Improving the quality of oral anticoagulant therapy

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CHAPTER 3

COMPARISON OF CONTROL AND STABILITY OF ORAL ANTICOAGULANT THERAPY USING ACENOCOUMAROL VERSUS PHENPROCOUMON

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ABSTRACT

Background/Purpose: Variability in the control of oral anticoagulant therapy has been associated with a heightened risk of complications. We compared control of anticoagulation between two com-monly used coumarins, phenprocoumon and acenocoumarol, and among anticoagulation clinics.

Setting/Patients: All qualifying patients managed at six regional anticoagulation clinics in the Netherlands.

Design: Retrospective cohort study using data for a three-year period from a computerised dosing and management system.

Measures:. Anticoagulation control expressed as the percent of time within the therapeutic range and stability expressed as the time-weighted variance in the international normalised ratio (INR)

Results: Data were available for 22,178 patients of whom 72% were treated with acenocouma-rol. INRs of patients who received phenprocoumon were within the therapeutic range 50% of the time compared with 43% for acenocoumarol (OR 1.32, 95% CI 1.24-1.41). Moreover, patients on phenprocoumon required 15% fewer monitoring visits and had more stable INR values. These observations were consistent for all six clinics. There were also sizable differences between the clinics with respect to control and stability of anticoagulation that were stable from year-to-year and were unrelated to the drug used.

Conclusions: With its longer half-life of three to five days, phenprocoumon produces more stable anticoagulation than acenocoumarol and should generally be the drug of choice when these are the available choices. The differences observed among clinics suggest that certain clinics employ policies and practices resulting in better control of anticoagulation.

INTRODUCTION

The indications for long-term therapy with coumarin anticoagulants have broadened con-siderably over the past few decades. Although this therapy has been made safer by improved laboratory testing and establishment of clear therapeutic ranges for intensity, a significant risk of complications persists. And despite these advances, the management of patients taking anti-coagulants is still suboptimal. In various studies of patients taking coumarin anticoagulants, the international normalised ratio (INR), used to monitor the intensity of anticoagulation, is outside the prescribed therapeutic range 10% to 70% of the time.[1] This is undesirable because INR values falling below the therapeutic range are associated with an exponentially increasing risk of recurrent thrombosis and values above the range place patients at a heightened risk of bleeding.[2-5] In addition, there is considerable evidence to suggest that increasing variability in a patient's INR values is also associated with a greater risk of hemorrhagic and thrombotic complications. [6-10]

Earlier studies have suggested that the level of control of anticoagulant therapy may be related to the specific coumarin drug that is administered. In direct comparisons, coumarin compounds with a long halflife, such as phenprocoumon, have been reported to provide greater stability of the INR and a higher proportion of INR measurements within the therapeutic range compared with agents, such as acenocoumarol, that have a short halflife. Despite these findings, in countries where both agents are available, many practitioners prefer acenocoumarol. This may be due to the perception on the part of practitioners that because of its short halflife of eight to ten hours, it is easier to adjust the dosage of acenocoumarol, and, if necessary, to rapidly discontinue therapy than is the case for phenprocoumon with its halflife of six days.

Using data from six anticoagulation clinics in the Netherlands, we performed a retrospective cohort study to compare the relative control and stability of the INR among patients taking either acenocoumarol or phenprocoumon. We were also interested in learning whether there were consistent differences in manner in which anticoagulation was managed among the six clinics.

PATIENTS AND METHODS

Setting and Patients

Two oral anticoagulant agents are available in the Netherlands, acenocoumarol (Sintrom mitis®) and phenprocoumon (Marcoumar®). The management of patients who are prescribed these agents is performed at one of 63 regional anticoagulation clinics located throughout the country. Although each centre operates independently, many use one of several available computerised systems to assist with dosing of anticoagulants. One of these is the TRODIS system, used by 13 clinics. (TRODIS, Infotrom, Leiden, The Netherlands). TRODIS evaluates recent INR results and in about onehalf of cases makes a dosage recommendation that can be modified by the physician.[3] In the other half of cases, consisting mainly of patients who are unstable, who have had complications or for whom the prescription of other medications has changed, the physician adjusts the dosage without a recommendation from the system.

