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ORIGINAL ARTICLE

Quality control of oral anticoagulation with vitamin K antagonists in primary care patients in Poland: a multi-centre study

Jolanta Sawicka-Powierza[1], Krzysztof Buczkowski[2], Sławomir Chlabicz[1], Zbigniew Gugnowski[3], Katarzyna Powierza[4], Alicja Małgorzata Ołtarzewska[1]

[1]Department of Family Medicine, Medical University of Bialystok, Bialystok, Poland
[2]Department of Family Medicine, Collegium Medicum, Nicolaus Copernicus University, Torun, Poland
[3]Family Practice Centre, Gizycko, Poland
[4]Medical student, Medical University of Bialystok, Białystok, Poland

Abstract

Background: Vitamin K antagonists (VKAs) remain the mainstay of anticoagulation therapy, which requires monitoring of international normalised ratio (INR). Quality of oral anticoagulation, clinical benefits, and the risk related to VKA use are determined by the time in therapeutic range (TTR).

Aim: The aim of this study was to assess the therapeutic quality of oral anticoagulation and to determine the factors that affect the incidence of INR outside the recommended range in primary care patients undergoing long-term VKA therapy in Poland.

Methods: A multi-centre cross-sectional analysis was carried out in 15 general practices from three voivodeships of Poland. At the planned time, INRs measured closest to the designated date in all patients were assessed in terms of being within the therapeutic range. TTR was determined as the percentage of visits with INR in therapeutic range on a given date.

Results: Overall, 430 patients aged 70.3 ± 12.7 years (222 men aged 72 ± 12.8 years and 208 women aged 68.5 ± 12.4 years) were included in the study. In the groups with INR below, within, and above therapeutic range, the patients' age was 67.3 ± 13.4, 72 ± 12, and 70.5 ± 13 years ($p = 0.001$), respectively. TTR for all the participants was 55%. Statistically significant factors associated with INRs outside the therapeutic range were: age below 60 years (compared to older persons; $p = 0.003$), more or less frequent INR control compared to the recommended intervals of four to eight weeks ($p < 0.001$), and the type of the VKA used, i.e. acenocoumarol compared to warfarin ($p < 0.001$). Logarithmic regression analysis showed that the use of acenocoumarol compared to warfarin, increased the chances of INRs below therapeutic range (odds ratio [OR] 3.19; 95% confidence interval [CI] 1.65–6.16), while male sex increased the probability of INR being above this range (OR 2.01; 95% CI 1.12– 3.59).

Conclusions: The TTR in primary care patients on VKA therapy was 55%. Better quality of oral anticoagulation with VKA could be achieved by using warfarin instead of acenocoumarol, proper INR monitoring in the recommended interval of four to eight weeks, and tighter INR control in younger and male patients.

Key words: vitamin K antagonists, primary care, time in therapeutic range, quality of oral anticoagulation

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INTRODUCTION

Vitamin K antagonists (VKAs) have constituted the mainstay of anticoagulation therapy for many years, despite the introduction of the so-called new oral anticoagulants (non-vitamin K antagonist oral anticoagulants) that do not require laboratory monitoring of anticoagulant effects. There are two VKAs available in Poland, warfarin and acenocoumarol. Warfarin has a half-life of 36 h to 42 h, and acenocoumarol 6 h to 8 h. Both drugs are administered in the treatment and prevention of venous thromboembolism, in the prevention of systemic

Address for correspondence:
Jolanta Sawicka-Powierza, MD, Department of Family Medicine, Medical University of Bialystok, ul. Mieszka I 4B, 15–054 Białystok, Poland, e-mail: jolasawicka@gmail.com

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embolism in patients with nonvalvular atrial fibrillation or valve diseases, and in patients with mechanical heart valve prosthesis. VKA treatment is effective in decreasing the risk of thromboembolic complications, but it also increases the risk of severe bleeding in those patients [1].

According to guidelines, VKA therapy effectiveness is measured by the international normalised ratio (INR) at intervals of four to eight weeks [1, 2]. Clinical benefits and the risk related to VKA use are determined by the time in therapeutic range (TTR). TTR in patients taking VKAs may be assessed by three different methods: 1) the fraction of INRs that are in the recommended range, 2) a cross-section of the patient's files [3], and 3) the Rosendaal linear interpolation method [4]. The advantages and disadvantages of each method have been widely discussed in literature [5–9]. However, according to comparative evaluation of TTR measurements, it is recommended that all three metrics be used to manage anticoagulation patients in a clinic or medical group practices [10].

The key reason for carrying out this study was the lack of multi-centre studies carried out by general practitioners aimed at evaluating anticoagulation effectiveness in Polish urban and rural populations. Most of the publications so far pertained to specialist care [11, 12] or to primary health care studies carried out in a single practice [13]. The aim of this study was to assess the therapeutic quality of oral anticoagulation and to determine factors that affect the incidence of INR outside the recommended range in primary care patients undergoing long-term VKA therapy in Poland.

