Research Article

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Prevalence of Hemorrhagic Accidents with VKA in the Cardiology Department of Chu Aristide le Dantec. Retrospective study of 60 cases (2016-2020)

Joseph Salvador Mingou[1], Ngor Ndeb Thiam[1], Marguerite Téning Diouf[2], Fatou Aw[1], Simon Antoine Sarr[1], Khadim Rassoul Diop[1], Malick Bodian[1], Mouhamadou Bamba Ndiaye[1], Maboury Diao[1] and Abdoul Kane[2]

[1]Cardiology Department, Aristide Le Dantec Hospital, Dakar, Senegal.
[2]Cardiology Department, Dalal Jam Hospital, Dakar, Senegal.

Correspondence
Joseph Salvador Mingou
Cardiology Department, Aristide Le Dantec Hospital, Dakar, Senegal.

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Abstract

Introduction: Hemorrhagic events with VKA are among the leading causes of iatrogenic events and are potentially serious. They represent a major problem in the management of VKA overdose. The objective of this study was to describe the epidemiological, clinical, paraclinical, therapeutic and evolutionary profiles of VKA bleeding events.

Methodology: This was a retrospective, descriptive, monocentric study over a four-year period from January 1, 2016, to December 31, 2020, in the cardiology department of the Aristide Le Dantec University Hospital. We included in our study all patients hospitalized for a bleeding event with proven VKA during the study period.

Results: A total of 60 patients were hospitalized for VKA bleeding events. The mean age of the patients was 54.2 years (20 and 79 years). The patients were predominantly female, with a sex ratio of 0.54:1. Most patients (67%) lived outside Dakar. The mean HAS-BLED score was 4.6 with extremes of 3 and 7. The CHA2DS2-VASc score had a mean of 3.63, with extremes of 2 and 7.

In biology, INRs were supra-therapeutic in all our patients, with a mean INR of 6.65. The lowest PT value was 3, while the highest value was 70, with a mean of 18.36.

The most commonly used VKA molecule was acenocoumarol (93.3%), followed by fluindione (5%) and warfarin (1.7%). The duration of treatment varied widely, with extremes of 2 weeks and 10 years. We classified the hemorrhages according to their type and location, so 88.3% had external hemorrhage while 11.7% had internal hemorrhage. The most frequent type of hemorrhage was hemoptysis (38.3%), followed by epistaxis (25%), then externalized digestive hemorrhage (33.3%), gingivorrhage (11.7%), Haemorrhagic stroke (10%) and a thigh hematoma (1.7%).

Therapeutically, all patients had received an INR check, discontinuation of VKAs and administration of vitamin K ampoules. Forty percent (40%) (n=24) received packed red blood cells. The evolution during hospitalization was favorable in 70% of cases. Complications included cardiovascular collapse in 3.3% (n=2). Hospital mortality was 26.7%.

Conclusion: VKA bleeding events are frequent and have a significant iatrogenic effect. In our study, they were more frequent in women and elderly subjects, and more often related to bleeding risk factors and irregular follow-up. The management of these events requires control of risk factors and early treatment.

KEYWORDS

Hemorrhage, Antivitamin K, Senegal.

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INTRODUCTION

Vitamin K antagonists (AVK) are anticoagulant medications used orally. They are used for the prevention and treatment of arterial and venous thrombosis. For more than six decades, vitamin K antagonists (VKA) have been the only class of oral anticoagulant available the market. Warfarin, acenocoumarol and fluindione have long represented the only alternative when oral anticoagulant treatment is necessary. Taking these molecules, the therapeutic benefit of which is no longer in doubt, nevertheless implies some constraints on use, notably the need for biological monitoring or compliance with certain dietary or therapeutic precautions, given the risk of interactions. Their effectiveness, in terms of reducing cardiovascular morbidity and mortality, has been widely demonstrated by robust clinical data [1]. The therapeutic index of this drug class remains low, and regular biological monitoring is necessary. The occurrence of bleeding under AVK, whether in the therapeutic zone or in an overdose situation, is an event with dramatic consequences and whose frequency is not negligible [2]. Indeed, hemorrhagic accidents at AVK constitute the leading cause of hospitalization for iatrogenic causes in France (17,000/year) and the third in the United Kingdom [3,4]. Very little data has been recorded in Africa, particularly sub-Saharan Africa.

The general objective of this study was to describe the epidemiological, clinical, therapeutic and progressive characteristics of patients presenting hemorrhagic accidents under AVK.

Then specifically to describe the prevalence of AVK use in the service and to identify the AVKs used.

