Oral Anticoagulant Treatment in Management of Elderly Patients with Atrial Fibrillation: Is It Beneficial or Detrimental?

Edwin Setiabudi, Idrus Alwi, Siti Setiati

ABSTRACT

Atrial fibrillation (AF) is supraventricular tachyarhythmia characterized by uncontrolled atrial activation, and deteriorates atrial function. In AF patients, increasing of age is related with enlarge left atrium (LA), diminished flow velocity of left atrial appendage (LAA), and spontaneously contrast echo, with other factors which are predisposition for LA thrombus. In AF patients, thromboemboli after cardioversion without anticoagulant administration is 1.5-3.0%. Elderly patient is not contraindication for anticoagulant, although higher risk for bleeding. For stroke prevention in >65 years of age whilst the patient is candidate for oral anticoagulant warfarin, it should be prescribed to reach INR 2.0-3.0. Some reports on anticoagulant evaluation (INR) and bleeding as complication of warfarin prescribed for AF treatment are not significantly different in elderly and younger patients.

Key words: atrial fibrillation, oral anticoagulant, geriatric.

INTRODUCTION

Anticoagulants are drugs of choice to prevent thromboembolism in atrial fibrillation (AF). The number of atrial fibrillation cases increases with age. Aging process will influence drug pharmacokinetics, i.e. drug absorption, distribution, metabolism, and excretion. Elderly patient usually has various types of diseases and anticoagulant treatment becomes a dilemma. In addition to the bleeding caused by anticoagulants, drug interaction of concomitant medications also becomes a serious problem. This article will discuss about the benefits and disadvantages of anticoagulant treatment in elderly patients with AF.

INCIDENCE OF AF IN ELDERLY PATIENTS

AF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation which results in decreased atrial mechanical function. The mortality risk is doubled in patient with AF compared to patient with sinus rhythm. Epidemiological data of Framingham Study indicated the incidence rate of AF, which had been accumulated during 22-year follow up period, was as high as 2.1% in male and 1.7% in female, and most AF cases were found in patients with 65-85 years of age group.

CLINICAL IMPLICATION OF AF

AF is a strong independent risk factor against embolic stroke event. The worst consequences of AF is thromboembolic stroke, which is usually derived from a thrombus at left atrial appendage (LAA). The other clinical implication, which especially occurs in AF with rapid ventricle response (usually has ventricle rate of >130 pulse per minute), may present as heart failure and tachycardia-induced cardiomyopathy.

Approximately two third to three fourth of ischemic stroke cases occur in non-valvular AF caused by embolic stroke. The risk for stroke in non-valvular AF patients is 5-7 times greater than in the patients without AF. Overall, 20-25% of ischemic stroke is caused by cardiogenic emboli.

The risk for stroke and thromboembolism in patients with AF is not equivalent. Patients with AF may be categorized into high-risk patient (with annual risk for stroke of 8-12%), moderate risk patient (annual risk for stroke of 4%) and low-risk patient (annual risk for stroke of 1%).

High-risk factors are:

1. Previous stroke/TIA (transient ischemic accident) or systemic emboli.
2. History of hypertension
3. Bad left ventricle systolic function
4. Age >75 years
5. Mitral valve rheumatic disease
6. Prosthetic cardiac valve

Moderate risk factors are:
1. Age 65-75 years
2. Diabetes mellitus
3. Coronary heart disease with good left ventricle systolic function

Low risk factors are:
1. Age <65 years
2. No other risk factors

The annual incidence of emboli in patients with mitral stenoses and AF is about 4-6%. There are risk factors that may cause stroke event in patients with non-valvular AF, i.e. previous stroke or TIA event (RR 2.5), diabetes mellitus (RR 1.7), history of hypertension (RR 1.6) and increased age (RR 1.4 for every decade).

Patients who have risk factor(s) for congestive heart failure or coronary arterial disease may experience stroke event approximately 3 times higher than patients without any risk factor. Echocardiography examination revealing left ventricle dysfunction and left atrium size >2.5 cm/m² is associated with spontaneous echocardiographic contrast, thrombus formation and emboli.

In patients with AF, there are independent predictors of spontaneous echocardiographic contrast, thrombus formation and emboli.