Patients are assigned to receive low intensity anticoagulation (INR 2.5 to 3.5) for atrial fibrillation and prophylaxis or treatment of venous thromboembolism. Patients are assigned to the high range (3.0 to 4.0) for reasons that include a mechanical valves, arterial thromboembolism (in the absence of atrial fibrillation), recurrent thromboembolism while being adequately maintained on a lower intensity of anticoagulation, among others.

We obtained anonymous, aggregated data from the TRODIS systems of six anticoagulation clinics widely dispersed over the country in the cities of Den Haag, Leeuwarden, Leiden, Lichtenvoorde, Schiedam and Utrecht. We selected these clinics because they represent a crosssection of Dutch anticoagulation clinics (e.g., rural and urban, university affiliated and not affiliated) and because their data could be readily extracted from TRODIS whereas the data could not readily obtained for the other clinics. All of the six clinics receive referrals of patients who reside in its geographic area from family physicians or specialists at local hospitals. The clinics in The Hague, Leiden and Utrecht are located in densely populated urban areas whereas the other three are situated in smaller, more rural cities. In the vast majority of cases, the indication for anticoagulation and the therapeutic range for the INR are established by the referring physician who also selects the drug (i.e., acenocoumarol versus phenprocoumon). The physician at the anticoagulation clinic manages the dosing and supervises the monitoring of therapy.

From each of the six clinics we obtained all available data for an inception cohort of all patients whose course of anticoagulation began between 1 January 1997 and 31 December 1999. We excluded patients whose course involved less than four monitoring visits or lasted four weeks or less. Patients who switched from acenocoumarol to phenprocoumon or vice versa were excluded.

Design, Measurements and Analysis

We conducted a longitudinal analysis comparing patients who took acenocoumarol with those who took phenprocoumon. We performed several analyses stratifying by intensity of therapy (low vs. high range), age, sex and anticoagulation clinic. In addition we compared the percent of INR measurements

that were within the therapeutic range and the percent of time spent in the therapeutic range for patients taking the two drugs. The latter was estimated by linear interpolation between successive INR measurements, calculating the portion of time during each interval that was spent inrange, summing across all intervals, and than dividing by the total duration of therapy.[11] We also computed the proportion of visits at which a change in dosage was prescribed and the average interval between visits. To test for differences we computed the unadjusted odds ratio (OR) and 95% confidence interval (CI).

To ascertain whether overall differences in the control of anticoagulation therapy observed among the six anticoagulation clinics were consistent, we examined all courses of therapy within each clinic separately for each of the three years studied. This was possible in all cases except for the first year of the study at one clinic that had not yet adopted standard target ranges for the INR.

To express the variability in INR values, we adapted a previously described method to characterise the degree to which a patient's prothrombin time ratio (PTR) deviates from his or her target PTR over time.[12] In this study, we adapted the formula to reflect variability in the INR over time per patient using the formula:

$$\sigma = \sqrt{\frac{1}{n-1}\sum_{i=2}^{n}\frac{(INR_i - INR_{i-1})^2}{\tau_i}}, \tau = t_i - t_{i-1}$$

where n is the number of all INR measurements before 31 December 1999 or when the course of therapy was terminated and t is the interval since the previous INR determination in days.

All of the foregoing analyses were performed using all available INR values except those gathered during the first four weeks of therapy. These were eliminated because INR values during this initial induction period are frequently out-of-range and we were most interested in studying patients during the time when their INR values would be expected to be stable. We also excluded periods of therapy that contained prolonged periods without an INR determination as these typically represent discontinuation of anticoagulation for surgery or other reasons.

RESULTS

A total of 22,178 patients were started on a coumarin anticoagulant during the period of study of whom 72% were treated with acenocoumarol and the remainder with phenprocoumon (Table 1). Seventy-eight percent of patients on acenocoumarol and 76% of those on phenprocoumon were assigned to the less intense range of therapy. There were substantial differences in the number of patients seen at the six anticoagulation clinics, ranging from 1773 to 5368 (Table 2). The average ages of patients on the two agents and assigned to the high and low ranges were similar. A slightly lower proportion of men were taking phenprocoumon than acenocoumarol.

