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Evaluation of the anticoagulant effect of vitamin K antagonists in patients with non-valvular atrial fibrilation

Ispitivanje antikoagulantnog efekta antagonista vitamina K kod bolesnika sa nevalvularnom atrijalnom fibrilacijom

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Abstract

Background/Aim. Despite the introduction of new oral anticoagulants (dabigatran, rivoroxaban, apixaban), vitamin K antagonists (VKA), such as warfarin and acenocoumarol are still the most widely used oral anticoagulants for the treatment of nonvalvular atrial fibrillation (NVAF). The time in therapeutic range (TTR) represents a measure of the quality of the anticoagulant effect of these drugs, and it is considered that the lower value of TTR is associated with the adverse effects of therapy. The aim of this study was to evaluate of the effectiveness of VKA therapy in patients with NVAF and to identify factors affecting the anticoagulation efficacy. M**ethods.** A retrospective study was conducted on a population of 725 outpatients with NVAF, treated with VKA and followed in the Blood Transfusion Institute of Niš, Serbia, from January to December 2017. Laboratory control of the INR was done from capillary blood of patients on Thrombotrack Solo (Axis Shield, Norway) and Thrombostat (Behnk Elektronik, Germany). Targeted therapeutic INR was between 2.0 and 3.0. For each patient all available INR values were evaluated to calculate the individual TTR according to the Rosendaal method. **Results**. The study included a total of 725 patients with NVAF which had 6,105 INR measurements, what was 8.13 ± 2.47 INR measurements per patient. The mean value of TTR and was 60.15 ± 17.52%, but 49.72% of patients had TTR less than 60%. Patients were at high risk of thrombosis in 6.15% of time (INR < 1.5) and high risk of bleeding in 2.2% of time (INR > 4.5). The most significant independent factors affecting the quality of VKA therapy were gender, arterial hypertension, diabetes mellitus and the use of amiodarone and antiplatelet drugs (aspirin, clopidogrel). **Conclusion.** The TTR is undoubtedly useful indicator of the VKA treatment effectiveness. The most important predictors of poorer efficacy of VKA therapy are: arterial hypertension, diabetes mellitus, patients' gender and the use of amiodarone and antiplatelet drugs (aspirin, clopidogrel). To improve the quality of VKA therapy, education of patients and better collaboration with them, as well as a successful teamwork of clinicians are also imperative.

Key words:
anticoagulants; atrial fibrillation; blood coagulation tests; dose-response relationship, drug; vitamin k.

Apstrakt

Uvod/Cilj. I pored uvođenja novih oralnih antikoagulantnih lekova (dabigatran, rivoroksaban, apiksaban), antagonisti vitamina K (AVK), kao što su varfarin i acenokumarol, još uvek su najčešće primenjivani oralni antikoagulantni lekovi u terapiji nevalvularne atrijalne fibrilacije (NVAF). Vreme u terapijskom opsegu (*Time in Therapeutic Range* – TTR) predstavlja meru kvaliteta antikoagulantnog efekta tih lekova, te se smatra da su niže vrednosti TTR udružene sa neželjenim efektima terapije. Cilj rada bio je da se utvrde efikasnost terapije AVK kod bolesnika sa NVAF i faktori koji utiču na kvalitet antikoagulantnog efekta tih lekova. **Metode**. Retrospektivnom analizom obuhvaćeno je 725 bolesnika sa NVAF koji su ambulantno praćeni u Zavodu za transfuziju krvi u Nišu, u periodu januar-decembar 2017. godine. Laboratorijsko određevanje međunarodnog normalizovanog

