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Novel Oral Anti Coagulants (NOACs) as Anti Thrombotic on Atrial Fibrillation Patients

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ABSTRACT

Atrial Fibrillation (AF) is an arrhythmia characterized by disorganization of atrial depolarization resulting in the impaired mechanical function of the atrium. Management of AF aims to prevent complications of ischemic stroke and systemic embolism, carried out by the administration of anticoagulant, warfarin, but warfarin has many side effects. New Oral Anticoagulants (NOAC) can be used as alternatives in preventing complications of AF.New anticoagulants such as dabigatran, rivaroxaban, and apixaban have better effects than other anticoagulants such as warfarin and have major side effects of bleeding and minimal relevant bleeding. Based on a national survey in Denmark to see a balance between stroke and intracranial bleeding, CHA2DS2-VASc 1 scores were only apixaban and both dabigatran doses (110 mg bid and 150 mg bid) which provided better clinical benefits than warfarin, but if the CHA2DS2- score VASc ≥2 of all NOACs is superior to warfarin. Atrial fibrillation can cause ischemic stroke and systemic embolism. New Oral Anticoagulant (NOACs) can be used as a solution to prevent complications from AF with minimal side effects. It is expected that the presence of new anticoagulants can reduce the rate of ischemic stroke and ischemic embolism due to AF with minimal side effects of bleeding and other side effects.

Keywords: Anticoagulant, Atrial Fibrillation , NOAC, Warfarin

ABSTRAK

*Atrial Fibrilasi (AF) adalah suatu aritmia yang ditandai dengan disorganisasi dari depolarisasi atrium sehingga berakibat pada gangguan fungsi mekanik atrium. Penatalaksanaan AF bertujuan mencegah komplikasiyakni stroke iskemik dan emboli sistemik, dilakukan dengan cara pemberian anti-koagulan yakni warfarin. Pemberian warfarin memiliki banyak efek samping. Novel Oral Anti Coagulants (NOAC) dapat dijadikan alternatif dalam mencegah komplikasi AF. Anti-koagulan baru seperti dabigatran, rivaroxaban dan apixaban memiliki efektifitas yang lebih baik daripada anti-koagulan lainnya seperti warfarin dan memiliki efek samping perdarahan mayor dan perdarahan relevan yang minimal. Berdasarkan survei nasional di Denmark untuk melihat keseimbangan antara stroke dan perdarahan intra-kranial didapatkan bila skor **C**ongestive heart failure, **H**ypertension, **A**ge ≥75 years (skor 2), **D**iabetes mellitus, **S**troke history (skor 2), peripheral **V**ascular disease, **A**ge between 65 to 74 years, **S**ex Category (female) dan "**C**" adalah adanya disfungsi ventrikel kiri sedang hingga berat (Left Ventricular Ejection Fraction/LVEF ≤ 40%) CHA_2DS_2-VASc 1 hanya apixaban dan kedua dosis dabigatran (110 mg b.i.ddan 150 mg b.i.d) yang memberikan manfaat klinis yang lebih baik daripada warfarin, tetapi apabila skor CHA_2DS_2-VASc ≥2 seluruh NOAC lebih superior dibanding warfarin.AF dapat menyebabkan stroke iskemik dan emboli sistemik.NOAC dapat dijadikan solusi untuk mencegah komplikasi dari AF dengan efek samping yang minimal. Diharapkan dengan hadirnya anti-koagulan baru dapat menurunkan angka stroke iskemik dan emboli iskemik akibat AF dengan efek samping perdarahan dan efek samping lainnya yang minimal.*

Kata Kunci: Antikoagulan, Atrial Fibrilasi, NOAC, Warfarin

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INTRODUCTION

Atrial Fibrillation (AF) is an arrhythmia characterized by disorganization of atrial depolarization resulting in impaired atrial mechanical function. In electrocardiography (ECG) the picture of AF is characterized by the alternation of P waves by fibrillation or fast oscillation waves that vary in shape, amplitude or interval, followed by irregular ventricular responses, while atrio-ventricular (AV) conduction is still intact.[1]

AF is an arithmetic that is most often found in daily medical practice. The prevalence of AF reaches 1-2% and will continue to increase in the next 50 years. A study involving 5209 healthy research subjects (not suffering from cardiovascular disease) showed that in a 20-year period, the incidence of AF was 2.1% in males and 1.7% in females. In Indonesia, there was a significant increase in the percentage of the elderly population in Indonesia, namely 7.74% in the 2000-2005 range to 28.68% in the 2045-2050 range, so the incidence of AF would also increase significantly.[1,2]

