Pharmacotherapy of Atrial Fibrillation

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Abstract
Atrial fibrillation (AF) is the most common type of arrhythmia and its prevalence is increasing. The incidence of atrial fibrillation increases every year. Therefore, atrial fibrillation also causes increased mortality and morbidity, including the incidence of stroke, heart failure, hospitalizations, and decreased quality of life. Atrial fibrillation increases the risk of stroke by up to 5 times and is thought to cause 25 % of strokes and patients with atrial fibrillation have a 3 times higher risk of heart failure compared with patients without atrial fibrillation. Risk factors of atrial fibrillation are age, history of myocardial infarction, history of heart failure, obesity, cardiothoracic surgery, smoking, alcohol consumption, hyperthyroidism, congenital heart disease, chest infection, and family history. Pharmacotherapy of atrial fibrillation is generally the use of anticoagulants for stroke prevention, heart rate control, heart rhythm control and upstream therapy.

Keywords*: Atrial Fibrillation, AF, Classification, Pharmacotherapy*

I. INTRODUCTION

Atrial fibrillation is a continuous arrhythmia, where the occurrence of atrial activation disorder is characterized by loss of atrial contraction and irregular ventricular levels determined by AV nodal conduction (Michaud & Stevenson, 2015). Atrial fibrillation is the most common type of arrhythmia and its prevalence is increasing (Kirchhof, et al., 2016). Atrial fibrillation is experienced by 1 % -2 % of the world's population with an age range of 40-50 years, around 5 % -15 % aged > 80 years (Arbustini, Favalli, Narula, Disabella, & Grasso, 2017). In Indonesia, the presentation of the incidence of atrial fibrillation also increased, according to data from one Indonesian hospital showed that the incidence of atrial fibrillation increased every year, which was 7.1 % in 2010, increasing to 9.0 % (2011), 9.3 % (2012) and 9.8 % (2013) (Yuniadi, et al., 2014).

Atrial fibrillation causes increased mortality and morbidity, including the incidence of stroke, heart failure, hospitalizations, and decreased quality of life (Kirchhof, et al., 2016). Atrial fibrillation increases the risk of stroke by up to 5 times and is thought to cause 25% of strokes and patients with atrial fibrillation have a 3 times higher risk of heart failure compared with patients without atrial fibrillation (Yuniadi, et al., 2014; Michaud & Stevenson, 2015). On an electrocardiogram (ECG), the characteristic of atrial fibrillation is the absence of P wave consistency, which is replaced by a fibrillation wave that varies in amplitude, shape and duration. In normal NAV function, the atrial fibrillation is usually followed by a ventricular response that is also irregular, and often fast (Newby, Grubb, & Bradbury, 2014).

II. ATRIAL FIBRILLATION

A. Classification of Atrial Fibrillation

Clinically atrial fibrillation can be divided into 5 types according to presentation time, duration, and spontaneous discontinuation of atrial fibrillation episodes. Atrial fibrillation can experience progression from paroxysmal to persistent, persistent, long or permanent. All types of atrial fibrillation can be an initial presentation based on previous history. The following are the classifications (Kirchhof, et al., 2016):

1. First diagnosed atrial fibrillation, this type applies to patients who first arrive with clinical manifestations of atrial fibrillation, regardless of the duration or severity of the symptoms that appear.
2. Paroxysmal atrial fibrillation, atrial fibrillation that experiences spontaneous termination within 48 hours, but can continue for up to 7 days.
3. Persistent atrial fibrillation, atrial fibrillation lasting more than 7 days, including episodes that are terminated by cardioversion, either with medication or with direct current cardioversion, after 7 days or more.
4. Long-standing persistent atrial fibrillation, atrial fibrillation that lasts up to ≥1 years, and a cadence control strategy will still be applied.
5. Permanent atrial fibrillation, atrial fibrillation that is determined as permanent by doctors (and patients) so that the rhythm control strategy is no longer used. If the cadence control strategy is still used then atrial fibrillation falls into the category of long-standing persistent atrial fibrillation.

