



INADEQUACY OF VITAMIN K ANTAGONIST USE IN PATIENTS WITH ATRIAL FIBRILLATION – OVERVIEW OF EVERYDAY CLINICAL PRACTICE AT THE MERKUR UNIVERSITY HOSPITAL IN ZAGREB, CROATIA

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SUMMARY – Atrial fibrillation is the most common cardiac arrhythmia. It increases the risk of death and thromboembolic events. Vitamin K antagonists reduce these risks. Disadvantages of vitamin K antagonist therapy are narrow therapeutic range and interactions with drugs and food. In a single center prospective study, we enrolled 249 patients with atrial fibrillation over a 12-month period. The aim of our study was to evaluate vitamin K antagonist use regarding the indication and adequate dose. Data on 249 consecutive patients with atrial fibrillation were collected before general availability of novel oral anticoagulants. Out of 249 patients, 160 (64.2%) had indication for oral anticoagulant therapy. Only 81 (50.6%) patients had vitamin K antagonist in therapy, 12 (14.8%) of them in adequate dose. We also analyzed 129 patients aged over 75, of which 109 (84.4%) had absolute indication for oral anticoagulant therapy. Only 34 (31.2%) patients aged over 75 had been receiving vitamin K antagonist therapy and 6 (17.6%) had the International Normalized Ratio values within the proposed therapeutic interval. We found a significantly higher rate of anticoagulant therapy introduction in patients under 75 years ($p=0.03$), but there were no significant differences in the adequacy of anticoagulant therapy ($p=0.89$) between these two populations. Our results showed clear inadequacies of vitamin K antagonist treatment with a growing need for a wider use of novel oral anticoagulants.

Key words: *Atrial fibrillation; Thromboembolism; Vitamin K – antagonists and inhibitors; Anticoagulants*

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, primarily occurring in diseased, structurally altered heart¹. Bearing in mind the progressive aging of the population, this arrhythmia is becoming a

significant problem, both from the medical and public health viewpoint, especially if left untreated or if treated inadequately. The incidence of AF in the general population is 1%-2%, reaching up to 5%-15% in those over 80^{2,3}. The likelihood of fatal outcome is twofold and the risk of thromboembolic events fivefold greater in AF patients^{4,5}. The mentioned thromboembolic incidents carry a greater risk of both mortality and morbidity compared to patients without AF. The risk of complications does not depend on AF duration, its form or the presence of symptoms⁶. The risk of com-

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plications depends on the presence of comorbidity⁶. The presence of comorbidities, most commonly referred to as CHADS2 score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke [double weight]) or CHA2DS2 VASc score (congestive heart failure, hypertension, age ($>65=1$ point, $>75=2$ points), diabetes, previous stroke/transient ischemic attack (2 points); VASc (vascular disease [peripheral arterial disease, previous myocardial infarction, aortic atheroma], and sex category [female gender]) determines which patient has indication for use of anticoagulant therapy⁷. It has long been known that anticoagulant therapy significantly reduces the risk of death, as well as thromboembolic incidents⁸. Anticoagulant therapy or therapy with vitamin K antagonists (VKA) has been shown to be most effective in this indication, even in comparison with dual antiaggregation therapy⁹. Still, administration of VKA is anything but simple, considering the narrow therapeutic window demanding regular measurement of Prothrombin Time or International Normalized Ratio (PT/INR), as well as numerous interactions with food ingredients and other drugs. Many studies have shown that for this reason, VKA therapy is often not prescribed to patients in whom it is indicated and, when prescribed, is often inadequately dosed. In their study on 2587 patients, McCormick *et al.* showed that 42% of AF patients were receiving warfarin, suggesting that this therapy continued to be used at low levels for stroke prevention; when warfarin was prescribed, the recommended therapeutic range of INR was maintained approximately half of the time¹⁰.

A recently published BALKAN AF study, which also included patients from Croatia, showed a relatively high overall use of oral anticoagulants (OAC); 73.6% of study patients were receiving OAC, whereas VKA was administered to 60.9% and novel oral anticoagulants (NOAC) to 12.7% of study patients. When VKA was used, the quality of anticoagulation was poor, with less than one-third of patients having INR in the therapeutic range¹¹.