In patients with AF, there are independent predictors of spontaneous echocardiographic contrast which include LA size, LAA flow rate, left ventricle dysfunction, fibrinogen level, hematocrit, and aortic atherosclerosis. This phenomenon has been characteristic for regional coagulopathy and the dense echocardiography result in a patient reveals high thromboembolic risk.

The effect of elderly on increased AF risk is multi factorial. In patients with AF, increased age is associated with enlarged LA, reduced LAA flow, and spontaneous echocardiographic contrast and each of those factors predispose to LA thrombus formation.

AF TREATMENT

The management of AF treatment has long been a great challenge in cardiology. The main problem in management of AF is associated with rhythm management and thromboembolic prevention. The general strategy in AF management is pharmacologic treatment through rhythm control and rate control. Clinical trials results indicate no significant difference of both strategies regarding reduced mortality and increased survival rate.

However, pharmacologic treatment has some limitations such as drug intolerance, adverse effect, and pro-arrhythmia effect. Therefore, non-pharmacologic approach such as electrical cardioversion, permanent heart pacing, catheter ablations, Cox-Maze procedure turns out to be further alternative treatment.

CORRELATION BETWEEN CARDIOVERSION, THROMBOEMBOLISM, AND ANTICOAGULANT

Elective cardioversion is frequently done in order to restore the sinus rhythm in patients with persistent AF. However, cardioversion may have thromboembolic risk unless prophylactic anticoagulant is administered prior to cardioversion procedure. The possibility of thromboembolic risk is greater when arrhythmia has occurred more than 48 hours.

Thromboembolism is a complication that may occur after cardioversion procedure, i.e. electrical, pharmacological, or spontaneous cardioversion. The incidence of post-cardioversion thromboembolism in AF patients without anticoagulant treatment is approximately 1.5-3%.

Byekerland and Orning reported that the incidence of post-cardioversion thromboembolism without anticoagulant treatment was 5.3%, while in patients who had anticoagulant treatment the incidence was 0.8%.

After the cardioversion, mechanical contraction of left atrium has not recovered (atrial stunning) until 2-4 weeks of period. Hence, there is possibility of new thrombus formation during atrial-stunning period and to prevent thrombus formation provided that another AF occurs after the cardioversion.

Thrombus that formed at left atrium needs approximately 2 weeks of period to be organized and firmly attached on atrial wall so that it will not easily removed when the atrium contracts after regaining its sinus rhythm.

In patients with AF more than 48 hours or unknown period, we recommend warfarin treatment with INR
target of 2-3, which is administered 3 weeks before cardioversion and continued after the cardioversion for 4 weeks.

Manning suggested TEE (Transesophageal Echocardiography) examination prior to cardioversion. Heparin will be administered to the patients if there is no thrombus found and after the cardioversion. Anticoagulant treatment is administered until 4 weeks post-cardioversion.

In multiple studies for Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE), there was 0.8% thromboembolism incidence for TEE examination strategy, while conventional strategy showed 0.5% of incidence. Both strategies showed no significant difference. TEE examination strategy needs lesser time for cardioversion. AF that last less than 24 hours has a very low post-cardioversion thromboembolic risk (0.8%). In some cases, thrombus may be formed in AF with less than 48 hour duration and therefore anticoagulant treatment is recommended during peri-cardioversion period.

The following are grading/staging recommendations for AF cases based on EBM (evidence based medicine):

1. Grade A, if the data are acquired through double-blind randomized clinical trial.
2. Grade B, if the data are obtained from non-randomized trials with limited sample or observational note.
3. Grade C, if the data are obtained based on the experts consensus.

Recommended classification of indication based on ACC/AHA guidelines for the management of patients with atrial fibrillation:

- Class I: a condition in which there is an evidence and or general consensus that a procedure or treatment is beneficial and effective.
- Class II: a condition in which there is a contrary evidence and or different opinion on benefit/efficacy of a procedure or treatment
- Class IIa: a property which shows an evidence or opinion supporting a procedure or treatment
- Class IIb: Less benefit or efficacy determined by an evidence or opinion
- Class III: a condition which has evidence and or general consensus that a procedure or treatment is not beneficial/effective and in some cases it would be harmful.

