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INR control calculation: comparison of Dutch and international methods

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ABSTRACT

Results of trials with new oral anticoagulant drugs and vitamin K antagonists (VKA) might not be directly applicable to Dutch clinical practice due to the high level of control of anticoagulation in the Netherlands. In addition, the Dutch method for assessing anticoagulation control uses cross-sectional international normalised ratio (INR) test results while the method used in the trials is based on person-time.

To enable comparisons, the two calculation methods were applied to INR data of a cohort of 5422 atrial fibrillation patients treated with VKA.

Overall, 74% of test results and 77% of person-time were in the therapeutic range [2.0-3.5]. For the narrower target INR interval [2.5-3.5], 59% of test results and 61% of person-time were in range. It was only between two and six months after the start of treatment that the percentage of person-time in range was lower than the percentage of test results in range. Control of anticoagulation, expressed as a percentage of person-time spent in range, in this Dutch dataset was similar to recent trials with new oral anticoagulants, although it should be noted that the Dutch INR target is higher than the target in these trials. INR control as estimated by the two calculation methods (cross-sectional and longitudinal) was similar.

KEYWORDS

Anticoagulants, atrial fibrillation, INR, TTR, vitamin K antagonists

INTRODUCTION

With the introduction of dabigatran and rivaroxaban, new oral anticoagulant drugs became available in the Netherlands. These drugs are indicated for the prevention of thromboembolic disease following knee or hip replacement, based on comparative studies with low-molecular-weight heparin.[1] More recently, results were published from randomised trials comparing dabigatran, rivaroxaban or apixaban with warfarin (a vitamin K antagonist, VKA) for prevention of cerebrovascular accidents in patients with atrial fibrillation. These studies showed superiority or noninferiority with regard to reductions in stroke or systemic embolism rates and bleeding, compared with warfarin.[2-5]

Effectiveness and safety of VKA treatment depends, among other things, on the intensity of anticoagulation.[6] During VKA treatment, the clotting tendency of the patient's blood, expressed as international normalised ratio (INR), is monitored and VKA doses adjusted if necessary in order to achieve INR values within a specified therapeutic or target range. Different methods exist to assess the level of INR control: a cross-sectional method based on the proportion of INR test results in range[7] and a longitudinal method based on the proportion of person-time spent in range (time in therapeutic range, TTR).[8] The Dutch Thrombosis Service represents a unique, high-standard setting of care for monitoring and dosing of VKA treatment.[7] The reported percentage of cross-sectional INR test results in the therapeutic range is 70-80%.[9-11] The trials that compare the new oral anticoagulants with VKA treatment use the longitudinal method, which hampers extrapolation of internationally obtained results to the Dutch setting. When the level of INR control in the Netherlands differs from the trial settings, the results are not directly applicable. In addition, the therapeutic range in the Netherlands (INR 2.0-3.5) differs from the therapeutic range used in the trials (INR 2.0-3.0).

The aim of this study was to describe how the Dutch cross-sectional INR calculation and the longitudinal Rosendaal method (TTR) compare in order to enable comparisons of the Dutch setting with international studies.

MATERIAL AND METHODS

Data source

The PHARMO Institute was granted access to the data of the Dutch Thrombosis Service in the region of Eindhoven concerning clients using VKA and requiring regular monitoring of INR. For this study the data from 2007 to 2009 were analysed. Variables in the database included indication of type of VKA use, dosing schemes and INR measurements.