According to these findings and the results of previous studies having shown NOACs to be a safe and effective alternative to warfarin, the rate of prescribing NOAC has been increasing in clinical practice. There is also a reduction in major bleeding events associated with NOACs, fewer interactions with drugs and foods, and no requirement for routine blood monitoring¹¹.

The aim of our study was to assess the adequacy of VKA administration regarding the dose and indication in patients in our everyday clinical practice. It should be noted that our study was conducted before NOACs had become widely available.

Patients and Methods

This study retrospectively included 249 consecutive patients diagnosed with AF irrespective of its form and duration. The study was conducted at the Division of Cardiology, Merkur University Hospital, Zagreb, and the enrolment period was 12 months, from October 2010 to October 2011. The study was approved by the Hospital Ethics Committee and all patients provided their informed consent. Patients hospitalized for diagnostic or therapeutic procedures requiring discontinuation of OAC therapy were excluded from the study. All included patients were adult. The following data were collected: sex, age, anticoagulant therapy, antiaggregation therapy, PT/INR at arrival, and risk factors for development of thromboembolic events expressed by the CHADS2 score.

Results

The study included 249 patients, 104 (41.8%) female and 145 (58.2%) male, mean age 73.6 years. Baseline characteristics of the study population are shown in Table 1.

After being stratified by their CHADS2 score, 160 (64.2%) patients had an absolute indication for administration of OAC therapy (CHADS ≥ 2), 76 (30.5%) had relative indication (CHADS=1), while only 13 (5.2%) patients had no indication for OAC therapy (CHADS=0) (Fig. 1).

Table 1. Baseline characteristics of study patients

Study patients, N=249	n	%
Male	145	
Female	104	58.24
Mean age (years)	73.6	41.76
Heart failure	75	30.12
Hypertension	217	87.14
Age >75 years	129	51.80
Diabetes mellitus	61	24.49
Previous stroke	6	2.41

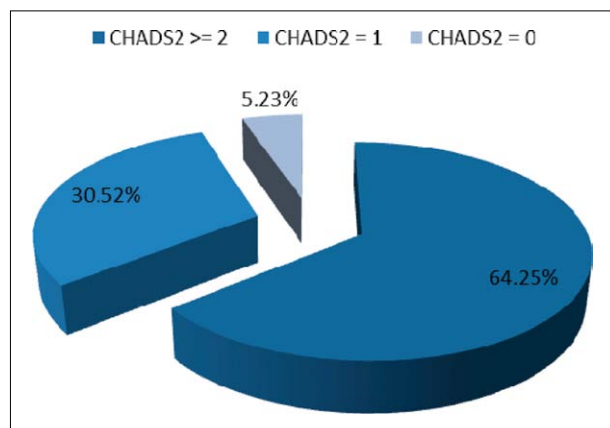


Fig. 1. Stroke risk profile of the study population.

Study population was also analyzed according to the CHADS2 stroke risk profile, and most of them had CHADS2 1 (30.5%) or 2 (30.9%) risk profile (Table 2).

Table 2. Patient stratification according to the CHADS2 stroke risk profile

CHADS2	n	%
0	13	5.22
1	76	30.52
2	77	30.92
3	64	25.70
4	10	4.02
5	9	3.61

CHADS2 = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke [double weight]

We further analyzed data on the adequacy of VKA administration regarding indication. Of the 160 patients with an absolute indication, only 81 (50.6%) patients were on VKA at the time of admission. To assess the adequacy of VKA therapy regarding the dose, we analyzed the percentage of patients satisfactorily saturated with warfarin based on their INR values. Only 12 (14.8%) of 81 (50.6%) patients on OAC therapy on admission had INR values within the proposed therapeutic interval of 2-3 (median 2.30). The remaining 69 (85.2%) patients had INR values beyond the therapeutic interval; 65 (80.2%) patients had INR less than 2 (mean 1.38) and four (4.9%) patients were VKA hypersaturated, with INR values >3 (mean 3.45) (Fig. 2).