The average interval between monitoring visits for patients receiving acenocoumarol was 14 days, which was 13% (two days) shorter than for patients receiving phenprocoumon. In addition, the proportion of visits at which a dosage adjustment was made was approximately 13% higher among patients receiving acenocoumarol (62% vs. 55% of visits). Yet, despite more frequent monitoring and adjustments of dosage, the INRs of patients taking acenocoumarol were within the therapeutic range only 43% of the time compared with 50% for phenprocoumon (OR 1.32, 95% CI 1.24-1.41). Similarly, 38% and 45% of all INR measurements were within range on the two drugs, respectively (OR 1.33, 95% CI 1.26-1.41). Moreover, variability in the INR as reflected by the timeweighted variance (s) was approximately 30% higher among patients receiving acenocoumarol (0.39 vs. 0.30). Similar differences in all these measures of the control and stability of anticoagulation were observed for patients managed within both the low and high INR ranges (Table 1).

Table 1. Characteristics of patients stratified by anticoagulant drug and intensity of therapy (Low range: INR 2.5 - 3.5, High range: INR 3.0 - 4.0)

	Acenocoumarol (n = 15,901)		Phenprocoumon (n = 6277)	
	Low Intensity	High Intensity	Low Intensity	High Intensity
Characteristic				
Number of patients	12,476	2615	4792	1485
Age at start of therapy (mean)	65	64	64	64
% male	39	65	45	65
Mean INR	2.7	3.2	2.9	3.4
Mean interval between INR measurements (d)	14	15	16	16
% of visits with dosage adjustment	61	66	55	54
% INRs in range	39	34	45	44
% of time INR in range	44	40	50	50
Mean s	0.38	0.45	0.29	0.33

Table 2. Mean interval between visits and variability in INR (s) according to type of coumarin anticoagulant, intensity of therapy and anticoagulation clinic*

	Anticoagulation Clinic					
	A	**B**	**C**	**D**	**E**	**F**
Total number of patients	2631	5368	1773	1409	5803	5104
Percent on phenprocoumon	1	64	13	8	41	2
Mean interval between visits (days)						
Acenocoumarol – low intensity	13	11	16	14	13	14
Phenprocoumon – low intensity	17	14	18	15	17	19
Acenocoumarol - high intensity	14	14	17	14	14	15
Phenprocoumon - high intensity	-	16	-	18	17	18
Variability in INR (s)						
Acenocoumarol – low intensity	.34	.40	.37	.40	.44	.37
Phenprocoumon – low intensity	.23	.28	.24	.28	.33	.22
Acenocoumarol - high intensity	.36	.48	.42	.44	.53	.40
Phenprocoumon - high intensity	-	.32	-	.29	.36	.32

**No data provided for cells with less than 20 patients*

We examined these differences at individual clinics and found that at every clinic with a sufficient number of patients on both drugs, the interval between visits was longer and variability in the INR was lower for patients taking phenprocoumon (Table 2). Similarly the proportion of visits involving a change in dosage was lower and the time spent within the therapeutic range was higher for patients on phenprocoumon (Figure 1).

Because we observed substantial differences between clinics with respect to the control of anticoagulation and variability of the INR, we compared them on an annual basis for the three years for which we collected data to determine if there was substantial year-to-year variation (Table 3). In some instances, an insufficient number of observations was available to obtain a stable estimate. However, based on the data that were available, there was minimal year-to-year variation within clinics and the observed differences in between clinics appeared to be relatively constant.