Patient selection

All VKA users with an indication of atrial fibrillation who attended the Thrombosis Service Region Eindhoven between 2007 and 2009 (study period) were eligible for inclusion in the study. Study patients started treatment in the study period, or before but continued attending the Thrombosis Service during the study period. Start of treatment was defined as the date of the first INR measurement after the date of registration at the Thrombosis Service. In order to obtain stable estimates of INR control, INR measurements performed within two months of the start of treatment were excluded. Treatment was defined as subsequent INR measurements during use of one specific VKA (acenocoumarol or phenprocoumon). A maximum gap of 12 weeks was allowed between measurements; if the gap was larger, treatment was assumed to be ended. Only the first treatment within the study period was included. Start of follow-up for the study was defined as the date of the first INR measurement in the study period, or the first measurement that was performed after at least two months of treatment for patients starting treatment in or just before start of the study period. Consequently, patients who had received less than two months of treatment were excluded. End of follow-up was defined as the date of the last measurement recorded at the Thrombosis Service, the last measurement under treatment with the specific VKA (switching of therapy), or the last measurement in 2009 (end of study period), whichever came first.

Study endpoints

The percentage of INR measurements within the therapeutic range and the percentage of person-time in the therapeutic range were calculated. The therapeutic and target ranges for atrial fibrillation as defined by the Federation of Dutch Thrombosis Services (the FNT; INR 2.0-3.5 and INR 2.5-3.5)[8-11] were used. Analysis of INR range 2.0-3.0 was not considered useful as the Thrombosis Service is not aiming at that range.

Data analysis

This study was a descriptive analysis of INR test results. Two calculation methods were applied: the percentage of INR measurements within therapeutic or target range using cross-sectional data and the percentage of time in therapeutic or target range based on longitudinal data.

INR test results within range (cross-sectional method)

The percentage of INR test results within range was calculated as described by Van Geest-Daalderop,[7] a method which is also used in the annual reports of the Dutch Thrombosis Service. The Thrombosis Service assesses overall treatment intensity twice a year, by taking the last INR of each patient before the prespecified assessment date and calculating the percentage of INR results within the therapeutic range.[7] In the current study, the data delivery dates of the Thrombosis Service Region Eindhoven are adopted: 31 March and 30 September. In each year during the study period, the last INR of each patient since the last data delivery date (and after at least two months of treatment) was included. The percentage of INR results within range was based on the mean of the included estimates (two per calendar year, in total a maximum of six).

Person-time in range (TTR, longitudinal method)

The percentage of total person-time spent within the therapeutic or target range was calculated as described by Rosendaal.[8] This method 'allocates the person-time between two measurements to particular INR values [...] by dividing the time between two measurements in days, and using small steps of 0.1 INR over the range of the time interval. [...].' In the current study all INR test results during follow-up were included; person-time was allocated to the therapeutic or target range according to the Rosendaal method and summed over all patients.

Stratified analysis

The calculation methods were performed overall and in the following strata: age at start of follow-up (<60, 60-69, 70-79, ≥80 years), VKA (acenocoumarol, phenprocoumon), time between start of treatment and INR measurements (2-6 months, >6 months) and calendar year of INR measurement (2007, 2008, 2009).

Statistical analysis

Data were analysed using SAS programs that are organised within SAS Enterprise Guide version 4.2 (SAS Institute Inc., Cary, NC, USA). Data management was conducted under Windows using SAS version 9.2.

RESULTS

In 2007-2009, 5921 AF patients were treated with VKA of whom 499 patients (9%) had received less than two months of treatment, which resulted in a study cohort of 5422 AF patients (see *table 1* for patient characteristics).

Table 1. *Characteristics of patients treated with VKA for atrial fibrillation*

	Study population n=5422
Gender, n (%)	
Men	2889 (53)
Women	2533 (47)
Age at start of follow-up	
<60	390 (7)
60-69	1013 (19)
70-79	1974 (36)
≥80	2045 (38)
Mean (± SD)	75 ± 10
Vitamin K antagonist, n (%)	
Acenocoumarol	4687 (86)
Phenprocoumon	735 (14)
Start of treatment, n (%)	
<2001	584 (11)
2001-2003	808 (15)
2004-2006	1744 (32)
2007-2009	2286 (42)
Follow-up in months	
0-12	1686 (31)
>12-24	1089 (20)
> 24-36	2647 (49)
Mean (± SD)	22 ± 13
End of follow-up, n (%)	
Last measurement recorded	1629 (30)
Switching of therapy	0 (0)
End of study period	3793 (70)
Number of INR measurements during follow-up, mean (± SD)	41 ± 25
Time between measurements in days, mean (± SD)	17 ± 5

SD = standard deviation.