PATIENTS AND METHODS

We carried out a descriptive, retrospective, single-center study carried out in the cardiology department of the Aristide Le Dantec university hospital center over a period of 4 years (from January 1, 2016 to December 31, 2020). The study focused on the files of patients hospitalized at the cardiological clinic of the Aristide Le Dantec University Hospital Center, who presented with a hemorrhagic accident with anti-vitamin K drugs. Data entry and analysis were carried out using Sphinx software. Millennium version 4.5.

RESULTS

In total, sixty (60) files were selected for this study with a female predominance (sex ratio/F of 0.54). The average age was 54.2 years (with extremes of 20 and 79 years). The most represented age group was those over 64 years (31.7%), followed by those between 45 - 54 years (21.7%), and 55 - 64 years (21.7%).

Patients who attended a French school represented 35% (n=21), while those who did not have access represented 65% (n=39).

Heart failure constituted the most frequent comorbidity with 39.4% of cases (n=13) followed by ischemic stroke 18.2% (n=6), myocardial infarction 18.2% (n=6).

Table 1: Distribution of antecedents.

Background	Workforce	Percentage
Heart failure	13	39.4 %
IDM	6	18.2 %
DALY	6	18.2 %
Pulmonary embolism	4	12.1 %
Neoplasia	4	12.1 %
Total	33	100%

Fifty (50) patients had already had a history of AVK accidents. Thromboembolic risk factors were dominated by hypertension and diabetes with 37.5% and 13.8% of cases respectively.

The average HAS-BLED Score was 4.6 (with extremes of 3 and 7).
The average CHA2DS2-VASc score 3.63 (with extremes of 2 and 7).

In our study population, the most frequent indications for anticoagulation were ACFA valve disease (33.3%) followed by ACFA in a healthy heart (31.7%) and then venous thromboembolism (VTE) (11.7%).

Valve replacements accounted for 8.3% of the population while intracardiac thrombi accounted for only 6.7%. Other indications were found (n=5) and represented 8.3% (chronic cor pulmonale, hypertrophic cardiomyopathy in ACFA, dilated cardiomyopathy with severe LV dysfunction, and ischemic cardiomyopathy with severe LV dysfunction).

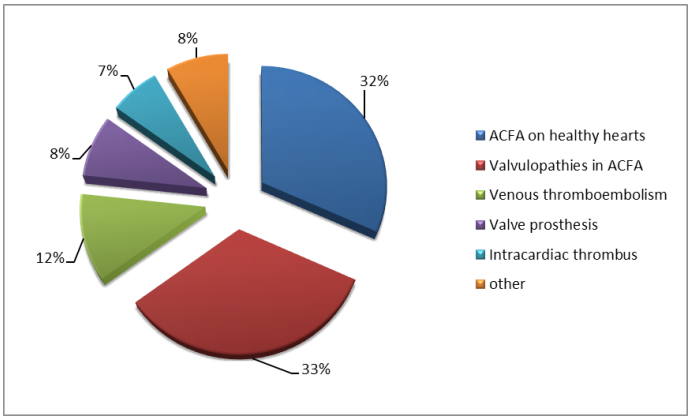


Figure 1: Indications for the use of AVK.

The mean value of the INR of our patients was 6.65 (with extremes of 4 and 12) and that of the prothrombin level was 18.36 ± 13.45 (with extremes of 3 and 70).

The most prescribed VKA was acenocoumarol in fifty-six patients (93.3%), followed by fluindione in three patients (5%), then warfarin in one patient (1.7%).

Table 2: Distribution of dosages of AVKs used.

Molecule	Dosage	Number (n=60)	Percentage
Acenocoumarol	4mg	39	65%
	3mg	7	11.7%
	2mg	9	15%
	1mg	1	1.7%
Fluindione	20mg	3	5%
Warfarin	5mg	1	1.7%

Thirty-nine of the patients on acenocoumarol 4mg took one tablet (4mg) (65%), nine patients took half a tablet (2mg) (15%), seven patients were on 3mg (11.7%) and only one patient was on 1 mg of acenocoumarol (1.7%).

The three patients on Fluindione all had the same dosage of 20 mg, and the patient placed on Warfarin had a dosage of 5 mg. Among the sixty patients on AVK, forty-two were taking one or more medications interacting with AVK, including antiplatelet agents (29.5%).