AF has varied clinical symptoms, the most common is palpitations. Other symptoms that are often found in the form of pre-syncope, weakness, dyspnea, dizziness and chest pain. Some patients with atrial fibrillation do not show typical symptoms of atrial fibrillation. Definitive diagnosis of AF is done using ECG. In ECG, the characteristic of AF is the absence of consistency of P waves, which are replaced by vibrational waves (fibrillation) which vary in amplitude, shape and duration. In normal atrio-ventricular (NAV) function, AF is usually followed by a ventricular response that is also irregular, and often fast.[1,2]

The risk of ischemic stroke and systemic embolism in patients with AF is based on a number of pathophysiological mechanisms, ie blood flow abnormalities characterized by static blood flow in the left atrium will cause a decrease in flow velocity in the left atrial auricle which can be seen as spontaneous echo-contrast on echocardiography.[3]

The management of AF aims to avoid complications that can occur, namely reducing the risk of ischemic stroke and other systemic emboli. In general the risk of stroke in AF is 15% per year which is around 1.5% in the 50 to 59 years age group and increases to 23.5% in the 80 to 89 years age group. While the average incidence of strokes and other systemic emboli is 5% (around 3-4%).[1,3]

Management given to AF patients is anti-thrombotic therapy that is used for stroke prevention in AF patients including anticoagulants and antiplatelets. Vitamin K antagonists (warfarin or coumadin) are the most widely used anticoagulant drugs for the prevention of strokes in AF. Although it has been used for a long time, warfarin therapy is definitely difficult to administer, because warfarin has a narrow therapeutic index, side effects and many metabolic variations that are difficult to estimate and usually require dose adjustments. For this reason alternative therapies are needed as anticoagulants which have effective work and minimal side effects. Novel Oral Anti Coagulants (NOACs) can be an alternative as anti-thrombotic therapy in AF patients.[2,3]

DISCUSSION

AF causes increased mortality and morbidity, including stroke, heart failure and decreased quality of life. Patients with AF have a risk of stroke 5 times higher and the risk of heart failure 3 times higher than patients without AF. Stroke is one of the most worrying complications of AF, because strokes caused by AF have a higher risk of recurrence. In addition, stroke due to AF resulted in death doubled and 1.5 times the cost of treatment.[1,3,4]

AF with other cardiovascular diseases such as hypertension, heart failure, coronary heart disease, hyperthyroidism, diabetes mellitus, obesity, congenital heart

disease such as atrial septal defects, cardiomyopathy, chronic kidney disease and chronic obstructive pulmonary disease (COPD). Symptomatic heart failure with functional class New York Heart Association (NYHA) II to IV can occur in 30% of patients with AF, but conversely AF can occur in 30-40% of patients with heart failure depending on the cause of heart failure. AF can cause heart failure through a mechanism of increased atrial pressure, increased cardiac volume load, valve dysfunction and chronic neuro hormonal stimulation. Distention in the left atrium can cause AF as occurs in patients with heart valve disease with a prevalence of 30% and 10-15% in the atrial septal effect. About 20% of the population of AF patients have coronary heart disease, although the link between AF itself and coronary perfusion is unclear.[2-4]

The management of AF aims to prevent complications. Antithrombotic therapy is the first choice used for prevention of stroke caused by AF. Anti-thrombotic therapies used for stroke prevention in AF patients include anticoagulants and antiplatelets. Another type of anti-thrombotic, thrombolytic, is not used for stroke prevention in patients AF.[1,3,4]

Vitamin K antagonists (AVK) such as warfarin and coumadin are the most widely used anticoagulant drugs to prevent strokes in AF. AVK such as warfarin plays a role in blood clotting, causing depletifactors II, VII, IX and X. Warfarin works in the liver by inhibiting the carboxylation of vitamin K from its precursor protein. The antithrombotic effect of AVK is only effective if there is a depletion of these four factors. This results in AVK taking several days to be effective as an anticoagulant. In addition, the use of AVK has many side effects in the form of bleeding. Five studies conducted by comparing AVK with placebo found that the major hemorrhage rate due to AVK was 1.3% per year compared to only 1% on placebo. Other additional evidence is that AVK is only effective as a stroke prevention when the time in therapeutic range (TTR) is 70%. TTR is the proportion of time when an International normalized ratio (INR) of 2-3 is reached compared to the overall length of time consuming AVK. This difficulty is compounded by the unavailability of INR inspection facilities in peripheral areas in Indonesia. Besides bleeding, AVK also has other side effects namely skin and tissue necrosis, alopecia, urticaria, dermatitis and can be hypersensitivity. Because of the side effects caused by AVK, New oral anticoagulants (NOACs) are needed with minimal side effects but have the same effectiveness as AVK.[4,5]

At present, in Indonesia there are 3 types of NOACs that exist in Indonesia that are not AVK, yakni dabigatran, rivaroxaban and apixaban.[3,5,6]