Recommended antithrombotic treatment in patients with AF based on ACC/AHA guidelines.\(^1\)

### Class I:

1. Administer antithrombotic agents (oral anticoagulants or aspirin) for all patients with AF to prevent thromboembolism, except for the Lone AF (A).
2. Individually select antithrombotic agents based on absolute and relative risk (RR) evaluation for stroke and bleeding as well as their benefits for certain patients. (A)
3. Long-term oral anticoagulant treatment with INR target of 2-3 in patients with high-risk for stroke, unless there is any contraindication. (A)
4. Alternative aspirin treatment for a dose of 325 mg/day in low-risk patients or in patients who have contraindication for oral anticoagulant (A).
5. Oral anticoagulant in AF patients with rheumatic disease of mitral valve or prosthetic valve (mechanic or tissue valve) (B).

The treatment will be given based on the target intensity of anticoagulant treatment in certain prostheses, but it should not be less than INR 2-3. (B)

### Class IIA:

1. INR target is less than 2 (1.6 – 2.5) for primary prevention of ischemic stroke and systemic emboli in patients > 75 years with consideration of increased risk for bleeding complication without any definite oral-anticoagulant contraindication (C).
2. Manage antithrombotic treatment in patients with flutter atrial in general in the same way as the AF (C).
3. Select antithrombotic treatment with comparable criteria other than AF pattern (that is for patients with paroxysmal, persistent or permanent AF) (B).

### Class IIB:

1. Suspend the anticoagulant treatment for a week in surgery or diagnostic procedures that may have risk for bleeding, without substituting heparin treatment in AF patients who have no mechanical prosthetic heart valve (C).
2. Administer intravenous or subcutaneous unfractionated heparin or LMWH in high-risk patients or when there is a serial of procedures require suspension of oral anticoagulant treatment over one week period (C).
3. Manage anticoagulant treatment (INR 2-3) in patients with coronary arterial disease (CAD) based on comparable criteria as the patients without CAD (C).

Low-dose aspirin treatment (less than 100 mg/day) or clopidogrel (75 mg/day) may be given
simultaneously with anticoagulant treatment. However, this strategy has not been adequately evaluated and it may be associated with increased bleeding-risk.

4. Administer aspirin as alternative treatment or primary prevention of stroke in patients < 60 years without any heart disorder or thromboembolic risk factors (Lone AF) (C).

**Class III:**

Long-term anticoagulant treatment to prevent stroke in patients < 60 years without any heart disorder (Lone AF) or thromboembolic risk factors (C).

Recommended antithrombotic treatment to prevent ischemic stroke and systemic emboli in AF patients who had cardioversion:38

1. Administration of anticoagulant agents associated with the utilized cardioversion method (electric or pharmacologic cardioversion) to restore sinus rhythm (B).

2. Administration of anticoagulant agents for at least 3-4 weeks before and after cardioversion (INR 2-3) in patients with AF which end >48 hours or indefinite duration (B).

3. Immediate cardioversion in acute (recent-onset) AF accompanied by signs or symptoms of hemodynamic instability which cause angina pectoris, myocardial infarct, shock or pulmonary edema without waiting for prior anticoagulant treatment (C)
   a. If there is no contraindication, administer bolus IV of heparin followed by intravenous heparin drip with adjusted dose corresponds to aPTT 1.5-2 times of normal level (B).
   b. Afterward, administer the oral anticoagulant agents (INR 2-3) for at least 3-4 week period in the same way as patients who had elective cardioversion (C).
   c. Until now, there are limited data supporting subcutaneous LMWH administration for such indication (C).

4. TEE screening in order to observe any thrombus in LA or LAA as another alternative method prior to anticoagulant treatment that routinely done preceding cardioversion (B).
   a. If there is no thrombus identified by IV unfractioned heparin, anticoagulants will be administered to the patients. Initially, bolus anticoagulant will be given and which will be followed by continuous intravenous drip with adjusted dose corresponds to aPTT 1.5-2 times of normal level prior to cardioversion (B).
   b. Afterward, it should be followed by oral anticoagulant agents (INR 2-3) for at least 3-4 week period if the patient undergoes elective cardioversion.
   c. Until now, there is limited data encouraging subcutaneous LMWH administration for such indication (C).
   d. If a thrombus is found in TEE examination, administer oral anticoagulants (INR 2-3) for at least 3-4 weeks before and after the patient has sinus rhythm (B).