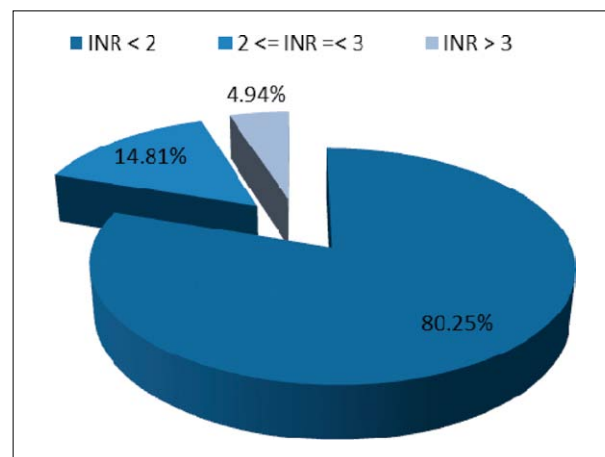


Fig. 2. Adequacy of vitamin K antagonist therapy according to INR values.

Knowing that age is an independent risk factor for thromboembolic events, we analyzed the patients aged over 75 as a separate group. Their stroke risk profile is illustrated in Figure 3.

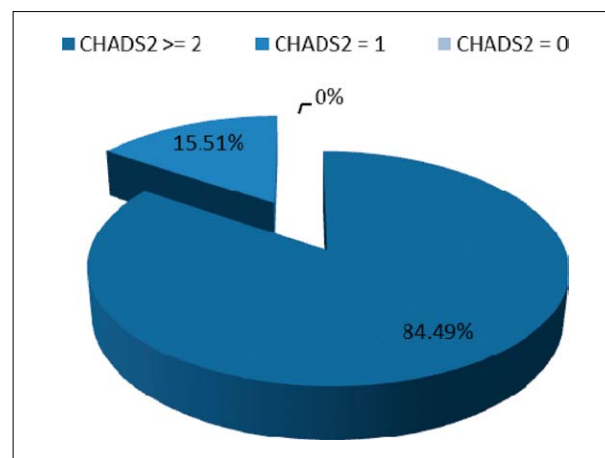


Fig. 3. Stroke risk profile in patients aged >75 .

The aforementioned group included 129 (51.8%) patients aged over 75, of which 109 (84.4%) had an absolute indication for OAC therapy and only 34 (31.2%) had been receiving VKA therapy. Only six (17.6%) patients had INR values within the proposed therapeutic interval, whereas the remaining 28 (82.4%) patients were inadequately saturated with VKA (Fig. 4).

We also found a significantly higher rate of anticoagulant therapy introduction in patients aged <75 as compared with those aged >75 ($p=0.03$), but there were no significant differences in the adequacy of anti-

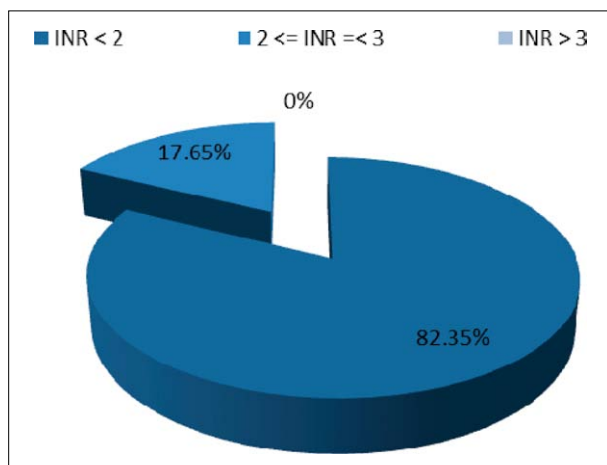


Fig. 4. Adequacy of vitamin K antagonist therapy according to INR values in patients aged >75.

coagulant therapy ($p=0.89$) between these two populations. According to CHADS2 score risk profile groups we did not find significant differences in the percentages of patients with oral anticoagulant therapy and percentages of those with appropriately regulated INR.

Discussion

Although the efficacy of warfarin in preventing stroke and systemic embolism in AF patients was demonstrated in a number of randomized controlled trials, there remains considerable uncertainty regarding adequacy of warfarin administration and dosage¹².

In our study, we found 160 (64.2%) patients with indication for OAC and only 50.6% of them had VKA in therapy and 14.8% in adequate dose. Similar results have been reported in some previous studies. The study carried out by McCormick *et al.* in 2587 patients showed that warfarin was prescribed to 42% of AF patients and the therapeutic range of INR values was maintained only 51% of the time¹⁰.

