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In-Depth Review of Stroke Prevention in Patients with Non-Valvular Atrial Fibrillation

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Abstract: Stroke is a common complication of atrial fibrillation that leads to high morbidity. Anticoagulation therapy significantly reduces the risk of stroke in a selected group of patients. The decision to start anticoagulation needs to be balanced with bleeding risk. During the past years, multiple oral anticoagulation agents were proven to be as effective as warfarin in multiple randomized clinical trials. The superior benefits of these agents over warfarin are lower risk of intracranial bleeding, stable blood level and no need for frequent blood monitoring. The non-pharmacological approach for stroke prevention is undergoing development and only use in the clinical trials. If proven to be beneficial, it will have great impact for the patient who is contraindicated for anticoagulation therapy. The objective of this article is to review the most current options for stroke prevention in patients with non-valvular atrial fibrillation.

Key words: Atrial fibrillation, HAS-BLED bleeding, stroke prevention, frequent blood monitoring

INTRODUCTION

Atrial fibrillation is a common health problem with estimated 1% prevalence in general population and more than 10% of people older than 80 years of age (Go *et al*., 2001; Krahn *et al*., 1995). Embolic stroke is a well known and fearsome complication of atrial fibrillation. It was estimated that every fifth stroke is due to atrial fibrillation. Recent data have shown that some cryptogenic stroke might actually be related or caused by subclinical atrial fibrillation (Healey *et al*., 2012). Stroke from atrial fibrillation usually has a more severe neurological deficit, higher rate of disability and mortality (Harrison and Marshall, 1984). Effective intervention can significantly decrease the rate of stroke. The decision to choose appropriate therapy has to be tailored for each patient by using various risk stratification scores and discussion with the patient.

Risk stratification: Who should receive stroke prophylaxis? Risk of stroke and risk of bleeding need to be taken into consideration when making a decision to start patient on anticoagulation. CHADS2 score is the most commonly used tools to stratify the risk of stroke. It comprises of 5 major risk factors for stroke which are age > 75 years, hypertension, history of congestive heart failure, diabetes and history of ischemic stroke/transient ischemic attack. Each of these parameters has a score of 1 except for a history of ischemic stroke/TIA that has a score of 2. Multiple cohort studies have shown the correlation between higher score and increase risk of stroke (Table 1).

The current atrial fibrillation management guideline from the American College of Cardiology and European Society of Cardiology recommends that a patient who has CHADS2 more than 1 should receive oral anticoagulant with vitamin K antagonist. For a patient who has CHADS2 score of 1 (moderate risk), the recommendation is to either use aspirin or vitamin K antagonist for stroke prophylaxis. This recommendation creates controversy for the physician caring for this group of patient. In the updated 2010 European Society of Cardiology guideline, the use of the CHA2DS2VASc score (Table 2) is recommended for this group of patient who has CHADS2 score of 0-1. It has incorporated other non-major risk factor which includes age between 65-75, female, history of coronary vascular disease. If the patient has CHA2DS2Vasc score more than 1, the oral anticoagulation should be considered. Another important point is that the risk of embolization is the same in patients with paroxysmal, persistent or permanent atrial fibrillation (Hart *et al*., 2000; Hohnloser *et al*., 2007).

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Table 1: CHADS2 score and risk of thromboembolic event

Score	Event rate without warfarin	Event rate with warfarin	Number need to treat
0	0.49	0.25	417
1	1.52	0.72	125
2	2.50	1.27	81
3	5.27	2.20	33
4	6.02	2.35	27
5 or 6	6.88	4.60	44

Table 2: CHA2DS2VASc score

Letter	Risk factor	Score
C	CHF	1
H	Hypertension	1
A2	Age	
	65-75	
	>75 years	1
		2
D	Diabetes	1
S2	Stroke/TIA history	2
VASC	Vascular disease history (prior MI, peripheral vascular disease and aortic plaque)	1

Table 3: HAS-BLED bleeding risk score

Letter	Clinical characteristic	Points
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly	1
D	Drugs or alcohol (1 point each)	1 or 2