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odnosa (*International Normalized Ratio* – INR) vršeno je iz kapilarne krvi bolesnika na aparatima Trombotrack Solo (*Axis Shield, Norveška*) i Thrombostat (*Behnk Elektronik, Nemačka*). Ciljni terapijski INR bio je između 2,0 i 3,0. Na osnovu svih dostupnih vrednosti INR za svakog bolesnika pojedinačno, određen je individulani TTR metodom po Rosendaal-u. **Rezultati.** Ispitivanjem su bila obuhvaćena ukupno 725 bolesnika sa NVAF kojima je u toku 2017. godine urađeno 6,105 kontrola INR (8,13 ± 2,47 INR kontrola po bolesniku). Srednja vrednost TTR bila je 60,15 ± 17,52%, ali je 49,72% bolesnika imalo TTR < 60%. Bolesnici su imali visok rizik od tromboze u 6,15% vremena (INR < 1,5), a u 2,2% vremena visok rizik od krvarenja (INR > 4,5). Najznačajniji nezavisni faktori koji su uticali na kvalitet AVK terapije bili su: pol i arterijska hipertenzija, dijabetes melitus, upotreba amiodarona i antitrombocitnih lekova (aspirin, klopidogrel). **Zaključak.** Parametar TTR je nedvosmisleno koristan pokazatelj efikasnosti antikoagulantnog efekta AVK. Najznačajniji prediktori lošije efikasnosti AVK su: pol, arterijska hipertenzija, dijabetes melitus, upotreba amiodarona i antitrombocitnih lekova (aspirin, klopidogrel). U cilju unapređenja kvaliteta primene i monitoringa antikoagulantnog efekta AVK neophodna je pravilna edukacija i bolja saradnja sa bolesnicima, ali i bolji timski rad kliničara.

Ključne reči:
antikoagulansi; fibrilacija pretkomora; krv, testovi koagulacije; lekovi, odnos doza-reakcija; vitamin k.

Introduction

Despite the implementation of new oral anticoagulants for the treatment of patients with atrial fibrillation or venous thromboembolism, vitamin K antagonists (VKA) such as warfarin, acenocoumarol and phenprocoumon are still the most widely used oral anticoagulants. The most common indications for their use are atrial fibrillation, mitral or aortic stenosis, mitral or aortic prosthetic valve, venous thromboembolism and intracavitary thrombosis [1, 2]. This therapy is long lasting, for months and years, and in some cases till the end of life. The mechanism of action of these drugs is based on their competition with the vitamin K and reduction the level of vitamin K dependent coagulation factors (FII, FVII, FIX, FX), an anticoagulant protein C and its cofactor protein S [3].

The use of VKA must be regularly and often laboratory controlled in order to ensure the adequacy of therapy and to avoid subdosing or drug overdose. The most commonly used test for the control of oral anticoagulant therapy is the prothrombin time (PT), expressed in international normalised ratio (INR) system, which provides an internationally standardized monitoring of the treatment. Therapeutic range for INR is from 2.0 to 3.5, depending on the indication for which the drug is used [4]. Therapeutic ranges are generally set up on the basis of clinical trials and are determined in order to achieve the required minimum coagulating effect for the prevention of recurrent thrombosis or lasting of existing thrombotic episodes. The treatment carries, on the one hand, the risk of bleeding, and on the other hand, the risk of thrombosis because warfarin and other VKA have a narrow therapeutic index and should be dosed within strictly defined ranges [3, 5].

The time in therapeutic range (TTR) is commonly used to evaluate the quality of VKA therapy and is an important tool for assessing the risks of this therapy. TTR estimates a percentage of time a patient's INR is within the desired therapeutic range and is widely used as an indicator of anticoagulation control [6–8]. Numerous studies have shown that higher TTR correlates with good clinical outcomes, and that there is a strong correlation between TTR and adverse events (bleeding, thrombosis). But although TTR is routinely assessed, there is no consensus on acceptable target for TTR in practice. Active-W study suggested a minimum TTR of 58% in order to show a benefit of oral anticoagulant therapy over antiplatelet therapy in terms of preventing vascular events [9], RE-LY study on Portuguese patients showed mean TTR of 61% [10, 11], Thrombosis Canada states that good INR control is when TTR is more than 60% [12], but there are studies that report elevated level of TTR of 74% as a measure of effective anticoagulation [8, 13]. It is known that many factors correlate with TTR, and the most important are age, sex, smoking, concomitant drugs, alcohol, comorbid medical and psychiatric conditions [14].

