

UNIT NO. 6

ATRIAL FIBRILLATION: AN OVERVIEW

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ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. In the past decade, there had been more than 1000 publications in the literature exploring this unique and fascinating arrhythmia, of which many aspects such as genetics and mechanisms, remain poorly understood. The growing interest and awareness of AF mirrors the global ageing population, coupled with new developments in both pharmacological and non-pharmacological therapies make treating this arrhythmia both fascinating and challenging.

SFP2010; 36(3): 27-30

SCOPE OF THE PROBLEM

The incidence and prevalence of AF are increasing in both developed and developing countries¹. Most population-based studies had been conducted in either United States or Western Europe²⁻⁴. These studies reflected a common trend, that in ageing populations and increase cardiovascular risk factors, in particular hypertension, the prevalence of AF will increase many fold. Based on the Framingham Heart Study, the lifetime risk for AF in adults age 40 was 26% for men and 23% for women⁵. In addition, the risk of stroke also mirrors the increase in age and AF of the population⁶. Therefore, the predictive impact on the economic burden of healthcare dealing with this arrhythmia is substantial as it accounts for at least one-third of all hospital admissions for arrhythmia-related diagnoses. It is therefore a major cause of hospitalization, morbidity and mortality^{7,8}. Despite a paucity of data for non-Caucasian populations, including Singapore, it is predicted that in general, the trend reflects a global phenomenon.

RISK FACTORS FOR AF

AF is associated not only with an older age group and hypertension, but also with heart failure, coronary artery disease and cardiomyopathies. In addition, obesity, diabetes mellitus, hyperlipidaemia, metabolic syndrome and chronic kidney disease have also been associated with AF⁹⁻¹¹. Meta-analyses of randomized controlled trials have also demonstrated relationship of AF to serious events in different vascular territories¹² in addition to the two fold increase in mortality¹³ and nearly five fold increase in stroke⁶.

CLASSIFICATION

For consistency and simplicity, AF is classified into 3 categories. Paroxysmal AF refers to episodes that terminate spontaneously and usually last less than 7 days. Persistent AF refers to episodes lasting more than 7 days, which may require either pharmacological or direct current cardioversion. Permanent AF implies failure of cardioversion or cardioversion not attempted¹⁴.

Non-valvular AF implies that the arrhythmia is not associated with rheumatic mitral valve disease, prosthetic valve or mitral valve repair.

Lone AF applies to AF in the younger age group with no evidence of any cardiopulmonary or systemic disease.

MANAGEMENT

The objectives of atrial fibrillation focus on 3 main areas: rate control, maintenance of sinus rhythm and prevention of thromboembolism. The strategies are not mutually exclusive and individualized tailored therapies for patients must be emphasized. The demographics, age, gender, concomitant cardiovascular risk factors and systemic diseases, socio-economic factors and presence of symptoms are key considerations in the decision-making process with the patient.

PREVENTION OF THROMBOEMBOLISM

Thromboembolic phenomena, especially stroke in the setting of AF pose both considerable morbidity and mortality consequences. The prevalence of both stroke and AF is age dependent. The risk of thromboembolism in non-valvular AF is similar regardless whether AF is paroxysmal, persistent or permanent¹⁵. In addition, strokes from AF are usually more serious than strokes from other causes¹⁶.

Risk stratification for thromboembolism in AF is therefore an extremely important aspect in the holistic management of this arrhythmia. Several randomized trials have looked into risk stratification scores for non-valvular AF. The most commonly accepted and widely used risk stratification strategy is the CHADS score¹⁷. The CHADS score is an acronym for: C (Congestive heart failure); H (Hypertension); A (Age greater than 75 years); D (Diabetes mellitus); S (History of stroke of transient ischaemic attack). Each letter is scored 1 point except for 'S' which is accredited with 2 points. Therefore the maximum CHADS score is 6. The risk of stroke increases with increasing CHADS score. Based on each individual's risk profile according to the score, either antiplatelet or anticoagulation should be recommended. For instance, if CHADS score is 0 or 1, antiplatelet therapy could be recommended. On the other

hand, if the CHADS score is 4 or greater, anticoagulation is strongly recommended. For CHADS score of 2 or 3, either antiplatelet or anticoagulation can be considered, though anticoagulation is the preferred choice if there was a history of stroke or transient ischaemic attack.

