Les facteurs associés à la qualité de l'anticoagulation chez les patients sous antivitamines K en Tunisie

Factors associated to adequate time in therapeutic range with oral vitamin K antagonists in Tunisia

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RÉSUMÉ

Introduction: La qualité de l'anticoagulation chronique et les facteurs prédictifs d'un niveau d'anticoagulation inadéquat chez les patients sous acénocoumarol n'est pas connu en Afrique du Nord.

Méthodes: Il s'agit d'une étude observationnelle réalisée entre novembre 2015 et le 30 novembre 2016. Les INR (International Normalized Ratio) ont été obtenus prospectivement et le TTR a été calculé selon la méthode Rosendaal.

Résultats: 215 patients ont été inclus dans cette étude, avec un âge moyen de 63 ± 0,8 ans. La prévalence d'une qualité anticoagulation inadéquate était de 78,1%; IC à 95% [72,2-83,2] (168 patients avec un TTR inférieur à 65%). Le TTR médian avec la méthode de Rosendaal était de 44,4%. Après ajustement multivarié, les variables associées à un niveau d'anticoagulation adéquat étaient: antécédents d'accédant vasculaire cérébral ischémique (OR ajusté égal à 4,3, IC 95%: 1,4-12,9), la prescription associée de traitement antiplaquettaire (OR ajusté égal à 3,5, IC à 95%: 1,1 -11,2), une dose journalière prescrite de coumarines inférieure à 6 mg (OR ajusté égal à 6,4, IC à 95%: 1,1-36) et un faible risque hémorragique évalué par le score HAS-BLED (OR ajusté: 0,5, IC à 95%: 0,3 -0,8).

Conclusion: La qualité de l'anticoagulation chronique sous acénocoumarol était sous-optimale. Les cliniciens et les patients devraient adopter des stratégies pour améliorer la qualité de l'anticoagulation et lutter contre les complications de l'anticoagulation chronique.

Mots-clés

Acenocoumarol; Temps dans la marge thérapeutique; Anticoagulation

SUMMARY

Introduction: The quality of chronic anticoagulation and predictor factors of poor anticoagulant control in patients under acenocoumarol were unknown in North Africa.

Methods: It is an observational study, carried out between November 2015 and November 30, 2016. The international normalized ratio (INR) values were prospectively obtained, and TTR was calculated using the Rosendaal method.

Results: Overall, 215 patients were included in this study, with a mean age of 63±0,8 years. The prevalence of poor anticoagulation control was 78.1%; 95% CI [72.2-83.2] (168 patients with TTR less than 65%). The median TTR with the Rosendaal method was 44.4%. After multivariate adjustment, variables significantly associated with adequate anticoagulation level were: history of ischemic stroke (Adjusted OR equal to 4.3, 95% CI: 1.4-12.9), associated prescription of antiplatelet therapy (Adjusted OR equal to 3.5, 95% CI: 1.1-11.2), daily prescribed dose of coumarins less than 6 mg (Adjusted OR equal to 6.4, 95% CI: 1.1- 36) and lower risk of bleeding assessed as HAS-BLED score (Adjusted OR: 0.5, 95% CI: 0.3-0.8).

Conclusion: The quality of anticoagulation management with VKA among outpatients who received acenocoumarol was suboptimal. Strategies should be undertaken by clinicians and patients to improve the quality of anticoagulation, to address challenges to adverse cardiovascular outcomes in individuals treated with chronic anticoagulation.

Key-words

Acenocoumarol, time in therapeutic range, anticoagulation

INTRODUCTION

Vitamin K antagonists (VKAs) remain the main therapeutic agents used to prevent thromboembolism in the world. Their efficiency and safety have been proved in multiple disease settings (1). However, VKAs have several limitations, including a narrow therapeutic window and numerous drug and dietary interactions. Maintaining therapeutic range in patients treated with VKAs has always been challenging and the potential consequences of deviating from the therapeutic range are deleterious. (2-6) Despite the many complexities associated with the use of VKAs, it remains a mainstay of anticoagulation therapy. Acenocoumarol, a derivative of coumarin, is the most VKAs used in Tunisia and preferentially used in some countries.

