Original Article

Optimal Choice of Pharmacological Therapy – Prevention of Stroke and Assessment of Bleeding Risk in Patients with Atrial Fibrillation

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Abstract

Background: The aim of the study was to highlight the importance of adequate anticoagulant therapy and the correlation of higher risk of stroke. **Methods:** This study analyzed data obtained from 103 patients with diagnosis of atrial fibrillation (AF) (39 of them had a stroke). Patients were divided into groups according to the $CHADS_2$, CHA_2DS_2-VASc, and HASBLED scores. **Results:** An analysis showed that anticoagulant drugs were more often prescribed to subjects <75 years of age ($P = 0.001$). Patients with a higher $CHADS_2$ score had a higher CHA_2DS_2-VASc score and vice versa (rho = 0.513; $P = 0.0001$). According to the CHA_2DS_2-VASc, 91.3% of the patients examined were prescribed an anticoagulant medication as a therapy at discharge from the hospital. The result was statistically significant compared to the practice where an anticoagulant was prescribed to 55.9% of high-risk subjects as estimated by the CHA_2DS_2-VASc score ($P < 0.05$). Our results also show that rivaroxaban is more commonly prescribed as a discharge therapy than warfarin ($\chi^2 = 12.401$; $P = 0.0001$). Furthermore, a significantly higher number of patients who were being prescribed aspirin (38.5%) had a stroke compared to 12.8% of patients who were being prescribed warfarin ($\chi^2 = 12.259$; $P = 0.0001$). **Conclusions:** Novel oral anticoagulants (NOACs) seem to be a better choice as a pharmacological therapy in the treatment of AF, due to a lack of adequate monitoring of patients' international normalized ratio (INR) values. CHA_2DS_2-VASc and HASBLED scores must be used as a part of routine clinical diagnostics when dealing with patients with AF.

Keywords: *Atrial fibrillation, hemorrhage, risk, stroke, therapeutics*

Background

Atrial fibrillation (AF) is the most common cardiac rhythm disorder associated with increased risk of mortality and morbidity from stroke and thromboembolism. The fundamental part of clinical management of AF involves decision-making of an appropriate oral anticoagulant (OAC) therapy, given that OAC therapy significantly reduces stroke (by 64%) and all-cause mortality (by 26%) in comparison to placebo or no treatment.[1–3] Almost all patients with AF have an increased risk of stroke, and anticoagulation therapy can reduce this risk.[3,4] HASBLED [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly >65 years, drugs/alcohol concomitantly] score allows clinicians to assess the bleeding risk and, importantly, allows clinicians to consider correctable bleeding risk factors. In patients with HASBLED score of ≥3, caution and regular examinations are recommended, as well as efforts to correct potentially corrective risk bleeding factors. High HASBLED score, by itself, should not be used as an indicator for excluding OAC therapy in patients. Instead, a HASBLED score should be used in estimating major bleeding risk in clinical practice.[5] Warfarin and other vitamin K antagonists (VKAs) were the first anticoagulants used in AF patients. VKA therapy reduces the risk of stroke by two-thirds and mortality by one-quarter compared with control (aspirin or no therapy).[3] Novel oral anticoagulants (NOACs), including direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, edoxaban, rivaroxaban, and betriaxaban, are suitable substitutes of VKAs, used for stroke prevention in patients with AF.[1,2,6] In $CHADS_2$ (congestive heart failure, hypertension, age of 75 years, diabetes