Current choice of anticoagulant is warfarin, a vitamin K antagonist. It is effective in reducing stroke in AF up to 68%¹⁸. However, this agent is far from ideal. It has a narrow therapeutic window and has numerous drug and food interactions. There is a wide variation in metabolism with the need for regular monitoring and dose adjustment. An ideal agent for stroke prevention in AF should be as safe and efficacious as warfarin. It should be orally administered with fixed dosing and no need for monitoring with a predictable response. In addition, it should have no food and drug interactions and importantly, minimal complications including bleeding risk. The undesirable characteristics of warfarin translate into real world practice. It is an alarming observation from clinical studies that deserving patients are not being prescribed warfarin^{19,21} or the International Normalised Ratios (INR) are not in the therapeutic range of 2 to 3^{22,23}. The consequences of sub or supra-therapeutic INR values had been described²⁴.

Dual antiplatelet agents

The quest for an alternative to warfarin for stroke prophylaxis in AF has been ongoing for the last decade. ACTIVE W trial was one of these earlier trials²⁵. The trial compared the use of warfarin compared to 2 antiplatelets, aspirin and clopidogrel in AF patients with similar risk profile for stroke. The trial was terminated prematurely due to safety reasons as it showed failure of aspirin/clopidogrel to prevent stroke, embolism, myocardial infarction and vascular death compared to warfarin. On the other hand, the sister arm, ACTIVE A investigated the use of aspirin alone compared with aspirin/clopidogrel combination in similar AF patients at high risk for thromboembolism who were deemed unsuitable for warfarin because of specific bleeding risk, physician assessment or patients' preference²⁶. There was a 28% relative risk reduction of stroke in the aspirin/clopidogrel combination arm compared to aspirin alone. However, there was also an increase risk of major bleeding up to 58%. Therefore, in view of the substantial risk of bleeding in the dual antiplatelet arm, one could then argue in preference of warfarin, which had been undoubtedly proven to be superior to dual antiplatelet therapy for stroke prophylaxis in AF.

Direct thrombin inhibitors

One of the earlier direct thrombin inhibitors, Ximelagatran, was studied in SPORTIF V²⁷. The trial result was in favor of Ximelagatran. However, the drug was withdrawn due to its toxic effects on the liver. Following SPORTIF series, the next direct thrombin inhibitor, Dabigatran, made headlines in the RELY trial²⁸. RELY was a non-inferiority trial which studied the efficacy of 2 different doses of Dabigatran compared to

warfarin in reduction of stroke or systemic embolism. The trial concluded that lower dose Dabigatran (110mg bd) had a similar rate of stroke as warfarin with a significant reduction in major bleeding. Higher dose Dabigatran (150mg bd) had significant reduction in stroke but similar risk of major bleeding compared to warfarin. Thus it could potentially be the alternative to warfarin in the future.

Direct Factor Xa inhibitors

These new agents are currently being studied and trial results are expected in the near future.

Non-pharmacological strategy for stroke prevention

The major source of clinically significant emboli is assumed to originate from the left atrial appendage²⁹. Mechanical devices to occlude the left atrial appendage had made this strategy a possible alternative for stroke prophylaxis, especially in high risk patients where warfarin may be contraindicated³⁰. However, the level of technical expertise, various operator learning curves and higher procedural complication rates may not make this strategy an attractive first line option based on risk-benefit ratio.

