

Do patients with a history of systemic embolism have better compliance in international normalized ratio control?

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What's new?

Among patients with AF chronic anticoagulant therapy with vitamin K antagonists (VKA) is suboptimal. Unfortunately, history of thromboembolic events did not cause better international normalized ratio (INR) control. Patients with a history of systemic embolism and very high risk for thromboembolic complications more often had INR below the therapeutic range than the rest of the patients with AF. It can be partly explained by the fact that patients with very

high thromboembolic risk at the same time usually have a high risk of bleeding. We may assume that patients with multiple factors associated with inadequate INR may not be ideal candidates for VKA therapy. These patients should be possibly considered for non-vitamin K antagonist oral anticoagulants (NOACs). Further efforts should be made in Poland to improve the quality of antithrombotic care in patients with AF treated with VKA.

Abstract

Background: Vitamin K antagonists (VKA) remain viable oral anticoagulants (OAC) for many patients because of their availability and cost.

Aim: The aim of the study was to assess the quality of VKA control in patients with atrial fibrillation admitted to the hospital and the influence of quality of VKA control on in-hospital mortality.

Methods: We retrospectively studied 907 patients with atrial fibrillation (AF). The INR was calculated as the prothrombin time ratio, which uses the International Sensitivity Index (ISI) for an exponent. We recorded one single measurement of INR on admission.

Results: A total of 422 patients with AF on VKA (245 male, 59%; mean age 71 ± 10 years) were included in the analysis. Of the total international normalized ratio (INR) values, 33% were in the therapeutic range of 2.0-3.0, 46% were below,

and 21% were above this range. Patients with $INR < 2$ more frequently had a history of systemic embolism (6% vs 2%; $p=0.04$). In the multivariate logistic regression model, odds of $INR < 2$ was higher in patients with a history of systemic embolism (OR = 2.95; 95% CI: 1.01-8.59; $p = 0.05$). INR control did not differ between patients with and without a history of stroke (29% vs 33%, $p = 0.7$). In patients with AF and a history of stroke, in-hospital mortality was significantly higher (8% vs 2%; $p = 0.04$).

Conclusions: Among patients with AF chronic anticoagulant therapy with VKA is suboptimal. Unfortunately, history of ischemic stroke did not cause better INR control. Patients with a history of systemic embolism and very high risk for thromboembolic complications more often had INR below the therapeutic range than the rest of the patients with AF.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and remains one of the major causes of stroke, systemic embolism, cardiovascular morbidity and mortality in the world [1]. This arrhythmia occurs in approximately 3% of the general population [2,3], with greater prevalence in the elderly and in patients with cardiovascular risk factors such as hypertension, heart failure, coronary artery disease, valvular heart disease, obesity, diabetes and chronic kidney disease [4-11].

Oral anticoagulation (OAC) is an effective therapy recommended for the prevention of thromboembolic complications such as ischemic stroke or systemic embolism in high-risk patients with AF [1]. Treatment with warfarin reduces all-cause mortality by 26% and the rate of stroke by 64% in this population [12-15]. Although non-vitamin K antagonist oral anticoagulants (NOACs – dabigatran, rivaroxaban, apixaban, edoxaban) are available, vitamin K antagonists (VKA – warfarin, acenocoumarol) remain a viable OAC for many patients because of their availability and cost [16, 17].

The therapeutic range for VKA therapy is defined in terms of the international normalized ratio (INR) [18,19].

Nevertheless, data coming from studies such as the GARFIELD-AF registry suggest that a large proportion of patients with AF have poor VKA control and these patients have higher risk of stroke or systemic embolism, major bleeding and all-cause mortality [20]. Patients after ischemic stroke are in a kind of vicious circle which indicates the high risk of recurrent stroke. Fifty percent of patients after ischemic stroke have another such event within the next five years [21, 22].

The aim of the study was general assessment of the quality of VKA control according to single measurement of INR on admission to the hospital in patients with AF according to the history of thromboembolic events. We also investigated the influence of quality of VKA control on in-hospital all-cause mortality in an AF population.

Methods

Study population

We retrospectively studied 907 patients with the diagnosis of AF hospitalized in the Reference Cardiology University Centre in Poland in the years 2016-2017. We excluded patients in whom oral anticoagulation was discontinued before admission to hospital due to planned procedures such as pacemaker implantation, implantable cardioverter-defibrillator implantation, implantation of devices for resynchronization therapy and percutaneous coronary interventions. There were the following reasons for admission to the hospital: paroxysmal symptomatic AF, persistent AF for electrical cardioversion, ablation of AF, exacerbation of heart failure, exacerbation of coronary artery disease, syncope, syncope with trauma, rhythm disturbances other than AF, uncontrolled hypertension.