**Class IIb:**

Cardioversion without TEE examination in the first 48 hours after AF (C).

a. In this case, anticoagulant treatment before and after cardioversion is optimal depends on other risk factor (C).

b. Anticoagulant is administered in patients with flutter atrial who are experiencing cardioversion in the same way as patients with AF (C).

**The Role of Anticoagulant in AF**

There are a lot of studies that evaluate the possibility risk of stroke in AF patients as well as the benefits of anticoagulant and antiplatelet treatment.25-31 Anticoagulant is very effective to prevent thromboembolic complications in AF.5 Five anticoagulant trials revealed 4.5% of annual stroke incidence in the control groups without anticoagulant treatment, but the risk was reduced to 1.4% (68% decrease) in warfarin group (60% reduced risk in male and 84% reduced risk in female). Aspirin for dose of 325 mg/day may reduce 44% risk. Annual incidence of major bleeding was 1% and 1.3% for the control group and warfarin group respectively. There was no different risk for stroke between paroxysmal (intermittent) AF and constant (chronic) AF. However, anticoagulant treatment to prevent ischemic stroke in AF patient was approximately 50% more effective than aspirin treatment. There was risk factor for intracranial bleeding caused by excessive anticoagulant treatment and uncontrolled hypertension. The risk of anticoagulant-induced cerebral bleeding was increased in elderly individuals, especially those who were treated with excessive anticoagulation treatment.

From these data and other data, it is obvious that antithrombotic treatment to prevent stroke in individuals <60 years without any clinical risk factor or structural heart disease (Lone AF) is not necessary because of the low risk. The incidence of stroke is also low (2% per year) in patients aged 60-75 years with Lone AF.

These patients are quite protected against stroke by aspirin...
treatment. In the very old AF patients (>75 years), anticoagulant treatment should be administered and monitored carefully because of increased risk for intracranial bleeding. Nevertheless, elderly patients with AF still possibly obtain beneficial effect of anticoagulant treatment, especially in those who have high-risk for stroke. Diet and drugs such as antibiotics and anti-arrhythmia agents (for example, amiodarone) may influence the effect of warfarin.

Antithrombotic treatment is recommended in: every patient with AF who has risk factor for stroke (previous stroke or TIA), heart valve disease, hypertension, diabetes, aged >65 years, left atrial enlargement, coronary arterial disease or congestive heart failure) should be treated by warfarin in order to achieve INR 2.0 – 3.0 in preventing stroke if the individual is a candidate for oral anticoagulant treatment.

Patients with contraindication of anticoagulant treatment should be considered for aspirin treatment. AF patients who have no previous risk factor and have low-risk for stroke (2% per year or less) can be protected from stroke by aspirin treatment. In patients aged >75 years, anticoagulant treatment should be used and monitored carefully so that the INR is maintained less than 3.0 because there is a risk of intracranial bleeding.8

The high-risk patients group should have chronic anticoagulant treatment considering that they will undergo cardioversion. Patients who are not included in low-risk patient group, i.e. patients with AF lasting more than 2 days should have three week warfarin treatment to achieve INR 2.0-3.0 prior to the elective cardioversion and treatment should be continued for 3-4 weeks after having regained the sinus rhythm. Other alternative strategy includes Transesophageal echocardiogram to remove atrial thrombus. It is obvious that this technique may predict the development of thromboembolism after the cardioversion in low-risk patients. Therefore, the patients should be immediately treated with heparin followed by therapeutic dose of warfarin.31 Anticoagulant treatment using heparin has been recommended in emergency cardioversion when 3 weeks anticoagulant treatment or transesophageal echocardiogram is not possible. No matter what strategy is used, anticoagulant treatment should be continued at least 4 weeks after cardioversion because the contractile function of atrium may not be fully recovered as before.32, 33

RECOGNIZING THE CHARACTERISTICS OF ORAL ANTICOAGULANT (WARFARIN)

Warfarin (Coumarin, Coumadin, Panwarfarin) is the most common oral anticoagulant because of single-dose warfarin that may provide stable anticoagulant effect. This may result from good oral absorption and its half-life in the circulation, i.e. less than 37 hours. Warfarin may also cause various adverse effects other than bleeding. Drug interaction of warfarin and other drugs may also occur. In general, compared to aspirin, high-intensity warfarin is more effective but it is associated with more possibility of bleeding. Low-intensity warfarin may have similar efficacy and safety to aspirin.