Apart from the 5 classifications mentioned above, there are also several additional Atrial Fibrillation classifications that are determined by the characteristics of the patient (Ryden, Cannom, & Fuster, 2006):

1. Lone atrial fibrillation: atrial fibrillation without being accompanied by other cardiovascular structure diseases, including hypertension, associated pulmonary disease or cardiac anatomic abnormalities such as left atrial enlargement, and under 60 years of age.
2. Non-valvular atrial fibrillation: atrial fibrillation that is not associated with mitral rheumatic disease, prostatic heart valve or mitral valve repair surgery.
3. Atrial Secondary Fibrillation: atrial fibrillation that results from a primary condition that triggers atrial fibrillation, such as acute myocardial infarction, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia or other acute lung diseases. While secondary atrial fibrillation associated with valvular disease is called valvular atrial fibrillation.

B. Etiology of Atrial Fibrillation

Patients with Atrial Fibrillation generally had cardiac structural abnormalities or systemic diseases such as hypertension, diabetes mellitus, left ventricular hypertrophy, hyperlipidemia, anemia, arthritis and others (Chugh, et al., 2014). In addition, risk factors for atrial fibrillation are age, history of myocardial infarction, history of heart failure, obesity, cardiothoracic surgery, smoking, alcohol consumption, hyperthyroidism, and family history (January, et al., 2014; Newby, et al., 2014)

III. PHARMACOLOGICAL TREATMENT OF ATRIAL FIBRILLATION

B. Anticoagulants for Stroke Prevention

Treatment in patients with atrial fibrillation is adjusted according to the symptoms that occur in the patient, the hemodynamic effects of atrial fibrillation, the duration of atrial fibrillation if there are persistent factors for stroke and other heart diseases. Atrial fibrillation increases the risk of stroke by 5 times and the incidence of stroke caused by atrial fibrillation continues to increase by 15 % - 25 % annually (Singer, et al., 2008; Michaud & Stevenson, 2015). Anticoagulation is recommended for patients with atrial fibrillation with a history of stroke, transient ischemic attack (TIA) or CHA2DS2-VASc scores of more than 2 (Brieger, et al., 2018). Oral use of anticoagulants in high-risk patients with atrial fibrillation includes vitamin K antagonists or recent anticoagulants including thrombin inhibitors (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban), but do not use antiplatelet agents (aspirin, clopidogrel) which have less substantial effect (Michaud & Stevenson, 2015).

Tabel 1. CHA2DS2-VASc score. Recommended use of anticoagulants (Bashore, Granger, Jackson, & Patel, 2016)

CHA2DS2-VASc score	Points
Heart failure or LVEF ≤ 40 %	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke, transient ischemic attack, or thromboembolism	2
Vascular disease (previous myocardial infarction, peripheral artery disease, or aortic plaque	1
Age 65-74 years	1
Female sex (but not a risk factor if female sex is the only factor)	1
Maximum score	9
CHA2DS2-VASc score = 0 : recommend no antithrombotic therapy	
CHA2DS2-VASc score = 1 : recommend antithrombotic therapy with oral anticoagulation or antiplatelet therapy but preferably oral anticoagulation	
CHA2DS2-VASc score = 2 : recommend oral anticoagulation	

Management of atrial fibrillation that induces a stroke which previously was classified into the CHA2DS2-VASc score (Tabel 1). Thus stroke risk stratification guidelines in patients with atrial fibrillation must be more inclusive of a variety of common stroke risk factors that will cover the entire spectrum of patients with atrial fibrillation. The CHA2DS2-VASc score includes common risk factors that are often found in daily clinical practice. CHA2DS2-VASc each letter is the beginning of certain words, namely Congestive heart failure, Hypertension, Age ≥ 75 years (score 2), Diabetes mellitus, Stroke history (score 2), peripheral Vascular disease, Age between 65 to 74 years, Sex Category (female). A history of heart failure is not a risk factor for stroke, but what is mean by the letter 'C' in the CHA2DS2-VASc score is the presence of moderate to severe left ventricular dysfunction (LVEF ≤ 40 %) or new heart failure patients requiring hospitalization regardless of the value of the ejection fraction. Female sex increases the risk of stroke independently, but women aged <

65 years and suffering from lone atrial fibrillation do not increase the risk of stroke so do not require anticoagulant therapy (Bashore, Granger, Jackson, & Patel, 2016).

