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Anticoagulation Quality Control in Primary Care with Vitamin K Antagonist

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Abstract

Introduction: Efficiency and safety of the treatment with oral anticoagulants are determined by the time that is kept in therapeutic range. Below the range, the efficiency is low or void, and when it exceeds the haemorrhagic risk is increased. There are different methods to value the quality control of anticoagulation. **Objectives:** To determine quality control of the anticoagulation in our area and if the different methods of control are comparable to Rosendaal. **Material and method:** A retrospective observational study of all the anticoagulated patients in our area (n=252). The variables considered were all INR values ("International Normalized Reason") and their respective dates, estimating the time in therapeutic range (TTR) by Rosendaal method, according to the fraction of INR in range, the average of all the INR and the cross-sectional analysis (last INR registered). We considered as "ideal control" if the TTR was >65% or if percentage of INR's determinations in range was >60%, during follow-up period of at least 6 months. **Results:** We realized 3.870 controls, in range 2.078 (53.70%). Average TTR was 64.30%, average INR in range: 89.68% and the percentage of patients with INR's last value in range: 67.86%. Patients with >60% of the INR in range: 41.27%. Patients with TTR>65%: 49.6%. **Conclusions:** One in every 2 anticoagulated patients does not get the minimal time recommended in therapeutic range to have the benefit from the anticoagulation. The fraction of total INR in range is the most nearly method to Rosendaal for a TTR ≥ 65. The last INR and the average value of the INR both overestimate the quality control.

Keywords: Quality control; Anticoagulants; International normalized ratio; Primary care; Rosendaal method

Introduction

The atrial fibrillation, valvular heart disease and the thromboembolic disease are responsible for an important morbidity and mortality in Western countries [1], therefore the prevention of its complications should be a priority objective of the health system.

The oral anticoagulants (OAC), vitamin K antagonists (warfarin and acenocoumarol) [2], used with remarkable success since more than 60 years ago to prevent thromboembolic disease; its narrow therapeutic margin and their many interactions both pharmacological as food make patients in treatment with OAC must be subjected to frequent checks of the prothrombin time, to determine that their INR (International Normalized Ratio) is kept in the proper range, which ensures a proper anticoagulation, minimizing the risk of bleeding [3].

Approximately between 0.7% and 1.8% of the Spanish population uses OAC [4,5]. At the beginning, due to the peculiarity of its management, the indication of treatment and follow-up of the patients was assumed by the haematology services, but today there are different organizational models [4,6-8]. At the hospital level, in Primary Care (PC), or mixed models. The use of the laptops coagulometres [9] improved accessibility in the models of control in PC and mixed, and even in some cases allowed the self-control of the own patient [10]. Currently, the monitoring model in PC [11] in our country reaches more than 72% [12].

therapeutic range, since the whole period which is below its range the effectiveness anticoagulant is low or zero and when it exceeds significantly increases the risk of bleeding. As to which method of measurement used to identify the patient that is properly anticoagulated there are several proposals: The percentage of determinations of INR in therapeutic range is a simple method to measure the quality of the control. However, has the disadvantage that the patients with more revisions, which are usually those who have more measurements outside of range, are most represented, so that this indicator tends to underestimate the degree of control [13]. In 1990, the International Society of Thrombosis and Hemostasia proposed another method of control: The cross-sectional analysis [14]. Choose a point in time and evaluates the last INR of each patient. In this way do not overstate the patients more revised. This method has the advantage of its simplicity and its calculation facility, but it has the disadvantage of assuming that a single point in time is representative of the rest, without taking into account the number of days within or out of range [13]. The British Committee for Standardization in haematology, in 2011, recommended to use the time in therapeutic range of Rosendaal (TTR) as an indicator of quality of control [15]; this method, calculates the proportion of time with an INR within the therapeutic range, assuming that between 2

consecutive tests the increase or decrease of the INR has a linear behavior [16].

To know the degree of control of the anticoagulation in our environment is important to consider improvement measures if necessary, and also to estimate the possibility of recommending the "new oral anticoagulants" or direct anticoagulants (DOAC), which do not require controls or dose modification to achieve its antithrombotic effect; as the evil control is one of the most important factors when devising them [17]. The value of the TTR that would define "good control" varies according to the different authors as might be established between the 45-50% [18,19], 60% [20-23], between 60 and 65% [24,25], or greater than 65% [17].