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mellitus, stroke) score, 1 point is given for a patient having congestive heart failure, hypertension, >75 years of age, and diabetes mellitus, while 2 points are added if a patient had a stroke or transient ischemic attack (TIA). The use of CHA_2DS_2-VASc [congestive heart failure, hypertension, age of ≥75 years (doubled), diabetes mellitus, prior stroke or TIA (doubled), vascular disease, age of 65–74 years, female] score is recommended only if $CHADS_2$ is <2.[2] The $CHADS_2$ and the CHA_2DS_2-VASc scores were originally created to evaluate a risk of stroke in patients with AF with the purpose of clarifying the requirement of antithrombotic therapy.[7,8] Compared with the $CHADS_2$ score, the use of CHA_2DS_2-VAS_C score considerably increases the number of AF patients for whom OAC is recommended.[8] The $CHADS_2$ scoring system has been criticized because it is not a good indicator for patients in the lower risk group, with $CHADS_2 = 1$, leaving too many patients in the group of aspirin versus OAC and may not predict a very low-risk group who need no treatment or aspirin. According to this score, it is considered that patients with a score of 0 do not need thromboprophylactic therapy, but that antiaggregation therapy could be prescribed.[2,9-11] All patients with a CHA_2DS_2-VASc score ≥2 should have anticoagulant medication included in their therapy, and patients with a score of 1 should be prescribed either an anticoagulant or an antiaggregation drug.[2] The CHA_2DS_2-VASc score is considered as a method of choice for deciding whether or not an anticoagulation therapy should be prescribed to a patient with AF. The CHA_2DS_2-VASc score enables the identification of patients who are indeed at a high risk of stroke and is valuable at directing a selection of applicable therapeutic approaches.[12] The $CHADS_2$ score is simple and easy to use; however, the CHA_2DS_2-VASc score enables a considerably more comprehensive risk of stroke evaluation and improves the accuracy at identifying low-risk patients who have AF.[12] The aim of this study was to evaluate the coherence of prescribing thromboprophylactic therapy in patients with AF by using clinical guidelines of the European Cardiology Society. In addition, the aim was to highlight the importance of adequate anticoagulant therapy and the correlation of higher risk of stroke. Furthermore, our aim was also to determine the most common comorbidities in patients with AF, to compare $CHADS_2$ and CHA_2DS_2-VASc score in patients with AF, to determine the value of a HASBLED score as a diagnostic tool for the assessment of the severity of the risk of bleeding, to determine the degree of prescription of NOAC in subjects with AF versus OAC. Moreover, the aim was also to compare the ratio of subjects who were pre-hospitalized with anticoagulants and those who have been prescribed anticoagulants after hospitalization and to determine the percentage of subjects with AF hospital treated with anticoagulants, which were within the INR 2–3 range.

Materials and Methods

Research is an observational, retrospective-prospective, and analytical study and included 103 patients (males 54 or 52.4% and females 49 or 47.6%), during period November 2016 to April 2017 (retrospective from November to January, and prospective from February to April). Out of 103 patients, 64 were hospitalized at the Clinic for Heart, Blood Vessel and Rheumatic Diseases, and 39 at the Clinic for Neurology, Clinical Center University of Sarajevo. They all had a diagnosis of AF, and patients from the Clinic for Neurology also had a stroke. The average age of the patients in the observed sample was 71.8 ± 10.1 (42–91 years). The inclusion criteria was diagnosis of AF. The exclusion criteria were incomplete medical history, absolute contraindications for prescribing anticoagulant therapy (active bleeding, neurosurgical surgery or intracranial hemorrhage in the past 7 days, hemorrhagic stroke, severe thrombocytopenia, and a history of heparin-induced thrombocytopenia in the previous 90 days). The subjects were excluded from the data analysis in case of lethal outcome and transfer to another clinic during hospitalization. Patients were divided into groups according to the $CHADS_2$, CHA_2DS_2-VASc, and HASBLED scores. $CHADS_2$ is taken as basic because it is the most common and the simplest for use. In order to calculate the score age, gender, presence of congestive heart failure, diabetes mellitus, stroke, myocardial infarction, and peripheral arterial disease were recorded. Urea and creatinine were monitored for the detection of renal failure, liver enzymes, labile INRs, bleeding history, as well as additional therapy that patients were taking were recorded. Anamnestic data also included consumption of alcohol. An ejection fraction <40% was scored according to the CHA_2DS_2-VASc score. A renal disease was recorded if the patient was on dialysis and if the creatinine level was >200 μmol/L. Liver disease was marked in case of cirrhosis, bilirubin two times the upper limit of the normal range (ULN), and AST/ALT/AP three times ULN. Labile INRs were considered as the INR values that were significantly out of the reference values of the therapeutic interval during hospitalization. The results are shown by tables and graphs using the number of cases, percentages, arithmetic mean (X) with standard deviation (SD), and extreme values (minimum–maximum). Chi-squared test was performed for analysis between groups, while correlation testing was performed with the Pearson's linear correlation coefficient. The values of $P < 0.05$ were considered as statistically significant.

Results

Table 1 shows types of pharmacological therapy prescribed to patients at discharge from the hospital, categorized according to the gender of the patients. Prescribing of warfarin, rivaroxaban, and antiaggregation therapy was noted. There were no statistically significant differences in the prescribing of different types of drugs according to gender ($P > 0.05$).