The risk of bleeding is another factor that needs to consider when starting the patient on anticoagulation. However, over concerns of the risk of bleeding may lead to underutilization of anticoagulation especially in the elderly population (Walraven *et al*., 2009). In the past, there was no bleeding risk scoring systems to help guiding the decision to start anticoagulation. HAS-BLED bleeding risk score (Table 3) is a simplified tool to help clinician estimate the risk of major bleeding (intracranial, hospitalization, hemoglobin decrease ≥2 g L^{-1} and/or transfusion) from oral anticoagulation which will help It comprises of 7 simple clinical characteristics and a score of 3 or more indicates high risk of bleeding (Lip, 2011).

Choices of anticoagulation: Warfarin is the drug of choice for stroke prevention in atrial fibrillation. During the past years, multiple alternative agents have been added to the armamentarium. The main advantages of these newer agents over warfarin are predictable effect with no need for monitoring, rapid onset of action, shorter half life and fewer food/drug interaction.

Warfarin: Warfarin has been used for stroke prophylaxis since 1954. Multiple studies had clearly shown its efficacy in mortality reduction and stroke prevention over anti platelet agent. It has multiple disadvantages despite its high efficacy. First, it required frequent monitoring of INR level to make sure that the patient is in therapeutic range. The term "Time in Therapeutic Range (TTR)" represents a percentage of time that the patient has INR in the range of 2-3. In SPORTIF III and V trials, patients with TTR less than 60% have higher annual rates of mortality and major bleeding compare with the group that has TTR more than 60 %. Even with the patient that has stable INR level, the recommendation is to check the INR every month. Second, each individual patient has a different response to the same dose of warfarin. This is due to differences in drug metabolism and interaction with food and other medication. Third, major bleeding which means bleeding that requires hospitalization, transfusion, or surgery, or involves particularly sensitive anatomic locations is the most fearsome complication of warfarin treatment. All of these disadvantages have lead to underutilization of warfare in the real world setting. One community database has shown that only 53% of patients received appropriate antithrombotic therapy according to CHADS2 score and 31% were classified as underrated (Gurwitz *et al*., 1997).

Dabigatran: Dabigatran is a direct reversal thrombin inhibitor. The first drug since warfarin that is approved by FDA for stroke prevention in atrial fibrillation. The efficacy of dabigatran has been demonstrated in the RE-LY trial (Connolly *et al*., 2009). In this study, 18,113 patients with nonvalvular atrial fibrillation were randomly assigned to receive dabigatran 110 mg, dabigatran 150 mg or warfarin and were followed for 2 years. It was found that dabigatran at the dose of 150 mg is more effective than warfarin in stroke prevention.

At 110 mg, it has the same efficacy (non-inferiority) compared to warfarin. Regarding the bleeding complication, dabigatran 150 mg has the same rate of major bleeding compared with warfarin while 110 mg doses has a much less bleeding episode compare to warfarin. FDA approves dabigatran 150 mg twice daily and 75 mg twice daily for patient with a creatinine clearance of 15-30 ml min^{-1}. The physician needs to be aware that the RE-LY trial excluded patient with creatinine clearance less than 30 ml min^{-1} and the approval of 75 mg twice daily dose was totally based on pharmacokinetic modeling not from the clinical trial. In Canada and United Kingdom, the use of dabigatran is contraindicated in patients with a creatinine clearance <30 ml min^{-1}. The RE-LY trial also showed a small increased but non statistically

significant risk of myocardial infarction with the use of dabigatran. Recently, metaanalysis that includes 7 trials of dabigatran (Uchino and Hernandez, 2012) shows a significant increase in risk of myocardial infarction or acute coronary syndrome. The physician should also take this into consideration when selecting a patient to receive dabigatran.

Dabigatran has a half-life of approximately 12-14 h and exert a maximum anticoagulation effect within 2-3 h after ingestion. It has to be taken twice daily. Because it is mainly renally excreted, abrupt decline in kidney function may lead to accumulation of the drug and increase risk of bleeding. The patient needs to be told to keep the medicine in the original bottle because it has a risk of breakdown when expose to moisture. The most common side effect of dabigatran is dyspepsia.