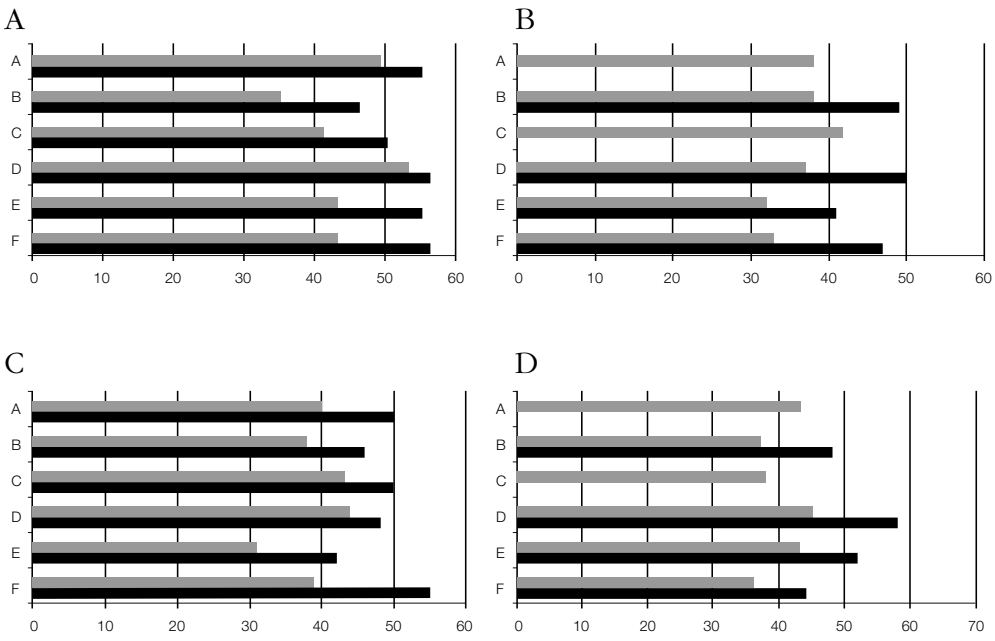

Figure 1: Frequency of dosage adjustments and percent of time INR within therapeutic range analysed according to anticoagulation clinic and coumarin anticoagulant used.
The letters A through F on the Y-axes represent individual anticoagulation clinics.
In each pair of bars, the upper bar presents data for acenocoumarol ( ) and the lower bar for phenprocoumon ( ).
The graph in upper left (A) displays the percent of monitoring visits at which no change in dosage was made for patients whose target INR was in the lower range.
The adjacent graph on the right (B) displays the same data for patients whose target INR was in the higher range.
The graph on the lower left (C) displays the percent of time during which the INR was within the therapeutic range for patients whose target INR was in the lower range.
The adjacent graph on the right (D) displays the same data for patients whose target INR was in the higher range.
No data are displayed for strata that contained fewer than 20 patients.

Table 3. Time-in-range and INR variability (s) stratified by coumarin drug, anticoagulation clinic and calendar year.

	A			B			C			D			E			F		
Year	**97**	**'98**	**'99**	**97**	**'98**	**'99**	**97**	**'98**	**'99**	**'97**	**'98**	**'99**	**'97**	**'98**	**'99**	**'97**	**'98**	**'99**
Percent of time-in-range																		
Acenocoumarol	51	49	45	35	35	37	40	42	41	52	52	49	*	45	41	41	42	41
Phenprocoumon	54	**	**	45	48	47	50	50	49	61	57	51	*	56	53	57	56	42
Variability in INR (s)																		
Acenocoumarol	.35	.35	.33	.40	.43	.41	.35	.37	.38	.39	.42	.42	*	.45	.48	.38	.38	.38
Phenprocoumon	.26	**	**	.29	.29	.29	.24	.24	.26	.24	.27	.35	*	.32	.35	.24	.28	.23

** Data from clinic F unavailable for 1997*

***No data provided for cells with less than 20 patients*

Discussion

In this study we used existing clinical data to compare the control of anticoagulation obtained using phenprocoumon and acenocoumarol. We found that patients treated with the former agent had consistent evidence of better control of anticoagulation and lower variability in their INR values. These findings are congruent with other studies that have compared these two drugs. Over 30 years ago, Breed and colleagues compared the stability and control of Thrombotest® results between 42 randomly selected patients who had been stably anticoagulated with acenocoumarol but were switched to phenprocoumon and 42 paired subjects who continued to take acenocoumarol.[13] During the subsequent six months the investigators observed that the patients who switched to phenprocoumon required about 10% fewer monitoring visits, were substantially more likely to have Thrombotest® results in the therapeutic range and had significantly lower variance in Thrombotest® results.[13] Other investigators over the past four decades have made similar findings as well.[11,14-17]

