
Bladder irrigation alone	34.0(102)	32.9(53)	36.8(7)	37.1(39)	20.0(3)	
Surgery	3.7(11)	3.7(6)	5.3(1)	2.9(3)	6.7(1)	
Unknown	15.7(47)	11.8(19)	26.3(5)	16.2(17)	40.0(6)	

Values are percentage (frequency)

Table 4: Outcomes after emergency department referral for severe gross hematuria while receiving antiplatelet drugs or oral anticoagulant.

Variables	Total N=300	Antiplatelet monotherapy N=161	Antiplatelet dual therapy N=19	Vitamin K Antagonist N=105	Direct oral anticoagulant N=15	*P*-value
Hospitalization	94.0(282)	95.0(153)	94.7(18)	92.4(97)	93.3(14)	0.75
Medical ward	49.8(140)	49.0(75)	38.9(7)	56.2(54)	28.6(4)	0.001
Surgical ward	40.9(115)	45.7(70)	61.1(11)	30.2(29)	35.7(5)	
ICU	1.4(4)	-	-	4.2(4)	-	
Observational unit	7.8(22)	5.2(8)	-	9.4(9)	35.7(5)	
Missing	(1)					
Length of stay (days)†	5[3-10]	5[3-8]	4[2-7]	7[3-14]	5[1-8]	0.12

Values are percentage (frequency) or median [Q1-Q3]. †1 missing value. ICU stands for intensive care unit.

3 months prior to hematuria). Of note, hematuria during hospitalization whereas patient was referred for another reason and intentional overdose of antithrombotic agents were excluded. All oral antithrombotic agents were included in the study: vitamin K antagonist, direct oral anticoagulants, antiplatelets agents (mono or dual therapy) and any combinations of these drugs.

The study received regulatory approval (*Commission Nationale de l'Informatique et des Libertés* "CNIL", #DR-2013-488 with subsequent substantial changes #DR-2016-489); ClinicalTrials.gov identifier: NCT02886533.

Outcomes

We first considered hospital outcome, focusing on ward type (medical or surgical), Intensive Care Unit (ICU) stay, Length Of Stay (LOS), and case fatality.

After hospital discharge, antithrombotic prescription was categorized into 3 classes according to SNIIRAM data for drug delivery in a 3-month follow-up period: no change, or class change when compared to the regimen before (drug delivery in a 3-month period before referral for severe gross hematuria), or discontinuation (no antithrombotic drug delivery in the following 3 months).

During a 3-month follow-up period after hospital discharge for severe gross hematuria, we retrieved SNIIRAM data on the occurrence of hospitalization for bleeding or ischemic events as coded in main discharge diagnosis (ICD-10).

No inform and signed consent was needed for the basic survey.

Statistical Analysis

Statistical analysis was performed from July 1 to October 31, 2022.

Clinical characteristics were described according to gender, whereas management and outcomes were described according to the type of antithrombotic drugs - Antiplatelet monotherapy or dual therapy, Vitamin K Antagonist (VKA) or Direct oral anticoagulant (DOAC)-. 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 across gender or across the type of antithrombotic drugs used chi-square test of Fisher exact test for categorical variables, Student t-test or analysis of variance for continuous variables with a gaussian distribution and Kruskal-Wallis test otherwise.

To estimate association between clinical predictors and antithrombotic prescription after hospital discharge (categorized as: no change, or class change when compared to the regimen before, or discontinuation, i.e. no antithrombotic drug delivery in the following 3 months), we ran a multivariable multinomial logistic regression model (generalized logit link) using "no change" as the reference category.

All statistical tests were two-tailed and P-values <0.05 were

Table 5: Independent factors associated with antithrombotic prescription thereafter among 279 patients referred for severe gross hematuria while receiving antiplatelet drugs or oral anticoagulant, and discharged alive based using multivariable multinomial logistic regression model with a generalized logit link (no change, n=161, as the reference category, discontinuation, n=41, and class change, n=77; 18 observations were deleted due to missing values for the response or explanatory variables).

Effect	Outcome	Unit	Odds Ratio Estimate	95% Wald Confidence Limits		Type 3 test *P*-value
MDRD	Class change vs. no change	- 15	0.95	0.85	1.09	0.001
	Discontinuation vs. no change	- 15	1.43	1.16	1.75	
OAC vs. AP	Class change vs. no change	1	5.87	3.22	10.7	<.001
	Discontinuation vs. no change	1	2.20	1.03	4.67	
Blood transfusion	Class change vs. no change	1	1.76	0.95	3.26	0.015
	Discontinuation vs. no change	1	2.81	1.34	5.89	

AP stands for antiplatelet, OAC for oral anticoagulant, MDRD for Modification of Diet in Renal Disease Study equation.

Table 6: Recurrences of hematuria and thrombotic events within 3 months according to antithrombotic prescription thereafter severe gross hematuria.