Oral anticoagulants inactivate vitamin K in liver microsomes and consequently disturb the formation of clotting factor dependent on vitamin K such as prothrombin. In addition, factor X may also reduce. Since prothrombin has a long half-life, prothrombin onset of action delays from 2 into 7 days.

After a rapid and complete absorption, nearly all of oral warfarin is bound to plasma albumin with 37 hours half-life. Warfarin is metabolized in liver microsomes and the end product is inactive metabolite excreted into urine and feces.

The standard procedures are as follows: administer 5 mg/day warfarin for 5 days, examine the prothrombin time every day until it shows a level in therapeutic range. Afterward, check it 3 times a week for 2 week period. For elderly patients and patients with increased bleeding risk, the initial dose is lower. Warfarin should be started at least 4 days before cessation of heparin so that coagulation factors that depend on vitamin K in the circulation is inactivated; heparin may be stopped soon after INR at therapeutic range for 2 days. Large primary dose may cause excessive reduce of prothrombin level and risk of skin necrosis which should be avoided. If only immediate effect is necessary, we should use a loading dose of warfarin 10-15 mg/day. Patients with heart failure or liver disease require lower dose. Usual maintenance dose is 4-5 mg every day, but it may vary from 1 mg to 20 mg per day. The wide range of dose means that the dose should be individually adjusted appropriate to the INR.

Warfarin effect is monitored by evaluating INR result. Prosthetic heart valve requires a more intense safe-anticoagulant treatment with quite varied recommended INR range, i.e. from 2.0 to 4.5, which includes lower INR range for bioprosthetic valve and mechanical aorta compared to the mitral valve.35 However, a meta-analysis of 23,145 patients recommended a higher INR range with the target >3.0.
Less intense anticoagulant treatment with INR 2.0-3.0 is suitable for DVT patients with pulmonary emboli who have thromboembolic risk, and patients who have thromboembolism have high-risk for stroke. The lowest INR limit in AF patients without heart valve disease is 1.5. Immediately after optimal warfarin need is identified, INR should only be evaluated for every 4-6 weeks.

Warfarin dose should be reduced in patients with congestive heart failure, alcohol-induced liver damage or malnutrition, renal disorder (which increases free drug fraction in the plasma). Thyrotoxicosis causes increase catabolism of vitamin K, therefore it requires less warfarin dose in contrast to mixedema.

In elderly patients, warfarin dose should be reduced because their response against warfarin increases with age. Excessive vitamin K diet (green salad) reduces warfarin efficacy. Alternating diet of high salad and low salad consumption will cause inappropriate INR control.

Warfarin may interact with approximately 80 kinds of drugs. The act of warfarin is inhibited by drugs reducing vitamin K and warfarin absorption such as colestiramine. Drugs such as barbiturate or fenitoin accelerate warfarin degradation in the liver. Drugs which may enhance the act of warfarin include cardiovascular drugs, allupurinol, quinidine, amiodarone and cephalosporine which inhibit vitamin K formation. Drugs reducing warfarin degradation and increased anticoagulant effect include various antibiotics such as metronidazole, cotrimoxazole and anti-ulcer drugs, i.e. cimetidine.

Antiplatelet agents such as aspirin, clopidogrel and NSAID (non-steroid anti-inflammatory drugs) increase the risk of bleeding, but it is varied among the patients. High-dose aspirin (> 1.5 g/day) may disrupt synthesis of clotting factor. It should be noted that we should provide awareness for the patients that they should not consume other drugs without any consultation during oral anticoagulant treatment, and clinicians should verify new drugs consumed by the patients. If there is any hesitation, INR should be monitored more frequently. INR monitoring is also required if there is alteration in anticipated diet such as during a trip.

Contraindications for warfarin treatment include stroke events that recently occur, uncontrolled hypertension, cirrhosis hepatic, and bleeding sites in gastrointestinal and genitourinary tract such as hiatus hernia, peptic ulcer, gastritis, gastroesophageal reflux with obvious bleeding, colitis, proctitis and cystitis. If anticoagulant treatment is considered necessary, the risk and benefit ratio should be evaluated carefully. Old age is not a contraindication for anticoagulant treatment although old age is more possible to have bleeding event.

