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UDC:

DOI: https://doi.org/10.2298/VSP181214008S

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
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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 non-valvular atrial fibrillation (NVAF). 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 study aim was to evaluate of the effectiveness of VKA therapy in patients with NVAF and to identify factors affecting the anticoagulation efficacy. Methods. A retrospective study was conducted on a population of 725 outpatients with NVAF, treated with VKA and followed in Blood Transfusion Institute of Niš 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 we evaluated all available INR values to calculate the individual TTR according to the Rosendaal method. Results. The study included a total of 725 patients with NVAF which had 6105 INR measurements, what is 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 a 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 are gender, arterial hypertension, diabetes mellitus and the use of amiodarone and antiplatelet drugs (aspirin, clopidogrel). Conclusion. The TTR is undoubtedly useful indicator of the effectiveness of VKA treatment. The most important predictors of poorer efficacy of VKA therapy are arterial hypertension, diabetes mellitus, patients' gender and the use of amiodarone and antiplatelet (aspirin, clopidogrel) drugs. To improve the quality of VKA therapy, education of patient and better collaboration with them, as well as a successful teamwork with clinicians are also imperative.

Key words: vitamin K antagonists; anticoagulation; time-in-therapeutic-range.

Apstrakt

Uvod/Cilj. I pored uvodenja novih oralnih antikoagulantnih lekova (dabigatran, rivoroxaban, apixaban), antagonisti vitamina K (AVK), kao što su varfarin i acenokumarol još uvek jesu najčešće primjenjivani oralni antikoagulantni lekovi u terapiji nevalvularne atrijalne fibrilacije (NVAF). Vreme u terapijskom opsegu (TTR-Time in Therapeutic Range) predstavlja meru kvaliteta antikoagulantnog efekta ovih lekova, te se smatra da su niže vrednosti TTR-a udužene sa neželjenim efektima terapije. Cilj ovog rada je bio utvrditi efikasnost AVK terapije kod pacijenata sa NVAF i izdvojiti faktore koji utiču na kvalitet antikoagulantnog efekta ovih lekova. Metode. Retrospektivnom analizom obuhvaćeno je 725 pacijenata sa NVAF koji su ambulantno praćeni u Zavodu za transfuziju krvi Niš u periodu januar-decembar 2017. godine. Laboratorijska kontrola INR-a radena je iz kapilarne krvi pacijenata na aparatima Trombotrack Solo (Axis Shield, Norveška) i Thrombostat (Behnk Elektronik, Nemačka). Ciljani terapijski INR je bio između 2,0 i 3,0. Na osnovu svih dostupnih vrednosti INR-a za svakog pacijenta ponašob je određen individuelni TTR metodom po Rosendaal-u. Rezultati. Ispitivanje je obuhvatio ukupno 725 pacijenata sa NVAF kod kojih je u toku 2017. godine urađeno 6105 kontrola INR-a,
što predstavlja $8,13\pm2,47$ INR kontrola po pacijentu. Srednja vrednost TTR-a je bila $60,15\pm17,52\%$, ali je $49,72\%$ pacijenata imalo TTR < $60\%$. Pacijenti su bili u visokom riziku za trombozu u $6,15\%$ vremena (INR < $1,5$), dok su u $2,2\%$ vremena bili u visokom riziku za krvarenje (INR> $4,5$). Najznačajniji nezavisni faktori koji utiču na kvalitet AVK terapije su: pol, arterijska hipertenzija, dijabetes, upotreba amiodarona i antitrombocitnih lekova (aspirin, klopidogrel). **Zaključak.** TTR je nedvosmisleno koristan pokazatelj efikasnosti antikoagulantnog efekta AVK. Najznačajniji prediktori lošije efikasnosti AVK su pol, arterijska hipertenzija, dijabetes, upotreba amiodarona i antitrombocitnih lekova (aspirin, klopidogrel). U cilju unapredjenja kvaliteta primene i monitoringa AVK antikoagulantne terapije neophodna je pravilna edukacija i bolja saradnja sa pacijentima, ali i uspešna interdisciplinarna saradnja sa kliničkim lekarima.