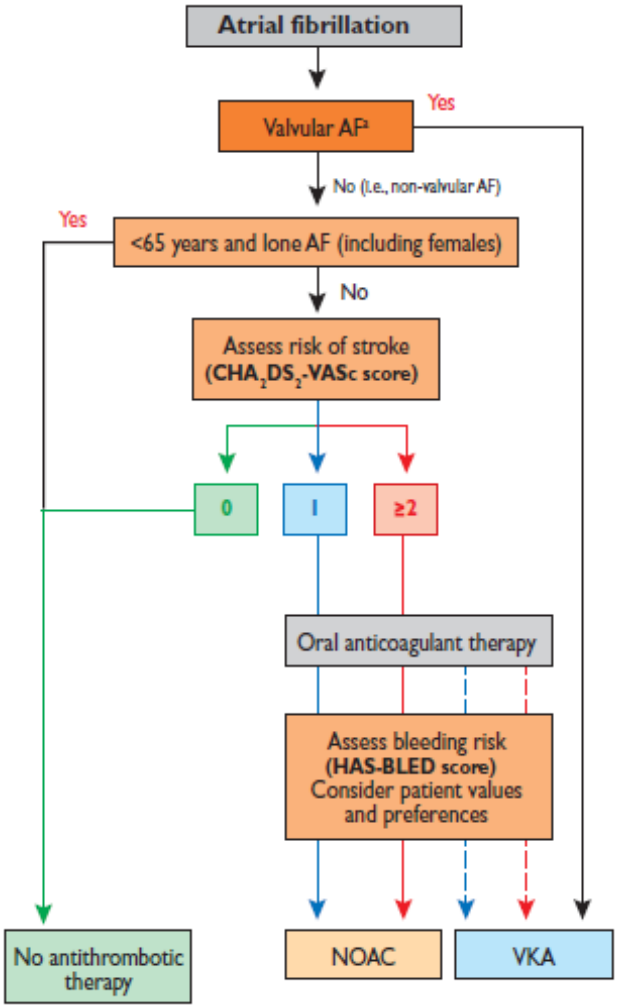

Figure 1. Selection diagram of anticoagulant therapy. NOAC: novel oral anticoagulants, VKA: vitamin K antagonists, solid lines: best choice, dashed lines: alternative choices (Camm, et al., 2012)

The decision to give thromboprophylaxis needs to be balanced with the risk of bleeding due to anticoagulants, especially intracranial bleeding that is fatal or causes disability. Figure 1 shows the algorithm for giving anticoagulants, HAS-BLED score, short for Hypertension, Abnormal renal or liver function, history of Stroke, history of Bleeding, Labile INR value, Elderly, and antithrombotic Drugs and alcohol have been validated in many cohort studies correlated well with intracranial hemorrhage. Evaluation of the risk of bleeding in each patient atrial fibrillation must be performed and if the HAS-BLED score is ≥ 3, special attention, periodic monitoring and efforts to correct risk factors that can be changed are needed. It is important to note that in the same HAS-BLED score, the risk of intracranial hemorrhage and other major bleeding with aspirin or warfarin is the same. The incorporation of CHA2DS2-VASc and HAS-BLED scores is very useful in the decision of thromboprophylaxis in daily practice (Bashore, Granger, Jackson, & Patel, 2016). Anticoagulant therapy used to prevent stroke in atrial fibrillation patients includes anticoagulants: vitamin K antagonists and new anticoagulants (Brieger, et al., 2018).

i. ***Vitamin K Antagonists:*** Vitamin K antagonists (warfarin) are the first anticoagulant drugs and are the most widely used for the prevention of stroke in atrial fibrillation. Therapy Vitamin K antagonists reduce the risk of stroke that has been used in many patients around the world with good results. Warfarin can reduce the risk of embolic stroke by 64 % and mortality rate by 26 % when used in non-valvular patients atrial fibrillation (Hart, Pearce, & Aguilar, 2007). However, the use of vitamin K antagonists is limited by a narrow therapeutic interval, so frequent monitoring and dose adjustment are needed, vitamin K antagonist therapy, when given with sufficient time, within the therapeutic range (TTR), effective for prevention of stroke in patients with atrial fibrillation. TTR is the proportion of time when INR 2-3 is reached compared to the total length of time consuming vitamin