Table 1: Types of pharmacological therapy according to gender

Therapy		Gender		Total
		Male	Female	
Warfarin	*N*	8	9	17
χ^2=0.549; *P*=0.304	%	14.8	18.4	33.2
Rivaroxaban	*N*	20	19	39
χ^2=0.235; *P*=0.425	%	37.0	38.8	75.8
Antiaggregation therapy	*N*	38	30	68
χ^2=0.958; *P*=0.221	%	70.4	61.2	66.0

Patients were divided in two groups: 1. patients <75 years of age and 2. patients >75 years of age. Out of 59 patients, 67.8% of them were under the age of 75 years received an anticoagulant drug, and out of 44 patients who were older than 75 years, 36.4% received an anticoagulant medication. Anticoagulant drugs were more often prescribed to subjects under 75 years of age compared to those older than 75 years with a statistically significant difference, $P < 0.05$ ($P = 0.001$). If the patients were divided into two groups, under 65 years and those who have 65 years or more, anticoagulant drug was prescribed in 61.3% of subjects who are younger than 65 years and in 51.4% of subjects who are 65 years or older. There was no statistically significant difference in the prescribing of anticoagulant drugs among younger and older patients, but anticoagulant drugs were more often prescribed to patients under 65 years ($P > 0.05$). The most common comorbidity was arterial hypertension in 77 (74.8%) patients, followed by valvular insufficiency (mitral and aortic insufficiency, 1–3 degrees) 56 (54.4%) patients, and stroke in 39 (37.9%) patients. Anemia was found in 12 (11.7%) patients and thyroid disorder in 8 (7.8%). Diabetes mellitus was present in 31 (30.1%) patients and hyperlipidemia was present in 16 (15.5%) patients. Persistent AF was observed in 80 subjects or 77.7%, permanent in 16.5% of subjects, and paroxysmal in 5.8% of subjects. In patients with AF, warfarin was prescribed in 16.5% of subjects, rivaroxaban in 37.9%, aspirin in 42.7%, statins in 47.6%, clopidogrel in 16.5%, digoxin in 54.4%, and some of the antiarrhythmic drugs were prescribed in 63.1% of subjects. The anticoagulant drug was given to 54.4% of the subjects. In permanent AF, warfarin was prescribed in 47.1% of subjects, rivaroxaban in 52.9%, aspirin in 70.6%, statins in 82.4%, clopidogrel in 5.9%, digoxin in 58.9%, and antiarrhythmic in 88.2% of subjects. In persistent AF, warfarin was prescribed in 11.3%, rivaroxaban in 37.5%, aspirin in 88.3%, statins in 38.8%, clopidogrel in 17.5%, digoxin in 52.5%, and antiarrhythmic drug in 100% of patients. In paroxysmal AF, no patient received warfarin or rivaroxaban, 83.3% received aspirin, 66.7% received statins, 33.3% clopidogrel, 66.7% received digoxin, and endoxaparin in all patients. Antiarrhythmic drug was prescribed in 100% of subjects with paroxysmal AF. Patients were also analyzed according to the $CHADS_2$ and CHA_2DS_2-VASc score. With a statistically significant difference ($P < 0.05$), 50% of patients with low risk in $CHADS_2$ score remained at low risk in the CHA2DS2-VASc score, while 25% of the subjects turned to medium and high risk. Medium-risk patients did not have a movement to low risk, while 19.4% remaining at medium risk and even 80.6% at high risk. Correlation analysis of $CHADS_2$ and CHA_2DS_2-VASc scores showing that there is a statistically significant association, patients with higher $CHADS_2$ score will have a higher CHA_2DS_2-VASc score and vice versa (rho = 0.513; $P = 0.0001$) [Figure 1].