**Ključne reči:**
vitamin K antagonisti, antikoagulantni efekat, vreme u terapijskom opsegu.

**Introduction**

Despite the implementation of new oral anticoagulants (NOAC) 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. 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 co-factor protein S. The use of VKA must be regularly and often laboratory controlled in order to ensure the adequacy of therapy and to avoid sub-dosing or drug overdose. The most commonly used test for the control of oral anticoagulant therapy is the prothrombin time (PT), expressed in 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. 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, so warfarin and other VKA have a narrow therapeutic index and should be dosed within strictly defined ranges.

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. The 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. RE-LY study on Portuguese patients showed mean TTR of $61\%$. Thrombosis Canada states that good INR control is when TTR is more than $60\%$, but there are studies that report elevated level of TTR on $74\%$ as a measure of effective anticoagulation. 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.

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

**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 Department for hemostatic disorders testings in Blood Transfusion Institute of Niš from January to December 2017. The study included patients of both sexes who had strictly determined diagnosis of 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 study and that control testing of INR would be done only at the Institute. We excluded patients who had discontinued treatment for any reason at any time of investigation, patients who have had interruption in taking VKA for any reason, patients who have done any of the control of INR in another facility, patients that had changed target INR during the investigation, as well as patients with INR > 6.0. We have characterized the demographic and clinical characteristics of the patients, as well as the use of other drugs (β-blockers, antiplatelet drugs, statins, amiodarone, ACE inhibitors).

Laboratory control of the INR was done from capillary blood of 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. 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 the 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 (SD). Qualitative characteristics of the investigated variables are given as frequency (N) and the percentage (%). The continuous data were analyzed using Chi-square 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 is “post-hoc” analysis from the prospective observational registry, we cannot exclude the presence of unmeasured selection bias, and statistical analyses were not specified before the data was seen, which could be some kind of study limitation.

**Results**

From the total of 725 patients in this study, there were 430 men (430/725 or 59.40 %) and 295 women (295/725 or 40.60 %). The average age of patients in the study 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.
During the one year follow-up of patients on VKA therapy a total of 6105 INR measurements were done, which is 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.

The mean TTR was 60.15±17.52%. More than a fifth of the time 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. Time in therapeutic range and time out of therapeutic range in investigated patients are shown in Figure 1.

Figure 1.

During the period of examination there were no major bleedings, while 65 patients (65/725 or 8.96%) had minor bleedings, mainly in the form of bruises, hematoma and epistaxis, whereas 4 patients (4/725 or 0.55%) had haematuria and 3 patients (3/725 or 0.41%) had bleeding from the gastrointestinal tract. After adjusting the dose of VKA bleedings were stopped.

Figure 2 shows distribution of TTR values, where we can see that 49.72% of patients have a TTR less than 60%, which means that almost half of the patients was at increased risk for serious complications of treatment.

Figure 2.

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 ($\chi^2$ (df = 9, N = 725) = 20.637; $p < 0.001$) and explained 57.81% of the variance of efficiency of VKA. The 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.

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 presents 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 has reduced a rate of stroke by 64% and mortality by 26% in this group of patients. 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 (ICH), 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 the patient was in an optimal INR range. However, although the 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 ROCKET-AF study the mean TTR was 55.2%, but the values in Western Europe and
North America were significantly higher, 63% and 64%, respectively 18. In ARISTOTLE
study the mean TTR was 66% 19, in RE-LY study 67.2%, with the highest values of 77% in
Sweden and 74% in Finland and Australia 20, 21. On the other hand, Gateman D et al
calculated the mean TTR in St. Paul Family Health Network in Ontario of 58.05%, while
the mean TTR in the study of Ciurus T et al is 76% that is considered to represent excellent
anticoagulation control 17. 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 co-morbidities 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 is the risk factor for complications of VKA treatment which may be potentially
very serious for the 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 has shown 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 of 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 potentiate the anticoagulant
effect of VKA and increases the risk for bleeding. A large number of studies showed 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 is being 1.8-fold increased, 3.5-fold increased in patients taking VKA and
clopidogrel, and 4-fold increased in patients taking triple therapy 10. Looking at the same
problem from the other hand, our recent investigation of different preparations of
acetylsalicylic acid in patients with stable coronary disease also has shown that there is an
increased effect of aspirin in patients receiving anticoagulant therapy, so there is an
increased risk for bleeding 27.

