ORIGINAL ARTICLE

Switching from acenocoumarol to warfarin in patients with unstable anticoagulation and its effect on anticoagulation control

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KEY WORDS

acenocoumarol, anticoagulation, INR, warfarin

ABSTRACT

INTRODUCTION Unstable oral anticoagulation increases the risk of thrombotic events and bleedings. Acenocoumarol use has been reported to be associated with two-fold higher risk for instability of anticoagulation control compared to warfarin administration.

OBJECTIVES The aim of the study was to evaluate the effect of introducing warfarin on anticoagulation control in patients with a variable response to acenocoumarol.

PATIENTS AND METHODS Sixty-eight subjects treated with acenocoumarol for 5 months or more and displaying intraindividual variability of international normalized ratio (INR) results were switched to warfarin. Unstable anticoagulation was defined as a failure to achieve a target INR within the preceding 3 months, i.e. ≥50% of 8 or more INR values below 2 or above 3.5. Patients with stable anticoagulation (<20% of out-of-range INRs), matched for age, gender, and anticoagulation indications, served as a reference group.

RESULTS Patients with unstable anticoagulation on acenocoumarol had higher body mass index ($p < 0.01$) and serum C-reactive protein levels ($p < 0.01$) compared to stable counterparts. The transition factor between acenocoumarol and warfarin was 1.8 (95% CI 1.69–1.96). The percentage time within the target INR range in patients with unstable anticoagulation was 40.2% at baseline and increased to 60.4% following 6 months on warfarin therapy ($p < 0.05$). The number of subjects with <20% of out-of-range INRs among individuals switched from acenocoumarol to warfarin was 22 (32.4%) vs. 63 (92.6%) in patients on stable anticoagulation after 6 months of follow-up ($p < 0.001$).

CONCLUSIONS Switching acenocoumarol to warfarin in patients with unstable anticoagulation can improve anticoagulation control.

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INTRODUCTION Vitamin K antagonists (VKAs) including warfarin (most commonly used worldwide), acenocoumarol, and phenprocoumon are highly effective in the prevention and treatment of thromboembolic disorders. The effectiveness and safety of oral anticoagulation is critically dependent on maintaining the prothrombin time, expressed as the international normalized ratio (INR).The current guidelines recommend a target INR of 2–3 for long-term oral anticoagulation in the secondary prevention of venous thromboembolism (VTE) and ischemic stroke in patients with atrial fibrillation.[1]

A dose of VKAs depends on several factors, predominantly diet and medications[2], or individual features such as age and body weight[3]. Genetic factors largely determine a dose of VKAs in patients regardless of the indication to anticoagulation.[4,5] Current evidence indicates that combined genotyping for the polymorphisms, CYP2C9*3 and –1639G>A or 1173C>T VKORC1 gene, predicts about 50% of the interindividual variability of the anticoagulation pharmacodynamic response.[6] The incidence of non-compliance among anticoagulated subjects has been estimated to be up to 30%.[7]

It has been shown that 10 to 30% of patients receiving long-term oral anticoagulation did not maintain stable anticoagulation monitored by measurement of INR, which increases the risk of thrombotic events or bleedings.[8,9] Several factors associated with unstable oral anticoagulation with several out-of-range INRs have been identified in case-control studies.[10] Increased odds ratio for unsuccessful INR control is more likely among patients professionally active or those with reduced mental capability impairing their compliance, and genetic cytochrome P450 CYP2C9 variants. Liver injury, renal insufficiency, or other concomitant diseases have not been reported to increase variability in anticoagulation control. This also held true for co-interventions.[10] Acenocoumarol (or acenocoumarin, the 4'-nitro analog of warfarin) is the most commonly used VKA in Poland, although in several countries, e.g. the United States of America, this anticoagulant agent is practically unavailable. Acenocoumarol use has been reported to be associated with more than twice higher risk for instability of anticoagulation control compared to warfarin administration (OR 2.63, 95% CI 1.23 –5.61).[10] To our knowledge, there has been no report which would specifically address the issue as to whether the switch from acenocoumarol to warfarin might improve anticoagulation control in everyday practice.

The aim of the study was to evaluate the effect of introducing warfarin in patients on chronic anticoagulant therapy with a variable response to acenocoumarol.

PATIENTS AND METHODS All eligible patients of both sexes aged ≤75 years were on chronic oral anticoagulation with acenocoumarol for at least 5 previous months and its expected duration was 6 months or more if their control of anticoagulation had been assessed as unsatisfactory and variable. Acenocoumarol was manual-dosed in an outpatient clinic.