The present work seeks to know the degree of control of our anticoagulated patients, followed entirely in PC in conditions of habitual clinical practice, using the Rosendaal method, the total percentage of determinations of INR, the transversal analysis (last INR) and the average value of the INR of last year.

Material and Methods

Observational study of a year of follow-up, with retrospective data gathered, through the clinical history computerized, in terms of habitual clinical practice.

Our influence area has 2 medical clinics and serves an urban population of 18.481 older than 14 years; we assessed all patients anticoagulation with warfarin or acenocoumarol of our area (n=307) regardless of the pathology that would lead to the treatment, the OAC prescribed and of the various ranges therapeutic indicated. To assess only to patients with a continued monitoring, we excluded those who have made less than 3 determinations of the INR during the study phase, and to those with a period>90 days between 2 determinations, as well as patients who were controlled exclusively at the hospital level (n=55). Therefore, of the 307 initial patients we selected a total sample of 252 patients valid for the study (Figure 1).

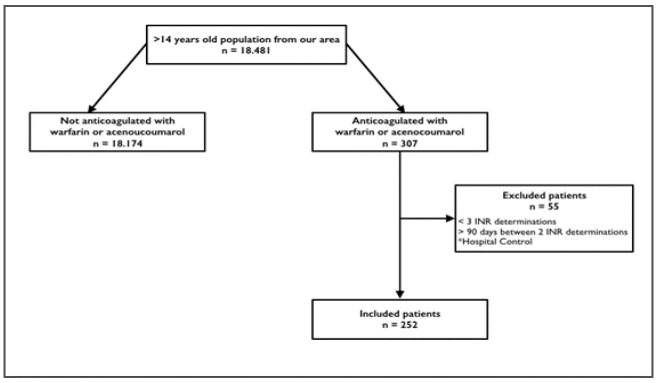

Figure 1: Selection of anticoagulated patients.

Although the criteria which determine that a patient has already exceeded the initial phase of pre-emption of dosage of treatment are highly variable (1-3 months or 3-5 controls) [20, 26,27], we take the view that in the 3 months prior to the start of the study to have at least 3 results of INR. Otherwise, it was assumed that it was a beginning of treatment, and excluded the first 3 controls, which are those that usually serve as reference to reach an acceptable control.

To evaluate the effectiveness of treatment was taken as reference the value of the INR, estimating the ranges of anticoagulation optimal for each patient depending on the primary pathology: for example, non valvular atrial fibrillation: 2-3; valvular atrial fibrillation: 2.5-3.5; thrombosis under anticoagulation: 2.5-3.5, etc. [3]. Therefore, to include patients with different pathologies, we can summarize by saying that our range of INR optimal ranged between 2 and 3.5, depending on the pathology that induced anticoagulation.

For each patient we obtained all the INR values registered with their respective dates, obtained in capillary blood by means of laptops coagulometre (CoaguChek1 S, Roche Diagnostics). Included socio-demographic variables (sex, age of the patients, treatment time with the OAC, indication, dose, type of OAC, number of INR determinations made and range of INR recommended), and associated comorbidities: arterial hypertension (HTA), diabetes mellitus (DM), dyslipidaemia (DL), heart failure (HF), COPD, hypothyroidism, dementia and depression.

The quality of the monitoring of follow-up of the OAC, main study variable, was measured using 4 different methods [13]: The TTR or Rosendaal method, which assumes an increase or decrease linear between 2 consecutive measurements of the INR [16]; the percentage of total INR in therapeutic range; the average value of all of the INR of each patient and the cross-sectional analysis, which calculates the percentage of patients in therapeutic range, valuing only the last INR registered.

There has also been an estimate of the percentage of patients with a TTR above the standards recommended by different authors in connection with the appearance of complications: Between 50 and 65% [17-25].

A descriptive analysis was made of the main variables of the study population, the continuous variables using the average and the standard deviation (SD), and the categorical through frequencies and proportions. The comparison of means was performed using Student t test for independent samples.