Demographic data such as age, sex, medical history and current OAC were determined for all patients. INR was recorded on admission. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the local ethics committee. The primary end-point was in-hospital mortality.

INR

The INR is calculated as the prothrombin time ratio (patient prothrombin time/mean of normal prothrombin time for laboratory) ISI, which uses the International Sensitivity Index (ISI) for an exponent, and is dependent on the specific reagents and instruments used in the measurement. We recorded one single measurement of INR on admission, which reflects the general effectiveness of anticoagulation.

Echocardiographic analysis

Left ventricular ejection fraction (LVEF) was assessed in transthoracic echocardiography using the modified biplane Simpson's method (Philips Ultrasound System EPIQ 7) and was derived in accordance with the recommendations of the European Society of Echocardiography [23].

Statistical analysis

Data are expressed as means and standard deviations (SD). Relative frequencies are used to present categorical variables. Student’s t test, the Wilcoxon rank-sum test and the chi-square test were used for statistical analysis where applicable. Logistic regression was used to test associations between variables and outcomes. Multinomial logistic regression was used to evaluate the association between variables and in-hospital mortality. A p value of less than 0.05 was considered as statistically significant. The statistical software StataIC (data analysis of statistical software) version 13, was used.

Results

Baseline characteristics

A total of 422 patients with AF on VKA (245 male, 59%; mean age 71 ± 10 years) were included in the analysis. Paroxysmal AF was present in 44% (n = 186), persistent in 10% (n = 42), permanent in 46% (n=194) of the patients. Hypertension was present in 74% (n = 312), diabetes in 27% (n=114), chronic kidney disease (CKD) in 24% (n = 101), ischemic heart disease (IHD) in 46% (n = 186) and chronic heart failure (CHF) in 72% (n = 304) of the patients. CHA2DS2-VASc score was 5.1 ± 1.8 and HAS-BLED score was 3.4 ± 1.4. Clinical characteristics of the population are shown in Table 1.

Table 1. Clinical characteristics of the population and comparison between patients with therapeutic and non-therapeutic INR

	All patients (n=422)	Therapeutic INR (n=139)	Non-therapeutic INR (n=283)	p-value
Females (%)	41	38	43	0.27
Age [years]	71±10	70±10	71±10	0.32
CHA2DS2-VASc score *	5.12±1.8	4.9±1.7	5.2±1.7	0.1
Type of AF				
Paroxysmal (%)	43	48	41	0.2
Persistent (%)	11	14	9	0.12
Permanent (%)	46	38	50	0.03
Hypertension (%)	74	72	76	0.38
Diabetes mellitus (%)	27	30	26	0.43
Coronary artery disease (%)	46	48	45	0.55
Chronic heart failure (%)	72	67	74	0.14
Chronic kidney disease (%)	24	22	25	0.62
Previous TIA/stroke (%)	6	5	6	0.7
Previous systemic embolism (%)	4	2	5	0.18
In-hospital mortality (%)	2	2	2	0.61

Data are presented as mean and standard deviation; AF – atrial fibrillation; TIA – transient ischemic attack

VKA control

Overall, the mean INR was 2.33 ± 1.3. Of the total INR values, 33% were in the therapeutic range of 2.0-3.0, 46% were below, and 21% were above this range.

Patients with good INR control less often had permanent type of AF (38% vs 50%; p = 0.03) (Table 1). In the multivariate logistic regression model, odds of the therapeutic range of INR was lower in patients with permanent AF (OR = 0.63; 95% CI: 0.41-0.97; p = 0.04) (Table 2).

Table 2. Multivariate regression model.

Odds of therapeutic INR in AF patients	OR	95% CI	p-value
Odds of therapeutic INR in AF patients	OR	95% CI	p-value
Age	0.99	0.97-1.02	0.8
Male	1.25	0.81-1.94	0.3
History of stroke	0.91	0.36-2.26	0.83
History of systemic embolism	0.45	0.12-1.59	0.21
Permanent type of AF	0.64	0.41-0.97	0.04
Odds of INR <2 in AF patients	OR	95% CI	p-value
Age	0.99	0.97-1.01	0.46
Male	1.06	0.71-1.59	0.77
History of stroke	2.03	0.86-4.80	0.1
History of systemic embolism	2.95	1.02-8.59	0.04
Permanent type of AF	1.08	0.73-1.61	0.68

AF – atrial fibrillation; OR – odds ratio; CI – confidence interval, INR – international normalized ratio

Patients with INR < 2 more frequently had a history of systemic embolism (6% vs 2%; p = 0.04) and had been treated with warfarin (39% vs 27%; p = 0.01). There were no differences in mortality (p = 0.8), CHA2DS2-VASc score (p = 0.7) or type of AF (p = 0.7). In the multivariate logistic regression model, odds of INR <2 was higher in patients with a history of systemic embolism (OR = 2.95; 95% CI: 1.01-8.59; p = 0.05) (Table 2).