Unstable anticoagulation was arbitrarily defined as a failure to achieve a target INR within the preceding 3 months, i.e. at least 50% of 8 or more INR values below 2 or above 3.5 (measurements performed in one- or two-week intervals). The INR values were determined by automated analyzers in large laboratories; for each patient, all INRs were measured using the same technique in the same laboratory. Patients who had stable anticoagulation, precisely defined as <20% of the last 6 or more INR values below 2 or above 3.5 within 3 to 6 months, and were matched for age, gender, and main anticoagulation indications served as a reference group.

Indications for long-term anticoagulation with VKAs were as follows:

1 an objectively confirmed episode of VTE

2 atrial fibrillation (AF) with or without cerebrovascular ischemic events

3 mechanical heart valve.

Exclusion criteria were as follows: known cancer or other severe concomitant diseases (renal failure [serum creatinine >120 umol/l], diabetes on insulin therapy, liver injury [alanine aminotransferase 1.5 times above the upper normal limit], autoimmune disorders, self-reported gastrointestinal disorders), acute illness, a history of bleeding requiring hospitalization, cognitive impairment, vegetarianism/veganism, a daily dose of acenocoumarol >12 mg, and use of drugs interfering with VKA metabolism such as barbiturates, carbamazepine, rifampicin, multivitamin supplements, and antibiotics (cardiovascular medications used on a long-term basis were allowed). Patients scheduled for major surgery or diagnostic procedure requiring discontinuation of anticoagulation within the study period and those who required stopping acenocoumarol before a 3-month period of unstable anticoagulation[11] were also excluded from the study. After obtaining written information in the form of a leaflet, all subjects were advised to refrain from products containing large amounts of vitamin K. Patients were asked about potential changes in diet, habits, co-medication, short-term illnesses, and scheduled invasive procedures at each visit.

Switching from acenocoumarol to warfarin (Warfin, Orion Pharma, Poland) was based on the manufacturer's instructions. Within the first month patients were asked to measure INRs at least once a week given at least 3 values within that month. Monitoring of anticoagulation was performed at least once a month. Follow-up period was 6 months.

All information regarding the quality of anticoagulation control during the 3 months before switching to warfarin and 6 months after initiation of this agent were recorded, including the number of visits, INR measurements, anticoagulant doses, time spent within and outside the therapeutic range. Stability of oral anticoagulation was evaluated based on the time in range, i.e. the proportion of time that patients had INRs within the recommended target range of 2–3, as described by Rosendaal et al.[12]

Routine laboratory tests, including hemoglobin, lipid profile, creatinine, glucose, fibrinogen, alanine aminotransferase (ALT), and C-reactive protein (CRP), were assayed by means of standard techniques in a single hospital laboratory.

Statistical analysis The Kolmogorov-Smirnov test was used to determine normal distribution. The Mann-Whitney U test or Student's t-test were used to test differences between groups as appropriate. The χ^2 test was used to compare categorical variables. The effect of the transition to warfarin was analyzed using Wilcoxon test for non-normally distributed data, otherwise with the t-test. A p-value <0.05 was considered statistically significant.

RESULTS Sixty-eight subjects treated with acenocoumarol and poor anticoagulation control were switched to warfarin and entered the final analysis. Characteristics of this group and

TABLE 1 Baseline characteristics of the study participants

	Unstable anticoagulation group (n = 68)	Stable anticoagulation group (n = 68)
age, years	57.4 ±12.3	58.3 ±13.3
males, n (%)	39 (57)	41 (60)
body mass index, kg/m^2	28.2 ±3.5[a]	26.1 ±2.9
current smokers, n (%)	16 (23.5)	24 (27.9)
diabetes, n (%)	8 (11.8)	7 (10.3)
hypertension, n (%)	38 (51.5)	33 (48.5)
venous thromboembolism, n (%)	33 (48.5)	28 (41.2)
atrial fibrillation, n (%)	27 (39.7)	29 (42.6)
prosthetic valve, n (%)	8 (11.8)	11 (16.2)
medications		
aspirin, n (%)	23 (33.8)	26 (38.2)
statins, n (%)	54 (79.4)	59 (86.8)
β-blockers, n (%)	51 (75.0)	55 (80.9)
angiotensin-converting enzyme inhibitors, n (%)	46 (67.6)	48 (70.6)
laboratory investigations		
total cholesterol, mmol/l	5.53 ±1.09	5.61 ±1.09
low-density lipoprotein cholesterol, mmol/l	3.38 ±0.83	3.47 ±0.78
high-density lipoprotein cholesterol, mmol/l	1.44 ±0.38	1.39 ±0.98
triglycerides, mmol/l	1.56 ±0.54	1.64 ±0.51
creatinine, umol/l	79.2 (62.1–97.4)	75.4 (60.2–95.6)
C-reactive protein, mg/l	2.14 (1.31–2.94)[a]	1.42 (1.03–2.42)
glucose, mmol/l	5.27 (4.02–6.83)	5.33 (4.12–6.68)
fibrinogen, g/l	2.54 ±0.49	2.45 ±0.44
hemoglobin, g/dl	13.2 ±1.5	13.8 ±1.7
alanine aminotransferase, IU/ml	26.3 ±2.6	25.7 ±2.9

