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Original article

Knowledge, attitude and practice of healthcare professionals on dose adjustment of acenocoumarol in Algeria

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Abstract: Acenocoumarol is the only oral antivitamin K anticoagulant prescribed and marketed in Algeria for the prevention and treatment of thromboembolic diseases. Nevertheless, the difficulty of handling this drug linked to a narrow therapeutic index and to great inter- and intra- individual variabilities of the response to the treatment poses a major public health issue because of its iatrogenic risk. To improve the management of patients on acenocoumarol and optimize its dosage adjustment and reduce iatrogenic secondary to vitamin K antagonists, our main objective work is to assess the knowledge, attitude and practice of health care professionals regarding this anticoagulant agent. We conducted a multicenter descriptive cross-sectional study from April to May 2021. We interrogated 152 health professionals of all ages, all sexes and all grades from different health departments in Oran City (Algeria) prescribing anticoagulants, through a validated questionnaire made up of 26 questions. Statistical analysis was achieved by SPSS version 20 software. Thus, 59.9% were women with a sex ratio of 0.67, 92.8% knew that acenocoumarol belongs to the antivitamin K class, 45.0% chose INR and PT as follow-up parameters, 36.0% chose INR alone and 78.9% were unaware of acenocoumarol dose adjustment algorithms as well as 82.0% were unaware of the existence of pharmacogenetics testing. 54.0% use the recommendations of the HAS for dosage adjustment of patients on acenocoumarol. 07.9% suggested using pharmacogenetic tests to improve the dosage adjustment of acenocoumarol, 06.6% suggested patient follow-up and 05.9% suggested therapeutic patient education as well as 74.3%, wanted to do training on. Therefore, this study highlighted gaps in the medical practice of physicians in terms of dosage adjustment, pharmacogenetics and its impact on dosage optimization. However, the evaluation of their knowledge was considered unsatisfactory. To overcome this lack of knowledge, it seems necessary to make physicians aware of the contribution of pharmacogenetics of acenocoumarol in Algeria.

Introduction

Vitamin K antagonists (AVKs) are among the anti-thrombotic drugs for oral administration, the most used in therapy for nearly 60 years which are characterized by a wide spectrum of indications

with a low cost [1, 2]. Moreover, even after the arrival of direct oral anticoagulants (ADO), AVKs are the most prescribed in the world and still constitute today [2]. Among the AVKs, acenocoumarol represents the only AVK molecule marketed in Algeria. From a pharmacodynamics point of view, the inter-individual variability of the response to AVK is considered to be a real public health problem. Indeed, the difficulty of handling the dosage of AVK in current practice is linked on the one hand, to the narrow therapeutic index and on the other hand, because of a significant variability that is explained by demographic factors, clinic-biological and therapeutic, as well as, by genetic factors recently identified [3, 4]. In Algeria, the corresponding epidemiological data are rare. However, a survey carried out at the level of the Hemobiology Department of University Hospital Center (CHU) of Oran, Oran City showed that only 26.0% of the patients have their AVK treatment in the therapeutic efficacy zone [5]. Furthermore, the concept of pharmacogenetics is a rapidly evolving science whose goal is to identify the genes that modulate the response to the drug. Two genes are mainly involved in the response to acenocoumarol: one coding for the vitamin K epoxide reductase (VKORC1) being the pharmacological target and the other coding for the cytochrome P450 2C9, (CYP2C9) involved in the metabolism of coumarin derivatives into inactive metabolites. According to the available data, both VKORC1 and CYP2C9 genotyping before the initiation of VKA treatment could optimize the dosage adjustment of these drugs and therefore improve therapeutic efficacy and reduce the risk of drug iatrogenesis [6 - 8]. The implementation of pharmacogenetics in the current medical practice depends on the prior knowledge of physicians. At the moment, little is known about attitude and understanding of pharmacogenetics testing among physicians, since pharmacogenetics is not part of routine clinical practice. Due to the extent of data in the field of anticoagulants and to improve professional practice and reduce iatrogenic secondary to VKAs, the present study was aimed to assess the knowledge, attitude, and practice of health professionals in Algeria.