K antagonists (Morgan, et al., 2009; Caterina, et al., 2012). Therefore, continuous dose management efforts must be made to obtain a target value of INR 2-3. The difficulty in using vitamin K antagonists in Indonesia is the unavailability of INR examination facilities in certain regions. In this regard it is also important to note the genetic factors in Indonesian ethnicity which are related to individual sensitivity to warfarin (Suriapranata, Tjong, & Wang, 2011).

ii. **Novel Oral Anticoagulants*:*** At present there are 4 new types of anticoagulants which are not vitamin K antagonists: apixaban, dabigatran, rivaroxaban, and edoxaban. Where 3 of them are in Indonesia, dabigatran, rivaroxaban, and apixaban. Dabigatran works by directly inhibiting thrombin while rivaroxaban and apixaban both work by inhibiting factor Xa. While edoxaban which is the latest anticoagulant is not yet available in Indonesia and the mechanism of action of this drug inhibits factor Xa (Kirchhof, et al., 2016)**.** Apixaban, rivaroxaban and dabigatran, , can be given if the INR target is not achieved with warfarin, but it is necessary to periodically examine kidney function. Dabigatran and rivaroxaban are not recommended in patients with atrial fibrillation with concomitant end-stage chronic renal failure or dialysis therapy because there is no clinical study, warfarin is the primary choice for patients in the group. Dabigatran and Rivaroxaban can be given to patients with chronic renal failure, but dosage adjusment needs to be done (January, Wann, Anderson, & Halperin, 2014). Clinical study ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboid Events in Atrial

Fibrillation) study compared comparing apixaban 5 mg twice a day with a dose adjustment of 2.5 mg twice a day if ≥ 80 years, body weight ≤ 60 kg or with serum creatinine 51.5 mg / dL (133 mmol / L) with warfarin dose adjusted to obtain INR 2–3 in 18201 AF patients non-valvular. There was a significant decrease in primary efficacy outcomes in the form of systemic stroke or emboli up to 21 % in the apixaban group compared to warfarin, a 31 % reduction in major bleeding events and a significant 11 % reduction in all causes (but not cardiovascular mortality). The incidence of hemorrhagic stroke and intracranial hemorrhage was significantly lower in the apixaban group but not for ischemic stroke. Apixaban is better tolerated than warfarin with fewer early discontinuities (25.3 % vs. 27.5 %) (Granger, et al., 2011)

Double blind study of ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) showed no difference in the primary safety endpoint namely a combination of major bleeding and clinically relevant bleeding but there was a decrease in fatal bleeding in the rivaroxaban group compared to the warfarin group. Therapeutic discontinuity occurs more frequently in rivaroxaban (23.9 %) than warfarin (22.4 %). Rivaroxaban has also been approved by The Food and Drug Administration (FDA) and European Medicines Agency (EMA) for stroke prevention in non-valvular AF, as well as in several other countries (Patel, et al., 2011).

Another study, RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapies with dabigatran etexilate), dabigatran etexilate has been approved by the FDA and EMA, as well as by several authorities of drugs and food of various other countries, for the prevention of stroke and thromboembolism. The European Medicines Agency establishes indications for 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 diabetes, coronary heart disease or hypertension. FDA approved a dose of 150 mg twice a day, and a dose of 75 mg twice a day. if there is severe renal impairment, whereas EMA approves a good dose of 110 mg twice a day and 150 mg twice a day (Connolly, Ezekowitz, Yusuf, Reilly, & Wallentin, 2010).

Table 2. Pharmacokinetic profile of anticoagulant drugs (Heidbuchel, et al., 2015).