Patients who received acenocoumarol more often had DM (31% vs 20%; p = 0.01), IHD (50% vs 38%; p = 0.02) and the therapeutic range of INR (58% vs 45%; p = 0.01) as compared to warfarin.

Male vs female

Female patients were significantly older (73 ± 9 vs 69 ± 10 years; p < 0.001), more often had hypertension (81% vs 70%; p = 0.01), a history of stroke (9% vs 4%; p = 0.03) and had a higher CHA2DS2-VASc score (5.9 ± 1.7 vs 4.5 ± 1.6; p < 0.0001) as compared to males. The value of INR control was similar between men and women (p = 0.2).

Patients with thromboembolic events

Ten percent of the patients had experienced thromboembolic events in the past. History of stroke was present in 6% (n

= 25) of the patients and history of systemic embolism in 4% (n = 16). Patients with AF and a history of stroke were more frequently male (p = 0.03) and had a higher CHA2DS2-VASc score (6.3 ± 2.1 vs 5.0 ± 1.1; p < 0.001). In this population in-hospital mortality was significantly higher (8% vs 2%; p = 0.04). INR control did not differ between patients with and without a history of stroke (29% vs 33%, p = 0.7). The percentage of patients within the therapeutic range on warfarin (29% vs 33%, p = 0.7) and acenocoumarol (54% vs 40%, p = 0.2) was similar.

In-hospital mortality

In the study population the in-hospital mortality was 2% (n = 8). The in-hospital mortality was higher in males (p = 0.001), patients with higher CHA2DS2-VASc score (p = 0.05) and with a history of stroke (p = 0.04). In the multivariate logistic regression model, odds of in-hospital death were higher only in males (OR = 0.09; 95% CI: 0.01-0.72; p = 0.024) (Table 3).

Table 3. Odds of in-hospital mortality.

	OR	95% CI	p-value
Age	1.02	0.95-1.10	0.47
Male	0.09	0.01-0.73	0.02
History of stroke	3.11	0.59-16.22	0.18
Permanent type of AF	1.22	0.33-4.51	0.76

AF – atrial fibrillation

Discussion

This study revealed that only 33% of the patients with AF admitted to the hospital had INR within the therapeutic range, the remaining patients showed inadequate therapeutic control. The only factor which significantly and negatively affected INR values within the therapeutic range was permanent type of AF. Patients with a history of systemic embolism and high risk for thromboembolic complications significantly more often had INR below the therapeutic range. History of ischemic stroke did not cause better INR control.

VKA is still used very frequently all over the world but maintenance of proper anticoagulant therapy is still a crucial problem. A study in which the authors enrolled 138 319 patients with AF on warfarin in the national assessment of warfarin therapy in the USA had a mean time in therapeutic range (TTR) about 54%. It improved with time on treatment, increasing from 48% for patients with less than 6 months of testing to 58% for those with more than 6 months of INR control. The number of patients assessed per physician practice was positively associated with TTR. Female sex, young age and low income were independently associated with poorer control of anticoagulant treatment with INR [24].

TTR is used in research studies, but rarely in clinical practice. In everyday clinical management we very often assess the latest INR. Individual TTR is calculated according to Rosendaal's linear interpolation method. [25]. This method is not ideal because it assumes that changes between consecutive INR measurements are linear over time. The method seems to allow the researcher to allocate a specific INR value to each day for each patient. TTR has crucial significance especially if anticoagulant therapy has just started.

Gurwitz et al. conducted a study that investigated the safety of warfarin therapy in the nursing home setting. The percentages of time in the less than 2, between 2 and 3, and more than 3 INR ranges were 36.5%, 49.6%, and 13.9%, respectively [26]. The Leiden Thrombophilia Study in patients with recurrent venous thrombotic events presented better INR control with TTR of 84% [27]. A study conducted by Cotte et al. revealed that the percentage of patients with poorly controlled treatment varied from 35% in the United Kingdom to 56% in Germany. The stroke rate was 0.5/100 person-years in patients with good control, compared with 1.0/100 in patients with poor control. The incidence of hemorrhage was 1.1 and 1.3 events/100 person-years, respectively. The authors underlined that INR in everyday community care is frequently outside the therapeutic range, and patients are exposed to an unnecessary risk of both stroke and bleeding [28].