A recently published BALKAN AF study showed some better results. This study enrolled 2712 patients from seven Balkan countries including Croatia; 73.6% of study patients had been receiving OAC and 60.9% had VKA, while NOAC were administered to 12.7% of study patients. The BALKAN AF study included 159 Croats and 134 (84.3%) of them had received OAC; 110 (69.2%) and 24 (15.1%) Croatian patients were administered VKA and NOAC, respectively. These results are newer, showing the situation in our

country to be better than our results, as we collected them before NOAC general availability in Croatia, so it might be the reason for differences. The distribution of VKA therapies in Croatia was similar as in other Balkan countries, i.e. Albania, Montenegro, Romania and Serbia, but our results were better as compared with Bosnia and Herzegovina and Bulgaria. The authors of the BALKAN AF study showed that AF patients from Bosnia and Herzegovina and Bulgaria more often received only antiplatelet therapy, mainly aspirin, especially AF patients aged over 80¹¹.

It is also known that VKA is highly effective in reducing the risk of stroke in older patients with AF. However, many studies found warfarin to be used continuously at low rates among elderly AF patients. Our results showed 33.9% of AF patients aged >75 to have received VKA and 16% of them had INR values within the proposed therapeutic interval. Failure to initiate VKA in elderly AF patients is related to a number of factors, including limitations of current therapies and the increased risk of major hemorrhage associated with advanced age. According to a recent study, about 33% of elderly patient hospitalizations due to adverse drug reactions, mostly hemorrhagic, are caused by warfarin, and another 13% by antiplatelet drugs, with a high risk for patients and costs for the society¹³. Fear from intracranial hemorrhage is a major factor in the widespread underuse of VKA in elderly people. One of four patients aged >80 also stops taking warfarin within the first year of initiation, predominantly because of these safety concerns¹⁴.

Interestingly, the 2008 Japanese AF guidelines do recommend an INR target of 1.6–2.6 in patients above 70 years¹⁵. However, the European and North American guidelines do not recommend lower INR levels in the elderly¹⁶. In addition, Hylek *et al.* demonstrated the INR above 2 to be associated not only with a lower risk of stroke, but also with a lower severity or risk of dying from stroke¹⁷.

According to our results and the results of these studies, NOAC should increase the use of antithrombotic therapy in the management of AF in older population. NOAC are easier to use and might offer similar or better levels of stroke prevention with a similar or reduced risk of bleeding than VKA.

Vitamin K antagonists were for a long time the only oral therapeutic option available for stroke prevention in AF patients. However, even after the intro-

duction of NOAC to everyday clinical practice, VKA continue to be frequently prescribed, primarily for their lower price. There is also a population of AF patients in whom VKA is the only treatment option. According to the ESC guidelines for treatment of AF, VKA remain the only treatment option with proven efficacy in patients with AF and mechanical valves or rheumatic mitral valve disease.

Oral anticoagulant therapy is recommended for men with CHA₂DS₂VASc score equal to or exceeding 1, as well as in women with CHA₂DS₂VASc score equal to or exceeding 2¹⁶. The efficacy of VKA in lowering the relative risk of developing thromboembolic events, the absolute annual risk of thromboembolic stroke and the frequency of lethal outcomes has been proven in many studies¹⁸. There are, however, many disadvantages regarding administration of VKA, namely, their narrow therapeutic window, interactions with drugs and foods, the need for frequent and regular laboratory testing, and large inter-individual differences in the dose required¹⁹⁻²¹.

Many studies have shown that these disadvantages are responsible for the inadequate frequency of prescribing VKA in patients in whom they are indicated on the basis of valid guidelines and when VKA are prescribed, it is very often in insufficient dose^{20,21}.

In this study, we wanted to point out the lack of indications for initiation of oral anticoagulant therapy, as well as the issue of maintaining optimal INR in the therapeutic range of 2-3. A total of 85.2% of patients who were on OAC therapy at the time of admission had INR outside the therapeutic range. Especially concerning was the fact that as little as 17.6% of patients in the >75 age group had INR within the prescribed range, considering that age is the most important predictive factor for development of stroke and major bleeding events in AF patients^{22,23}. This is why age over 75 was included in the CHA₂DS₂VASc score as an independent factor worthy 2 points, which makes it a reason enough in itself for initiation of OAC therapy. NOAC are a suitable alternative to warfarin for stroke prevention in AF patients and their use is increasing in everyday clinical practice. Studies such as ARISTOTLE, RE-LY, ENGAGE-AF-TIMI 48 and ROCKET-AF showed a significantly better efficacy compared to warfarin with equal or less risk of bleeding²⁴⁻²⁷. For this improved efficacy and equal or lower bleeding risk, we expect an increase in the use of NOAC resulting in better

patient compliance to therapy and better protection from thromboembolic events, which is especially important in patients aged >75.