Values are given as mean ±SD or median (IQR)

a intergroup difference at a p-value <0.05

similar patients with stable anticoagulation have been presented in TABLE 1. Baseline comparison of two groups differing with regard to stability of INR values showed that unstable anticoagulation was associated with higher body mass index and serum CRP levels. No differences in other variables were observed (TABLE 1). Duration of anticoagulation was similar in both groups (median 7 [5–10] vs. 8 [5–12] months).

Following 6 months of VKA switch all patients with unstable anticoagulation were taking warfarin. All routine tests yielded similar results compared to baseline values (data not shown). The transition factor between acenocoumarol and warfarin was 1.8 (95% CI 1.69 to 1.96). A mean dose of the latter anticoagulant was 7.61 ±1.28 mg/day (TABLE 2) and all but 5 patients took the same dose each day in contrast to 60 (88.2%) patients on acenocumarol from the control group who took varying doses in a three-day algorithms throughout the entire observation period. Doses of acenocoumarol remained unchanged in the stable anticoagulation group (TABLE 2). No thrombotic events or major bleedings were reported during the study. There were no INR values >5 during a 6-month follow-up. The percentage time within the target INR range improved significantly by 50.2% in the unstable anticoagulation group compared to the baseline values (p <0.01) and remained unaltered in stable controls on acenocoumarol (TABLE 2). A similar pattern of differences was observed for the percentage of time spent below and above the therapeutic range (TABLE 2). Standard deviation of INRs following introduction of warfarin decreased by 0.21 (p <0.001). The number of INR measurements and visits was similar before and after switch to warfarin in the unstable anticoagulation group and was higher while comparing to stable patients (TABLE 2). Following 6 months of follow-up the time spent within the target INR range vs. outside it remained unaltered in the reference stable anticoagulation group (TABLE 2). The percentage of subjects with <20% of out-of-range INRs from the group of individuals switched from acenocoumarol to warfarin was 32.4%, while at baseline none of patients met this criterion (TABLE 2). Still, a large percentage of unstable patients (67.6%) fulfilled the criteria for unsatisfactory anticoagulation control compared to patients on stable anticoagulation (>90%) throughout the entire analysis time (p <0.01).While dividing the whole group with unstable anticoagulation to subgroups with improved anticoagulation control on warfarin (n = 22) vs. their persistently unstable counterparts, we found that both subgroups were similar except for a higher prevalence of hypertension (p = 0.021), more frequent use of statins (p = 0.04) and aspirin (p = 0.042), and tendency to increased age in the former group (p = 0.07).

No significant differences in the level of anticoagulation control were found with regard to the main indication for anticoagulation both prior to and following switching to warfarin (data not shown).

DISCUSSION We demonstrated here that switching acenocoumarol to warfarin in patients with unstable anticoagulation can improve anticoagulation control. To our knowledge, there have been scanty data from interventional studies designed to compare the effect of the switch from one VKA to another in terms of stability of anticoagulation control. A few comparative analyses, mainly retrospective case-control studies on populations of rather limited sizes, have been published because acenocoumarol is used less and less frequently worldwide. Warfarin with a half-life of 36 hours has been reported to provide better anticoagulation stability combined with a lower bleeding risk compared to that observed while using a shorter half-life compound such as acenocoumarol (a half-life of 8 to 11 hours).[13] The advantage of warfarin has been at least in part attributed to fluctuations of the short-lived factor VII levels in plasma. However, other investigators failed to show significant differences in the stability

TABLE 2 Data on stability of anticoagulation control in both groups at baseline and 6 months after switching the unstable patients from acenocoumarol to warfarin