Materials and methods

We adopted a multicenter cross-sectional descriptive study for a period from April 1st, 2021 to May 13th, 2021, designed to evaluate the knowledge, attitude and practice (KAP survey) of 152 physicians from different sites: Oran University Hospital (EHU), Oran University Hospital Center (CHUC), Hospital of the General Directorate of National Security (DGSN), Oran University Regional Military Hospital (HMRUO), Local Public Health Establishment (EPSP) and Private sector. The study was carried out in the Pharmacovigilance Department of EHU from Oran. It included health professionals of all ages, all sexes and all grades from different departments prescribing anticoagulants in cardiology, cardiac surgery, vascular surgery, resuscitation, general surgery and internal medicine who agreed to fill the question sheet. This study excluded interns and those who refused to participate. This survey was carried out through a questionnaire of 26 questions which was self-designed and validated by 2 pharmacologists and 2 epidemiologists from EHU of Oran. The questionnaire has four sections; the first part represents the general data on the physicians, the second part evaluates knowledge of the physicians on acenocoumarol and the third part concerns the medical practices of the prescription of the drug. The fourth part aims to determine the attitude and expectation of the physicians toward the pharmaco-genetics of acenocoumarol.

Statistical analysis: The data collected was entered into SPSS version 20 software. Quantitative variables were represented as mean and standard deviation, qualitative variables were expressed as percentages. The crossing of several variables was tested by using the Chi-square test. A p-value of less than 0.05 is considered significant.

Results

Breakdown by survey site: This study was carried out on a small sample size of physicians (n = 152) of which 67.7% (n = 104) are working at the EHU of Oran and 17.4% (n = 26) of them are health care

professionals working at the CHU level with a response rate of 85.5%.

Demographic and occupational description: There was a female predominance of 59.9%. The sex ratio (M : F) was 0.67. The mean age of the study population was 30.9 ± 1.2 (25 - 72 years). The study mainly affected health professionals whose age was less than 30 years old with a percentage of 71.1% (n = 108). Most of the participants were from the internal medicine department at 13.2% (n = 20) followed by departments of general surgery at 12.6% (n = 18) and cardiology at 11.3% (n = 17). The other departments with a frequency of 38.8% represented subsequent: neurosurgery, neurology, pneumology, nephrology, hepatobiliary surgery, thoracic surgery, urology, hematology and hemo-biology. 140 of the physicians who took part in this survey answered all the questions and 73.7% of physicians had experience of less than five years.

Evaluation of knowledge of health professionals: 92.8% of the participants knew that acenocoumarol belongs to the class of AVKs. The results of the cross-referencing of the knowledge of the class of acenocoumarol concerning the different specialties are represented in **Figure 1** with p = 0.256. 45.0% of the physicians engaged in this survey (n = 68) chose INR and PT as monitoring parameters for acenocoumarol followed by 36.0% who chose INR alone. As for the rate of adaptation of monitoring of biological parameters: 75 of the total physicians followed their patients twice a week and 36 of the physicians followed them once a week. More than half of the physicians surveyed (78.9%) declared that they do not know dose adjustment algorithms of acenocoumarol. The dose adjustment algorithms cited by physicians are shown in **Table I**.

