Towards improvement of oral anticoagulant therapy

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CHAPTER 5

Prediction of Haemorrhagic and Thrombotic Events in Patients with Mechanical Heart Valve Prostheses Treated with Oral Anticoagulants

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J Thromb Haemost. 2008;6(3):451-6

Abstract

Background Variability in the intensity of anticoagulant therapy is considered a risk factor for complications, but it is unclear how best to quantify variability.

Objective We evaluated the association of three methods to measure variability with complications of oral anticoagulant therapy**.**

Methods We conducted a nested case-control study within a cohort of patients with prosthetic heart valves. 210 patients with a first haemorrhagic or thrombotic event during follow-up were selected with two controls per case, matched on age and sex. We calculated the time spent at an INR below, above and between 2.5 and 4.0; the variance growth rate according to three different methods (A, B1, B2), of which method A combines variability and time in range and methods B1 and B2 purely look at variability.

Results Odds ratios of the variance growth rates for thrombotic events for patients in the 2nd and 3rd tertile varied between 2 and 3, with the highest odds ratio for complications for the method that purely looked at variability. For haemorrhagic complications highest odds ratios were found for measure A which also incorporated time in range, with ORs of 2.6 (CI95 1.3-5.1) and 3.1 (CI95 1.6-6.0) for the 2nd and 3rd tertile as compared to the first. The combination of time spent out of range with the highest tertile of variability increased the risk 2.6-fold (CI95 1.6-4.2) as compared to subjects with stable anticoagulation within the target range.

Conclusion Unstable anticoagulation was associated with haemorrhagic and thrombotic complications. Method A was best associated with complications, but methods B1 and B2, in combination with time spent in range were equally well associated. As we prefer to disentangle variability and intensity of anticoagulation, we propose to use methods B1 or B2 to reflect pure variability of oral anticoagulant therapy.

Introduction

Oral anticoagulants are among the most frequently prescribed drugs worldwide. They are proven to be effective in the treatment of venous thrombosis as well as for prevention of both venous and arterial thrombotic events in patients who are at increased risk[1-3]. While oral anticoagulants decrease the risk for a thrombotic event by inhibiting coagulation, through the same mechanism they increase the risk of severe or even fatal haemorrhage. Approximately 1% of patients will suffer from such a complication of oral anticoagulant therapy per year [4,5].

Given the severity of these adverse events it is of great importance to identify patients who are at highest risk to experience such an event so that precautions can be made. Several studies investigated potential risk factors for haemorrhagic complications, such as increased age, indication for anticoagulant therapy and the use of interacting medication [6-8]. Variability in the intensity of anticoagulant therapy (expressed as the International Normalized Ratio (INR)), as first described by Fihn and colleagues, is considered a risk factor for developing haemorrhagic or thrombotic complications [9]. They investigated whether the variance growth rate was associated with haemorrhagic events in a retrospective cohort of patients using oral anticoagulants for various indications. This variance growth rate is a measure of the time weighted variance of the INR around the target INR and reflects the degree to which a patient's achieved INR deviates from his or her target INR over a prolonged interval. Fihn and colleagues found that patients with a variance growth rate in the highest tertile had a 1.6 times higher risk of experiencing a haemorrhagic event compared to patients in the lowest tertile. Cannegieter radically modified the formula of Fihn and used the degree to which a patient's INR deviates from the previous one, and this variance growth rate does not depend on the target INR [10]. With this formula a patient is defined stable if his or her INRs are around the same value every time, even if this means that, for

example, the INR is constantly above the upper limit of the therapeutic range. Later, Fihn described a third method to calculate the variability in INR [11]. This variance growth rate is approximately the same as the method of Cannegieter, with small differences in the denominator. Variability of the INR, calculated with any of these methods has been shown to be associated with an increased risk of developing a haemorrhagic event with odds ratios varying from 1.6 to 3.0 [9-11], but it is not clear which one is best associated with such events.

Another method to assess the quality of the anticoagulant treatment is the linear interpolation method, which reflects the time spent within the target range, rather than the variability [9,12]. It has been shown that patients who spent less than 45% of the time inside the therapeutic range have a relative risk of 2.8 (95% CI 1.9-4.3) for developing an adverse event compared to patients who spent over 65% in range [13].

