Atrial fibrillation

Atrial fibrillation is a very common finding in the older population affecting about 5% of people over 65 years and almost 10% of those over 80 years. Thus, patients aged 80 years of age and over now account for about 36% of all cases. This is expected to increase to 53% by 2050.[1]

Eduard Shantsila Postdoctorate Research Fellow, University of Birmingham Centre for Cardiovascular Sciences,City Hospital, Birmingham
Alena Shantsila Research Fellow, University of Birmingham Centre for Cardiovascular Sciences,City Hospital, Birmingham
Gregory YH Lip Professor of Cardiovascular Medicine, University of Birmingham Centre for Cardiovascular Sciences,City Hospital, Birmingham
email: shantsila@yandex.ru

Atrial fibrillation (AF) is the commonest sustained cardiac rhythm disorder, which is associated with a high risk of mortality and morbidity. Ageing is associated with diffuse cardiac changes such as degenerative changes in the sinus node and supraventricular conduction system, atrial fibrosis, and elevation of left ventricular diastolic pressure that can result in an increased propensity to AF.[2] Risk factors for AF such as hypertension, heart failure, coronary artery disease and diabetes mellitus are common in older people and these factors, as well as advanced age itself, have been identified as strong predictors of the stroke risk.

AF can also be secondary to various systemic or respiratory illnesses, chronic alcohol excess as well as to some reversible conditions such as thyrotoxicosis and acute poisoning with alcohol or illicit drugs. Timely addressing of the primarily problem can prevent AF relapses.

The presence of AF may reduce left ventricular ejection fraction by 15-20%, mostly in those with poorly controlled heart rate. In the absence of antithrombotic therapy, the annual risk of stroke in patients with nonvalvular AF increases from about 5% in patients less than 65 years of age to about 8% in patients 75 years of age or older.[3] AF accounts for only 1·5% of strokes in patients 50–59 years of age, but the proportion increases more than 15-fold to 23·5% among patients 80–89 years of age.[4] Women over the age of 75 years are at particularly high risk for stroke in the setting of AF.[5] Of note, stroke developed secondary to AF is associated with higher morbidity and mortality.

Several guidelines for the management of AF are available. In the UK, the National Institute for Health and Clinical Excellence (NICE) guidance on the management of AF was published in June 2006 and serves to provide an evidence-based framework to guide AF management.[6]

Diagnosis

Although AF can often be detected simply by irregular pulse and heartbeats the diagnosis of AF requires documentation of the arrhythmia by an ECG (absence of P waves). An ECG should be performed on all patients where a diagnosis of AF is suspected. In patients with suspected paroxysmal AF, a 24-hour Holter monitor is useful for diagnosis in those with symptomatic episodes less than 24 hours apart, while longer periods of monitoring are required in those with less frequent episodes. In patients with previous AF episodes, ECG monitoring may help to detect asymptomatic AF paroxysms.[7] A detailed history and a previous ECG can help estimate duration of the arrhythmia. Careful attention should also be given to comorbidities and complications, which are more common in the older person. A transthoracic echocardiogram should be performed in most patients with AF for the diagnosis of underlying structural heart disease and to aid the planning of long-term management strategies.

Classification

The temporal classification of AF can help to define the objectives of management and therapeutic

strategies. Paroxysmal AF defines the episodes that terminate spontaneously within seven days. AF is termed persistent if its duration is for more than seven days and electrical or pharmacological cardioversion is required to terminate the arrhythmia. Permanent AF is defined as chronic AF, where cardioversion is not successful or deemed inappropriate, eg. due to persistence of the AF for more than 12 months.

Management

Rhythm control

Rhythm control in AF aims to restore sinus rhythm and prevent recurrences of the arrhythmia. Cardioversion of AF can be achieved electrically or pharmacologically. Given that the majority of older people have concomitant structural heart disease, antiarrhythmic drugs such as amiodarone or sotalol can be administered to increase success rate of cardioversion once this is to be attempted.[8] However, long-term maintenance of sinus rhythm after successful cardioversion also remains problematic, and many older patients will require long-term antiarrhythmic drugs to reduce the frequency of relapses. Typically only about half of patients maintain sinus rhythm at 12 months. Re-consideration of the pros and cons of a repeated cardioversion for every AF relapse should be considered individually on older patients. Generally attempts to maintain sinus rhythm should be considered in symptomatic patients, in those with treatable precipitants or congestive heart failure.