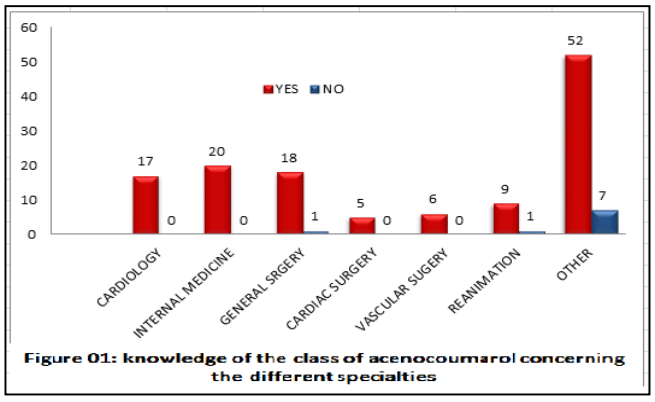

Figure 01: knowledge of the class of acenocoumarol concerning the different specialties

TABLE I: Dose adjustement algorithms cited by physicians

Algorithms adaptation	Effect
Administration 1 day / 2	1
Association of a heparin	1
Increase/decrease ¼ tablet (1mg)	1
Depending on INR	2
INR:1 /INR: 2 or 3 venous pathology	1
According to the recommendations	3
No answer	16
Total	25

Concerning pharmacogenetics tests, 82.0% of the physicians questioned did not know if there were pharmacogenetics tests for dosage adjustment of acenocoumarol and the large majority of the physicians (80.3%) did not know if the leaflet for acenocoumarol contained the notion of genetic variability. 28 of the physicians questioned found that pharmacogenetics allowed an understanding the variability of the pharmacological response and the prediction of the dose necessary to reach equilibrium (18.4%). 17 physicians affirmed that it made it possible to understand pharmacological variability only (11.2%).

Medical practice concerning the prescription of acenocoumarol: Among all the physicians surveyed, 76.3% prescribed anticoagulants, on an of average per month (n = 116), 44.7% prescribed this drug for less than five patients per month (n = 68), 17.1% prescribed it for five to 10 patients per month (n = 26), a small proportion of the physicians prescribed it for more than 10 patients per month (n = 22, 14.5%). The intersection between the prescription rate of acenocoumarol and the different specialties is shown in **Figure 2** with a p = 0.001.

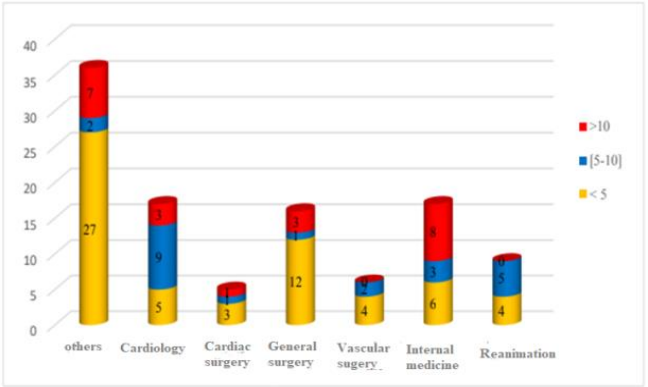

Figure 02 : Prescription rate of acenocoumarol and the different specialties

An analysis of the present data showed that the majority of the prescribing physicians initiated acenocoumarol with a dose of one mg (n = 89, 59.0%), 28.9% initiated it with a dose of two mg (n = 44), 02.0% initiated it with three mg (n = 03) and only 01.3% of the physicians initiated it with a dose of four mg (n = 02). 66.0% of the participants said the starting dose differs depending on the diagnosis and the individual. The crossing between initiation dose and its characteristics is shown in **Table II**.

TABLE II : Choice of the initiation dose according to its characteristics

Characteristics of the initial dose	Initial dose
Standard dose	P=0,398
Dose that differs according To th diagnosis and the individual	P= 0,049
Tolerated dose	P=0,281

More than half of the physicians (52.0%) said they used INR and PT for monitoring their patients. Only 04.5% said they used the three parameters INR, TP and TQ. Regarding the link between the physicians' knowledge of the drug acenocoumarol monitoring parameters and their application in their medical practice, there was a significant relationship between knowledge of acenocoumarol monitoring parameters and their application in practice with a value of p = 0.024 (**Figure 3**).