Results

Of the total of 307 anticoagulation therapies with vitamin K antagonists, 252 met the criteria of selection, with an average age 73.4 ± 11.8 years; 57.14% women and 42.86% men. We analysed an average of 314 ± 85 days per patient and each patient was 15.36 ± 5.45 annual checks, which represents 3,870 determinations. The principal indications of treatment with OAC were: atrial fibrillation (AF) (66.27%), prosthetic valves (PV) (17.06%), deep vein thrombosis (DVT) (9.52%) and pulmonary thromboembolism (PTE) (3.97%). In regard to the comorbidities, as was to be expected, the frequency of chronic disease in the study population is high and many of the patients have several associated pathologies; HTA was present in 61.9% of patients, DM in 25.4% and DL in 24.21% ; 10.32% presented these 3 risk factors together; also present

were: Renal Failure (RF): 14.68%; COPD: 11.11%; HF: 9.13%; dementia: 4.76%; depression: 4.37%; hypothyroidism: 4.36% and ischemic heart disease (IHD): 3.57% (Figure 2).

The global TTR by Rosendaal method was 64.30%. As we mentioned earlier, there is no consensus about the cut-off or percentage from which it is considered that a patient is well controlled, so that varies according to the sources consulted from the 50% [18,19] to over 65% [17,24,25].

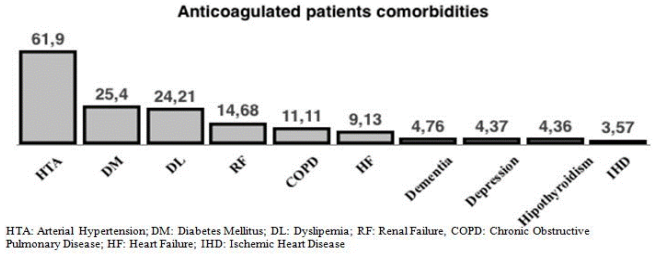

Figure 2: Anti-coagulated patients comorbidities.

If in our results we apply the lower cut, TTR above 50%, the percentage of patients with good control would be 76.98% and if we apply the more restrictive test of TTR greater than 65%, the percentage of patients with good control would fall to 49.60%. The results with the other methods used were: patients with more than 60% of total INR in therapeutic range 41.27%, the average value of the INR of each patient: 89.68% in range and the cross-sectional analysis, considering if the last value of the INR was in range: 67.86% (Figure 3).

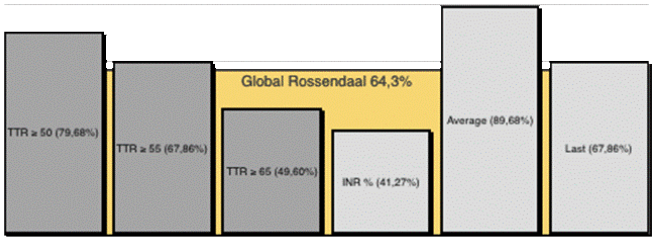

Figure 3: Anticoagulation control according to the types of methods used (n=252).

The global TTR by Rosendaal method was 64.30%. The percentage of patients with TTR above 50% was 79.68%; with TTR ≥ 55% was 67.86%, and with TTR over 65% was 49.60%. The percentage of patients with more than 60% of total INR in therapeutic range was 41.27%; The percentage with the average value of the INR of each patient was 89.68%, and the percentage with the last value of the INR in range was 67.86%.

In addition, the degree of control of all patients globally, we analyse in each one of the pathologies that led to the indication of the anticoagulation: AF, PV, DVT and PTE (Figure 4).

Discussion

In spite of the fact that the standardized method of linear interpolation of Rosendaal is recommended to evaluate the quality of the anticoagulation [17], this is a complex method, and perhaps that is why there are few jobs that use it in clinical practice conditions in PC [28-30]. Recently Alonso Roca et al. [31] applied it in a broad population of the Community of Madrid, but unlike us, they only value patients whose therapeutic range objective is between 2 and 3, discarding the rest, and do not consider the average value of the INR of each patient as a possible measure of control.