Although not easily achieved, high anticoagulation control, expressed as the time spent within the therapeutic range (TTR), has a paramount effect on patient outcomes, reducing stroke events and mortality rate (7). Time in therapeutic range (TTR), is a way of summarizing INR control over time, is mainly calculated according to F.R. Roosendaal's algorithm with linear interpolation (8).

It is important to keep in mind that real-world patient populations are more complex than those in controlled studies, with multiple comorbidities. Numerous registries and surveys have been described in Europe, Asia, North and South America but no data on the quality of anticoagulation control achieved in patients receiving routine medical care is available in North Africa.

Literature review reveals poor quality of anticoagulation control with VKAs, especially in developing countries where the lack of an efficient communication physician-patient, the lack of adherence to the prescribed treatment and the lack of continuous surveillance and educational support, are key factors missing. (9)

In Tunisian health care facilities, no published data in this concern are available and the adherence level of outpatients to their oral VKAs prophylactic treatment is completely unknown.

Therefore, we conducted this study in one of the most frequently visited university hospital in Tunisia, located in Tunis the capital city, to assess the prevalence and predictor factors of poor anticoagulant control in patients under VKAs prophylactic treatment, prescribed for different indications, in order to generate targeted recommendations and to improve the quality of oral anticoagulation in our department.

METHODS

Study design and population

It is an observational study, carried out in the cardiology department of La Rabta university Hospital in Tunisia, between November 2015 and November 30, 2016.

Were included outpatients (age ≥ 18 years old), followed in the daily specific INR- consultation in our department, who received uninterrupted oral VKAs (coumarins) for at least 6 months with more than four documented measures of INR separated by 60 days at least.

For these patients, coumarins were prescribed for one or more of these indications: valvular and non-valvular atrial fibrillation (AF), prosthetic heart valves, deep vein thrombosis and pulmonary embolism.

Patients with communication problems and/ or patients with mental disorder, who were not able to answer different items of the questionnaire, were not included.

Socio-demographic characteristics (age, gender, educational level) and baseline clinical characteristics including the main indication of prescription of VKAs, the medical history, the onset date of oral VKAs use, were collected for all enrolled patients. For patients with non valvular AF, stroke and hemorrhagic risks were evaluated respectively using CHA2DS2-VASc score (10) and HAS-BLED scores (11). The SAMe-TT2R2 score was also calculated in non valvular AF patients to predict which patients on oral anticoagulation with vitamin K antagonists (VKAs) will reach an adequate time in therapeutic range (TTR) (> 65%). (12)

The INR target for atrial fibrillation, deep vein thrombosis, pulmonary embolism, was 2–3. INR target for mechanical valve replacement in aortic position was 2.5–3.5. Whereas INR target of 3–4.5 was used for mechanical valve replacement in mitral position, and for dual aortic and mitral mechanical valve replacement.

Quality of Anticoagulation

For each patient, the periodic INR testing was reported in every consultation during the study period. The estimated time spent in the TTR was assessed by the Rosendaal method which is a linear interpolation to assign an INR value to each day between successive observed INR values (8). Poor anticoagulation control was defined as an estimated TTR ≤ 65%.[6;13;14] We used this cutoff based on ACTIVE W trial (6) and two reviews, that indicated a TTR close to 66% was a benchmark for high-quality anticoagulation.(13;14)

Data entry and Statistical Analysis

Data entry and all statistical analyses were performed using SPSS software version 20.0. A 2- sided P value of <0.05 was considered to be significant for all analyses. Quantitative variables showing normal distribution with Kolmogorov Smirnov test were presented as mean ± standard deviation (SD). Categorical variables were presented as proportions (percentages) with a 95% confidence interval (95% CI) calculated with Open Epi software. Baseline characteristics were compared between patients with adequate (TTR > 65%) and inadequate (TTR ≤ 65%) using the Pearson chi-square test (χ^2) for categorical variables and the Student's t test for quantitative variables. Logistic regression analyses were performed for multivariate adjustment, including variables with recognized clinical relevance with VKA control and those with a P value <0.2 in univariate analysis. Results are presented as adjusted odds ratios (ORa) with its 95% confidence intervals (95% CI).