In this study we evaluated the three variability measures to asses which one is most associated with the occurrence of a haemorrhagic or a thrombotic event in patients with mechanical heart valve prostheses. We included the time spent in therapeutic range in our analyses since this is the established method in literature to reflect the quality of oral anticoagulant therapy.

Patients and Methods

Patients were participants of the LAVA study, a large cohort study consisting of all patients with mechanical heart valve prosthesis treated in four regional anticoagulation clinics between 1985 and 1993 [14]. The main objective of this study in 1608 patients was to determine the optimal level of anticoagulation for this indication. For all patients the following data were collected: date of birth, sex, all INR measurements with corresponding date, all hospital admissions and deaths. Additional information concerning the hospital admissions were collected from

hospital or general practitioners files. Outcome events were all thrombotic and haemorrhagic events during follow up with cerebral infarction defined as a neurologic deficit of sudden onset documented by CT-scanning (presence of infarction or absence of haemorrhage) or autopsy, peripheral emboli as acute peripheral ischemia proven by angiography, operation or autopsy, valve thrombosis defined as valve impairment by deposition of thrombus on the valve, proven at operation or autopsy, intracranial and spinal haemorrhage defined as neurologic deficit of sudden or subacute onset, confirmed by CT-scanning, surgery or autopsy, and major extracranial haemorrhage as an acute haemorrhagic event that led to death or to hospital admission for treatment of the haemorrhage as the most important reason for hospitalization (haemorrhage that led to hospital admission for diagnostic procedures only was not considered major). Out-hospital haemorrhages of all possible origin, i.e. also traumatic, were included. All strokes that could not be categorized as haemorrhagic or ischemic were designated “unclassified strokes”.

We conducted a nested case-control study within the LAVA cohort. Cases were all patients who experienced a first thrombotic or haemorrhagic event during follow-up. For each case two control persons were selected who were free of a haemorrhagic or thrombotic event at the time of the event of the case, but who were at risk, i.e., they were using oral anticoagulants at that date. For control subjects the index-date was the date of the INR measurement closest to the event date of the case. Control patients were matched on age and sex. A control could be selected more than once or become a case at a later date.

For each patient we calculated the variability of the INR according to three different methods; the variance growth rate by Fihn, the variance growth rate by Cannegieter and the variance growth rate again by Fihn. The formulas used to determine these measures are shown in box 1.

Box 1. Formulas of the variability measures

Variance growth rate Fihn (method A)

$$\sigma^2 = \frac{1}{n}\sum_{i=1}^{n}\frac{(\mathrm{INR}_i - \mathrm{target}_i)^2}{\tau_i}$$

Variance growth rate Cannegieter (method B1)

$$\sigma^2 = \frac{1}{n}\sum_{i=1}^{n}\frac{(\mathrm{INR}_{i+1} - \mathrm{INR}_i)^2}{\tau_{i,i+1}}$$

Variance growth rate Fihn (method B2)

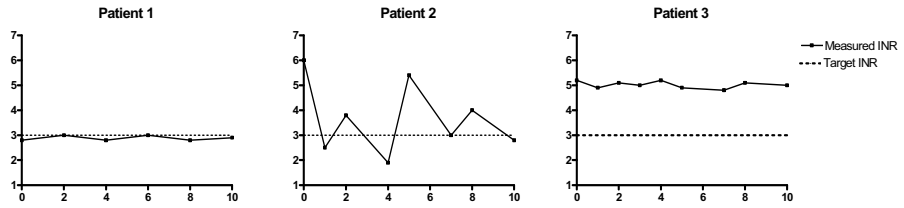
$$\sigma^2 = \frac{1}{n-1}\sum_{i=1}^{n}\frac{(\mathrm{INR}_{i+1} - \mathrm{INR}_i)^2}{\tau_i}$$

*n is the number of INR measurements, τ is the time in weeks between the present and previous INR measurement.