The most common complication is bleeding, while unusual but serious complication is warfarin-induced skin necrosis. The etiology has not been known yet. Such complication may occur between the 3rd and the 8th day of treatment. Deficiency of protein C may become a predisposition factor, especially when high-dose warfarin is initiated after cardiopulmonary bypass (lower protein C level). The best protection is by commencing lower dose of warfarin and also protected by heparin treatment. Continue heparin treatment although necrosis occur, reduce the dose up to approximately 2 mg/day, cover it with heparin, and slowly increase the warfarin treatment until several weeks.

In excessive hypoprothrombinemia without bleeding or only mild bleeding, the treatment may be repeated in consideration with reducing dose or dose cessation. Bleeding risk may be reduced dramatically by reducing INR from 3.0 – 4.5 to 2.0 – 3.0, which usually can be achieved by reducing warfarin dose merely 1 mg/day. INR level of 9 (in the case without any bleeding) may be arranged by dose cessation and return to lower dose of warfarin. If there is a bleeding or INR > 9, administration of oral vitamin K₁ may reduce the INR in 24 - 48 hours. For emergency cases, administration of subcutaneous vitamin K gives various results; therefore, it should be avoided. Moreover, slow intravenous vitamin K administration (5 to 10 mg for more than 30 minutes) is more recommended.

AF is one of indication for anticoagulant treatment of warfarin in addition to post acute myocardial infarct (along with heart failure or thrombus), low ejection fraction, vein thromboembolism, stenoses or regurgitation of mitral valve, hypertension heart disease, dilatation cardiomyopathy, bradycardia/tachycardia syndrome, ASD, prolapse of mitral valve, and primary pulmonary hypertension. AF which is not accompanied by heart disorder such as thyrotoxicosis is rarely caused by emboli. However, in elderly patients, AF without any heart disorder (Lone AF) may increase the risk for stroke, therefore anticoagulant or aspirin treatment is still recommended.

**BLEEDING COMPLICATION CAUSED BY ANTICOAGULANT TREATMENT IN ELDERLY PATIENTS**

Braun reported that there was no significant difference in bleeding caused by long-term anticoagulant treatment (approximately 7 years) between elderly patients (> 70 years) compared to general population.
Copland also reported that there was no significant difference between elderly patients (>75 years) compared to younger age group in evaluation of anticoagulants (INR) and the occurred bleeding as complication of AF treatment using oral warfarin.38

In addition, O’Callaghan suggested less-aggressive oral anticoagulation treatment in elderly patients (>65 years) although his result in elderly patients and patients under 65 years showed no significant difference in bleeding complication caused by oral anticoagulant treatment. Bleeding in elderly groups is more likely caused by NSAIDs.39

A study conducted by Tom et al. in 1994-1998 involved 4202 patients who received oral anticoagulant and categorized them into 4 groups based on their age, i.e.: 842 patients who were <60 years, 1200 patients who were 60-70 years, 1464 patients who were 71-80 years and 696 patients who were >80 years. Mean value for incidence rate of major bleeding was increased gradually in accordance with the age of studied groups, i.e. 1.5/100 patients/year in the <60 years group up to 4.2/100 patients/year in the >80 years group, with hazard ratio of 2.7 (95% CI 1.7 – 4.4). Mean value for incidence rate of thromboembolism was increased gradually in accordance with the age of studied groups, i.e. 1.0/100 patients/year in the <60 years group up to 2.4/100 patients/year in the >80 years group, with hazard ratio of 2.2 (95% CI 1.2 – 4.2).40

Van der Meer observed patients who underwent operation or did not receive anticoagulant treatment. In every increased age of one decade after 40 years of age, there is more than 46% severe bleeding complication.41 Moreover, in the patients who had received anticoagulant as treatment for thrombosis prevention, the bleeding complication also depends on age.42

CONCLUSION

Dose adjustment of oral anticoagulants in elderly patients with AF is very useful to prevent ischemic or hemorrhagic stroke. Such dose adjustment is striven to achieve balance, i.e. to prevent ischemic stroke in one hand and to prevent bleeding complication in the other hand.

Maximal protection against ischemic stroke in AF patients can be obtained by INR 2.0 – 3.0.

REFERENCES