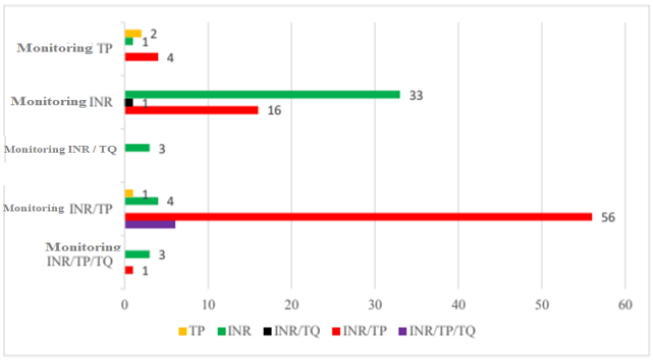

Figure 03 : Relationship between knowledge of acenocoumarol monitoring parameters and their application in practice

Among the physicians questioned, 28.0% declared that they measure the biological assessments at 48 hours after each modification of the dose or prescription which could interact with the drug acenocoumarol and 07.0% affirmed that they measure them on the fourth day of the initiation of treatment with only 04.0% of the physicians measured these parameters on the fourth day after the initiation of processing and 48 hours after each modification. About the duration of INR instability in the patients: 37.5% (n = 57) of the physicians declared that they have patients with an average duration of instability of two weeks and 19.7% have patients with an instability duration of one week (n = 30). Almost all the physicians (n = 126, 82.9%) observed adverse effects in patients with an INR outside the range. Bleeding was the adverse effect most observed by physicians with a frequency of 82.9% (n = 126). According to the results of the analysis concerning the process of dosage adjustment of acenocoumarol carried out by the physicians questioned is: in the event of INR off target, 20.4% of the physicians adapted the dosage by adjusting with the level of 1/4 tablet (**Table III**). Of these physicians, 54.0% said they used the HAS recommendations for dose adjustment of patients on acenocoumarol followed by those who used the ANSM recommendations.

TABLE III: Dosage adjustment of acenocoumarol in case of off-target INR

DOSAGE ADJUSTMENT	FREQUENCE %
Increase / decrease ¼ tablet	20,4
Adaptation according to INR	9,9
cardiology / reanimation opinion	3,9
intake skip	2,6
discontinuation of treatment	2
Adaptation according to INR, intake skip, administration of vitamin k	1,3
Increase / decrease ¼ tablet, intake skip	1,3
Increase / decrease ¼ tablet, discontinuation of treatment	1,3
optimize compliance	1,3
discontinuation of treatment/ HBPM	0,6
discontinuation of treatment/ lovenox/ administration of vitamin k	0,6
other attitudes	17,25
No answer	35,55
Total	100

The crossing between the initiation dose and the recommendations is shown in **Figure 4** with a significant level of p = 0.327. The intersection between the criterion for choosing the initiation dose and the recommendations is shown in **Figure 5** with p = 0.815. 38.0% of the physicians observed resistance in their patients, 31.0% stated that they mainly observed hypersensitivity and 27.0% of the physicians had patients who had toxicity following this treatment.