Table 2. *Percentages of test results (cross-sectional) and person-time (longitudinal) in range*

	Cross-sectional method	Longitudinal method
	INR test results within range n (%)*	Person years within range n (%)
Total	12,064 (100)	9742 (100)
INR 2.0-3.5 (therapeutic range)	8963 (74)	7487 (77)
INR 2.5-3.5 (target range)	7166 (59)	5915 (61)

***One measurement per patient per six months.**

The study population included slightly more men (53%) than women (47%). Mean age was 75 (± 10) years. Acenocoumarol was the primary VKA used in this population (86%); none of the patients switched preparations during the study period. Most patients started treatment in or just before the study period; 26% had been on treatment for more than four years and 11% had been on treatment for more than six years at the start of the study period (1 January 2007). Mean follow-up was 22 (± 13) months; for most patients (70%) follow-up ended on 31 December 2009 (end of study period). Mean time between INR measurements was 17 (± 5) days.

The estimates of INR control as determined by the cross-sectional and the longitudinal calculation methods were similar, within the therapeutic range INR (2.0-3.5) as well as in the target range INR (2.5-3.5) (*table 2*). The percentages of INR values within range were 74% and 59%, respectively, and the percentages of person-time within range were 77% and 61%.

In *table 3* and *table 4* various subgroup analyses are shown for both ranges. Similar or somewhat more control of INR was observed when excluding the first 2-6 months of treatment from the longitudinal calculation; for the cross-sectional method results did not differ between the 2-6 and >6 month treatment period.
From 2007 to 2009, the level of INR control was stable when determined by the cross-sectional calculation method (73-75% of values were in range). However, INR control improved when determined by the longitudinal calculation method: from 72% of person-time in range in 2007 to 80% of person-time in 2009. Between study years no differences were observed in the mean INR result, number of measurements per patient, time between measurements or the distribution of measurements by time since the start of treatment.

DISCUSSION

The aim of this study was to compare two calculation methods for assessing INR control in order to enable comparisons of the Dutch setting to international studies with new oral anticoagulants. These calculations were performed on the same dataset and with the therapeutic as well as the narrower target range for AF. Overall, the two calculation methods gave similar estimates. The longitudinal method gave slightly higher INR control estimates, likely due to the fact that INR values were weighted by the amount of person-time (and patients are sent home for a longer period when INR values are stable and in range), whereas in the cross-sectional analysis each INR value was equally eligible for selection while more measurements are performed when INR values are out of range. Another study comparing the methodologies found that the longitudinal method yielded lower estimates than the cross-sectional method, which is in contrast to our study.[12] The reason for the lower TTR results from the longitudinal method in that study was not clear.

Table 3. *Percentages of test results (cross-sectional) and person-time (longitudinal) in the therapeutic range (INR 2.0-3.5) by age, VKA preparation, and treatment phase*

	Cross-sectional method – INR tests		Longitudinal method – person-years	
	INR (2.0-3.5) / total*	**(% within range)**	**INR (2.0-3.5) / total**	**(% within range)**
<60 years	606 / 808	(75)	449 / 587	(77)
60-69 years	1670 / 2209	(76)	1375 / 1760	(78)
70-79 years	3410 / 4499	(76)	2879 / 3723	(77)
≥80 years	3277 / 4548	(72)	2784 / 3673	(76)
Acenocoumarol	7606 / 10,315	(74)	6302 / 8260	(76)
Phenprocoumon	1357 / 1749	(78)	1185 / 1482	(80)
2-6 months	800 / 1075	(74)	484 / 755	(64)
> 6 months	8163 / 10,989	(74)	7003 / 8,986	(78)