Dabigatran Etexilate

Dabigatran are NOACs which directly inhibit thrombin. The RE-LY (Randimized Evaluation of Long-term anticoagulant therapist Y with dabigatran etexilate) study compared the dose of dabigatran etexilate with adjusted dose warfarin. For primary efficacy endpoints in the form of stroke and systemic embolism, dabigatran given at a dose of 150 mg b.i.d found that dabigatran was superior to warfarin, without significant differences in the primary safety endpoint in the form of major bleeding. Hemorrhagic stroke and intracranial hemorrhage rates are lower in dabigatran compared to warfarin and have a lower risk of major bleeding than warfarin. Based on the results of the RE-LY study, dabigatran etexilate has been approved by the drug authorities of several countries in Europe such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The EMA determines the use of dabigatran for non-valvular AF with at least one of the following risk factors: history of stroke, transient ischemic attack (TIA) or systemic

embolism, LVEF <40%, symptomatic heart failure and age ≥75 years or ≥65 years but accompanied by one of the risk factors such as diabetes, coronary heart disease or hypertension. The FDA approves a dose of 150 mg b.i.d and a dose of 75 mg b.i.d in the event of severe renal impairment, while the EMA approves a dose of 110 mg b.i.d or 150 mg b.i.d.[3-5]

Rivaroxaban

Rivaroxaban works by directly inhibiting factor Xa. A study comparing the use of rivaroxaban with a dose of 20 mg o.d. (15 mg o.d. when creatinine clearance count is 39-49 ml / min) compared with warfarin in 14264 high-risk AF patients. From the results of the study found no decrease in mortality or ischemic stroke but there is a significant decrease in hemorrhagic stroke and intracranial hemorrhage. There was no difference in the primary safety endpoint that was a combination of major bleeding and clinically relevant bleeding but there was a decrease in fatal bleeding in the rivaroxaban group. Rivaroxaban has also been approved by the FDA and EMA for stroke prevention in non-valvular AF.[1,4-6]

Apixaban

A study was conducted on 5599 AF patients who were not suitable for AVK therapy given apixaban (5 mg bid with adjusted dose to 2.5 mg bid when age ≥80 years old, body weight ≤60 kg or serum creatinine ≥1.5 mg / dL) or given aspirin (81-324 mg / day with 91% drinking ≤162 mg / day). After a 1.1-year observation period, the study was terminated earlier because there was a significant reduction of 55% in the primary endpoint in the form of a stroke or systemic embolism in the apixaban group compared with aspirin, with no difference in the incidence of major and intracranial hemorrhage. Apixaban is better tolerated than aspirin with a drug withdrawal rate of 17.9% compared to aspirin which reaches 20.5%.[4-6]

Meanwhile another study compared apixaban [5 mg bid with dose adjustment to 2.5 mg bid if ≥80 years old, body weight ≤60 kg or with serum creatinine ≥1.5 mg / dl (133 mmol / L)] with warfarin dose adjusted to obtain a value of INR 2-3 in 18201 non-valvular AF patients. There was a significant reduction in primary efficacy outcomes in the form of stroke or ischemic embolism of up to 21% in the apixaban group compared to warfarin, a 31% reduction in the incidence of major bleeding and a significant 11% reduction in all-cause mortality. The incidence of hemorrhagic stroke and intracranial hemorrhage is significantly lower in the apixaban group but not so for ischemic stroke. Apixaban was better tolerated than warfarin with little early discontinuity (25.3% vs 27.5%). Apixaban has also received EMA and FDA approval for indications of stroke prevention in non-valvular AF.[2,3,8]

New anticoagulant drugs are proven to be non-inferior to warfarin with better safety. On this basis NOACs are preferred over warfarin in the majority of non-valvular AF patients. There are no further studies that compare among NOACs, but in terms of major hemorrhage rates of dabigatran 110 mg b.i.d and apixaban are lower than other NOACs.[8,9]

Based on a national survey in Denmark to see the balance between stroke and intracranial hemorrhage obtained only apixaban and both dabigatran doses (110 mg b.i.d and 150 mg b.i.d) which provide better clinical benefits than warfarin.[5,7,8]

CONCLUSION

Atrial Fibrillation (AF) is an arrhythmia characterized by disorganization of atrial depolarization resulting in impaired atrial mechanical function. AF can cause ischemic strokes and systemic embolism. Prevention of the occurrence of ischemic stroke and systemic embolism is done by administering anti-coagulants such as vitamin K antagonists such as warfarin.

But warfarin has several dangerous side effects such as can cause bleeding. For this reason, another alternative is needed to prevent ischemic stroke and systemic embolism with minimal side effects.Novel Oral Anti Coagulants (NOACs) can be used as a solution to prevent complications from AF with minimal side effects. In Indonesia at this time, circulating 3 types of NOACs namely dabigatran, rivaroxaban and apixaban which have better effectiveness than warfarin with minimal bleeding side effects.

SUGGESTION

It is expected that the presence of NOACs can reduce the number of ischemic strokes and ischemic embolism due to AF with side effects of bleeding and other side effects.

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