The aim of this study was to evaluate the effectiveness of VKA therapy and to identify factors affecting anticoagulation efficacy in patients with NVAF.

Methods

A retrospective study was conducted on a population of 725 outpatients with atrial fibrillation, treated with VKA [warfarin (Farin®), acenocoumarol (Sintrom®, Sinkum®, Acenokumarol®)] and followed in the Department for Hemostatic Disorders Testing in the Blood Transfusion Institute of Niš, Serbia from January to December 2017. The study included patients of both sexes who had strictly determined diagnosis of nonvalvular atrial fibrillation (NVAF) and indication for the use of VKA (the target INR 2.0–3.0), patients who were expected to take VKA throughout the whole period of the study and that control testing of INR would be done only at the mentioned Institute. We excluded patients who had discontinued treatment for any reason at any time of investigation, patients who had interruption in taking VKA for any reason, patients who made any of the control of INR in another facility, patients who had changed target INR during the investigation, as well as patients with INR > 6.0. We recorded demographic and clinical characteristics of the patients, as well as the use of other drugs (beta-blockers, antiplatelet drugs, statins, amiodarone, ACE inhibitors).

Laboratory control of the INR was done from capillary blood of the patients on Thrombotrack Solo (Axis Shield, Norway) and Thrombostat (Behnk Elektronik, Germany). For each patient we evaluated all available INR values to calculate the individual TTR according to the Rosendaal method [15]. This method uses linear interpolation to assign an INR value to each day between successive observed INR values [INR-DAY software program (Dr FR Rosendaal, Leiden, Netherlands)]. The primary outcome was to determine TTR, and the secondary outcomes were to determine time under (INR < 2.0) and over therapeutic range (INR > 3.0), time with increased thrombotic risk (INR < 1.5) and time with increased hemorrhagic risk (INR > 4.5), as well as to determine independent factors for increased risk of worse anticoagulation therapy.

Statistical analysis was performed using Statistical Package for Social Science (SPSS Software GmbH, Germany), version 15.0. The results are presented in tables and graphs, using the mean values and standard deviations. Qualitative characteristics of the investigated variables are given as frequency (n) and the percentage (%). The continuous data were analyzed using χ^2 test. Multivariate logistic regression analysis was performed to identify independent risk factors for TTR < 60%. The results were considered to be statistically significant at a $p < 0.05$. Since it was "*post-hoc*" analysis from the prospective observational registry, we could not exclude the presence of unmeasured selection bias, and statistical analyses were not specified before the data were seen, which could be some kind of study limitation.

Results

Out of the total of 725 patients in this study, there were 430 (59.40%) men and 295 (40.60%) women. The average age of patients was 71.05 ± 10.42 years, range from 22 to 88 years. There was no statistically significant difference in the age structure of patients by gender ($t = 1.125$; $p = 0.043$). Table 1 shows the main characteristics of the patients.

Table 1

Characteristics of patients with nonvlavular atrial fibrillation (n = 725)

Characteristics	Values
Age (years)	71.05 ± 10.42
Gender (male/female)	430 (59.40) / 295 (40.60)
Previous stroke/TIA	111 (15.35)
Hypertension	524 (72.30)
Previous AMI	232 (32.00)
Vascular disease history	138 (19.10)
Diabetes mellitus	162 (22.40)
Concomitant drugs	
β-blockrers	624 (86)
statins	565 (78)
aspirin	275 (38)
clopidogrel	152 (21)
amiodaron	138 (19)
ACE-inhibitors	522 (72)

***Note*: Values are given as number (percentage) of the patients or mean ± standard deviation.**
AMI – acute myocardial infarction; TIA – transient ischemic attack; ACE – angiotensin-converting enzyme.