Patients were distributed according to the severity of the risk of stroke estimated by $CHADS_2$ score. The patients were most often placed into the high-risk group, 68 or 66% of them, 31 or 30.1% of them at the middle-risk group, and only 4 or 3.9% of them belonged to the low-risk group. Anticoagulants in discharge therapy were prescribed to 3 patients with low risk (75%), to 15 patients with medium risk (48.4%), and to 38 patients with high risk (55.9%). Comparing the practice of doctors with the guidelines of the European Cardiology Society, according to $CHADS_2$, all high-risk patients should have anticoagulants in discharge therapy, and in reality it was prescribed only to 38 patients (55.9%). There is a statistically significant difference between what is recommended in guidelines and the actual state ($\chi^2 = 38.4906$ $P < 0.05$). In medium-risk patients, anticoagulant was prescribed in 45.2% of cases. In patients with low risk there is no need for anticoagulants, but it was prescribed in three cases (75%) for patients enrolled in the study. According to CHA_2DS_2-VASc, only 2 patients were at low risk, 7 with medium risk, and 94 were at high risk. According to this score, 91.3% of our patients had to have an anticoagulant medication in discharge therapy. The result was statistically significant compared to the practice where the anticoagulant was given to 55.9% of high-risk subjects estimated by CHA_2DS_2-VASc score ($P < 0.05$). Comparing the relation between pre-hospital and post-hospital prescribing of anticoagulant therapy, 19 (33.9%) of patients who were previously on anticoagulant therapy remained on the same and after hospitalization, and 37 (66.1%) of patients who were not previously on anticoagulants received them after hospitalization. There is a statistically significant difference between pre-hospital and post-hospital prescribing of anticoagulants where significantly higher number of subjects received it after hospitalization ($\chi^2 = 28.7037$ $P = 0$). Prior to hospitalization, 19 (18.4%) patients were on warfarin, 64 (62.1%) on aspirin, and 20 patients did not have any thromboprophylactic therapy, 19.4% of them. Warfarin was used in 17 subjects (16.5%) and rivaroxaban in 39 subjects (37.9%). Patients were without therapy in 47 subjects (45.6%). With statistically significant differences,

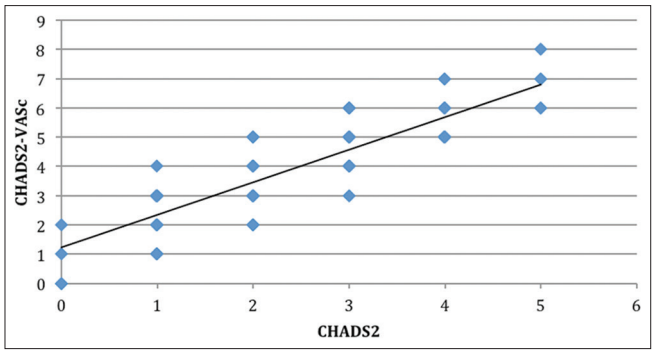

Figure 1: Correlation between $CHADS_2$ and CHA_2DS_2-VASc score (rho = 0.513; *P* = 0.0001)

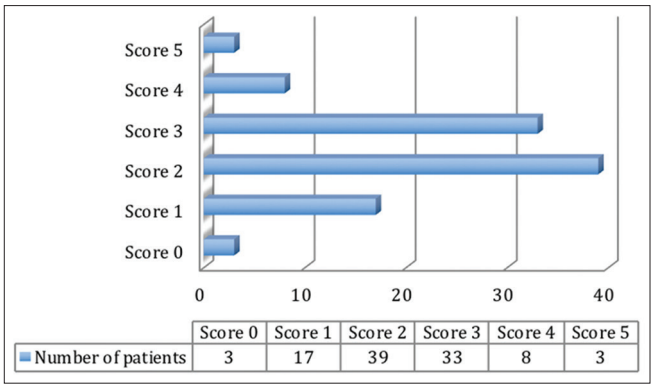

Figure 2: HASBLED score in patients

rivaroxaban is more commonly used in discharge therapy than warfarin (χ^2 = 12.401; *P* = 0.0001) 42.1% of patients who were pre-hospitalized with warfarin were treated with rivaroxaban after hospitalization. About 57.9% of them did not receive the drug. The result was not statistically significant (χ^2 = 0.1781, *P* = 0.673). Analyzing the discharge therapy of the patients in terms of anticoagulant therapy, 16.5% of the patients received warfarin (VKA), 37.9% rivaroxaban (NOAC), and 45.6% of the subjects did not receive either of these drugs. Enoxaparin was used during hospitalization in 64.1% of subjects.