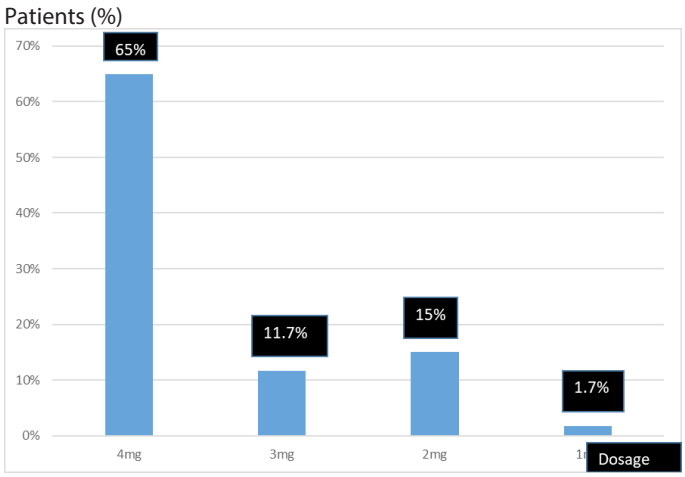


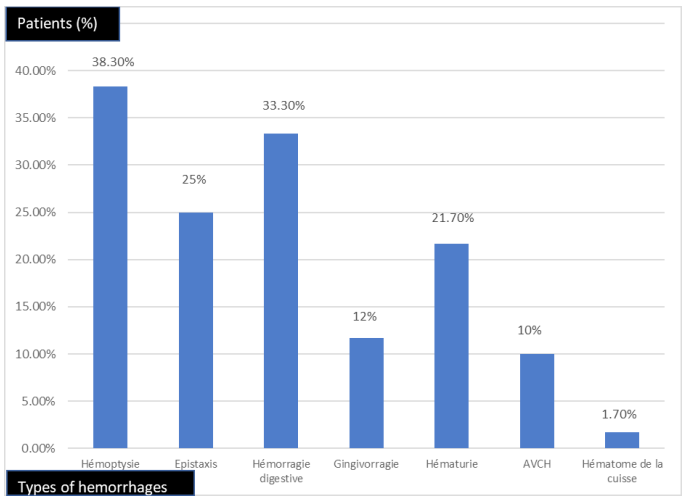
Figure 2: Patients on acenocoumarol.

Table 3: Distribution of drugs interacting with AVK.

Drugs interacting with AVK	Workforce	Percentage
Antiplatelet aggregation	28	29.5%
Statins	18	18.9%
Other medications that do not interact with AVKs	13	13.7%
Non-steroidal anti-inflammatories	10	10.5%
Propanolol	8	8.4%
No medication	18	18.9%

Fifty-three of our patients (88.3%) had external hemorrhage, while 7 of our patients (11.7%) had internal hemorrhage, these hemorrhages were variously associated.

We counted 23 hemoptysis (38.3%), 15 epistaxis (25%), 20 externalized digestive hemorrhages (33.3%), 7 gingivorrhagia (11.7%), 13 hematuria (21.7%), 6 AVCH (10%), and a hematoma of the thigh (1.7%).



AVCH: hemorrhagic stroke

Figure 3: Distribution of types of internal and external hemorrhages.

The support consisted of:

- A stoppage of the AVK: 100%
- Administration of vitamin K: 100%
- A packed blood cell transfusion: 40% (n=24)
- The use of fresh frozen plasma was not mentioned in any records.

The evolution was marked by the occurrence of death in 26.7% of patients, or 16 patients; 02 patients or 3.3% of patients had developed complications such as cardiovascular collapse in whom the emergency had been lifted and followed by a good evolution. The evolution was also favorable for the rest of the patients.

DISCUSSION

The use of AVK is widespread in developed and developing countries [5], the study of the national survey on adverse events linked to care (ENEIS) shows that the leading cause of hospitalization for events Serious adverse events involve anticoagulants, of which VKAs represent the majority [6].

The average age of our population was 54.2 years with the most represented age group being over 64 years (31.7%), comparable to the Moroccan population whose average age was 51.9 years. This average age was younger than in a French study on AVK accidents where the average age was 72.5 years [7].

Our population was predominantly female, i.e. a sex ratio of 0.54, which is strictly identical to the sex ratio found in a prospective descriptive study on a sample of 80 patients at the IBN SINA University Hospital in Morocco in 2019 having found 35% men and 65% women [8]. This sex ratio is also comparable to that found in the study carried out in the cardiology department of the Principal Hospital of Dakar in 2016, which was 0.65 with a study population composed of 61 men and 93 women [9]. It is, however, different from that of the French population under AVK, where 51.7% of patients under AVK are men [7], and from that of a case control study carried out in the cardiology department of the Avicenne military hospital in Marrakech in Morocco, where we note a slight male predominance in the group of cases with a percentage of 53% compared to 51% in the group of controls [10].

Certain specific clinical conditions are recognized as risk factors for bleeding in the event of treatment with AVK. The factors identified are high blood pressure, diabetes, cerebrovascular pathologies, serious cardiac pathologies, history of gastrointestinal bleeding, recent myocardial infarction, severe anemia, the presence of a pathology neoplastic, and renal (serum creatinine > 1.5 mg/dl) or hepatic insufficiency [11,12]. In our series, 34.5% of patients were hypertensive, 12.6% were diabetic, 12.1% had a history of neoplasia, and 6.9% of our patients had renal failure, which is consistent with the data from the literature [13-15].