The probable basis for improved control and stability is the longer half-life of phenprocoumon (144 hours) compared with that of acenocoumarol (8-10 hours). Studies by several investigators have indicated that the very short half-life of acenocoumarol fails to maintain suppression of factor VII levels which rebound in the interval between doses.[17] The role of a longer half-life is further supported by studies demonstrating that warfarin, with a half-life of 36 hours, also provided greater control and stability than acenocoumarol.[18-20] There are few data available about possible differences between phenprocoumon and acenocoumarol in relation to the frequency and severity of drug-drug interactions which could also influence overall stability.

We also observed apparent differences in the degree of control and variability of the INR among the clinics we studied. The fact that these disparities were observed across years and for both acenocoumarol and phenprocoumon, suggests that they may reflect genuine differences in the techniques and procedures used to manage patients. They may also reflect differences in setting. One clinic, for example, is located at a major medical centre where surgical procedures are performed and a greater proportion of patients may have their anticoagulation interrupted and restarted. All of the other clinics are based in community settings.

Our observations serve to extend those of other investigators who have found that organised anticoagulation clinics appear to provide management that is of higher quality than that received by patients who are managed outside of such clinics.[1] We found that even among such clinics, there appear to be potentially important variations in the average level of control of the INR. To the extent that such variations reflect divergent policies and practices, it may be possible to identify optimal management strategies employed by certain clinics. It is worth noting, however, that the overall level of control of the INR, represented by the percent of time in range, that we observed was somewhat lower than reported in other settings. This in, in part, reflects that narrow therapeutic range used in Netherlands.

This study has several potential shortcomings that require comment. First, patients were not randomly assigned to therapy and it is conceivable that patients who were prone to be unstable were preferentially placed on the shorter-acting acenocoumarol in the hope

that the dosage could be adjusted more readily. It appears, however, that the choice between these drugs was made more on the basis of generic local preferences and that bias by indication was unlikely. Second, it is also conceivable that the relative experience of the different anticoagulation clinics in managing the two drugs played a role in the quality and stability of anticoagulation control, i.e., clinicians who were more familiar with one drug possessed greater proficiency in its use than they would in using the other drug. However, the consistent differences we observed across all clinics lend little credence to this hypothesis. In fact, the relative level of control among clinics was similar for both drugs. And third, this study did not address a number of factors that could potentially induce variability in the control of anticoagulation. For example, van der Meer and colleagues demonstrated a limited relationship between adherence and stability in the INR level.[21] Given an equivalent level of noncompliance, patients on phenprocoumon would be less apt to display wide swings in the INR. Similarly, with its short duration of effect, acenocoumarol might be presumed to be more susceptible to variations in the intake of vitamin K that can, in turn, cause the INR to vary.[22] And fourth, we did not examine the incidence of hemorrhagic or thrombotic complications for the two drugs. However, excessively high and low values of the INR have been shown to be closely associated with the risk of bleeding and thrombotic events, respectively.[1-4] Although, in one study, the rate of bleeding complications was actually slightly lower among patients taking acenocoumarol compared with phenprocoumon.[23]

Despite these theoretical shortcomings, this study has several strengths. First we obtained complete, clinical data on large groups that constituted essentially the entire populations of anticoagulated patients residing in six geographic regions. Second, the results that we observed were nearly uniform across all six anticoagulation clinics and were consistent with earlier studies.

Taken as whole, the results of this analysis and those published by other authors indicate that phenprocoumon should ordinarily be regarded as the first-line agent in circumstances where acenocoumarol is the only other option. Interestingly, this same recommendation was made in the past but exerted little apparent influence on practice.[24] Clinical concerns about the long half-life of phenprocoumon should be obviated by studies demonstrating the effectiveness of low doses of vitamin K in rapidly and safely reversing coumarin anticoagulation.[25-29] Whether control and stability with phenprocoumon is better or worse than that achieved with warfarin, which has a half-life that is intermediate between phenprocoumon and acenocoumarol, is a subject for further study.

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