For rhythm control in patients with paroxysmal AF, a β-blocker would be the initial treatment option. However Class Ic antiarrhythmic drugs, such as flecainide, amiodarone or dronedarone can be considered if β-blockers are ineffective or contraindicated. The perceived reasons for the restoration and maintenance of sinus rhythm include the relief of symptoms, improvement of exercise tolerance and quality of life, the possible reduction of thromboembolic risk and the avoidance of tachycardia-induced cardiomyopathy. However, the evidence from clinical trials suggests the contrary.[9-10] These trials show that a rate-control strategy is non inferior to a rhythm control approach for mortality. The latter even appeared to be less cost-effective and tended to be associated with more thromboembolism, hospital admission and adverse drug effects.

The large AFFIRM trial demonstrated equivalent survival in patients randomly assigned to rate-control and rhythm-control strategies.[11] But according to a sub-analysis of the AFFIRM trial in patients 65 years or older, rhythm control was associated with higher mortality compared with rate control strategy.[11] At the same time, the sinus rhythm was an independent predictor of improved survival in AF patients.[12] This discrepancy may stem from the higher vulnerability of the elderly population to the side effects of the antiarrhythmic drugs. In this respect, the recent ATHENA study has demonstrated that dronedarone may reduce hospitalisations and cardiovascular mortality as compared with placebo in patients with AF.[13]

Rate control

The aims of the rate control approach are to minimise the symptoms associated with the tachycardia and prevent the haemodynamic consequences of an uncontrolled tachycardia. Generally the criteria of desirable heart rate control would be between 60 and 90 beats per minute at rest and less than 110 beats per minute during exercise. β-blockers or rate-limiting calcium channel blockers should be administered as the preferred initial rate control therapy in most patients. β-blockers may offer an additional benefit in patients with co-existing coronary artery disease or systolic heart failure. Rate limiting calcium channel blockers (diltiazem and verapamil) are also effective and a safe option to reduce ventricular rate in older patients, even in hyperadrenergic settings.[14] Where monotherapy inadequately controls the heart rate, combination therapy with β-blockers or rate-limiting calcium channel blockers and digoxin should improve heart rate control. If heart rate control still remains problematic specialist referral is indicated, and additional drugs, eg. amiodarone, or nonpharmacological measures may be indicated.[15] Where urgent pharmacological rate control is required in the acute setting, an intravenous β-blocker (eg. esmolol or metoprolol) or rate-limiting calcium channel blocker (eg. verapamil) can be used. Intravenous amiodarone is a good alternative where β-blockers or calcium channel blockers are contraindicated or ineffective.

Antithrombotic therapy

Adequate antithrombotic therapy is critical for stroke prevention in all AF patients. Patients with paroxysmal

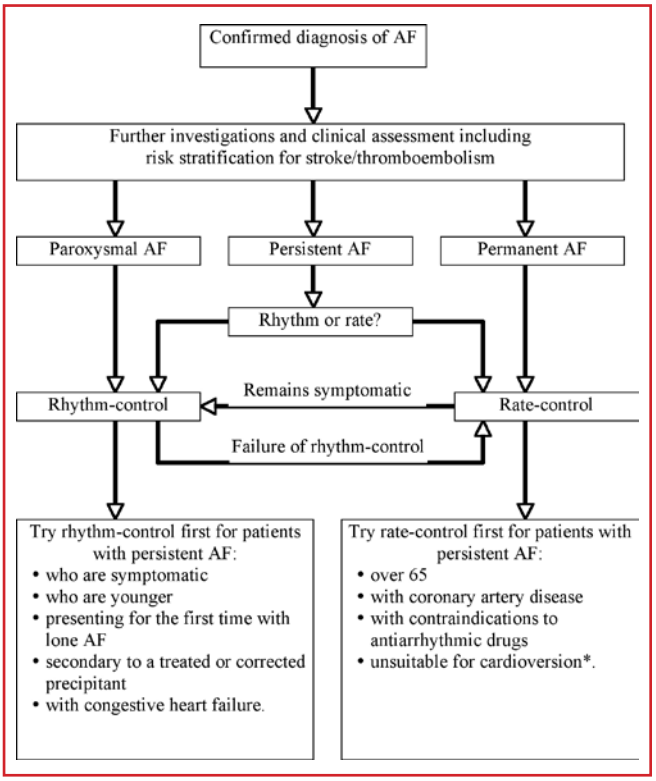

Figure 1: Treatment strategy decision tree.[6]