Figure 2 shows the structure of the patients according to the HASBLED score. Most of the patients had HASBLED score 2 and it was evaluated as such in 37.9% of subjects, followed by a score 3 in 32% of the subjects, while the smallest number of patients had a score of 0 and 5 (2.9% of the patients). About 38.5% of those previously treated with aspirin had a stroke. With statistically significant difference (*P* < 0.05), a significantly higher number of aspirin patients (38.5%) had stroke compared to 12.8% of patients on warfarin (χ^2 = 12.259; *P* = 0.0001). In addition, none of the patients who were on the warfarin did not regularly control the INR values. No patients who had a stroke were previously on rivaroxaban. All patients had an ischemic stroke. Of the 19 patients who were previously treated with warfarin, 7 or 36.8% of them had INR values 2–3 within admission, and 63.2% were outside this interval. An INR interval was also observed in subjects treated with warfarin during hospitalization. About 77% of subjects had INR values 2–3, and INR values were not in reference ranges in 23% of the total number of those treated with warfarin. The mean platelet count was 244.9 ± 78.7 with a minimum of 119 and a maximum of 471. The average duration of hospitalization was 13.5 ± 6.5 days with the shortest duration of hospitalization of 1 day and maximum of 32 days with the largest number of patients with a duration of hospitalization between 7 and 15 days. Conversions of AF to the sinus rhythm of the subjects were recorded in 41 or 39.8% of cases. Patients who did not have hyperlipidemia received statins in therapy in 38.6% of cases.

Discussion

In the overall sample in our study, men were slightly more represented than women, which is in correspondence with the previously published studies according to which men have a greater incidence of AF than women.[13] The absolute number of men and women becomes almost equal as the incidence of AF increases dramatically with age, and in the group of patients who are older than 75 years of age, there is a greater number of women diagnosed with AF.[13] AF is associated with increased morbidity, such as heart failure and stroke. Contemporary studies show that 20–30% of patients with an ischemic stroke have AF diagnosed before, during, or after the initial event. White matter lesions in the brain, cognitive impairment, decreased quality of life, and depressed mood are common in AF patients, and between 10–40% of AF patients are hospitalized each year.[2] Female AF patients who have additional risk factors for stroke (e.g., older age) are also at a greater risk than men of having a stroke, even those who received warfarin therapy. Women diagnosed with AF can be more symptomatic than men and are typically older and have more comorbidities. Bleeding risk on anticoagulation therapy is similar in both sexes, but it is estimated that women often do not receive specialist care and rhythm control therapy.[2] The most common comorbidity in our study was arterial hypertension, followed by valvular insufficiency, stroke, anemia, and thyroid disorders. Anemia carries a greater risk of thromboembolic complications in patients with AF, and these patients need to be monitored more frequently.[14] Severe anemia is an independent predictor of large bleeding.[15] TSH levels should be routinely performed in patients with AF, however, this is necessary only for newly diagnosed patients and in patients with a history of thyroid disorders.[16]

In patients with hypothyroidism, and those who are taking coumarin derivatives, it is necessary to monitor INR values frequently, because hypothyroidism reduces the efficacy of coumarin preparations.[17] Frequent monitoring of INR values is also necessary in patients who are being co-prescribed warfarin and methimazole