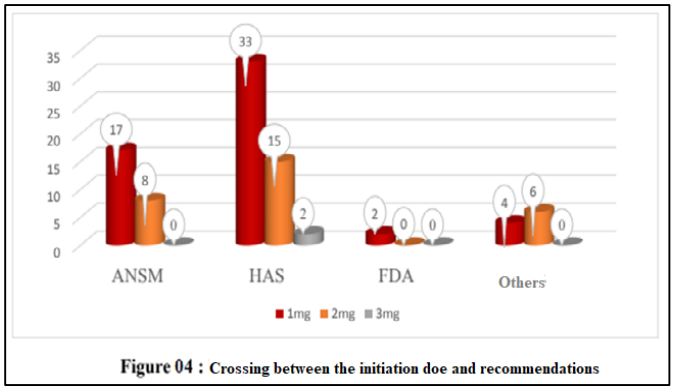

Figure 04 : Crossing between the initiation doe and recommendations

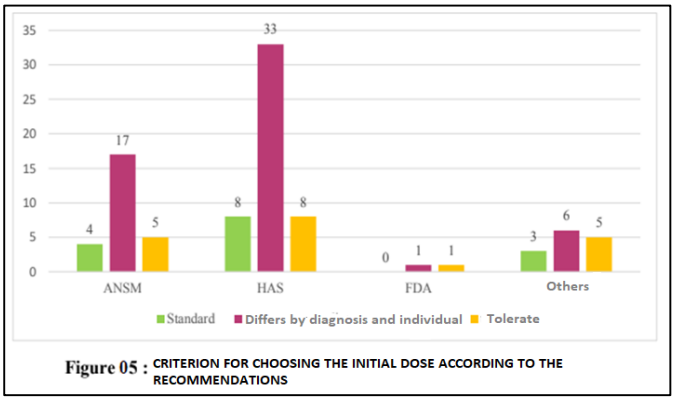

Figure 05 : CRITERION FOR CHOOSING THE INITIAL DOSE ACCORDING TO THE RECOMMENDATIONS

Attitude and expectation of healthcare professionals: According to current data, 07.9% of the participants suggested using pharmacogenetics tests in the medical practice to improve the dose adjustment of patients on acenocoumarol, 06.6% suggested monitoring the patient while proportion of 05.9% opted for therapeutic patient education. Almost half of the participants (48.0%) expressed their desire to apply pharmacogenetics tests in their clinical practice against 08.6% and a large majority of physicians (74.3%) wanted to do training course on the pharmacogenetics of acenocoumarol. Thus, a link between physicians' knowledge of pharmacogenetics tests, acenocoumarol dosage adjustment algorithms and the presence of the concept of genetic variability on the package leaflet and the desire to train on the latter is given in **Table IV**.

TABLE IV: Relationship between pharmacogenetics knowledge and pharmacogenetics training

Pharmacogenetics training	P
Knowledge of acenocoumarol dosage algorithms	0,642
Knowledge of pharmacogenetic testing for adapting dosage of acenocoumarol	0,321
presence of the notion of Pharmacogenetic in the instructions for acenocoumarol	0,522

Discussion

This study was marked by the significant participation of physicians from the EHU which is the site of the main study followed by the CHUO and to a lesser degree to other health structures with female predominance. The findings corroborate a Chinese study concerning the knowledge, attitude and practice of physicians toward anticoagulant treatment for non-carriers of the valve of atrial fibrillation of which female predominance [9]. The average age of physicians was 30.9 ± 1.2 years with 71.1% of physicians under 30 years old in line with previous studies [10 - 11]. 03.9% were over 45 years old, contrary to Ye et al. [9] where physicians were aged older. Most physicians surveyed were specialists in internal medicine then cardiology and general surgery. This agrees with the findings in Qatar where the physicians recruited were from internal medicine and cardiology [13]. The majority of physicians were residents followed by assistant physicians. This is because resident physicians are the most accessible and numerous physicians compared to other categories of practitioners which is in line with [13]. Almost all physicians had less than five years of experience as the majority were residents, unlike [9] whose recruited physicians had more than ten years of experience. Regarding an evaluation of the knowledge of health professionals, present data showed that most physicians know that acenocoumarol belongs to the AVKs class against a few who thought that this molecule is heparin or ADO. Though, no significant relationship was observed between knowledge of the class of acenocoumarol and the specialty. Physicians recruited knew that among the parameters used in the treatment monitoring, the combination of PT with INR occupied the first place, second with INR and third on three parameters INR, TQ and PT. Monitoring of acenocoumarol is based on the combination of the three parameters INR, TQ and PT at the same time which is essential for better management of treatment [11]. A small proportion of physicians who knew them testified to the lack of information and knowledge of physicians about this drug. Concerning knowledge of the frequency of control of these parameters, the