	Unstable anticoagulation group (n = 68)	Stable anticoagulation group (n = 68)
	prior to switching to warfarin	continued acenocoumarol
number of visits, n	2.3/month[a]	1.0/month
number of INR, n	2.3/month[a]	1.3/month
percentage of time		
within the target INR range	40.2%	87.5%
below the target INR range	35.7%	10.1%
above the target INR range	24.1%	2.4%
number of subjects with <20% of out-of-range INRs, n (%)	0 (0)	68 (100)
daily dose, mg	4.22 ±0.82	3.96 ±0.94
	following switching to warfarin	continued acenocoumarol
number of visits, n	2.5/month[a]	0.8/month
number of INRs, n	2.8/month[a]	1.3/month
percentage of time		
within the target INR range	60.4%[a]	91.1%
below the target INR range	18.9%[a]	6.8%
above the target INR range	20.7%[a]	2.1%
number of subjects with <20% of out-of-range INRs, n (%)	22 (32.4)[a]	63 (92.6)
daily dose, mg	7.61 ±1.28[a]	4.06 ±0.83

Values are given as mean ±SD or otherwise stated.

a intergroup difference at a $p < 0.05$

Abbreviations: INR – international normalized ratio

of anticoagulation control with an almost identical percentage of therapeutic prothrombin time at the similar mean number of visits per patient.[14] These discrepancy might be explained by different characteristics of the study population, for example we excluded patients who started anticoagulation as they were prone to greater variation in INRs and higher frequency of INR measurements. Furthermore, the definitions of unstable/stable anticoagulation control differed somewhat from those used in other studies, and some other measures of unstability, e.g. weekly dose changes (at least 15% of the previously prescribed coumarin weekly dose) in at least 40% of visits during the previous 4 months as a measure of anticoagulation stability[10] have not been used.

Of note, we have identified potential factors that increase the likelihood of improved chronic anticoagulation as a result of warfarin use instead of acenocoumarol. Higher prevalence of hypertension, more frequent use of statins and aspirin, and tendency to increased age observed in patients who became stable in terms of anticoagulation control on warfarin at 6 months seem to indicate that older patients with more comorbidities, taking more medications, could benefit from introducing a VKA taken in the same dose each day, which eliminates the risk of errors in dosage of VKAs. Tendency to better anticoagulation control in pensioners compared to working subjects had been reported previously.[10] Larger studies, however, are needed to validate this hypothesis.

The frequency of INR testing was comparable during administration of acenocoumarol and the subsequent warfarin. Exclusion of new patients starting oral anticoagulation permitted to avoid a population of subjects usually displaying a large variability of INRs. We cannot exclude the possibility that additional visits at a clinic and contact with physicians contributed to the improved anticoagulation control as observed by Palareti et al.[10], although no specific interviews or questionnaires evaluating knowledge or compliance were used in this study. Moreover, a subgroup of patients with artificial heart valves (n = 19) was also included although for this population a range of INR 2.5–3.5 is recommended; exclusion of these patients did not affect final results of the study.

In order to transform the warfarin dose to the acenocoumarol one, we used the transition factor between two VKAs of 1.5–2.0 depending on the last daily dose (acenocoumarol dose was multiplied by 1.5–2.0), and the final transition factor of 1.8 in this study was also identical to that of 1.85 published in 2008.[15] Our findings confirmed a practical utility of the transition factor calculated recently by van Leeuwen et al.[15]

It is known that intraindividual variation of INRs over time is multifactorial and a spectrum of the established predisposing factors is wide. Factors that have not been specifically addressed in this analysis were changes in physical activity, alcohol intake, socioeconomic status and the level of proper education.[16,17] Recently, it has been demonstrated that the use of a specific validated anticoagulation algorithm is likely to increase the number of patients with satisfactory anticoagulation control.[18,19]

An interesting observation is the fact that anticoagulated patients with variable INRs on acenocoumarol had enhanced inflammatory state as evidenced by significantly higher CRP levels, though they were largely below 3 mg/l, which excluded a major infection or typical inflammatory disease that was undiagnosed. Moreover, leaner subjects tended to have more stable anticoagulation control, which might suggest that some unreported changes in diet, including additional food intake, could contribute to variation in INRs in overweight patients. Given the fact that adipose tissue is a major source of interleukin-6 which stimulates hepatic CRP synthesis, both observations might be interrelated, although they are preliminary and should be specifically addressed in a larger study. It should be stressed that there was no difference in acenocoumarol dose between patients with stable and unstable anticoagulation, which is in line with previous studies.[10]