The study carried out in Poland by Dereziński et al. analyzed the effectiveness of anticoagulation in primary care. They analyzed 964 INR measurements and found that only 56.84% of them were within the therapeutic range during the one-year follow-up. Moreover, they found no correlation between the number of INR measurements and effectiveness of treatment. The minority of patients (30%) had more than 70% of INR measurements within the limit of the therapeutic range [29].

Similar results were presented by Sawicka-Powierza et al., where the TTR value in 430 patients was 55% [30]. It is noteworthy that in the above-mentioned study male gender was the only obvious and significant independent predictor of INR results above the upper limit of the therapeutic range. In our study INR control was similar among both sexes.

Community-based practice data presented good quality of anticoagulation in patients on warfarin with mean TTR of 66.5% [31]. According to the ORBIT-AF registry only 59% of all INR values were in the therapeutic range. Warfarin patients followed at special anticoagulation clinics had higher median TTR (69%) than those patients not followed at such clinics (66%) [32]. In this registry patients with poorer control were more often female, nonwhite and had less college education.

Nevertheless, a report from the Swedish quality register Auricula showed that efficient warfarin therapy with a mean TTR of 76.5% is possible to achieve in routine clinical care with unselected patients. Moreover, the authors claim that warfarin treatment with proper therapeutic values of INR performs well, and should not be ruled out in favor of NOACs although NOACs according both to randomized trials and registries are safer than warfarin, because they cause significantly fewer major bleeding events and especially dramatically reduce the rate of intracranial bleeding [33]. Some NOACs even have their specific reversal agents – idarucizumab for dabigatran and andexanet alfa for rivaroxaban – which raises safety of the anticoagulant treatment especially in the case of life-threatening bleeding or emergency settings [34]. Although NOACs are nowadays the preferred therapeutic option according to European Society of Cardiology guidelines, patients with markedly reduced renal function, especially with eGFR < 30 ml/min, benefit from VKA treatment [35]. Also patients after kidney transplantation are limited to use of VKA [36, 37, 38]. From

the latest trials we know already that NOACs combined with antiplatelet agents cause significantly less bleeding than combination of warfarin and antiplatelet agents [39].

Generally the poor control of anticoagulant treatment with VKA can be partly explained by the fact that patients with very high thromboembolic risk at the same time usually represent high risk of bleeding. We may assume that patients with multiple factors associated with inadequate INR may not be ideal candidates for VKA therapy. These patients should be possibly considered for NOACs. Further efforts should be guaranteed in Poland to improve the quality of antithrombotic care in patients with AF treated with VKA.

What is the way to improve the quality of the anticoagulation therapy apart from strict INR control then? Undas et al. observed that switching acenocoumarol to warfarin in patients with unstable anticoagulation improves the quality of anticoagulation. The factor of transition between acenocoumarol and warfarin was assessed as 1.8. The TTR in patients with poor anticoagulation was 40.2% at baseline and rose to 60.4% during 6 months on the treatment with warfarin ($p < 0.05$) [40]. In our study the percentage of patients within the therapeutic range on warfarin and acenocoumarol was similar. However, individuals with INR below 2 on admission were more often treated with warfarin. Type of VKA did not influence the in-hospital mortality.

It is worth noting that in our population with a history of stroke in-hospital mortality was significantly higher (8% vs 2%; $p = 0.04$). Patients with AF and a history of stroke were slightly older, more often had the permanent type of atrial fibrillation, and had a significantly higher CHA₂DS₂-VASc score (6.3 ± 2.1 vs 5.0 ± 1.1 ; $p < 0.001$), which means that they more often had significant comorbidities such as coronary artery disease, diabetes mellitus, and chronic kidney disease. Although the differences were numerically higher, they did not reach statistical significance. There are very scarce data in the literature on prognosis in patients with a history of stroke during hospitalizations due to other reasons than stroke as compared to the rest of the population with AF.

We believe that these data are of value in the population of patients with AF treated with vitamin K antagonist oral anticoagulants. The strength of our study is the inclusion of 'real-world' patients treated with vitamin K antagonist oral anticoagulants admitted to the hospital for various reasons except for elective procedures.

This study has all the limitations of an observational study as the decision about antithrombotic treatment and the doses of the drugs were entirely at the discretion of the treating physician. We did not have enough data to analyze a long follow-up. Unfortunately data regarding the therapy and the baseline laboratory tests are not available. We would like underline that conclusions regarding outcome data should be evaluated with caution due to the retrospective nature of the study.

In conclusion, among patients with AF chronic anticoagulant therapy with VKA is suboptimal. Unfortunately, a history of ischemic stroke did not cause better INR control. Patients with a history of systemic embolism and very high risk for

thromboembolic complications more often had INR below the therapeutic range than the rest of the patients with AF.

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