Ethical considerations

Since it is an observational and not an interventional study, no requirement to be approved by the ethical committee of our university hospital. Besides, we opted not inform patients about this follow-up in the beginning of the study, to avoid any observational bias that could underestimate the poor adherence to VKAs anticoagulation (15). At the end of the study period, patients were contacted and informed about the study aim, and their oral consent was obtained to use these data for this work.

RESULTS

Study population characteristics

Overall, 215 patients were included in this study, with a mean age of 63±0,8 years (Min 27, Max 93) and a sex-ratio F/M equal to 1.4. Clinical characteristics are depicted in Table 1.

Adherence level to oral anticoagulation with coumarins

The prevalence of poor anticoagulation control was 78.1%; 95%CI [72.2-83.2] (168 patients with TTR less than 65%). The median TTR with the Rosendaal method was 44.4%, Inter quartile Range IQR (33.3%-60%). None of the INR values were within range in 1.4% of the sample and only 4.4% had all their INR measurements within the therapeutic range.

Table 1: Patients' characteristics

Variable	
Patients (n)	215
Age (years± SD)	63±0.8
Male gender (n, %)	87 (40.5)
Education level (%)	
illiterate	49.7
Primary school	36.2
Secondary school	13.2
University degree	0.7
Hypertension (n, %)	93 (43.4)
Diabetes (n, %)	40 (18.6)
Dyslipidemia (n, %)	40 (18.6)
Smoking (n, %)	43 (20)
History of ischemic stroke (n, %)	49 (22.9)
History of haemorrhagic stroke (n, %)	45 (21)
History of coronary heart disease (n, %)	21 (9.8)
History of cardiac failure (n, %)	47 (23.5)
History of renal failure (n, %)	15 (7)
Indication for coumarins (n, %)	
AF*	107 (49.8)
Mechanical valve prosthesis	33 (15.3)
AF* + Mechanical valve prosthesis	62 (28.8)
Others	13 (6)
Duration under coumarins (years±SD)	6±9.7
Association of antiplatelet therapy (n, %)	35 (16.4)
Daily dose of coumarins ≥ 6 mg (n, %)	43 (20)
More than 3 drugs (n, %)	72 (35.1)
AF scores**	
CHAD2S2-VASC (embolic risk)	3±0.13
HAS-BLED (bleeding risk)	1.6 ±0.08
SAME TTR	2.1±0.07

* Atrial fibrillation
** were calculated only for patients with non valvular Atrial fibrillation

Predictive factors for obtaining a correct time in therapeutic range

Unadjusted analyses depicted in Table 2 revealed higher control levels for patients with no mechanical valve prosthesis (69.2% TTR ≥ 65% Vs 52.9% TTR < 65%; non adjusted OR equal to 2.1 CI 95% [1.1 – 3.9]) and for patients receiving daily dose of coumarins less than 6 mg (91.5%

Table 2: Predictive factors for obtaining a correct therapeutic range for patients under coumarins (Univariable analysis)

Variable	Group 1 (TTR ≤ 65%)	Group 2 (TTR > 65%)	P-value
Age (years±sd)	62.5±1.2	60.9±1.4	0.4
Male gender (%)	42.3	34	0.2
Education level – higher education (%)	64.9	74.5	0.1
Hypertension (%)	41.7	48.9	0.6
Dyslipidemia (%)	17.3	23.4	0.4
Diabetes mellitus (%)	18.5	19.1	0.7
Smoking (%)	20.8	17	0.2
History of ischemic stroke (%)	20.8	30.4	0.1
History of hemorrhagic stroke (%)	22.8	14.9	0.2
Presence of mechanical valve prosthesis (%)	47.1	30.8	**0.04**
Daily prescribed dose < 6 mg	76.8	91.5	**0.01**
Associated antiplatelet therapy (%)	14.5	23.4	0.1
Duration under coumarins (years)	21±12.4	8±0.9	0.3
More than 3 drugs under use	32.7	43.5	0.1
CHA2DS2-VASC risk score*	2.9±0.2	2.8±0.1	0.9
HAS-BLED risk score *	1.7±0.1	1.4±0.1	0.1
SAME TTR score*	2.11±0.1	2.13±0.09	0.8

· Calculated only in non valvular atrial fibrillation

TTR ≥65% Vs 76.8 % TTR <65%; non adjusted OR equal to 3.5 CI 95% [1.2 – 10.5]). None of cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, and smoking) or poly medication was significantly associated with higher control level.