In our study, the most frequent indications were valvular heart disease in complete arrhythmia due to atrial fibrillation (33.3%), complete arrhythmia due to non-valvular atrial fibrillation (31.7%) and then venous thromboembolism (11.7%). These data are similar to literature data which shows a predominance of atrial fibrillation [16,17].

Conventionally we note that there is an increased risk of hemorrhagic events with AVK when initiating treatment. This phenomenon is linked to the instability of the INR at the start of treatment [18].

It has been shown in a study that the treatment initiation period particularly exposes the patient to overdoses and complications. Indeed, 68% of patients who started AVK treatment for less than 3 months had developed a hemorrhagic accident and the probability of developing a hemorrhage under AVK during this period is 6 times higher than during prolonged treatment [19].

Other studies report that the duration of treatment does not seem to be linked to the incidence of bleeding [18], which is consistent

with the results of our work, where we find 68% of cases who had presented a hemorrhagic event between the first year and the five years following the initiation of treatment with AVK, 27% of cases bled less than 1 year after the start of treatment, and 5% of patients presented a hemorrhagic accident after more than 5 years of treatment. The ENEIS study shows that 19% of serious adverse events linked to AVK are associated with inappropriate use of the therapy, characterized by inappropriate prescription, administration or monitoring or by an absence of treatment linked to poor patient compliance, an absence of prescription or administration [6].

The combination of AVK with antiplatelet agents (aspirin, clopidogrel) greatly increases the risk of bleeding via inhibition of platelet function. A recent case-control study shows that multiple medications are directly involved in exposure to the risk of bleeding during treatment with AVK [20]. The same study reports that the AVK-antiplatelet association was found for 7 of the 34 cases, or 20.6% of the cases, and for 6 of the 70 controls, or 8.6% of the controls ($p = 0.114$) [20].

In our study, 70% of patients were taking medications interacting with AVK at the time of the hemorrhagic accident including antiplatelet agents (29.5%), statins (18.9%), nonsteroidal anti-inflammatories (10.5%), and propranolol (8.4%), which is consistent with literature data.

In our series, the INR was supratherapeutic in 100% of cases, with an average of 6.65 for all of our patients, similar to the data from a French study which found an average of 6 for the INR [21]. Above 4.5, the risk of bleeding is increased. Below 2, the thromboembolic risk is increased depending on the indication [22].

The risk of bleeding (whatever its severity) increases by a factor of 30 for an INR greater than 4 in the event of atrial fibrillation [23]. For intracranial bleeding, the annual incidence rate would increase from 0.5/100 patient years (INR < 4) to 2.7 (INR between 4 and 4.5) to reach 9.4 (INR > 4.5), an increase of a factor of 20 [24,25].

Blas- Châtelain C et al., report that the risk of serious bleeding is 3.9 times higher when the HAS-BLED score is greater than or equal to 3 [26].

The data found in our study are thus correlated with these studies with an average HAS BLED score of 4.6 for our patients.

The incidence of hemorrhagic accidents does not appear to be linked to the type of molecule. However, certain genetic characteristics, such as the presence of CYP2C9*2 or 3* polymorphisms, or the T allele of the VKOR-1 gene could increase the risk of bleeding in patients treated with AVK. Poor compliance and insufficient therapeutic education may also be to blame. Finally, alcohol intoxication and the occurrence of trauma are risk factors that are still discussed [27,28].

For hemorrhagic manifestations, the estimation of the severity of the hemorrhage complicating oral anticoagulation does not follow internationally recognized criteria. Certainly, if most authors agree to classify hemorrhages into fatal, major and minor, the criteria for defining a major hemorrhage are not unanimously accepted [29].

In our study, all our patients benefited from stopping the AVK, and had frequent biological checks. Administration of vitamin K1 ampoules was carried out in all our patients, and 40% received a transfusion of packed red blood cells.

Direct Oral Anticoagulants (DOACs) are an alternative to VKA treatment, their recent extension of indication in the prevention of ischemic strokes (DALYs) in patients with non-valvular atrial fibrillation (AF), and in curative treatment deep vein thrombosis (DVT) and pulmonary embolism (PE) with better tolerance, has increased their prescription [30-31].

CONCLUSION

AVKs have significant iatrogenicity. These hemorrhagic accidents at AVK are therefore frequent, and their management requires controlling the risk factors. In our study, they were more frequent in women and elderly subjects, and more often linked to bleeding risk factors and irregular follow-up. However, the advent of DOACs constitutes an alternative to treatment with AVK; There is currently the problem of their accessibility in Sub-Saharan Africa due to their high cost.

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