Medication	Warfarin	Apixaban	Rivaroxaban	Dabigatran
Bioavailabillity	100 %	50 %	66% without food. Almost 100% with food	3 – 7 %
T max (h)	72 – 96 %	3	2.5 - 4	1 - 2
Absorbtion with food	No effect	No effect	39 % more	No effect
Distribution (% protein bound)	99 %	87 %	95 %	35 %
Vd (L)	10	21	50 - 55	60 – 70
Metabolism	CYP2CP (primary)	CYP3A4 (primary)	CYP3A4 (primary)	Hepatic esterase
t½ (h)	40	8 - 15	5 – 9 (Young)	12 - 17

			11 - 13 (Elderly)	
Renal excretion	92 %	25 %	35 %	80 %

C. Control of Heart Rate

Heart rate control using beta blockers, non-dihydropyridine calcium antagonists, and others (Table 3) is recommended for patients with paroxysmal, persistent, or permanent atrial fibrillation with stable hemodynamic conditions (January, Wann, Anderson, & Halperin, 2014)

Tabel 3. Dosage for controlling heart rate (Camm, et al., 2012)

Class	Drug	Intravenous Dosage	Oral Dosage
Beta Blocker	Propranolol	-	10 - 40 mg, 3 times a day
	Carvedilol	-	3.125 - 25 mg, 2 times a day
	Atenolol	-	25 - 100 mg, once a day
	Bisoprolol	-	5 - 10mg, once a day
Calcium channel antagonists (*non-dihydropyridine)*	Verapamil	0.075 - 0.15 mg / kgBB iv in 2 minutes	40 mg (2 times a day) to 240 mg once a day (Extended Release)
	Diltiazem	0.25 mg / kg BW bolus in 10 minutes, followed by 0.35 mg / kgBB	30 mg (3 times a day) to 120 mg once a day (Extended Release)
Others	Amiodaron	5 mg / kg in 1 hour and 50 mg / hour for maintenance	100 - 200 mg (once a day)
	Digoksin	0.5 - 1 mg	0.125– 0.5 mg

D. Control of Heart Rhythm

The main purpose of heart rhythm control is to reduce symptoms due to atrial fibrillation. This strategy was chosen for patients who still experience symptoms even though rate control therapy has been performed optimally. The first choice for therapy with rhythm control is with antiarrhythmic drugs, Amiodaron is the most powerful antiarrhythmia preventing atrial fibrillation recurrence after successful cardioversion (Lafuente, Valembois, & Bergmann, 2015). Changing atrial fibrillation to sinus rhythm (cardioversion) using the drug is most effective within 7 days after atrial fibrillation. But pharmacological cardioversion is less effective in persistent atrial fibrillation (Gillis, Verma, Talajic, Nattel, & Dorian, 2011). Pharmacotherapy of rhythm return to the sinuses has the advantage of reducing the risk of thromboembolism, improving hemodynamics by restoring 'atrial kick', preventing the occurrence of a rapid ventricular response that can induce cardiomyopathy due to tachycardia, and preventing atrial remodeling which can increase atrial size and cause atrial cardiomyopathy (Boos, Carlsson, & More, 2003).

E. Upstream Theraphy

Upstream therapy at atrial fibrillation aims to prevent or inhibit the process of myocardial remodeling due to hypertension, heart failure, or inflammation. Some of the therapies included in this group are angiotensin conversion enzyme inhibitors, angiotensin receptor blockers, antagonists aldosterone, statin, and omega 3. Angiotensin conversion enzyme inhibitors and angiotensin receptor blockers inhibit the arrhythmogenic effects of angiotensin II, including preventing atrial fibrosis and hypertrophy, oxidative stress, and inflammation. Its use as primary prevention is mainly in patients with hypertension, heart failure, and other risk factors for coronary heart disease. Angiotensin conversion enzyme inhibitors and angiotensin receptor blockers should be used in patients with recent atrial fibrillation in heart failure patients with decreased ejection fraction and hypertension with left ventricular hypertrophy (Camm, et al., 2012).

IV. CONCLUSION

Atrial fibrillation is a continuous arrhythmia, where the occurrence of atrial activation disorder is characterized by loss of atrial contraction and irregular ventricular levels determined by AV nodal conduction. Symptoms in most patients with atrial fibrillation use heart rate control. In patients with atrial fibrillation and there are additional risk factors for stroke, anticoagulants are recommended, where previously the clinicians have considered the benefits and harms of using the drug.

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