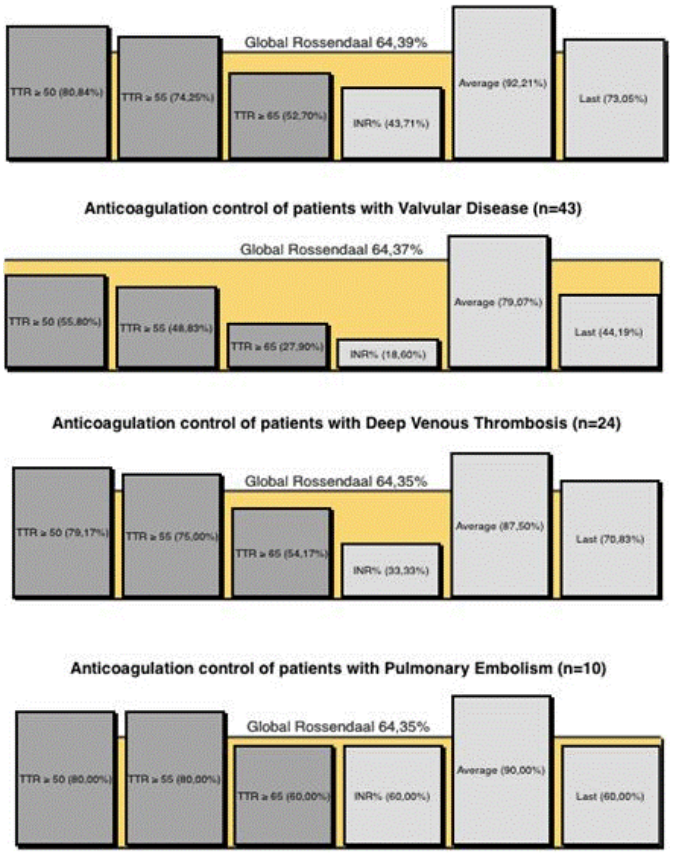

Figure 4: Anticoagulation control of patients with atrial fibrillation (n=167).

Likewise extend in ± 0.2 the therapeutic range, in what they call "range set" (value between 1.8 and 3.2) for a possible margin of coagulometre mistake, this setting is reflected in their results in an increase of the Rosendaal overall 15%, so that if we assume a similar behavior in our study, the Rosendaal global that we have obtained from the 64.30% could be placed in a 73.9%.

With regard to the set of previously published studies, our result is similar in relation to the prevalence of the use of the OAC (1.66% of our population) [4,8,29,30] to the age of the patients (73.4) and his comorbidity, but with a greater number of annual checks (15.36), which perhaps best represents the welfare activity and follow-up of these patients in PC, since they are not infrequent situations of evil control that routinely make which anticipate some records. Also, we have only found 2 jobs where it includes patients with pathologies subsidiaries of an INR different to 2-3, one of them made in our province [29] and another in the Netherlands [19], and

curiously are those who have obtained a value of Rosendaal similar to our (47.5% *vs.* 49.6 of TTR>65% and TTR global 65% *vs.* our 64.3, respectively). Anyway our results are very similar to those published studies (Table 1) unlike the made in Sweden in 2011 [26] that get a level of quality very much higher than the rest (76.2%). Also, are similar or even better than those obtained in the clinical trials of the DOAC [32-34], which is surprising, since in a clinical trial control of the OAC would be carried out with a closer follow-up of the patients that in our clinical practice.

The quality of anticoagulant control in Spanish PC has questioned in 2013 [35]. Probably due to the use of measures that are not the most adequate, as the percentage of patients with the last 2 or 3 INR in range [36]. The present work shows that the degree of control obtained is in line with multi-centre studies from other European countries with a higher sample (Table 1).

The calculation of the TTR according Rosendaal is quite complex, so that it is not always possible to obtain it. In these cases, some authors recommend the use as a control measure the value of the last INR [31]. Based on our results, we believe that the value closest to the TTR is the percentage of determinations of INR in range, taking into account that the latter underestimated the degree of control [13,30] (41.27 *vs.* 49.60 in the present work). Our data show that both the last value of INR and especially the average of all the INR overestimate the degree of control of our patients in more than 50%. Matching data in part with those obtained by Schmitt et al. [37], in a study where with the Rosendaal method obtained worst degree of control that with the percentage of INR and with the cross-sectional analysis of the last INR.

It should be noted that the worst degree of control we have in those patients that present PV, as in the rest of pathologies studied the TTR $\geq$ 65 was around 50%, while in these patients is only 27.9% (Figure 4). We do not know what the difference found can be attributed to; it could seem logical that when having a optimum range of INR higher (2.5-3.5) more difficult to keep it in the time, anyway, whatever the cause poses for us to analyse these results in a specific study of the degree of anticoagulation in this pathology.

The implication that these results can have in our decision-making can be important, especially in patients "poorly controlled", since we can question if we must stop the treatment with the OAC or recommend a DOAC. It is therefore necessary to define a single standard of TTR and express the results as a percentage of patients above or below it. In general, the standard is established on the basis of the appearance of a higher frequency of complications, but as we see, it can vary between 50 and 65% [18-25], and depending what point of court chooses, results can be very different as is reflected in Figure 3. The Spanish Health Ministry sets a cut-off point of 65% [17], basing this recommendation only in the study of Connolly et al. [24]. However, this study, which effectively uses a critical value of 65%, also provides that with the 58% the benefit is higher than double antiagregatión, and in their own conclusions show the standard between 60 and 65%. Therefore the recommendation of our ministry is much stricter than the study on which it is based.