During the one year follow-up of patients on VKA therapy, a total of 6,105 INR measurements were done, which was 8.13 ± 2.47 INR measurements per patient. Average number of days between INR measurements was 34.89 ± 17.26. Characteristics of anticoagulant therapy during the investigated period are shown in Table 2.

Table 2

Characteristics of anticoagulant therapy in patients with nonvalular atrial fibrillation (n = 725)

Characteristics	Values
Total number of INR mesurements	6,105
Number of INR mesurements per patient	8.13 ± 2.47
Number of days between INR measurements	34.89 ± 17.26
Drug	
warfarin	436 (60.10)
acenokoumarol	259 (39.90)
Daily dose of drug (mg)	
warfarin	4.7 ± 1.26
acenokoumarol	3.58 ± 1.47

***Note*: Values are given as number (percentage) of the patients or mean ± standard deviation.**
INR – international normalized ratio.

The mean TTR was 60.15 ± 17.52%. More than a fifth of time, the patients had INR under therapeutic range (INR < 2.0 in 21.05% of time), while in 18.10% of time, patients had INR > 3.0. A high risk of thrombosis (INR < 1.5), patients had in 6.15% of time, and in 2.20% of time, they were at high risk of bleeding (INR > 4.5).

During the period of examination there were no major bleedings, while 65 (8.96%) of the patients had minor bleedings, mainly in the form of bruises, haematoma and epistaxis, whereas 4 (0.55%) of the patients had haematuria and 3 (0.41%) of the patients had bleeding from the gastrointestinal tract. After adjusting the dose of VKA, bleedings were stopped.

Distribution of TTR values is shown in Figure 1. It can be seen that 49.72% of the patients had TTR less than 60% which means that almost half of the patients was at increased risk for serious complications of treatment.

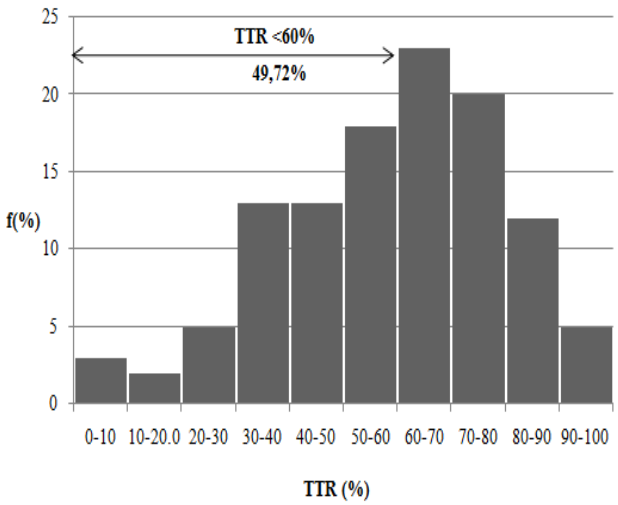

Fig. 1 – Histogram with relative frequencies of time in therapeutic range (TTR).

Table 3 shows logistic regression model of independent factors for the assessment of increased risk of poor effect of anticoagulation therapy. The whole model was highly significant [χ^2 (df = 9, n = 725) = 20.637; $p < 0.001$] and explained 57.81% of the variance of efficiency of VKA. Factors that gave statistically significant contribution to the model were: gender, arterial hypertension, diabetes mellitus and the use of amiodarone, aspirin and clopidogrel.