	Total N=297	Discontinuation N=42	Class change N=81	No change N=174	*P*-value
Recurrences of hematuria	14.1(42)	11.9(5)	17.3(14)	13.2(23)	0.62
Thrombotic events	2.0(6)	4.8(2)	3.7(3)	0.6(1)	0.06

Values are percentage (frequency) Thrombotic events were ischemic heart disease (n=3), cerebral infarction (n=2) and arterial embolism (n=1).

considered significant. Statistical analyses were performed using SAS software 9.4 (SAS Institute, Cary, N.C., USA).

Results

Clinical Characteristics

Over the study period, 400 patients referred for severe gross hematuria while receiving antithrombotic drugs were included. Considering stable antithrombotic regimen over 3 months before hematuria and no other concurrent bleeding 300 patients remained eligible. Clinical characteristics are reported in Table 1. There were 260 (87%) males, and 40 (13%) females; mean age was 78.8±10.1 years. Only 36 patients (12%) had a recent (within 3 months) history of hematuria (non-severe by design). The three most frequent comorbidities were arterial hypertension (60.3%), malignant disease (35.7%) and coronary artery disease (33.7%). Charlson's comorbidity index was low (index ≤2 for 67.3% of patients).

Urologic diseases identified through discharge diagnosis (ICD-10 codes) for the current or previous hospital stays are listed in Table 2. No underlying urologic disease was identified in 123 male patients (47%) and 33 female patients (82%) at that time. In the remaining 137 male patients, a cancer was coded in 45 (25.4%) patients, mainly bladder cancer. A non-malignant prostatic disease was coded in 39 (28.5%) patients.

The distribution of antithrombotic agents was as follows: 180 patients with antiplatelet agents (161 patients with monotherapy, 19 with dual therapy), 120 patients with oral anticoagulants (105 with VKAs, 15 with DOACs). Characteristics of antithrombotic regimens, presumed indications and self-reported duration are reported in Supplementary Material Table S1. The CHA2DS2VASc score was globally high, with a score equal to 2 in more than 50% of patients with atrial fibrillation.

Management

By design, all patients were referred to emergency department. The hemostatic management is reported in Table 3, part A. Blood transfusion was needed in 37% of patients with a median number of 2 red cell packs, without statistically significant difference in patients receiving antiplatelet agents or oral anticoagulants (p=0.06). In patients receiving VKAs, vitamin K was used in 28.6% of patients and prothrombin complex concentrate only in 10.5% of patients. Table 3, part B shows the urological management. Bladder irrigation alone was needed in 34% of patients. Nearly half of patients (46.6%) required endoscopy with or without surgical procedure (tumor removal, polyp ablation). Surgery alone, without endoscopy, was needed in only 3.7% of patients. No statistically significant difference in the urological management was detected when comparing antithrombotic regimens.

Outcomes

Outcomes after emergency department are shown in Table 4. Almost all patients (94%) needed hospitalization. Among those hospitalized patients, type of ward distribution was significantly different when comparing antithrombotic regimens (*P*=0.001). Pairwise post-hoc showed statistically significant difference between VKA and antiplatelet agents (*P*=0.006), VKA and DOAC (*P*=0.038), DOAC and antiplatelet agents (*P*=0.003), and DOAC and dual antiplatelet regimens (*P*=0.027).

Two-hundred and ninety-seven patients were discharged alive. Considering antithrombotic prescription thereafter we observed no change in 174 patients (58.6%), antithrombotic class changes in 81 patients (27.3%) and discontinuation in 42 patients (14.1%). Predictors of antithrombotic prescription are shown in Supplementary Material Table S2. Using multivariable multinomial logistic regression, we identified three independent predictors for antithrombotic prescription: Modification of Diet in Renal Disease (MDRD) (*P*=0.001), antithrombotic class (*P*<0.001) and need for bleed transfusions (*P*=0.015) (Table 5). For every decrease of 15 units in MDRD, discontinued prescription was 1.4 times as often then unchanged prescription. Compared to unchanged prescription, discontinued prescription was twice as often among patients previously receiving an oral anticoagulant than among those receiving an antiplatelet agent, and was 2.8 times as often among patients who had blood transfusion than among those who had not; furthermore, changed prescription was nearly six times as often among patients previously receiving an oral anticoagulant than among those receiving an antiplatelet agent.

During the three months following discharge for severe gross hematuria, whatever the antithrombotic prescription there after, 6 thrombotic and 44 bleeding events were identified, of which 42 (14.1%) were recurrences of hematuria. Recurrences of hematuria and thrombotic events within 3 months according to antithrombotic prescription thereafter are shown in Table 6. Identified urologic diseases according to hematuria recurrence within 3 months are displayed in Supplementary Material Table S3.