The potential disadvantages of our study included the fact that we used CHADS₂ score instead of the currently recommended CHA₂DS₂VASc score to assess the indication for therapy. It is known that the CHA₂DS₂VASc score is significantly more sensitive in recognizing high-risk patients. We assume that by using the CHA₂DS₂VASc score, the number of patients requiring anticoagulation therapy would be even higher, which would make our results yielding an even worse ratio of VKA use according to indication.

However, at the time when this study was performed, the CHADS₂ score was still valid and as such was calculated in all patients at admission. The final statistical analysis of the data collected was also based on the CHADS₂ score. The attempt of subsequent insertion of data required to calculate the CHA₂DS₂VASc score in a short pilot project was found to be unsuccessful since the required clinical data were not routinely recorded at the time. Considering that even the results based on the CHADS₂ score showed inadequate use of VKA, we deem them sufficient to conclude that VKA therapy was inadequate in our patients. It should be emphasized that the number of patients included in this study was relatively small. Considering better availability of NOAC, a greater number of patients will require data collection over a longer period of time, as well as a greater number of institutions involved in this potential research project.

Conclusion

In conclusion, our study showed the use of VKA in Croatia to be probably inadequate. Such results should direct us towards improving screening of patients in need of anticoagulant therapy, as well as better control of therapy administration. These results probably support the need for a more frequent use of NOAC, which would make at least some of the above mentioned VKA therapy disadvantages less pronounced.

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Sažetak

NEDOSTATNA PRIMJENA ANTAGONISTA VITAMINA K
U BOLESNIKA S ATRIJSKOM FIBRILACIJOM – PRIKAZ REZULTATA IZ KLINIČKE PRAKSE
U KLINIČKOJ BOLNICI “MERKUR”, ZAGREB

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Atrijska fibrilacija je najučestalija aritmija koja povećava rizik smrti i tromboembolijskih incidenata. Antagonisti vitamina K smanjuju taj rizik. Problem terapije s antagonistima vitamina K je uska terapijska širina i brojne interakcije s lijekovima i hranom. Cilj ovoga istraživanja bio je utvrditi dostatnost primjene antagonistata vitamina K s obzirom na indikaciju i dozu. Prikupljeni su podaci 249 bolesnika s atrijskom fibrilacijom hospitaliziranih u Kliničkoj bolnici “Merkur” u razdoblju od 12 mjeseci i to prije šire dostupnosti novijih oralnih antiokoagulansa. Od svih bolesnika, 160 (64,2%) ih je imalo indikaciju za primjenu oralne antikoagulantne terapije, a tek je njih 81 (50,6%) imalo antagonist vitamina K u terapiji. Samo 12 (14,8%) bolesnika je uzimalo antagonist vitamina K u dostatnoj dozi, a 129 (51,8%) ih je bilo iznad 75 godina starosti. Njih 109 (84,4%) je imalo indikaciju za oralnu antikoagulantnu terapiju, a samo 34 (31,2%) ih je uzimalo antagonist vitamina K, od kojih je 6 (17,6%) imalo INR u terapijskim vrijednostima. Statistička analiza podataka pokazala je da su bolesnici mlađi od 75 godina češće uzimali indiciranu oralnu antikoagulantnu terapiju u odnosu na bolesnike starije od 75 godina ($p=0,03$), dok nije bilo statistički značajne razlike u dostatnoj primjeni antikoagulantne terapije između ovih dviju populacija ($p=0,89$). Naši rezultati jasno pokazuju nedostatnost primjene antagonistata vitamina K kao i potrebu bržeg prijelaza prema terapiji novijim oralnim antikoagulansima.

Ključne riječi: *Atrijska fibrilacija; Tromboembolija; Vitamin K – antagonisti i inhibitori; Antikoagulansi*