If we opted for the 65% recommended, we can conclude that approximately 50% of our patients are not well controlled, in spite of achieving a global control of the OAC nearly optimal, both when compared with similar international studies (Table 1), as with the clinical trials of the DOAC. Definitively, the control of our patients treated with OAC, and followed exclusively in PC has an acceptable quality. However, despite a good overall accessible and integral control, there are a percentage of patients poorly controlled that can consider certain measures of improvement: Training, assistance in computer systems of control, etc.

Country	N	INR Range	TTR Rosendaal	Reference
Wales	2.223	2-3	67.9	Jones et al. [38]
Holand	2.304	2-3.5	65	Veeger et al. [19]
France	278	2-3	55	Amouyel et al. [18]
UK	27.458	2-3	63.1	Gallagher et al. [22]
Sweden	18.391	2-3	76.2	Wieloch et al. [26]
USA	392	2-3	56.7	Han et al. [39]
Germany	525	2-3	68.1	Mueller et al. [23]
Portugal	377	2-3	60.3	Caldeira et al. [40]
Spain (Madrid)	49.312	2-3	66.8	Chronos-Tao [31]
Spain (Galicia)	511	2-3	57.3	Anfagal [30]
Spain (Madrid)	65	2-3	56.3	Habashneh et al. [28]
Spain (Granada)	368	2-4	54.3	Fernández et al. [29]
Spain (Granada)	252	2-3.5	64.3 73.9	Present work with «range set»
INR: International Normalized Ratio; TTR: Time in Therapeutic range; «range set» [value between 1.8 y 3.7] for a possible margin of coagulometre mistake [31]				

Table 1: Studies made in different countries using the Rosendaal method [time in therapeutic range].

At this point, we ask ourselves what else we can do, because our attitude to these patients do not usually be another that raise or lower the dose of the drug, according to the result of the last INR, using systematic and standardized algorithms and advance or postpone the date of the next revision. And we must not forget that the result are not affected just by the dose of the OAC employed, but also there are interference and interactions with food and with other drugs common in this

type of patients, and as not, with the degree of therapeutic compliance [5].

So it only remains for us to consider if, in spite of everything, there will not always be a significant number of patients that we do not get the optimum control. And if this is so, to what extent we must raise the use of the DOAC. Today, within the situations in which can be seen as the DOAC as a therapeutic option within the National Health System, are those patients in whom, while in treatment with OAC, it is not possible to maintain a control of INR range (2-3 in case of AF) despite a good therapeutic compliance. Considering that the control of INR is suboptimal when the TTR is less than 65%, calculated by the Rosendaal method. In those cases in which this method is not available, it is considered that the control of INR is suboptimal when the percentage of INR values within therapeutic range is less than 60% [17].

Following this policy, with the data of our work, approximately between 50.4 and 58.73% of the studied patients (patients not controlled according to TTR or percentage of INR in range, respectively) would be candidates to replace its treatment by the "new" DOAC. In this case, it would be needed to also consider the budgetary impact that may involve this change. It would therefore be advisable to have an analysis that identifies groups of priority patients for these new treatments and thus allow establishing a rational strategy for its use in the National Health System (NHS) in the authorised indications.

Limitations of the Study

In the majority of work of this type usually have a selection bias of the patients, since the professionals involved on a voluntary basis, are usually the most involved in the pathologies objective of study, being in general their patients something better controlled than in the rest of professionals who do not participate. Including all the anti-coagulated patients in our area we have tried to minimize this type of bias.

Another bias of inclusion that we assume is having selected only to patients who are controlled exclusively in PC, lacking the necessary data in the controlled patients in the hospital.

Conclusions

In the literature there are different methods to assess the degree of control of the anti-coagulated patients, but currently the TTR calculated by the Rosendaal method is the most accurate, since other way of control offer very different and no individualized results. In this sense, the last INR and the average value of the INR both overestimate the quality control. But the fraction of total INR in range establishing the court in 60%, could be used in it default. At last, one out of 2 anti-coagulated patients in our area has a lower control of their INR, and what is worse, we do not know exactly what we can do to improve it.

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