Table 3

Logistic regression model of independent factors for assessing the efficiency of vitamin K antagonists

Factors	OR	95% CI	*p*
Age	1.223	0.065–8.480	0.092
Gender	3.870	1.065–12.060	0.040
Previous stroke/TIA	1.590	0.951–2.682	0.076
Hypertension	2.082	1.049–4.133	0.036
Previous AMI	0.502	0.050–2.880	0.061
Diabetes mellitus	3.100	2.330–4.150	0.240
Amiodarone	11.360	4.870–26.520	< 0.001
Aspirin	4.820	1.150–20.190	0.031
Clopidogrel	5.200	1.520–12.760	0.008

OR – odds ratio; CI – confidence interval; TIA – transient ischemic attack; AMI – acute myocardial infarction.

Discussion

Anticoagulant drugs are used in the treatment or prevention of thromboses and thromboembolic complications. Traditional VKA, which have been in use for over 50 years are the gold standard in therapy for all that time. They provide the necessary protection from thromboembolic events and have proven to be sufficiently effective over many years of use. One of the most common indications for VKA therapy is atrial fibrillation and guidelines recommend that patients who are at low risk may be treated only with aspirin, while in patients at high risk, it is recommended to use VKA [2, 16, 17]. Anticoagulant therapy reduces stroke rate by 64% and mortality rate by 26% in this group of patients [18]. But, VKA therapy has disadvantages and the most important are: unpredictable response, narrow therapeutic window, routine monitoring, slow start/stop action, often dose adjustment, numerous interactions with food and drugs, resistance to warfarin, procoagulant effect of warfarin at the beginning of the therapy. However, the most severe complication of VKA therapy is intracranial hemorrhage, whose rate is about 1% in clinical studies [19].

The efficiency and safety of VKA depend strongly on the TTR value, which is a measure of the period in which a patient is in an optimal INR range. However, although TTR is generally accepted as a measure for monitoring of the anticoagulant effect of drugs and the successful conduction of this therapy, there are no strengthened data what is accepted value of TTR. Recent trials related to the introduction of new oral anticoagulants have provided data of actual TTR values in different countries of the world. In the ROCKET-AF study, the mean TTR was 55.2%, but the values in Western Europe and North America were significantly higher, 63% and, the mean TTR was 66% [21], in the RE-LY study 67.2%, with the highest values of 77% in Sweden and 74% in Finland and Australia [10, 11]. On the other hand, Gateman et al. [8] calculated the mean TTR in the St. Paul Family Health Network in Ontario of 58.05% [8], while the mean TTR in the study of Ciurus et al. [1] is 76% that is considered to represent excellent anticoagulation control [1]. According to our study, the mean value of TTR is 60.15% during a follow-up of one year, and it is lower than that reported from big clinical trials, but still correlates with the number of the existing data in the literature. Also, the value is greater than the minimum TTR of 58% at which there is a benefit of anticoagulant therapy over antiplatelet therapy in terms of preventing vascular events [9]. Especially important result of our study was the fact that 49% of patients had TTR less than 60%, indicating that almost half of the patients were at increased risk of serious adverse events, both of bleeding and thrombosis.

This fact imposes a deeper analysis of management of the anticoagulant therapy in our institution, which involves the study of the relationship between patient and transfusion physician, identifying and understanding the factors which may have the influence on the quality of the therapy, the behavior of the patients in accordance with established criteria, as well as the modification of VKA therapy in accordance with comorbidities and other drugs that must be introduced into therapy afterward. The INR values that are out of therapeutic range require high-speed control (in a short period of time), which enhances the number of patients on a daily and monthly basis, increasing the cost of treatment, and, additionally, they are the risk factor for complications of VKA treatment which may be potentially very serious for patients.