Discussion

We reported on 300 patients referred for severe gross hematuria while receiving antithrombotic agents. We observed that urologic disease was not diagnosed in 52%, mostly in women (82.5% in women versus 47.3% in men). Management complied with usual practice: Vitamin K antagonist reversal was in accordance to recommendations and urological management complied with usual practice [22,24].

Contrary to Satasivam et al., the rate of bladder irrigation alone was lower in our study (34% vs 85%) regardless of the type of antithrombotic agent or combination of agents used [25]. Lastly, we identified three independent predictors of antithrombotic prescription there after: an altered renal function, the type of antithrombotic and the need for blood transfusions.

Guidelines are unanimous in support of urologic evaluation for hematuria irrespective of the presence of antithrombotic agents [14,24,25]. Antithrombotic-associated hematuria is often precipitated by a significant pathological lesion. In this context, malignancy is the most relevant cause of hematuria especially in patients taken antithrombotic agents compared with patients without [6,17]. Evaluation failed to reveal a significant pathologic finding in 3% to 82% of cases [13,26,27]. In a prospective analysis of 1930 patients with hematuria, evaluation with abdominal radiography, renal ultrasound, urography and cystoscopy found no diagnosis in 52.4% of patients with macroscopic hematuria, without difference in patients taken anticoagulant or not [16]. In a meta-analysis including 22 studies describing 175114 patients with hematuria and antithrombotic agents, an urologic pathology was diagnosed in only 44% of patients [14]. Our results are in line with these studies [25,26]: 11.7% of bladder cancer, a prostatic disease was identified in 18.1% of male patients, mostly benign prostatic hyperplasia.

With regard to antithrombotic prescription thereafter, assessment of the individual risk of both bleeding and thromboembolism must be undertaken [6]. The risk assessment included gender, indication of antithrombotic therapy, type of antithrombotic agent, and underlying urological pathology. Individual risk assessment led to maintain antithrombotic therapy in 255 out of 297 (85.8%, with no change in 2/3 and class change in 1/3), and to discontinue it in 14.1%.

We observed that an altered renal function and the need for blood transfusions were associated with antithrombotic prescription thereafter. Blood transfusion, hemoglobin level and renal function as well as hemodynamic parameters are indeed correlated with the severity of gross hematuria.

Oral anticoagulation was a strong predictor of antithrombotic prescription thereafter. Our study was in line with a previously reported higher bleeding risk of VKAs compared to DOACs [7,14]. Type of anticoagulation (VKA, DOAC, antiplatelet agent in dual regiment or not) is strongly correlated with underlying cardiovascular disease. When a change was considered, VKA has been often replaced by parenteral anticoagulation. Parenteral anticoagulant or DOAC rather than continuing VKA was already suggested [25,28].

Within a 3-month follow-up period, hematuria recurrence rate was 14%, and we were not able to detect an association with antithrombotic prescription. Causes of recurrent hematuria appear multifactorial involving probably urological malignancy [29].

Clinical Implications

AT therapy is an important aggravating factor for bleeding. In the context of severe gross hematuria associated with ATs, very few studies reported the therapeutic decision thereafter [6,25]. We think that reassessment of AT therapy should be included in the management of severe hematuria before discharge. In this context, we found 3 factors that led to treatment changes: altered renal function, oral anticoagulant and need for bleed transfusions. These factors allowed to change or discontinuation of AT treatment in more than 40% of cases. In patients referred to ED for severe hematuria, especially when a therapeutic modification was decided, a close monitoring is required over the following months. With holding (at least temporarily) or modifying AT regimen after the acute phase of a severe hematuria 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, urologist, careers, patients and their family.

Strengths and Limitations

Some strengths can be highlighted. All hematuria events were medically validated using a strict definition of major bleeding, 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 antithrombotic therapy for 3 months before hematuria, and then hematuria recurrence without attrition bias.

There were several limitations to the present study. We were not able 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 is 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.

Conclusion

Based on a large prospective cohort of patients referred for severe gross hematuria while receiving a stable antithrombotic therapy, we observed that antithrombotic therapy was discontinued for at least three months in 14%. Renal function, need of red cell transfusion, reflecting hematuria severity, and type of antithrombotic agents, correlated with underlying cardiovascular disease, were independently association with antithrombotic prescription thereafter. Observed predictive factors are valuable but further studies are required before firm conclusion being drawn.

Author Statements

Author's Contributions

J. Bouget, E. Oger and L-M. Scailteux participated in the analysis and interpretation of the data and the drafting of the manuscript. J. Bouget and E. Oger participated in the study concept and design. J. Bouget, E. Oger, F. Balusson, P-M. Roy, D. Viglino, L. Pavageau, K. Lacut, Z.E. Khene and L-M. Scailteux participated

in the critical revision of the report. E. Oger, and F. Balusson participated in the statistical analyses.

Availability of Data and Material

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.

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Conflict of Interest and source of founding

The authors declare that they have no conflict of interest.

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