METHODS

Study population

A multi-centre cross-sectional analysis of all patients on long-term VKA therapy was performed in 15 general practices in three Polish voivodeships (Podlaskie, Kujawsko-Pomorskie, and Warminsko-Mazurskie) in March 2015.

Five general practices were randomly chosen from each voivodeship. The total population of the three voivodeships was 4,725,877 people. The number of patients in practices that participated in the study amounted to 27,168, of whom 511 individuals were receiving long-term VKA therapy. Target INR range was from 2.0 to 3.0 or from 2.5 to 3.5. Patients' data were retrieved from electronic databases of primary care practices participating in the study. The obtained data contained information about sex, age, place of residence, education, frequency of INR ratio examination, recommended therapeutic range of INR, indications for anticoagulant treatment, administered medication (warfarin or acenocoumarol), and INR values. The main exclusion criterion from the study was single or dual antiplatelet therapy. In addition, individuals on treatment for less than three months, patients whose therapy had to be discontinued due to scheduled invasive procedures, and individuals who failed to report for the scheduled INR measurement were excluded from the study.

Overall 511 patients on long-term VKA therapy from 15 general practices were enrolled, which constituted approximately 1.9% of the practices' population. Of the 511 subjects 81 were excluded, i.e. 31 individuals treated for less than three months, 16 patients whose therapy was discontinued due to invasive procedures, and 34 individuals who failed to show up for the test on the scheduled date.

Measurements

All patients undergoing long-term VKA treatment performed their INR measurements within the scheduled time, which allowed a standardised comparison of prothrombin time regardless of the reagent used. A cross sectional method for % INR within therapeutic range (percentage of visits within the range on a given date) was used to calculate TTR. This method was calculated by taking INRs of the patients whose values were within range at one point in time (the INR measurement that was closest to the midpoint of the scheduled date ± seven days) divided by the total number of INRs measured in all patients during that time [3].

Statistical analysis

Patients with INR values within therapeutic range and those with INR values out of range were compared with the t-Student test. The correlation between pairs of variables was evaluated using the Pearson χ^2 test. The impact of different independent factors on the dependent variable 0–1 was evaluated with logarithmic regression analysis. A p-value < 0.05 was considered statistically significant.

Informed, written consent was obtained from each subject. The Ethics Committee of the Medical University of Bialystok approved the study (R-I-002/478/2014).

RESULTS

The study group included 430 patients aged 70.3 ± 12.7 years (222 men aged 72 ± 12.8 years, and 208 women aged 68.5 ± 12.4 years). Patients over 60 years of age constituted 80.9% of the examined population. The most common indication for a long-term VKA therapy was stroke prevention in patients with nonvalvular atrial fibrillation. The recommended target INR range in the majority of patients was between 2.0 and 3.0. Most of the patients reported for INR control in the recommended intervals of four to eight weeks. Acenocoumarol was the most commonly administered VKA in our study group (Table 1).

Time in therapeutic range in all the participants was 55% and did not significantly differ between the voivodeships. INR within the therapeutic range was found in 54.7% of patients (105 men, 130 women), below the range in 30.9% (66 men, 67 women), and above in 14.4% (37 men, 25 women). The age of patients with INR values below, within, and above the therapeutic range was 67.3 ± 13.4, 72 ± 12, and 70.5 ± 13 years ($p = 0.001$), respectively. The highest value

Table 1. Baseline characteristics of patients on long-term vitamin K antagonist (VKA) treatment (n = 430)

Characteristics	N (%)
Participants (total)	430 (100%)
Sex:	
Male	222 (51.6%)
Female	208 (48.4%)
Age [years]:	
< 50	31 (7.2%)
50–59	51 (11.9%)
60–69	107 (24.9%)
70–79	143 (33.2%)
≥ 80	98 (22.8%)
Education level:	
Higher	109 (25.4%)
Secondary	167 (38.8%)
Basic	154 (35.8%)
Place of residence:	
City ≥ 300,000 residents	232 (54%)
City < 300,000 residents	142 (33%)
Village	56 (13%)
Target therapeutic range of INR:	
2.0–3.0	380 (88.4%)
2.5–3.5	50 (11.6%)
Indication:	
Nonvalvular atrial fibrillation	283 (65.8%)
Venous thromboembolism	97 (22.6%)
Mechanical heart valves and others	50 (11.6%)
Frequency INR ratio examination:	
More than every 4 weeks	81 (18.8%)
In the interval of 4 to 8 weeks	316 (73.5%)
Less than every 8 weeks	33 (7.7%)
Type of VKA:	
Warfarin	91 (21.2%)
Acenocoumarol	339 (78.8%)
Voivodeship of Poland:	
Podlaskie	165 (38.4%)
Warminsko-Mazurskie	149 (34.6%)
Kujawsko-Pomorskie	116 (27%)

Data are shown as number (percentage). INR — international normalised ratio

of INR was 8.85, while the lowest was 0.86. During the study, we did not detect any thromboembolic and haemorrhagic complications among patients with INR outside the therapeutic range. However, a high risk of developing thromboembolic complications was observed in 7.4% of the individuals (16 men and 16 women) with INR ≤ 1.5, while a high risk of developing haemorrhagic complications was found in 2.6% of patients (seven men, four women) with INR ≥ 4.5.