recommendations of the ANSM require that the first control must be carried out after the third intake of AVK (that is to say the morning of the fourth day). The second control is carried out according to the results of the first INR to assess anticoagulant efficacy (depending on the case between three and six days after the first control). Subsequent checks should be carried out once or twice a week until INR stabilizes, then a progressive spacing up to a maximum interval of one month [10]. This study showed that physicians have insufficient notions of the rhythm of monitoring the biological parameters of patients under acenocoumarol. When it comes to dose adjustment algorithms, most physicians said they are unaware of them. It is noted that even physicians who claimed to know them, the majority could not cite the dosing algorithm. Regarding pharmacogenetics tests, Most of the physicians participating in the survey did not know that pharmacogenetics tests for acenocoumarol are needed. The minority who knew them mentioned the INR and PT as genetic tests. This indicated that physicians have shortcomings in genetic testing and pharmacogenetics remains poorly understood in the healthcare structure [14]. These are similar to a study in the United States where there is a low use of pharmacogenetics testing and lacking information on pharmacogenetics testing [15]. However, others conducted in the United States between 2010 and 2013 reported a higher level of knowledge [12]. In addition, most physicians did not know whether the instructions for acenocoumarol contained the notion of genetic variability, contrary to a study in Kuwait [16] on the knowledge, perception and confidence of physicians and pharmacists towards the practice of pharmacogenetics. Where half of the physicians were aware that the package inserts for warfarin contained a warning of altered metabolism in some people with specific genetic variants. Little physicians questioned that pharmacogenetics assists in understanding of the variability of the pharmacological response and the prediction of the dose necessary to reach equilibrium. A few physicians affirmed that it made it possible to understand only the pharmacological variability and few agreed on the fact that it made it possible to avoid the appearance of adverse effects. The subjects of this survey were unaware of the great benefits that pharmacogenetics can bring to medical practice which demonstrates the need to educate physicians and inform them of its benefits, thus, the present data were inconsistent with other studies. A study conducted in Ethiopia on the knowledge of health professionals, their attitudes and interest towards pharmacogenetics showed most of the participants are aware of its importance in various fields of clinical practice [5]. This is in line with assessing the knowledge of pharmacogenetics by healthcare professionals [10, 17].

Data from medical practice concerning acenocoumarol showed a majority of physicians prescribed anticoagulants. This is similar to data in Saudi Arabia on the evaluation of the knowledge and attitude of physicians regarding the use of oral anticoagulants in patients with atrial fibrillation, of which the majority of the participants prescribed anticoagulants [11]. The prescription of acenocoumarol was significantly associated with the physician specialty. This can be explained by the fact that the use of acenocoumarol is more important than in specialties dealing with thromboembolic diseases, specifically cardiology and internal medicine. It is noticed that more than half of physicians initiate treatment with a dose of one mg followed by two mg. An Indian study, based on physician's knowledge and practice of oral anticoagulant therapy showed more than half of the participants said the initial dose of acenocoumarol was two mg [14]. With ANSM recommendations, the initial dose is conclusive and should be as close as possible to the equilibrium dose [9]. As for the question concerning the criteria for choosing the initiation dose, more than half of physicians affirmed that the dose differed according to diagnosis and individual. Due to significant interindividual variability, the dosage of acenocoumarol is strictly individual, it must be adapted according to the biological results [18]. A study on the knowledge of physicians and patients about oral anticoagulants showed that almost all of the physicians do not have correct knowledge of the