RATE VERSUS RHYTHM

The controversial issue of rate control versus rhythm conversion has been lingering even up till today. The main question has been whether leaving a patient in AF and maintaining adequate ventricular rate control is a preferred option than maintenance of sinus rhythm either via electrical or pharmacological means. The AFFIRM³¹ and RACE³² trials were designed to address this issue. In the AFFIRM trial, the overall mortality was not significant between the rate control and rhythm control groups. Conversely, in the rhythm control group, there were more hospitalizations and deaths compared to the rate control group. There was no difference in the rate of stroke between the 2 groups. Similarly, RACE also demonstrated that rate control was not inferior to rhythm control for prevention of death and morbidity. However, in these and other smaller trials, the subset of younger patients, female gender and paroxysmal AF were not well represented. Therefore, whilst rate control with stroke prophylaxis may be the preferred strategy for the majority, there is a definite role in conversion and maintenance of sinus rhythm in a highly symptomatic population group. These 2 studies also surfaced the notion that all anti-arrhythmic drugs have considerable adverse effects and maybe even pro-arrhythmic in certain subset of patients. There were no considered 'safe' anti-arrhythmic drugs and this may have resulted in comparative outcomes with the rate control group. Conventional anti-arrhythmics that were used in the rate versus rhythm trials include Class Ic and Class III (amiodarone, sotalol) drugs. The CASS³³ trial demonstrated increase in mortality when certain classes of anti-arrhythmics were used in the setting of structural and coronary artery disease. The recent publication

of ATHENA³⁴ raised hopes of an amiodarone equivalent drug, dronedarone. The chemical structure of dronedarone is similar to amiodarone but without the presence of the iodine moiety, thus causing fewer side effects. ATHENA showed a reduction in cardiovascular risk hospitalization in high-risk patients with AF in the dronedarone group versus placebo. However, this drug is a less effective anti-arrhythmic than amiodarone and contraindicated in patients with NYHA Class IV or acute decompensated heart failure³⁵. Therefore, dronedarone trades safety for efficacy compared to amiodarone, which has potential adverse effects.

The alternative to drug therapy to maintain sinus rhythm is a non-pharmacological approach. Radiofrequency ablation for AF has been a hot topic of much interest, research and discussion particularly in the arena of cardiac electrophysiology. A seminal paper more than a decade ago demonstrated that the foci for AF arose from the pulmonary veins³⁶. Since then, numerous research and publications have been made concerning permanent cure for AF by radiofrequency ablation and electrical isolation of pulmonary veins. Success rates are favorable for paroxysmal compared to persistent or permanent AF in high volume centres with experienced operators. Current guidelines recommend ablation for AF as a second line therapy in patients who have failed at least 1 anti-arrhythmic drug³⁷.

Rate control in AF is usually achieved with beta-blockers, calcium channel blockers and agents with effects on the atrioventricular node. There had been no clear indication of an ideal heart rate for permanent AF, for which rate control is usually the preferred strategy. Most authorities recommend heart rate of between 60 to 80bpm at rest and 90 to 110bpm during exercise. The recent RACE II³⁸ suggested that lenient was as good as strict ventricular rate control in AF. The lenient strategy (resting heart rate <110bpm) was non-inferior to the strict approach (resting heart rate <80bpm and heart rate goal during moderate exercise <110bpm) for a composite primary end point that included cardiovascular death, heart failure hospitalization, stroke and other major events. The rate control strategy should be individualized with most patients being able to achieve lenient rate control. However, a stricter control should be strongly advocated if patients are symptomatic, develop heart failure or have elevated heart rates during exercise.

UPSTREAM THERAPIES FOR THE PREVENTION OF AF

Angiotension converting enzyme inhibitors (ACEIs) and angiotension receptor blockers (ARBs) as well as statins and fish oils have been observed in preventing AF in several small experimental studies. These classes of agents were postulated to have impact on the electrical heterogeneity of the atria through anti-proliferative, anti-fibrotic and anti-inflammatory effects. However, recent publications failed to show any benefit with the ARBs^{39,40}.