All the participants were analysed for factors that could cause INR to fall out of therapeutic range. It was found that statistically significant factors contributing to INRs outside range were as follows: age — individuals up to 60 years showed a worse INR control compared to older persons; more or less frequent INR control than in the recommended intervals of four to eight weeks, and type of applied VKAs — worse anticoagulation control was observed in patients taking acenocoumarol compared to those on warfarin (Table 2).

In further analysis, in which INR within the therapeutic range (dependent variable) was assumed as 0 and INR outside the range (below and above) was assumed as 1, significant independent predictors leading to INRs outside the therapeutic range were established using logarithmic regression analysis. It was observed that both administration of acenocoumarol and male sex were significant independent predictors of INRs outside the therapeutic range, while age between 60 and 69 years compared to age < 50 and ≥ 70 years decreased the probability of INRs being outside the therapeutic range. Moreover, assuming the dependent variable INR in therapeutic range as 0 and INR below as 1, the use of acenocoumarol was an independent predictor of INRs below the range, while age > 60 years decreased the odds ratio of INRs below the therapeutic range. Similarly, assuming the dependent variable INR within therapeutic range as 0 and INR above the range as 1, male sex was the only significant independent predictor of INRs being above therapeutic range (Table 3).

DISCUSSION

This study showed that TTR in primary care patients on long-term VKA therapy in Poland was low, at 55%. Only 235 of the 430 patients in the study had INR within the therapeutic range; the remaining patients showed inadequate therapeutic control. Patients whose INR was outside the range were at risk for thromboembolic or bleeding complications. This study also determined which factors significantly affected INR values; they included: age up to 60 years, more or less frequent INR control than in recommended intervals of four to eight weeks, and type of applied VKAs (acenocoumarol vs. warfarin). The use of acenocoumarol was a significant independent predictor of INR values below the range, and male sex was the only significant independent predictor of INR being above the therapeutic range.

Maintenance of adequate anticoagulation among patients on VKAs is a worldwide problem. Comparable results to ours have been shown in other studies, with a mean TTR of 53.7% [14] and 49.6% [15]. On the other hand, some authors presented good quality anticoagulation in patients on warfarin, with a mean TTR of 66.5% [16] and even TTR of 84% in the Leiden Thrombophilia Study [17]. A study conducted

Table 2. Factors affecting the incidence of international normalised ratio (INR) within and outside the therapeutic range

Characteristics	INR within the therapeutic range	INR outside the therapeutic range	p
Participants (total)	235 (54.7%)	195 (45.3%)	
Sex:			0.093
Male	105 (50.5%)	103 (49.5%)	
Female	130 (58.6%)	92 (41.4%)	
Age [years]:			**0.003**
< 50	12 (38.7%)	19 (61.3%)	
50–59	17 (33.3%)	34 (66.7%)	
60–69	64 (59.8%)	43 (40.2%)	
70–79	81 (56.6%)	62 (43.4%)	
≥ 80	61 (62.2%)	37 (37.8%)	
Education level:			0.168
Higher	68 (62.4%)	41 (37.6%)	
Secondary	86 (51.5%)	81 (48.5%)	
Basic	81 (52.6%)	73 (47.4%)	
Place of residence:			0.647
City ≥ 300,000 residents	232 (54%)	101 (43.5%)	
City < 300,000 residents	142 (33%)	66 (46.5%)	
Village	56 (13%)	28 (50%)	
Indication:			0.060
Nonvalvular atrial fibrillation	166 (58.7%)	117 (41.3%)	
Venous thromboembolism	47 (48.5%)	50 (51.5%)	
Mechanical heart valves and others	22 (44%)	28 (56%)	
Frequency INR ratio examination:			**< 0.001**
More than every 4 weeks	33 (40.7%)	48 (59.3%)	
In the interval of 4 to 8 weeks	192 (60.8%)	124 (39.2%)	
Less than every 8 weeks	10 (30.3%)	23 (69.7%)	
Type of VKA:			**< 0.001**
Warfarin	65 (71.4%)	26 (28.6%)	
Acenocoumarol	170 (50.1%)	169 (49.9%)	