7
Gender also stands out as a significant predictor of bad anticoagulation, which shows 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 confirmed this fact and have shown that women are at greater risk of AF-related stroke during VKA treatment, as a result of poor anticoagulant effect of warfarin\textsuperscript{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 \textit{et al} have shown that hypertension is associated with lower TTR\textsuperscript{14}, while on the other side Veterans Affairs Study to Improve Anticoagulation (VARIA)\textsuperscript{30} this relationship didn't confirm. This investigation has shown that arterial hypertension is a predictor of poor anticoagulation, and possible explanation of this influence may be associated with interaction of drugs\textsuperscript{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\textsuperscript{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 (DOAC) or new oral anticoagulants (NOAC) (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 the VKA, lower incidence of bleeding, especially intracranial or gastrointestinal, have fewer interactions with food than VKA, achieve faster antithrombotic effect and there is no need for regular monitoring because of predictable pharmacokinetics\textsuperscript{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), high risk of bleeding, and/or potential drug-drug interactions.

### Conclusion

The TTR is undoubtedly useful and beneficial 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 (aspirin, clopidogrel) drugs. To improve the quality of VKA therapy, an education of patient and better collaboration with them, as well as a successful team-work with clinicians are also imperative.

### Acknowledgement

This work was supported from the Ministry of Education, Science and Technological Development of the RS (Project No 175 061, 43 012 and 41004).
References


Table 1. Characteristics of patients (N = 725)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%) / Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.05±10.42</td>
</tr>
<tr>
<td>Gender (Male/female)</td>
<td>430 (59.40%) / 295 (40.60%)</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>111 (15.35 %)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>524 (72.30 %)</td>
</tr>
<tr>
<td>Previous AMI</td>
<td>232 (32.00 %)</td>
</tr>
<tr>
<td>Vascular disease history</td>
<td>138 (19.10 %)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>162 (22.40 %)</td>
</tr>
<tr>
<td>Concomitant drugs:</td>
<td></td>
</tr>
<tr>
<td>β-blockerRs</td>
<td>624 (86 %)</td>
</tr>
<tr>
<td>Statins</td>
<td>565 (78 %)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>275 (38%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>152 (21%)</td>
</tr>
<tr>
<td>Amiodaron</td>
<td>138 (19%)</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>522 (72%)</td>
</tr>
</tbody>
</table>

AMI – acute myocardial infarction
TIA – transient ischemic attack
### Characteristics of anticoagulant therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%) / Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>725 (100%)</td>
</tr>
<tr>
<td>Total number of INR measurements</td>
<td>6105</td>
</tr>
<tr>
<td>Number of INR measurements per patient</td>
<td>8.13±2.47</td>
</tr>
<tr>
<td>Number of days between INR measurements</td>
<td>34.89±17.26</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>436 (60.10%)</td>
</tr>
<tr>
<td>Acenokoumarol</td>
<td>259 (39.90%)</td>
</tr>
<tr>
<td><strong>Daily dose of drug</strong></td>
<td></td>
</tr>
<tr>
<td>Warfarin (mg)</td>
<td>4.7±1.26</td>
</tr>
<tr>
<td>Acenokoumarol (mg)</td>
<td>3.58±1.47</td>
</tr>
</tbody>
</table>
Fig. 1 – Time in therapeutic range (TTR) and time out of therapeutic range in investigated patients (%).
Fig. 2 – Histogram with relative frequencies of TTR.
<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.223</td>
<td>0.065–8.480</td>
<td>0.092</td>
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<tr>
<td>Gender</td>
<td>3.870</td>
<td>1.065–12.060</td>
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<tr>
<td>Previous stroke/TIA</td>
<td>1.590</td>
<td>0.951–2.682</td>
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<td>Hypertension</td>
<td>2.082</td>
<td>1.049–4.133</td>
<td>0.036</td>
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<td>Previous AMI</td>
<td>0.502</td>
<td>0.050–2.880</td>
<td>0.061</td>
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<tr>
<td>Diabetes mellitus</td>
<td>3.100</td>
<td>2.330–4.150</td>
<td>0.240</td>
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<tr>
<td>Amiodarone</td>
<td>11.360</td>
<td>4.870–26.520</td>
<td>&lt;0.001</td>
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<td>Aspirin</td>
<td>4.820</td>
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<tr>
<td>Clopidogrel</td>
<td>5.200</td>
<td>1.520–12.760</td>
<td>0.008</td>
</tr>
</tbody>
</table>

OR - Odds Ratio.