The variance growth rate by Fihn reflects the degree to which a patient's INR deviates from his or her target INR over a prolonged period. Using this formula for variability, a patient is most stable when his or her INRs are close to the target INR. We will refer to this method as method A from now on. The variance growth rate by Cannegieter reflects the degree to which a patient's INR deviates from the previous one. This formula is a reflection of the true variability not taking into account the intensity of anticoagulation. With this formula a patient is most stable if his or her INRs are around the same level even if this means the INR is constantly above the upper limit of the target range. The 2nd variance growth rate by Fihn is approximately the same as the formula used by Cannegieter, with minor differences in the denominator. Given the minor differences between the formula of Cannegieter and the 2nd formula of Fihn, we will refer to these methods as method B1 and method B2 respectively. Examples of the three measures of variability are given in box 2. Time in, above and below an INR range of 2.5-4.0 was calculated using the linear interpolation method [12]. With this method the

time between two measurements is divided in days and it assumes that the INR value between two measurements will vary linearly from the first, to the value of the second measurement. This way we can calculate how many days were spent at different INR values. Although the target range at the time of the study (1985-1993) was an INR between 3.6 and 4.8 we considered the actual optimal INR range as was determined in 1996; i.e. the level at which least complications occur (INR between 2.5 and 4.0).

Box 2. Example of three patients with target INR 3.0 and the values of three different methods to calculate the variance growth rate.



Method A = 0.01	Method A = 1.04	Method A = 3.23
Method B1= 0.01	Method B1= 4.06	Method B1 = 0.03
Method B2 =0.01	Method B2= 4.64	Method B2 = 0.03

We calculated all these measures for four different time windows; one year, 6 months, 3 months and 6 weeks prior to the time of the event. For each time window only subjects were included who had INR measurements during the whole period of that time window. The INR measurement at the time of the event was not included in the calculations for the various effect measures, because this was not a routinely measured INR.

The values of the variance growth rates and the percentage of time spent in, above and below INR range 2.5-4.0 were divided into tertiles (good, medium, poor) based on the distribution in the control persons. To asses whether being out of range along with a high variability is predictive we also studied the combination of the time spent at INR 2.5-4.0 and the variability calculated according to method B1 (method A includes the achieved INR and is therefore unsuitable to disentangle variability and time in range). For this combination we divided the time spent at INR 2.5-4.0 into two groups; patients in the good and medium group were considered to be frequently in range and patients in the poor group to be frequently out of range. The variance growth rate was divided into unstable (poor group) or stable (good and medium group). ORs were calculated for patients with high variability who were in INR range 2.5-4.0, patients who were stable but outside the range of INR 2.5-4.0 and those who were both unstable and outside INR range 2.5-4.0, all with stable patients in the INR range as reference category. To investigate whether the effect is specific for the period directly preceding the event, we analysed the different quarters of the year prior to the event. Additional, we did separate analysis for phenprocoumon and acenocoumarol users.

We performed a matched analysis calculating odds ratios (OR) and 95% confidence intervals (95%CI) using conditional logistic regression models. For all variability measures the lowest tertile is the reference category (which is the low-risk group according to our hypothesis). For the time in therapeutic range the highest tertile is the low-risk group and this was chosen to be the reference category. We performed separate analyses for haemorrhagic events and thrombotic events, as well as an analysis in which the two were combined. For the subgroup analysis for the type of vitamin K antagonist we performed logistic regression analysis adjusting for the matching factors sex and age. The conditional logistic regression models were done with the STATA 8.0 SE software (StataCorp LP, Tx,

USA), logistic regression analysis was performed with the statistical package SPSS version 14.0 (SPSS Inc, Chicago, Ill).

Results

Among the 1608 patients in the LAVA cohort there were 210 first events, consisting of 154 haemorrhagic events and 42 thrombotic events. Fourteen strokes could not be classified as either a haemorrhagic or an ischemic event. Thirty-three patients experienced an intracranial or spinal haemorrhage and 121 an extracranial haemorrhage. The thrombotic and embolic events were almost all cerebral infarctions (n=40) except for two patients who had a peripheral embolism.

Four hundred and twenty control subjects were matched to the 210 cases. One hundred and seventeen patients were selected more than once as a control, of whom12 patients were selected three times. Thirteen control patients became a case at a later date. There were slightly more women than men, 53.1% versus 46.9%. Median age was 66 years (IQR 58 – 72). General characteristics of cases and controls are shown in table 1.

Table 1. General characteristics of cases and control subjects.