Data are shown as number (percentage). VKA — vitamin K antagonist

Table 3. Predictors of the incidence of international normalised ratio (INR) outside, below, and above the therapeutic range in vitamin K antagonist (VKA) treated patients assessed in logarithmic regression analysis

Variables		β	OR (95% CI)	P
Predictors affecting the occurrence of INR outside range vs. INR within the range (n = 430)				
Age [years]	60–69	–0.49	0.61 (0.39–0.98)	**0.039**
Sex	Male	0.41	1.51 (1.02–2.25)	**0.041**
Type of VKA	Acenocoumarol	1.0	2.73 (1.63–4.56)	**< 0.001**
Predictors affecting the occurrence of INR below range vs. INR within the range (n = 368)				
Age [years]	60–69	–1.0	0.37 (0.19–0.7)	**0.003**
	70–79	–0.83	0.44 (0.23–0.81)	**0.009**
	≥ 80	–1.17	0.31 (0.15–0.63)	**0.001**
Type of VKA	Acenocoumarol	1.16	3.19 (1.65–6.16)	**0.001**
Predictors affecting the occurrence of INR above range vs. INR within the range (n = 297)				
Sex	Male	0.3	2.01 (1.12–3.59)	**0.018**

CI — confidence interval; OR — odds ratio

in primary care patients of four European countries (France, Germany, Italy, and the United Kingdom) showed that the proportion of patients with poorly controlled anticoagulation varied from 34.6% in the United Kingdom to 55.8% in Germany [18].

Only a few studies aimed at the evaluation of TTR have been carried out in Poland. Dereziński et al. [13] analysed the effectiveness of oral anticoagulation in 104 patients in the population of a single general practice. They analysed 964 INR measurements among patients and found that only 548 (56.84%) of them were in the therapeutic range during a one-year observation [13]. This result was consistent with the outcome of our study. Ciurus et al. [11] examined 149 warfarin-treated patients in a cardiology clinic and showed that anticoagulation assessment was satisfactory and mean TTR was 76% ± 21%. Undas et al. [12] demonstrated an improvement in anticoagulation quality in 68 patients by switching from acenocoumarol to warfarin and obtaining an increase in TTR from 40.2% to 60.4% during six months of follow-up. The authors suggested that switching from acenocoumarol to warfarin in patents with unstable anticoagulation could improve oral anticoagulation control [12]. Because a different method of determining TTR was used, it was difficult to compare these results with ours. However, better anticoagulation quality in patients on warfarin was also noted in our study, and the use of acenocoumarol was a significant independent predictor of increased odds ratio of an INR below the range. Despite various methods, the conclusions of this study were consistent with our findings.

It seems that in Poland acenocoumarol treatment was applied in the majority of ambulatory patients, although application of VKA with a longer half-life, such as warfarin, is in accordance with recommendations [10]. The use of warfarin instead of acenocoumarol in the first phase of improving anticoagulation in patients of general practitioners seems to be a simple method to implement. Other studies also confirm our findings, where overall treatment quality was much better in patients on warfarin compared to individuals on acenocoumarol [19].

We also revealed that patients aged up to 60 years had worse oral anticoagulation control than older individuals. Similar results were presented by other authors, who also suggested that younger age was associated with poorer anticoagulant control [14], that patients aged ≥ 65 years had higher TTR value than patients < 65 years, and that age had an influence on TTR through greater drug adherence [20].

More or less frequent INR control than in the recommended intervals of four to eight weeks could indirectly influence the stability of anticoagulation treatment by too rare or too frequent changes in the VKA dose. Our observations are confirmed by the observational study in which authors suggested that better INR control could be much improved by changing the warfarin dose only when INR is 1.7 or lower and 3.3 or higher [21].

There are some limitations to our study. The comparison of our TTR values with the results obtained using other methods may raise some concerns. Using the traditional method (the fraction of INRs within range), TTR was calculated by taking the number of INRs within therapeutic range for all patients divided by the total number of INRs measured during the selected time interval. It is a simple method and can be compared to the approach used by us. As regards the linear interpolation Rosendaal method, TTR was calculated using the INR-DAY software. Here, it is assumed that a linear relationship exists between two INR values and allows a specific INR value to be assigned to each day for each patient. In the study by Schmitt et al. [9] no differences between cross-section and fraction of methods were found. However, a low TTR with the use of the Rosendaal method compared to other methods was observed but reasons for this observation remained unclear [9]. Barbui et al. [7] found no differences between TTR values in the method based on calculation of the fraction of INRs within range and the linear interpolation method.

In conclusion, TTR in primary care patients on long-term VKA therapy was 55%. Better therapeutic quality control of oral anticoagulation with VKAs can be achieved using warfarin instead of acenocoumarol, proper measurements of INR in the recommended intervals of four to eight weeks, and tighter INR control in younger and male patients.

Conflict of interest: *none declared*

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