and persistent AF have a risk of stroke similar to patients with permanent AF and those without symptoms similar to symptomatic patients.[16] High efficacy of antithrombotic therapy for stroke prevention in AF is supported by strong evidence from large clinical trials. In a meta-analysis of 13 trials including over 14,000 participants, an adjusted-dose of warfarin (INR 2-3) prevented two thirds of cases of ischaemic stroke or systemic thromboembolism and significantly reduced all-cause mortality.[17] Of note, warfarin is superior to aspirin in reducing the risk of ischaemic stroke by approximately 40%.[17] Although the risk of major anticoagulation-related bleeding is twice as high in those over 80 years compared to younger patients (1·9 versus 0·9%, respectively) the total health benefits are still strongly in favour of anticoagulant therapy.[18] The high efficacy of anticoagulation over aspirin in older patients (age >75 years) has been recently confirmed in the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) trial.[19] Of note, no significant difference in major bleeding events were observed between the anticoagulation and aspirin groups. In real

life, many older patients cannot benefit from adequate anticoagulation either because of its underprescription or poor tolerance. Among hospitalised elderly patients with AF, the proportion of those discharged on warfarin was 75% of those 65-69 years of age, 59% of those aged 70-79 years, 45% of those aged 80-89 years, and only 24% of those aged over 90 years.[20] Given that in the AFFIRM trial, the vast majority of strokes in both arms of the study occurred in patients who stopped warfarin or had sub-therapeutic INR there is a pressing need for alternative stroke prevention strategies for this growing patient population.[20-21] Optimistic results of the recent and ongoing clinical trials give hope that novel oral anticoagulants (eg, dabigatran etexilate) would allow prevention of thromboembolism in AF at least as effectively and safely as it can be done with warfarin but without the need of regular blood monitoring.[22]

Can we improve our stroke and bleeding risk assessment of patients with AF?

In order to improve the selection of truly "low-risk" patients, a new stroke risk stratification schema, the CHA2DS2-VASc score has been proposed (Figure 2).[23] This score complements the commonly used CHADS2 schema by consideration of additional stroke risk factors. Oral anticoagulation therapy is indicated in "high risk" AF patients (score ≥2), whilst for those who are truly "low risk" (CHA2DS2-VASc score = 0), no antithrombotic therapy is recommended. For those with a CHA2DS2-VASc score=1, oral anticoagulation or aspirin may be used, with a preference for oral anticoagulation.[23,24] Similarly, current guidelines do not formally recommend a bleeding risk score, given the lack of available validated and simple bleeding risk stratification systems. More recently, a new user-friendly bleeding risk score scheme, called HAS-BLED—Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (eg. age >65), Drugs/alcohol—has been proposed.[25] One point is awarded for each factor that is present. The HAS-BLED score predicts those with a "high risk" of bleeding (ie. HAS-BLED score ≥3) who require extra caution (rather than contraindication) following initiation of antithrombotic therapy, given that both warfarin and aspirin have the same rates of major bleeding, especially in the elderly.

Letter	Clinical characteristics	Points awarded
The CHA2DS2-VASc schema for stroke risk assessment		
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A	Age ≥ 75	2
D	Diabetes mellitus	1
S	Stroke/TIA/TE	2
V	The CHA2DS2-VASc schema for stroke risk assessment	1
A	Age 65–74	1
Sc	Sex category (i.e. Female gender)	1 Maximum 9 points
The HAS-BLED bleeding risk score*		
H	Hypertension	1
A	Abnormal renal and liver function (one point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age .65)	1
D	Drugs or alcohol (one point each)	1 or 2 Maximum 9 points

Figure 2: Stroke and bleeding risk assessment

Non-pharmacological approaches

Atrioventricular nodal disease frequently co-exists with AF and this should be considered in any patient reporting dizziness or blackouts. Importantly, many drugs prescribed for AF increase the refractory period of the AV node and therefore may unmask a previously unrecognised conduction disorder. These patients should be offered pacemaker implantation, which then allows suppression of tachyarrhythmias with appropriate drug dosages. For patients who remain highly symptomatic or whose rate or rhythm control is difficult despite optimal pharmaceutical therapy, electrophysiological or surgical options should be considered.