For patients with non valvular AF, none of CHAD2S2-VASC score, HAS-BLED score or SAMe-TT2R2 score was significantly associated with higher control levels.

After multivariate adjustment (Table 3), variables significantly associated with adequate anticoagulation level were: history of ischemic stroke (Adjusted OR equal to 4.3, 95% CI: 1.4-12.9), associated prescription of antiplatelet therapy (Adjusted OR equal to 3.5, 95% CI: 1.1-11.2), daily prescribed dose of coumarins less than 6 mg (Adjusted OR equal to 6.4, 95% CI: 1.1- 36) and lower risk of bleeding assessed as HAS-BLED score (Adjusted OR: 0.5, 95% CI: 0.3-0.8).

DISCUSSION

The current study is unique from North African region that assesses the quality of anticoagulant therapy in patients receiving a long term acenocoumarol, using the method of Rosendaal et al.(8) Our study identified factors associated with adequate anticoagulation level in patients on chronic VKA. To assess the quality of acenocoumarol therapy, TTR value of 65% was used to assess the efficiency anticoagulation control. The quality of anticoagulation assessed in Tunisian patients under AVK was suboptimal as the prevalence of poor anticoagulation control was 78.1%. The median TTR with the Rosendaal method was 44.4%, Inter quartile Range IQR (33.3%-60%). After multivariate adjustment variables significantly associated with adequate anticoagulation level were history of

Table 3: Predictive factors for obtaining a correct time in therapeutic range for patients under coumarins (Multivariable analysis)

Variable	P-value	Adjusted OR*	95% CI**
History of ischemic stroke	0.009	4.3	[1.4 - 12.9]
HAS-BLED risk score	0.013	0.5	[0.3 - 0.8]
Associated antiplatelet therapy	0.030	3.5	[1.1 - 11.2]
Prescribed dose < 6 mg/day	0.035	6.4	[1.1 - 36]
Smoking	0.2	0.4	[0.1 - 1.6]
More than 3 drugs under use	0.2	1.8	[0.6 - 4.8]
Presence of mechanical valve prosthesis	0.2	0.4	[0.1 - 1.8]
History of hemorrhagic stroke	0.7	0.8	[0.2 - 2.9]
Male gender	0.8	0.9	[0.3 - 2.7]
Education level – higher education	0.8	1.1	[0.4 - 2.7]

*Adjusted Odds-ratio
** 95% Confidence Interval

ischemic stroke, associated prescription of antiplatelet therapy, daily prescribed dose of coumarins less than 6 mg and lower risk of bleeding assessed as HAS-BLED score.

The TTR obtained in the present study was suboptimal as the results documented in other studies (16-21). These anticoagulation reports from Africa [16;21], Korea [20], North America (17;18) Saudi Arabia (20) were relatively poor outcomes when compared to a similar study in Europe in which Maeder et al reported a median TTR of 69% (51–89%), and TTR ≥65% in 61% of patients in Eastern Switzerland (22).

A wide variation between countries in the success of maintaining the INR of patients with AF in the therapeutic range , have been demonstrated by Connelly et al (6) and Van Spall et al (4), respectively in the ACTIVE W and RELY trials. Mean TTR varied between countries from 46% to 78%. A lower mean TTR were identified in South Africa and Brazil. A higher mean value were showed in United Kingdom and Sweden (6). A wide variation exists among physician practices, hospitals, and healthcare systems in quality of anticoagulation control (6; 7). In RELY study; Van Spall et al (4) have demonstrated considerable regional variation in both TTR and the percentage of algorithm-consistent warfarin dosing decisions. Only 55 of 6022 included patients were African. The mean (SD) TTR ranged from a low of 54 (21) % in East Asia to 73 (15) % in North Europe. Mean (SD) percentage of algorithm-consistent warfarin dose changes ranged from a low of 55 (21) % in East Asia to 68 (17) % in North Europe.

In the studies reported above in the discussion, warfarine was the used molecule to anticoagulate patients. However, in this study, acenocoumarol was the unique VKA used. A shorter half-life of acenocoumarol compared to warfarin may result on a poor quality of anticoagulation control. (23; 24)

Recently; Bryk AH et al (25), have showed a similar quality of anticoagulation assessed by TTR in AF patients on acenocoumarol as compared to warfarin (66.5 ± 14.3 vs 66.7 ± 13.3, p= 0,09) in a Brazilian population.