Great variations in the values of TTR show that the anticoagulant effect of VKA is affected with a great number of factors. Our investigation showed that gender, arterial hypertension, diabetes mellitus and the use of amiodarone, aspirin and clopidogrel were associated with lower probability of staying within the target INR. The strongest independent factor for bad anticoagulation control was use of amiodarone, which is the most widely used antiarrhythmic in atrial fibrillation. It is known that amiodarone has a negative impact on the anticoagulant effect of VKA, because it inhibits the hepatic metabolism of warfarin, potentiating its anticoagulant effect and resulting in high INR values and increased risk of bleeding [22, 23]. The same effect has the concomitant use of antiplatelet therapy (aspirin and/or clopidogrel), which also potentiates the anticoagulant effect of VKA and increases the risk for bleeding. A large number of studies have shown that although this combination of drugs can potentially prevent both thromboembolism and atherothrombotic events, it is also associated with an increased risk of severe bleeding and requires careful consideration of all the risks and benefits [24, 25]. A large, nationwide investigation in Denmark showed that a risk for severe bleeding in patients taking VKA and aspirin was 1.8-fold increased, 3.5-fold increased in patients taking VKA and clopidogrel, and 4-fold increased in patients taking triple therapy [26]. Looking at the same problem from the other hand,

our recent investigation of different preparations of aspirin (acetylsalicylic acid) in patients with stable coronary disease has also shown that there is an increased effect of aspirin in patients receiving anticoagulant therapy, so there is an increased risk for bleeding [27].

Gender also stands out as a significant predictor of bad anticoagulation implying that women respond poorer to VKA treatment, so there is far more difficult to achieve good control than in men. The reason for this effect is unclear, but previous studies have confirmed this fact and have shown that women are at greater risk of atrial fibrillation-related stroke during VKA treatment, as a result of poor anticoagulant effect of warfarin [14, 28, 29].

The impact of arterial hypertension on anticoagulant therapy has not been precisely defined, although it has been studied in numerous investigations. Therefore, Apostolakis et al. [14] have shown that hypertension is associated with lower TTR, while on the other side, the Veterans AffaiRs Study to Improve Anticoagulation (VARIA) [30] did not confirm this relationship. Our investigation showed that arterial hypertension is a predictor of poor anticoagulation, and possible explanation of this influence may be associated with interaction of drugs [31]. Finally, diabetes mellitus, as a predictor of the poorer effect of VKA is associated with increased levels of the procoagulant clotting factors (FII, FVII) and a decrease of anticoagulants, such as thrombomodulin, with abnormal fibrinolytic pathway and decreases fibrinolysis [32, 33]. In these patients, most often there is a disorder of renal function, which leads to the abnormal elimination of these drugs and the poorer anticoagulant effect.

Since of the various effects of VKA and the impact of a number of factors to this therapy it is developed a new era of anticoagulation which is a crucial for all patients who do not have sufficient anticoagulant protection or where the TTR is less than 60%. These are direct oral anticoagulants or new oral anticoagulants (also called a target-specific anticoagulants): on one side, dabigatran, which is a direct inhibitor of thrombin, and on the other side inhibitors of FXa: rivaroxaban, apixaban, edoxaban. A number of meta-analyses have shown that these drugs have a better safety profile than VKA, lower incidence of bleeding, especially intracranial or gastrointestinal, have fewer interactions with food than VKA, achieve faster antithrombotic effect, and during their use, there is no need for regular monitoring because of predictable pharmacokinetics [34–36]. Compared with warfarin, dabigatran is associated with a reduced risk of ischaemic stroke, intracranial haemorrhage and mortality, but with an increased risk of major gastrointestinal bleeding. It is the only anticoagulant with a specific antidote idarucizumab. Inhibitors of FXa are recommended for patients with mild renal impairment (only 1/3 of the drug is renal eliminated), and those with high risk of bleeding, and/or potential drug-drug interactions.

Conclusion

The TTR is undoubtedly proved and useful indicator of the effectiveness of VKA anticoagulant treatment. The most important predictors of poorer VKA therapy efficacy are: arterial hypertension, diabetes mellitus, patients' gender and the use of amiodarone and antiplatelet drugs (aspirin, clopidogrel). To improve the quality of VKA therapy, an education of patient and better collaboration with them, as well as a successful team-work of clinicians are also imperative.

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