Recent studies though preformed on a limited number of patients suggest that catheter ablation can provide a similar level of control of AF in elderly patients as in younger patients. Although two relatively small studies reported the possibility of discontinuation of anticoagulation if sinus rhythm is maintained at three to six months after successful AF ablation, it is still to be proven if warfarin cessation is justifiable and would balance the risk of ablation-related complications that appear to be higher in older patients.

Conclusion

It is important to point out that as both current pharmacological and electrophysiological approaches remain unsatisfactory, appropriate antithrombotic

therapy is vital to prevent thromboembolic complications. Trials of novel antiarrhythmic and antithrombotic drugs are ongoing, and hopefully these will improve the management of this common cardiac arrhythmia.

We have no conflict of interest

References

1. Go A, Hylek E, Phillips K, et al. Prevalence of diagnosed atrial fibrillation in adults. *JAMA* 2001; **285**: 2370–75
2. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation* 2003; **107**: 139–46
3. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; **154**: 1449–57.
4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; **22**: 983–88
5. Fang MC, Singer DE, Chang Y, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation* 2005; **112**: 1687–91
6. National Collaborating Centre for Chronic Conditions. Atrial fibrillation: National clinical guideline for management in primary and secondary care. Royal College of Physicians, 2006
7. Hindricks G, Piorkowski C, Tanner H, et al. Perception of atrial fibrillation before and after radiofrequency catheter ablation: relevance of asymptomatic arrhythmia recurrence. *Circulation* 2005; **112**: 307–13
8. Singh BN, Singh SN, Reda DJ, et al; Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) Investigators. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med* 2005; **352**: 1861–72
9. Testa L, Biondi-Zoccai GG, Dello Russo A, et al. Rate-control vs. rhythm-control in patients with atrial fibrillation: a meta-analysis. *Eur Heart J* 2005; **26**: 2000-6
10. de Denus S, Sanoski CA, Carlsson J, et al. Rate vs rhythm control in patients with atrial fibrillation: a meta-analysis. *Arch Intern Med* 2005; **165**: 258–62
11. Wyse DG, Waldo AL, DiMarco JP, et al. Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002; **347**: 1825–33
12. Corley SD, Epstein AE, DiMarco JP, et al., AFFIRM Investigators. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation* 2004; **109**: 1509–13
13. Coletta AP, Cleland JG, Cullington D, Clark AL. Clinical trials update from Heart Rhythm 2008 and Heart Failure 2008: ATHENA, URGENT, INH study, HEART and CK-1827452. *Eur J Heart Fail* 2008; **10**: 917–20
14. Lim H, Hamaad A, Lip G. Clinical review: clinical management of atrial fibrillation—rate control versus rhythm control. *Critical Care* 2004; **8**; 271–79
15. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. *Circulation* 2000; **101**: 1138–44
16. Flaker GC, Belew K, Beckman K, et al; AFFIRM Investigators. Asymptomatic atrial fibrillation: demographic features and prognostic information from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 2005; **149**: 657–63
17. Lip GYH, Edwards SJ. Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. *Thrombosis Research* 2006; **118**: 321–33
18. Poli D, Antonucci E, Grifoni E, et al. Bleeding risk during oral anticoagulation in atrial fibrillation patients older than 80 years. *J Am Coll Cardiol* 2009; **54**: 999–1002
19. Mant J, Hobbs FD, Fletcher K, et al; BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007; **370**: 493–503
20. Hylek EM, D'Antonio J, Evans-Molina C, et al. Translating the results of randomized trials into clinical practice: the challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. *Stroke* 2006; **37**: 1075–80
21. Sherman DG, Kim SG, Boop BS, et al; National Heart, Lung, and Blood Institute AFFIRM Investigators. Occurrence and characteristics of stroke events in the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) study. *Arch Intern Med* 2005; **165**: 1185–91
22. Ahrens I, Lip GY, Peter K. New oral anticoagulant drugs in cardiovascular disease. *Thromb Haemost.* 2010; **104**: 49–60
23. Fauchier L, Lip GY. Guidelines for antithrombotic therapy in atrial fibrillation: understanding the reasons for non-adherence and moving forwards with simplifying risk stratification for stroke and bleeding. *Europace* 2010; **12**: 761–63
24. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010; **137**: 263–72
25. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess one-year risk of major bleeding in atrial fibrillation patients: The Euro Heart Survey. *Chest* 2010. In press.