CONCLUSION

AF is the most common cause of arrhythmia in hospital and primary health care settings. The incidence and prevalence of AF will increase exponentially in the future. Recent advances and new developments in pharmacological as well as non-pharmacological treatments have made treating this arrhythmia a worthwhile task in order to reduce the associated morbidity and mortality.

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LEARNING POINTS

- **The objectives of atrial fibrillation focus on 3 main areas: rate control, maintenance of sinus rhythm and prevention of thromboembolism.**
- **The risk of thromboembolism in non-valvular AF is similar regardless whether AF is paroxysmal, persistent or permanent.**
- **An ideal agent for stroke prevention in AF should be as safe and efficacious as warfarin. It should be orally administered with fixed dosing and no need for monitoring with a predictable response. In addition, it should have no food and drug interactions and importantly, minimal complications including bleeding risk.**
- **Rate control in AF is usually achieved with beta-blockers, calcium channel blockers and agents with effects on the atrioventricular node.**
- **The rate control strategy should be individualized with most patients being able to achieve lenient rate control. However, a stricter control should be strongly advocated if patients are symptomatic, develop heart failure or have elevated heart rates during exercise.**

ASSESSMENT OF 30 MCQs**FPSC NO : 36****MCQs on Cardiovascular, Risk Factors, and Consequences****Submission DEADLINE : 13 September 2010****INSTRUCTIONS**

- With effect from 1st April 2008, the College Assessment of 30 MCQs has gone paperless.
- To submit answers to the following multiple choice questions, you are required to log on to the College Online Portal (www.cfps2online.org)
- Attempt ALL the following multiple choice questions.
- There is only ONE correct answer for each question.
- The answers should be submitted to the College of Family Physicians Singapore via the College Online Portal before the submission deadline stated above.

- In the INTERHEART Study by Yusuf et al published in 2004, a study of 52 low- and middle-income countries, the five established risk factors - tobacco use, lipids, hypertension, diabetes, and obesity - predict approximately X% of the population attributable risk of acute myocardial infarction. What is X?**
 - 20%.
 - 40%.
 - 60%.
 - 80%.
 - 100%.
- An adult male who is a current smoker wishes to know what is reduction of coronary artery disease risk which may occur if he were to stop smoking. He has not had an acute myocardial infarct. Which one of the following effect sizes of reduction of risk can be expected?**
 - 35%.
 - 40%.
 - 45%.
 - 50%.
 - 55%.
- Coronary artery disease in Singapore is the third major cause of hospitalization in the last three years. Over this period, what is the trend of hospitalization for this condition?**
 - Rising.
 - Falling.
 - Static.
 - No clear trend.
 - None of the above.
- From the National Health Surveillance Survey 2007 in Singapore, what is the trend of physical inactivity in the population with regards to the age-standardized prevalence of 2001 and 2007?**
 - Drop by 6.4%.
 - Increase by 0.4%.
 - Increase by 0.7%.
 - Drop by 7.3%.
 - None of the above.
- In a study by Chan et al on myocardial infarction patients admitted to a local tertiary hospital, it was noted that 83% of patients younger than 45 years and 72% of patients 45 years and older with X were left untreated. What is X?**
 - Diabetes mellitus.
 - Hyper-uricaemia.
 - Hypertension.
 - Hyper-triglyceridemia.
 - Hyperlipidemia.
- Which one of the following statements regarding recent studies in hypertension is TRUE?**
 - As we age, it is normal and acceptable to have a higher blood pressure.
 - Cardiovascular risks begins to increase from blood pressures of 130/90 mmHg.
 - For every 2 mmHg reduction in systolic blood pressure, cardiovascular mortality is increased by 7-10%.
 - For each 20 mmHg increase in systolic pressure, mortality from ischaemic heart disease or stroke is doubled.
 - None of the above.