Rivaroxaban: The most recent oral anticoagulant approved for thromboembolic prevention in nonvalvular atrial fibrillation. The efficacy of rivaroxaban was shown in ROCKET AF trial (Patel *et al*., 2011). In this study, 14,264 patients were randomly assigned to receive either rivaroxaban 20 mg daily (15 mg daily if creatinine clearance is 30-49 ml min^{-1}) or warfarin (target INR 2.0-3.0). After median follow-up of 707 days, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding. However, the time in therapeutic range in warfarin group was only 55% which raised a concern for interpretation of the trial result. In the RE-LY study, the time in therapeutic range was 64%.

Rivaroxaban is an oral direct factor Xa inhibitor. It is not recommended for those with creatinine clearance less than 15 ml min^{-1} (Fox *et al*., 2011). We expect to see more safety data from real-world experience because it has been approved for less than a year at the time that this article is prepared.

Apixaban: Another oral direct factor Xa inhibitor that showed efficacy in a randomized controlled trial. It is in the process of obtaining approval from FDA. It has been approved in Europe. Its efficacy has been demonstrated in ARISTOTLE trial (Granger *et al*., 2011). In this randomized, double-blind trial, 18,201 patients were assigned to either apixaban 5 mg twice daily or warfarin (target INR 2-3). After median follow-up of 1.8 years, stroke and systemic embolism were significantly reduced in the apixaban group (noninferiority compared with warfarin). The rate of bleeding was also significantly lower. In addition, compared to all the above mentioned studies (RE-LY and ROCKET AF), ARISTOTLE was the only study that demonstrates a reduction in all cause mortality compared with warfarin.

These newer oral anticoagulants give the patient more convenient compared with warfarin. However, there is no clear consensus or guideline on the management of bleeding complication from these newer agents. The basic available coagulation studies couldn't correctly evaluate the activity of these agents when patient present with bleeding. Ecarin clotting time was shown to have a linear correlation with dabigatran level but it is not widely available. Also, there is no specific antidote to reverse the effect of these newer anticoagulation. Clinicians should also consider this fact when starting their patients on these newer agents.

Non-pharmacological therapy: Approximately 20% of patients with atrial fibrillation have a relative or absolute contraindication to anticoagulant therapy. The management to minimize embolization risk in this group of patients is unclear. Studies have shown that 90% of left atrial thrombi form in the left atrial appendage. This leads to the thought that excision or closure of the left atrial appendage should reduce the risk of thromboembolic complication. Various surgical techniques were used which include LAA excision or closure by suturing. These procedures are only performed in patients who are undergoing cardiac surgery for other indications. In a retrospective analysis, surgical left atrial appendage ligation or amputation decreases the incidence of embolic events (3 VS 17%) LAA closure can also be achieved by a percutaneous procedure using a specially designed device to trap blood clots before they exit the LAA. WATCHMAN-R device (Atritech company) was evaluated in the PROTECT AF noninferiority study (Holmes *et al*., 2009). After a mean follow-up of 18 months, the device was noninferior to warfarin in term of stroke, cardiovascular death and systemic embolism.

The major complication was pericardial effusion. It hasn't been approved by the FDA and should only be considered in highly selected patients in whom long-term anticoagulation therapy is contraindicated.

CONCLUSION

Atrial fibrillation is responsible for 15% of total strokes and the number of thromboembolic episodes in the USA has been estimated at about 75,000 annually. It is important to identify the patient at high risk for stroke with the use of CHADS2 or CHA2DS2Vasc score and start prophylaxis with anticoagulation therapy. To start anticoagulation, the risk of

thromboemboli should be significantly outweighing the bleeding risk. Beside warfarin, dabigatran and rivaroxaban were recently approved for this indication. These newer oral anticoagulant provide patients with more convenient because no blood monitoring is necessary and they have less interaction with other drugs or food. We expect to see more safety data from a post marketing surveillance study in the larger population. The physician should also concern about the fact that there is no clear consensus on treatment of bleeding complication from this newer agents and the fact that there is no antidote and effective monitoring when compared with warfarin.

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