In this study; the potential reasons for low TTR might be: low educational and socioeconomic level of our population, prolonged duration of INR monitoring due to patient load, lack of time to well communicate information about benefits of coumarins and risks of poor anticoagulation, absence of a standard protocol for acenocoumarol therapy management and lack of an anticoagulation clinic at the studied hospital.

Level of patient education and lack of time to well communicate information about benefits of coumarins and risks of poor anticoagulation may affect the anticoagulation level. Lack of knowledge about food and drug interactions, and lack of knowledge about the appropriate therapeutic range are explanations for inadequate level of anticoagulation, as 49,7% of our population study are illiterate. We believe that patient education during clinic visits is an essential part of the management. One can argue that nonadherence, and lack of knowledge about narrow therapeutic window and numerous drug and dietary interactions, may be a major contributing factor for lower TTR readings in our patients.[26] In a busy clinic, time assigned for each patient may hinder patient education.

A previous study showed that limited health literacy is associated with poor anticoagulation control for patients on warfarin therapy (27-29). Lack of medication understanding may hinder the safe and effective use of this narrow therapeutic index drug. Being unaware of a medical diagnosis, such as AF, can be problematic as it likely implies a lack of understanding of the health risks that are associated with the diagnosis and potential therapeutic options that may lead to an increase in overall risk of morbidity, mortality, and cost of care. (30)

Martins et al (29) showed that inadequate health literacy was highly prevalent in a cohort of 422 impoverished Brazilians receiving anticoagulation with warfarin. No association between health literacy and percentage of time in therapeutic range was demonstrated. They postulated that high-quality anticoagulation clinics may contribute to overcome the identified disadvantages of inadequate health literacy. (31)

Three primary factors have been reported to be associated with patient nonadherence to anticoagulation medication, including patient's perception and knowledge about its purpose, their understanding of both the risks and benefits associated with the use of anticoagulants, and their socioeconomic status. (32)

Paper-based and/or computerized software models of acenoucoumarol-dosing protocols, use of point of care testing, anticoagulation management services with dedicated personnel (i.e. anticoagulation clinics), self-management patients trained by e-learning or by group training (eHealth programme) are recommended tools to provide a systematic approach to improve anticoagulation management services. (33)

An opposite finding was showed in a recent review by Clarkesmith et al. (34) They have demonstrated that there is insufficient evidence to draw definitive conclusions regarding the impact of educational or behavioral interventions on TTR in AF patients receiving oral anticoagulant therapy. Thus, more trials are needed to examine the impact of interventions on anticoagulation control in AF patients and the mechanisms by which they are successful. It is also important to explore the psychological implications for patients suffering from this long-term chronic condition.

The low TTR might be also due to less frequent monitoring (1INR within 63 days) (16). TTR can be increased with more frequent INR monitoring (35).

Different patient characteristics are possible reasons for discrepant control levels. Poor control has been reported among populations affected by com

orbidities (17; 18; 36). In our study, we analyze individual comorbid condition as reason for poor control but we did not found significant association between the level of anticoagulation and the majority comorbidities or CHAD2S2-VASC score. Only a history of ischemic stroke was associated with adequate level of anticoagulation. It is extremely important to keep optimal TTR in these patients to ovoid stroke recurrences (2-6).

In Fantasia trial, Patients with TTR < 70% had more prevalent cardiovascular risk factors, e.g. diabetes, chronic kidney disease, or peripheral artery disease (all P < 0.05) as well as a low level of education (P = 0.019). Patients with TTR < 70% had higher mean CHA2DS2-VASc (3.8± 1.6 vs. 3.6± 1.6; P=0.014) and HAS-BLED scores (2.1± 1.1 vs. 1.9± 1.0; P= 0.002), respectively (36).

Patients with daily prescribed dose of coumarins more than 6 mg and higher risk of bleeding assessed as HAS-BLED score have poor level of anticoagulation. These patients are under anticoagulated, may be to reduce bleeding risk perceived as high by the clinician.