***One measurement per patient per six months.**

Table 4. *Percentages of test results (cross-sectional) and person-time (longitudinal) in target range (INR 2.5-3.5) by age, VKA preparation, and treatment phase*

	Cross-sectional method – INR tests		Longitudinal method – person-years	
	INR (2.5-3.5) / total*	**(% within range)**	**INR (2.5-3.5) / total**	**(% within range)**
<60 years	470 / 808	(58)	349 / 587	(60)
60-69 years	1310 / 2209	(59)	1083 / 1760	(62)
70-79 years	2779 / 4499	(62)	2301 / 3723	(62)
≥80 years	2607 / 4548	(57)	2182 / 3673	(59)
Acenocoumarol	6030 / 10,315	(58)	4933 / 8260	(60)
Phenprocoumon	1136 / 1749	(65)	982 / 1482	(66)
2-6 months	604 / 1075	(56)	347 / 755	(46)
>6 months	6562 / 10,989	(60)	5567 / 8986	(62)

***One measurement per patient per six months.**

In the two to six months after start of treatment, the two calculation methods resulted in different estimates of INR control likely due to the difference in selection of measurements. In the cross-sectional method, the last INR value of each patient in the database within a prespecified time period was selected for analysis, i.e. relatively late in the treatment period. Assuming improvement of INR control over the 2-6 month treatment period, the resulting estimate is higher than when calculated using all measurements between 2-6 months of treatment, as was done in the longitudinal method. After six months of treatment, anticoagulation is more stable and this difference was no longer present.

We also observed improving INR control over the study years 2007 to 2009 by the longitudinal calculation method but not by the cross-sectional method. The reason for this difference is unclear.

As described in the Thrombosis Service reports,[9-11] INR control was better under phenprocoumon than under acenocoumarol.

This study was based on data from the Thrombosis Service Region Eindhoven which monitors anticoagulation treatment of about 10,000 patients each year, and is therefore among the larger services in the Netherlands. The proportions of patients with arterial indications (86-87%) and atrial fibrillation (60-65% of arterial indications) are similar to the national median proportions over the study years (83-85% and 62-66%, respectively). The percentages of phenprocoumon users in this particular centre were 18-19% over the study years, which is above the national median of 9-12%. The percentage of INR results within range are, however, representative of the Netherlands: 77-78% of INR test results from long-term

patients were within the therapeutic range compared with the national median of 78-80%.[9-11]

Besides a different method to calculate INR control, the trials with new anticoagulants used a different therapeutic range. In these studies, patients with atrial fibrillation received warfarin under a therapeutic range of INR (2.0-3.0) while the Thrombosis Service has an INR target range (2.5-3.5) and a broader therapeutic range (2.0-3.5). The target range is set higher than the internationally advised target range to prevent inadequate anticoagulation (INR <2.0).[13] Quality estimates obtained for the Thrombosis Service in our study were 74% of INR values and 77% of person-time within therapeutic range (2.0-3.5) and 59% of INR values and 61% of person-time within target range (2.5-3.5). The trials reported 64%,[3] 62%[4] and 55%[5] of person-time within therapeutic range INR (2.0-3.0). Hence, compared with the target range in the Thrombosis Service, two of three trials reported slightly higher INR control.[3,4] However, given the broader therapeutic range in the Netherlands and the fact that these studies used selected populations, it may be more appropriate to conclude that the level of INR control was similar for the different settings. Although they used various calculation methods, INR ranges and indications for anticoagulation, other studies on Dutch data have reported estimates which are lower or equal to the estimates calculated in this study.[7,14-22]

In conclusion, the cross-sectional and longitudinal methods to assess INR control during anticoagulant therapy show similar results. Hence, the difference in calculation method is not a major limitation for comparing trial results with Dutch clinical practice.

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