		Cases (n=210)	Controls (n=420)
Age			
	Median (IQR)	66 (58-72)	66 (58-72)
Sex			
	Male (%)	99 (46.1)	198 (46.9)
	Female (%)	111 (53.1)	222 (53.1)
Position of heart valve			
	Aortic (%)	111 (52.9)	233 (55.2)
	Mitral (%)	68 (32.4)	133 (31.7)
	Both (%)	30 (14.3)	52 (12.4)
Coumarin			
	Phenprocoumon (%)	171 (81.1)	356 (85.2)
	Acenocoumarol (%)	37 (17.2)	62 (14.6)
	Other/ Unknown (%)	2 (1.0)	2 (0.2)

Table 2 shows ORs for haemorrhagic events for all measures (154 cases, 308 controls). The measures were generally most clearly predictive during the time window of three months, while associations became attenuated when the variance growth rates were calculated over longer time intervals. The risk of a haemorrhagic event was highest among patients who spent relatively little time within INR range 2.5-4.0. Method A, which incorporates both time in range and variability was most clearly associated with the risk of haemorrhage. In the time window of three months we found an OR of 2.6 (95%CI 1.3-5.1) for patients in the 2nd tertile and an OR of 3.1 (95% CI 1.6-6.0) for patients in the highest tertile compared to patients in the lowest tertile. The methods that only looked at variability were associated with a 1.6-fold increased risk of haemorrhage in the highest tertile compared to the lowest for a 3-months time window. Odds ratios for all measures for thrombotic events are given in table 3 (42 cases and 84 matched controls).

Table 2. Odds ratios for tertiles of the different measures for all haemorrhagic events

		One year		6 Months		3 Months		6 Weeks	
	Tertile	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Time at INR 2.5-4.0	Good	1.0	-	1.0		1.0		1.0	
	Medium	1.3	0.7-2.2	1.4	0.8-2.4	1.5	0.8-2.7	1.9	0.9-4.3
	Poor	1.8	1.1-3.2	1.6	0.9-2.7	2.6	1.4-4.8	2.3	1.1-4.9
Time above INR 4.0	Good	1.0		1.0		1.0		1.0	
	Medium	1.0	0.6-1.7	1.0	0.6-1.8	1.1	0.6-1.9	2.5	1.1-5.6
	Poor	1.4	0.8-2.4	1.3	0.8-2.2	1.9	1.1-3.8	2.5	1.2-4.9
Method A	Good	1.0		1.0		1.0		1.0	
	Medium	1.2	0.7-2.1	1.9	1.1-3.4	2.6	1.3-5.1	1.8	0.9-3.7
	Poor	1.4	0.8-2.4	1.9	1.0-3.3	3.1	1.6-6.0	1.4	0.7-2.8
Method B1	Good	1.0		1.0		1.0		1.0	
	Medium	0.9	0.5-1.6	1.1	0.7-2.0	1.2	0.6-2.1	0.8	0.4-1.6
	Poor	0.9	0.6-1.6	1.5	0.9-2.6	1.6	0.9-2.8	1.3	0.7-2.6
Method B2	Good	1.0		1.0		1.0		1.0	
	Medium	1.0	0.6-1.7	1.1	0.6-1.9	1.2	0.7-2.3	0.8	0.4-1.5
	Poor	0.9	0.6-1.6	1.5	0.9-2.6	1.5	0.9-2.7	1.4	0.7-2.7

Table 3. Odds ratios for tertiles of the different measures for all thrombotic events

		One year		6 Months		3 Months		6 Weeks	
	Tertile	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Time at INR 2.5-4.0	Good	1.0	-	1.0		1.0		1.0	
	Medium	1.8	0.6-5.3	0.8	0.3-2.2	1.3	0.4-3.8	1.1	0.2-4.8
	Poor	1.4	0.5-4.0	0.7	0.3-1.9	1.5	0.6-4.2	0.9	0.2-4.3
Time below 2.5	Good	1.0		1.0		1.0		1.0	
	Medium	1.3	0.4-4.5	-				-	
	Poor	2.0	0.8-4.8	2.2	0.9-5.6			1.6	0.3-8.0
Method A	Good	1.0		1.0		1.0		1.0	
	Medium	1.5	0.6-4.0	1.3	0.5-3.6	2.1	0.7-6.1	3.2	0.6-16.9
	Poor	1.4	0.5-4.0	1.7	0.5-5.4	1.5	0.5-4.4	1.8	0.4-8.1
Method B1	Good	1.0		1.0		1.0		1.0	
	Medium	0.7	0.3-2.0	3.0	0.9-10.1	3.0	0.8-10.8	0.5	0.1-2.1
	Poor	0.9	0.4-2.5	1.7	0.5-5.6	3.2	1.0-11.1	0.5	0.1-1.8
Method B2	Good	1.0		1.0		1.0		1.0	
	Medium	0.9	0.3-2.3	2.0	0.6-6.4	2.1	0.6-6.8	0.2	0.03-0.9
	Poor	1.0	0.4-2.7	1.3	0.4-4.3	2.5	0.8-7.7	0.4	0.1-1.7