Patients with high daily prescribed dose of coumarins (> 6 mg) may have genetic factors associated with resistance to anticoagulation and consequently to a poor anticoagulation level.(37;38)

Contribution of genetic factors to the level of anticoagulation was not evaluated in this study.

Surprisingly; prescription of antiplatelet therapy was associated with adequate anticoagulation level.

In various independent cohorts, the SAMe-TT2R2 score has shown good capacity to discriminate patients with a good TTR (≥ 65–70%;) a SAMe-TT2R2 score of .2 is associated with a poor TTR, and as these patients are exposed to more thromboembolism and bleeding, intense efforts to improve TTR by education or choosing a direct oral anticoagulant (DAO) would be better initial options. (39)

In our study, the SAMe-TT2R2 score cannot predict the anticoagulation quality.

The only VKA assessed by Apostolakis et al. (12) was warfarin. The capacity of SAMe-TT2R2 to discriminate patients with a good TTR on acenocoumarol has not been largely validated.

The SAMe-TT2R2 score has been demonstrated to have a modest ability of predicting stable anticoagulation control in patients treated with acenocoumarol (40).

Recently Bryk AH et al (24) have compared the predictive ability of SAMe-TT2R2 score in AF patients treated with acenocoumarol versus warfarin on a long-term basis. This study showed that common and clinical risk factors incorporated in the SAMe-TT2R2 score are less effective in predicting unstable anticoagulation in AF patients on acenocoumarol as compared to warfarin.

Analysis of TTR showed that an important percentage of patients exhibit, on average, suboptimal quality of anticoagulation. Managing anticoagulation outside of a clinical trial or anticoagulation clinic is associated with poorer INR control as is initiation of therapy in patients who are VKA-naïve. (7)

These results should contribute to improve our clinical practice Tajer C et al (41) proposed action on both institutional and individual levels. Creation dedicated anticoagulation clinics with establishing treatment algorithms. Algorithms to establish how frequently patients should attend control visits and how VKA doses should be changed influence TTR levels (4). Patient education either using e learning or group training should performed to reduce health literacy and to obtain adequate adherence to VKA. More frequent controls might be an alternative for these unstable patients to ensure a higher TTR. Patients with inadequate control of INR levels, despite adequate adherence to VKA treatment should be switched to direct oral anticoagulants (DOA) agents. In our National healthcare system, like the majority of North African healthcare systems,choosing a DOA would be better initial option, however limited by economic and financial issues.

The present study has a number of limitations. First, the number of patients was relatively small and based on certain inclusion criteria (e.g., availability of four or more INR). While we attempted to include as many clinic patients as possible, we do recognize the possibility of selection bias. Participants with greater comorbidities and disability, and potentially those with lower health literacy, may have been less likely to had opportunities for enrolment. Likewise, we do not have information on individuals who were candidates for anticoagulation but not enrolled in our department, regardless of health literacy level. Second, the observation period was relatively short. A recent study has shown that patients with a stable INR in the therapeutic range over a certain period will not necessarily maintain this good INR control in the coming months (42). Thus, TTR needs to be assessed repeatedly during long-term VKA therapy to make sure that treatment is effective and safe.

Third, patient compliance would have been a key variable in the present study setting. Unfortunately, there was no information on compliance. Finally, our study was performed in one single institution in Tunisia, and thus findings cannot automatically be applied for entire Tunisia. The generalizability of our study to higher socioeconomic cohorts, or across other Tunisian regions or to other North African nations remains unknown.

Finally, while we sought to include relevant sociodemographic and clinical measures, we expect there was residual confounding from variables, such as social determinants of health and genetic factors that were not collected in this investigation.

CONCLUSION

To our knowledge, this is the first study examining the quality of anticoagulation in North Africa. This study provides important information about quality of chronic anticoagulation control of patients on acenocoumarol, who receive medical care within a large tertiary care hospital in Tunisia and provide an important and novel benchmark for patient anticoagulated in this middle-income country. It can be concluded that the quality of anticoagulation management with VKAs among outpatients who received acenocoumarol was suboptimal. This was reflected by low TTR.

Critical urgent next steps are to create specific anticoagulation clinics with establishing treatment algorithms and improving acenocoumarol-specific education in order to address challenges to adverse cardiovascular outcomes in individuals treated with anticoagulation.

Competing interests

The authors declare no competing interest

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