corresponding dose of warfarin [14]. There was a significant relationship between the initiation dose and its difference according to the individual and the diagnosis. More than half of physicians said they only use INR and PT for monitoring their patients in their medical practice. Few said they used three parameters INR, PT and TQ, we noticed that physicians do not use TQ contrary to the literature requirements. A significant relationship between knowledge of acenocoumarol monitoring parameters and application in medical practice was found. For frequency of measurement of these assessments, about a third of the physicians carried out the control on the second day after the start of treatment or modification of dosage and 05.0% on the fourth day of treatment. To international recommendations (ANSM, HAS, FDA, SFC, ESC, etc.), the control must be carried out on the fourth day after taking acenocoumarol to detect individual hypersensitivity: INR greater than two announces an overdose of acenocoumarol. After a change in dosage, the first control must be done three days after change in dose; the controls must be repeated until stabilization according to recommendations of the ANSM [9]. In practice, the balance of the treatment is sometimes obtained only after several weeks. All physicians observed adverse effects in patients with INR outside the range: hemorrhage was the most frequently observed effect who especially observed thrombosis which is similar to that in India [14]. Another study was conducted on exploring the obstacles to optimal anticoagulation for atrial fibrillation [19] in the United States where the main concern of physicians regarding VKAs is the risk of bleeding. VKAs are medication accidents in France, because of hemorrhagic complications. In 1998, according to a survey by the network of Regional Pharmacovigilance Centers, hemorrhagic accidents linked to VKAs were the highest rate of hospitalization for iatrogenic effects [20].

About the modalities of dose adjustment of acenocoumarol, it is observed heterogeneity in terms of dose adjustment. For recommendations used in the dose adjustment, there is a discrepancy in the adoption of the prescription guidelines and dose adjustment of acenocoumarol, hence a need to harmonize the prescription guidelines. Present data are consistent with a survey conducted on the evaluation of the management of overdose and bleeding with VKAs in the emergency department of the University Hospital of Nancy where HAS recommendations are known [21]. Data showed the absence of a significant relationship between recommendations used and the initiation dose and with criteria also for choosing the initiation dose. Regarding response variations of acenocoumarol, half of the physicians observed resistance in their patients while fewer declared they observed hypersensitivity. Various factors may be at the origin of these variations, among other genetic factors, playing a primordial and obvious role in these variations, in particular, the CYP2C9*2 and *3 polymorphism and the VKORC1 polymorphism justifying the establishment of these genetic tests in the handling of AVK treatment. The current study is interested in the means of improving dosage adjustment of acenocoumarol proposed by physicians and found that despite the lack of knowledge on the pharmacogenetics by physicians, many of them suggested means to improve patient dose adjustment. Almost half of the participants expressed a desire for pharmacogenetics tests in clinical practice against the third who were reluctant. What remains a positive attitude about pharmacogenetics, demonstrates that some physicians are aware of the relevance of pharmacogenetics and the great benefits it can bring to their daily practice. According to a survey conducted in Ethiopia, all the participants showed a positive attitude. For example, all healthcare professionals believed that pharmacogenetic testing could help reduce the adverse effects of drug treatments and agreed that such testing would optimize drug dosing and improve drug efficacy [5]. Interestingly, most of the participants were in favor of carrying out training on pharmacogenetics of acenocoumarol, this proves that a new concept has caught their attention and they hope to know more about it. No major relationship was detected between the wish to follow training on pharmacogenetics and dose adaptation algorithms used, knowledge of pharmacogenetic tests and the notion of genetic variability on the leaflet.

Conclusion: Knowledge of Algerian health professionals on essential notions indicating direct impact on beneficial optimization of acenocoumarol as monitoring parameters and frequency. This study highlights shortcomings in the practice of managing acenocoumarol treatment: discrepancy in the best dose for treatment initiations and absence of standard dose adjustment algorithms. In addition, the discrepancy in the prescription reference systems adopted at the level of the various services of health structures of Wilaya of Oran and the absence of notions of pharmacogenetics testing. Thus, it would be essential to develop and implement an education program for health professionals to deepen their knowledge of pharmacogenetics and its impact on daily medical practice to secure pharmaceutical care.

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Author contribution: SA conceived and designed the study. FH & BF collected, contributed in analysis and interpretation of data. All authors have drafted and revised the manuscript as well as approved the final version of the manuscript and agreed to be accountable for its contents.
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Ethical issues: Including plagiarism, informed consent, data fabrication or falsification and double publication or submission have completely been observed by authors.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Author declarations: The authors confirm that all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals have been obtained.

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