As we found in the analysis with haemorrhagic events, the measures were generally most clearly predictive of an event during the time window of three months and this risk was highest in patients who spent least time in the target zone. Variability method A, that combines variability and time in range showed increased risks with an OR of 1.5 (95% CI 0.5-4.4) for patients in the highest tertile compared to the lowest. The two methods that purely looked at variability now had higher odds ratios, of, for method B1 3.0 (95% CI 0.8-10.8) and 3.2 (95% CI 1-9.8) in the 2nd and highest tertile compared to the lowest tertile and 2.1 (95% CI 0.6-6.8) and 2.5 (95% CI 0.8-7.7) for method B2. Odds ratios for the combination of haemorrhagic and thrombotic events are shown in table 4. Adjustment for the value of the INR at the last measurement before the index date did not affect the outcomes, except in the analysis of thrombotic events where the ORs became more distinct.

Table 4. Odds ratios for tertiles of the different measures for all adverse events

		One year		6 Months		3 Months		6 Weeks	
Time window	Tertile	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Time at INR 2.5-4.0	Good	1.0	-	1.0		1.0		1.0	
	Medium	1.3	0.8-2.1	1.3	0.8-2.1	1.6	1.0- 2.8	2.0	1.0- 4.0
	Poor	1.5	1.0-2.4	1.4	0.9-2.1	2.5	1.5- 4.3	1.9	1.0- 3.8
Time above 4.0	Good	1.0		1.0		1.0		1.0	
	Medium	1.1	0.7- 1.7	1.0	0.6- 1.6	1.2	0.7-1.9	2.6	1.3-5.1
	Poor	1.3	0.8- 2.0	1.1	0.7-1.7	1.9	1.2-3.1	1.6	0.9- 2.9
Time below 2.5	Good	1.0		1.0		1.0		1.0	
	Medium	1.2	0.7-2.2	-					
	Poor	1.6	1.1-2.4	2.0	1.3- 2.9	1.9	1.2- 3.0	1.1	0.6- 2.0
Method A	Good	1.0		1.0		1.0		1.0	
	Medium	1.3	0.8- 2.0	1.7	1.1-2.8	2.8	1.5– 4.9	1.6	0.9- 2.9
	Poor	1.4	0.9- 2.2	1.8	1.1- 3.0	3.1	1.7-5.4	1.4	0.7- 2.6
Method B1	Good	1.0		1.0		1.0		1.0	
	Medium	0.9	0.6- 1.5	1.3	0.8-2.0	1.4	0.8- 2.4	1.0	0.5- 1.7
	Poor	1.0	0.6- 1.6	1.5	0.9-2.3	1.8	1.1- 3.0	1.3	0.7- 2.3
Method B2	Good	1.0		1.0		1.0		1.0	
	Medium	0.9	0.6-1.5	1.2	0.7- 1.9	1.5	0.9- 2.6	1.0	0.5- 1.7
	Poor	1.0	0.6-1.5	1.5	0.9- 2.3	1.8	1.1- 2.9	1.1	0.6- 2.0

Subsequently, we combined the pure variability methods (B1 and B2) with the time spent in and outside the INR target range of 2.5 and 4.0. The risk of a haemorrhagic or thrombotic event was increased 2.6-fold (95%CI 1.6-4.2) for those in the highest tertile of variability and lowest time-in-range tertile as compared to subjects with stable anticoagulation who were usually within the target range (table 5). Variability within an INR range of 2.5 – 4.0 did not affect risk. Again, the effect was only seen in the three months directly preceding the event. In a subgroup analysis of phenprocoumon and acenocoumarol users we found similar results for all measures, but the associations were more pronounced in acenocoumarol users.