- 7. Which of the following statements regarding the HYVET study is TRUE?**
- (A) It was undertaken in elderly subjects above 65 years with hypertension.
 - (B) The active treatment group was given the diuretic Indapamide only.
 - (C) The control group received Perindopril.
 - (D) There was a 10% reduction in the primary end point of fatal or nonfatal strokes.
 - (E) It demonstrated that antihypertensive treatment with indapamide, with or without perindopril, in persons 80 years of age or older is beneficial.
- 8. Which of the following statements regarding the ACCOMPLISH trial is TRUE?**
- (A) It compared treatment with either benazepril plus amlodipine or benazepril plus hydrochlorothiazide.
 - (B) It was a randomised, double-blind trial involving 1,500 hypertensive patients.
 - (C) This trial was terminated early at mean follow-up of 24 months.
 - (D) The benazepril-hydrochlorothiazide group had 2.2% fewer events than the benazepril-amlodipine group.
 - (E) The benazepril-hydrochlorothiazide combination was shown to be superior to the benazepril-amlodipine combination.
- 9. Which of the following statements regarding the ARBITER6-HALTS trial is TRUE?**
- (A) The primary end point was major adverse cardiovascular events.
 - (B) The secondary end point was change in carotid artery intima-media thickness.
 - (C) Extended-release niacin was compared with ezetimibe when combined with statin therapy.
 - (D) Ezetimibe therapy led to regression of carotid intima-media thickness and fewer clinical cardiovascular events.
 - (E) Niacin failed to reduce or halt progression of carotid intima-media thickness.
- 10. Which of the following regarding use of Telmisartan for hypertension treatment in patients who have vascular disease or diabetes with end-organ damage is TRUE?**
- (A) Ramipril better tolerated than telmisartan.
 - (B) Telmisartan is less effective than Ramipril in reducing cardiovascular events.
 - (C) Combination therapy of Telmisartan and Ramipril does not increase hypotension or renal dysfunction.
 - (D) Telmisartan compared to placebo had no significant effect on the reduction of hospitalisations for heart failure.
 - (E) None of the above.
- 11. The goal of diabetic therapy in patients with diabetes mellitus is a glycated haemoglobin of LESS THAN:**
- (A) 5.5%.
 - (B) 6.0%.
 - (C) 6.5%.
 - (D) 7.0%.
 - (E) 7.5%.
- 12. The lipid abnormalities commonly associated with diabetes mellitus are:**
- (A) Decreased Apo-b lipoprotein.
 - (B) Increased HDL.
 - (C) Decreased VLDL.
 - (D) Increased LDL.
 - (E) Increased serum triglycerides.
- 13. Which of the following statements is TRUE?**
- (A) Diabetics with raised serum cholesterol are at marginally increased risk from cardiovascular events.
 - (B) Studies show that total serum cholesterol mirrors risk from coronary artery mortality.
 - (C) The DECODE study found that when pre-diabetics progresses to frank diabetes, cardiovascular mortality remains the same.
 - (D) The MRFIT study found that there was linear relationship between coronary heart disease and serum cholesterol down to 70mg/dl.
 - (E) Stroke accounts for 40% of all diabetic mortality.
- 14. Metabolic syndrome consists of :**
- (A) Hyperlipidaemia.
 - (B) Increased waist circumference.
 - (C) Insulin resistance.
 - (D) Hypertension.
 - (E) All of the above.
- 15. Which of the following regarding diabetic treatment is TRUE?**
- (A) Intensive glucose lowering leads to decreased mortality.
 - (B) Lifestyle changes are very successful for reducing HBA1C.
 - (C) Sulphonylureas remain first line in the management of diabetes.
 - (D) Macrovascular complications are the major cause of diabetic mortality.
 - (E) Microvascular complications are the major cause of diabetic mortality.
- 16. Chronic Kidney Disease (CKD) in Diabetics can arise from multiple causes, which of the following is TRUE?**
- (A) Diabetic nephropathy is the only main cause of CKD.