Several methodological limitations of the study should be acknowledged. First, the study population was small and follow-up period was short. It

is not clear if the use of warfarin instead of acenocoumarol is benficial in subjects with a late-onset variation in anticoagulation control. Because of the limited sample size, the subgroup analysis, including that based on indications for anticoagulation, could not be considered as reliable and larger studies are needed to validate observations derived from the current analyses. Second, INRs were determined in several local laboratories using likely different reagents. Moreover, data on the specific external laboratory quality control were not available. Third, since it has been demonstrated that lower intake of dietary vitamin K is associated with the risk of having INRs outside the recommended range and vitamin K supplementation (100–150 micrograms daily orally) improves stability of anticoagulation among patients with unexplained variability in response to VKAs[20], it might be speculated that low-dose vitamin K administered to some of the study participants can reduce variability in anticoagulation control. In the present study, dietary vitamin K intake by a questionnaire or targeted interview has not been assessed. Likewise, a potential impact of genetic factors, particularly allelic variants of cytochrome P450 2C9[10], has not been evaluated.

Concluding, we showed that in a subgroup of patients within the first year of anticoagulation with variable INR values transition from acenocoumarol to warfarin can improve control of anticoagulation. Such an improvement is more likely in older patients with comorbidities. However, a substantial percentage of patients on long-term coumarin therapy tend to have out-of-range INRs despite switching from one VKA to the other. Although recent advances in the development of new anticoagulants allow us to predict that some patients in whom good anticoagulation is a challenge will benefit from emerging, novel therapeutic options[21], now it should be highlighted that patient education with better INR monitoring, preferably at anticoagulation clinics, and control of lifestyle changes are of paramount importance in most anticoagulated patients with poor anticoagulation control.

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ARTYKUŁ ORYGINALNY

Zmiana acenokumarolu na warfarynę u pacjentów o niestabilnej antykoagulacji i jej wpływ na kontrolę antykoagulacji

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SŁOWA KLUCZOWE

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STRESZCZENIE

WPROWADZENIE Niestabilna antykoagulacja zwiększa ryzyko powikłań zakrzepowych i krwawień. Wykazano, że stosowanie acenokumarolu wiąże się z dwukrotnie większym ryzykiem stwierdzenia niezadawalającej kontroli antykoagulacji w porównaniu ze stosowaniem warfaryny.

CELE Celem badania była ocena efektu wprowadzenia warfaryny na kontrolę antykoagulacji u chorych, u których obserwowano zmienność odpowiedzi na acenokumarol.

PACJENCI I METODY Zastąpiono acenokumarol warfaryną u 68 pacjentów leczonych przeciwkrzepliwie przez co najmniej 5 miesięcy, a u których wyniki oznaczenia INR (*international normalized ratio* – INR) były zmienne. Niestabilną antykoagulację zdefiniowano jako nieosiągnięcie docelowych wartości INR w poprzedzających 3 miesiącach, tj. ≥50% spośród 8 lub więcej wyników INR poniżej 2 lub ponad 3,5. Pacjenci, u których antykoagulacja była stabilna i byli dobrani pod względem wieku, płci oraz wskazania do leczenia przeciwkrzepliwego stanowili grupę kontrolną. Pacjentów obu grup obserwowano przez 6 miesięcy.

WYNIKI Pacjenci cechujący się niestabilną antykoagulacją w czasie leczenia acenokumarolem mieli większy wskaźnik masy ciała ($p < 0,01$) i stężenie białka C-reaktywnego ($p < 0,01$) w porównaniu z osobami ze stabilną antykoagulacją. Przelicznik przy zmianie acenokumarolu na warfarynę wyniósł 1,8 (95% CI 1,69 to 1,96). Odsetek czasu, w którym pacjenci mieli INR w zakresie docelowym wynosił wyjściowo w czasie stosowania acenokumarolu 40,2% i zwiększył się do 60,4% po 6 miesiącach w czasie stosowania warfaryny ($p < 0,05$). Liczba pacjentów, u których zastąpiono acenokumarol warfaryną, a <20% ich wartości INR przekraczało zakres docelowy, wynosiła 22 (32,4%) w porównaniu z 63 (92,6%) chorymi o stabilnej antykoagulacji po 6 miesiącach ($p < 0,001$).

WNIOSKI Poprawę kontroli antykoagulacji można uzyskać, zamieniając acenokumarol na warfarynę u pacjentów ze zmiennymi wynikami INR.

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