Table 5. Odds ratios for the combination of time in therapeutic range and variability calculated with method B1.

Time in therapeutic range*	Variability**	OR_{Haem}	95%CI	OR_{throm}	95%CI	OR_{total}	95%CI
In range	Stable	1.0	-	1.0	-	1.0	-
	Unstable	1.0	0.5-2.0	1.1	0.4-3.5	1.2	0.7-2.1
Outrange	Stable	1.6	0.9-3.1	0.8	0.3-2.6	1.5	0.9-2.6
	Unstable	2.7	1.4 - 4.9	2.5	0.8-7.9	2.6	1.6-4.2

*In range are patients with a time in therapeutic range in the 2nd and highest tertile, outrange are patients in the lowest tertile.
** Stable are patients who have a variance growth rate calculated with method B1 in the lowest or 2nd tertile, unstable are patients in the highest tertile.

Discussion

In this study of 630 subjects with mechanical heart valve prostheses we found that unstable anticoagulation was associated with an increased risk of haemorrhagic and thrombotic complications. Both variability and time spent outside the target range affected risk. The variance growth rate described by Fihn, method A, incorporates both aspects of instability, and was therefore most clearly associated with complications of anticoagulant therapy, especially haemorrhagic episodes. Thrombotic events were most clearly predicted with variability calculated with method B1 and B2, which only concern variability of the INR and not the time within range. The optimal time window to determine these measures was three months.

Periods of time outside the therapeutic range are intrinsically related to the treatment and therefore not avoidable. The problem is to have an instrument to quantify them to obtain a better quality of anticoagulation in order to reduce adverse events. Several studies have been done to investigate potential instruments to quantify this quality, and research concerning this topic is ongoing. Our study

showed similar results as the previous studies have shown [9-11,13]. From these studies we knew that the measures we evaluated could predict which patients were at increased risk, but we did not know which one was best associated since they have never been compared directly to each other. In another study it was shown that patients with episodic overanticoagulation had an increased risk of both haemorrhagic and thrombotic events [15]. The authors suggest that this phenomenon reflects instability of anticoagulation. These results are in line with our findings, since the variability measures increase when patients have episodes of high INR levels.

Overall, the variability according to method A was best associated with complications of oral anticoagulant therapy. However, this method is a composite of time in range and variability. When we combined the methods that only looked at variability with a measure of time in range, this predicted equally well. The importance of the association of risk of the methods that only look at the variability of the INR, is that we show this is a risk factor per se, added to the risk of under- and overanticoagulation. When we adjusted for the value of the last INR before the index date the effect did not disappear, which teaches us that an INR within the therapeutic range in patients with high variability in INRs can not be interpreted the same way as in patients who are very constant in their INRs. Remarkably, the achieved intensity of anticoagulation was less important in predicting thrombotic events than haemorrhagic events.

The lack of association in the time windows of one year and six months may be the result of the dilution of the effect of the variability measures when calculated over a prolonged period. This is also supported by the results of our analysis of quarters of the year prior to an event, where we only found an association in the three months directly preceding the event. Remarkably, a six weeks time window had little association. This may be the result of the limited

number of INRs which are available in such a period. Time between two visits can be as long as six weeks, so in a time window of 6 weeks prior to the event, few patients will have sufficient INR measurements to reliably calculate the various measures. Consequently, three months is the optimal time window to predict thrombotic and haemorrhagic risk by variability.

We have shown that unstable anticoagulation is associated with haemorrhagic and thrombotic complications. The variance growth rate calculated by method A is best associated with complications. However, this method does not inform us on the reason for the increased risk. Since methods B1 and B2 in combination with the time spent at INR 2.5- 4.0 are equally well associated, we prefer to disentangle variability in and intensity of anticoagulation. Disentangling the variability and the time in therapeutic range gives us the opportunity to target more directly either the instability or the inadequate level, hence possibly preventing these events. Therefore we propose to use the variance growth rates by Cannegieter or Fihn, methods B1 and B2 to reflect the variability of oral anticoagulant therapy.

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