during treatment of Graves' disease.[18] An alternative drug to methimazole, in combination with warfarin, can be lithium.[19] In patients with thyroid disorders, it is suggested that the thyroid hormone status should be regularly monitored in the patients taking warfarin, especially if amiodarone is co-prescribed with warfarin.[20] Hypertension is the first risk factor for the occurrence of AF and it is the most common comorbidity, as demonstrated in the current study. Angiotensin-converting-enzyme inhibitors (ACEIs), which are the most commonly prescribed agents for the treatment of hypertension, are also part of a pharmacological therapy of AF.[21] ACEIs or angiotensin II receptor blockers (ARBs) may reduce recurrent AF after cardioversion, if they are included in the therapy together with an antiarrhythmic drug.[2] Diabetes mellitus is one of the important risk factors for AF, while AF is a strong and independent risk factor in cardiovascular morbidity and mortality in patients with diabetes. Oxidative stress, conexin remodeling, and glycemic fluctuations are implicated in the pathophysiology of AF in diabetes.[22] Diabetes mellitus is included as a risk factor in the $CHADS_2$ score, and is also observed as a prothrombotic condition due to numerous changes in primary and secondary hemostasis. No studies have yet been able to evaluate the efficacy of medicines used to control blood glucose on the risk of thromboembolic complications in patients with AF.[23] Diabetic retinopathy, a measure of disease severity, does not increase the risk of ocular bleeding in patients receiving anticoagulant therapy. Hyperlipidemia was found in 15.5% subjects in our study, and chronic obstructive pulmonary disease (COPD) in 13.6% of subjects. AF is common in patients with chronic lung disease and is associated with P-wave dispersion.[24] The risk of developing AF is 1.8 times higher in patients with forced expiratory volume 1 (FEV1) between 60 and 80% compared to FEV1 >80%, while a risk of hospitalization due to AF in the same group of patients is 1.3 times higher.[25] Impaired pulmonary function is an independent predictor for the onset of AF.[25] Enoxaparin may be a better choice of a drug in controlling the lipid status of hemodialysis patients with diabetes mellitus and hyperlipidemia.[26] In patients with COPD, chronic hypoxia and hypercapnia stimulate the hematopoietic function, resulting in compensatory polycythemia and increased blood viscosity. Since the blood flow is slower and there is an imbalance in the acid–base status, the COPD represent a hypercoagulable state.[27] It has been demonstrated that the use of low-molecular-weight heparin (LWMH), in combination with the standard pharmacological therapy, is useful in the prevention of these complications.[28] The correlation analysis between the $CHADS_2$ on admission and CHA_2DS_2-VASc shows that there is a statistically significant association between the two scores, i.e., that patients with higher $CHADS_2$ score have higher CHA_2DS_2-VASc score.[29] The mortality of patients with AF is higher (up to twice as high in the Framingham study) in relation to the population without AF.[30] Increased mortality is largely associated with thromboembolic complications of AF, primarily stroke. Paroxysmal AF has the same risk of cerebral thromboembolism as the persistent or permanent AF. Accordingly, the only therapy that clearly affects the prognosis of AF, i.e., it reduces mortality, is an antithrombotic therapy.[31] Many studies have also shown inadequate prescribing of anticoagulant therapy according to the $CHADS_2$ score.[7,32] The ESC guidelines recommend estimating stroke risk in AF patients based on the CHA_2DS_2-VASc score.[2] The bleeding risk in patients taking aspirin is not different to the bleeding risk in patients on VKA or NOAC therapy, while VKA and NOACs, but not aspirin, appear to effectively prevent strokes in AF patients.[2] An OAC therapy should be considered for men with a CHA_2DS_2-VASc score of 1, and women with a score of 2, balancing the expected stroke reduction, bleeding risk, and patient preference.[2] It is important to note that age (≥65 years of age) is related to relatively high and continuously increasing stroke risk.[2] An individualized approach should be the basis for making the decision to include anticoagulation therapy in patients with only one CHA_2DS_2-VASc risk factor (excluding female sex). Female sex does not appear to increase a risk of stroke in absence of other stroke risk factors.[2] A possibility of life-threatening hemorrhage is the most frequent reason for not including anticoagulation therapy in the treatment of patients with AF. Therefore, for the purpose of an appropriate risk assessment of bleeding, based on the results of the recent research called the EuroHeart Survey that involved 3978 subjects, a simple score system was created under the acronym HASBLED (abnormal liver and renal function, stroke, bleeding, labile INR, elderly, drugs, and alcohol).[33] In addition, the so-called ATRIA score for bleeding assessment that scored anemia, severe renal insufficiency, age >75 years, pre-bleeding, and hypertension were proposed in 2011. However, studies have shown that the HASBLED score is better at assessing bleeding risk with a significant statistical difference.[34] Its better predictive value seems to be due to the inclusion of diabetes, heart failure, and left ventricular dysfunction.[35] A HASBLED score which is higher than 3 does not mean that an anticoagulant therapy is contraindicated, but instead that administering an anticoagulant greater assessment of the benefit of an anticoagulant therapy for a specific patient. The HASBLED score also seems to be better than the HEMORR(2)HAGES rapid score (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke).[36] Furthermore, it is only the

HASBLED score that demonstrated a significant predictive performance for intracranial hemorrhage.[36]

Conclusions

In medical practice, non-adherance to the recommendations for prescribing appropriate pharmacological therapy to patients with AF is common. NOACs seem to be a better choice of pharmacological therapy due to a lack of regular monitoring of INR values in patients on warfarin therapy. An anticoagulation therapy should be prescribed to all patients with a risk of stroke. Although individual approach to a patient's therapy is imperative, CHA_2DS_2-VASc and HASBLED score should be used as a part of routine clinical diagnostic when dealing with patients with AF. A multidisciplinary approach to the patients diagnosed with AF requires adequate treatment of comorbidities to reduce the lethal outcome.

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Conflicts of interest

There are no conflicts of interest.

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