Research Review Speaker Series™

The four pillars of non valvular atrial fibrillation management

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About the speaker

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Dr Stiles is the Director of Electrophysiology for the Midland region of NZ. He trained in Otago, Waikato, Edinburgh, Leicester and Auckland before completing his PhD in AF and Flutter at Adelaide University. He has interests in ablation of arrhythmia and cardiac device management. He is Chair of the Scientific Publications and Document Writing Committee for the Asia Pacific Heart Rhythm Society. He can sometimes be seen cycling Waikato roads, looking for lost golf balls or yelling at the Blackcaps.

The 2017 Goodfellow Symposium was held in Auckland on March 24-26, 2017. The Symposium presented a multi-disciplinary programme catering for general practitioners, primary health care nurses, urgent care physicians, registrars, specialists and others primary health care professionals. Dr Martin Stiles discussed the four pillars of atrial fibrillation (AF) management: anticoagulation, rate control, rhythm control and lifestyle modification (adapted from ESC Guidelines 2016). His talk addressed each of these approaches with evidence base for their application in General Practice. His presentation was supported by Boehringer Ingelheim.

1 ANTICOAGULATION

CHA_2DS_2VASc Score

The CHA_2DS_2VASc score estimates the risk of stroke in patients with clinically proven AF, and guides anticoagulation treatment. A high score corresponds to a greater risk of stroke, while a low score corresponds to a lesser risk of stroke. Patients are scored for each of the following conditions: **C**ardiac failure (1 point); **H**ypertension (1 point); **A**ge (1 point for ≥65 years and an additional point ≥75 years); **D**iabetes (1 point); **S**troke or TIA (2 points); **V**ascular disease (1 point); **S**ex **c**ategory (female 1 point, male 0 points).

- For a CHA_2DS_2VASc score of 0, no anticoagulation is required (outside the setting of cardioversion or ablation, where different rules apply).
- For a CHA_2DS_2VASc score of 1, treatment will depend on patient and physician preference. However, if the score of 1 is due to female gender only, stroke risk is low and no treatment is required.
- For a CHA_2DS_2VASc score ≥ 2, anticoagulation is recommended, once the bleeding risk is considered.

Warfarin: effectiveness and limitations

It is well known that warfarin is more effective than placebo, monitored warfarin is more effective than low dose warfarin, and that warfarin is more effective than aspirin or the combination of aspirin and clopidogrel. Until recently there were no better therapeutic options, but now the novel anticoagulants (NOACs) are available.

Warfarin has a slow onset of action. Because of genetic variations in metabolism, it has variable dose requirements. Due to its multiple food and drug interactions and narrow therapeutic index, frequent coagulation monitoring is necessary.[1-3]

Novel anticoagulants

The properties of NOACs are shown in Table 1. Large phase 3 trials in tens of thousands of patients have shown that, for the endpoint of stroke or systemic embolism, high-dose dabigatran (150mg bd) and apixaban are superior to warfarin while low-dose dabigatran and rivaroxaban are equivalent to warfarin. For the endpoint of major bleeding, low-dose dabigatran (110mg bd) and apixaban are superior to warfarin while high-dose dabigatran and rivaroxaban are equivalent to warfarin. Meta-analyses also show a benefit regarding total mortality for NOACs versus warfarin. From a clinical perspective, if a patient has a higher bleeding risk perhaps one would choose low-dose dabigatran with equivalent efficacy to warfarin but a lower bleeding risk. Conversely, patients with high stroke risk and few bleeding risk factors may choose high-dose dabigatran.

New Zealand dabigatran experience

The New Zealand dabigatran experience has been interesting to say the least. In the first two months from 1 July 2011, 7000 patients started treatment with the NOAC. However, an audit revealed 78 bleeding episodes, including 12 that were major.[4] Four contributing factors were identified, including prescriber error, impaired renal function, patient age and lack of a reversal agent.

Availability of reversal agents

Availability of specific NOAC reversal agents marks the next phase in anticoagulation care. With the approval of idarucizumab, dabigatran is the first and only NOAC with a specific reversal agent. The ideal reversal agent has no procoagulant effects, is easy to use, specifically targets the NOAC, acts immediately, and has a predictable response and sustained effect.

The RE-VERSE AD study enrolled 503 patients taking dabigatran who presented to hospital with life-threatening emergencies, either bleeding or requiring emergency surgery.[5] A 5 g dose of idarucizumab resulted in immediate and complete reversal of dabigatran anticoagulation in 98.6% of patients. The mean time to cessation of bleeding in patients presenting with uncontrolled bleeding was <3.5-4.5 hours. The operator judged intraoperative haemostasis as "normal" in 92% of evaluable patients presenting for emergency surgery or a procedure other than bleeding. No safety concerns have been identified to date.

Table 1. Properties of novel anticoagulants [6-8]

	Dabigatran		Apixaban	Rivaroxaban
Target	IIa (thrombin)		Xa	Xa
Hours to C_{max}	2		3-4	2-4
Half-life (hours)	12-14		12	9-13
Renal elimination	80%		27%	33%
THERAPEUTIC OUTCOMES VERSUS WARFARIN				
	High dose	Low dose		
Stroke or systemic embolism	Superior	Equivalent	Superior	Equivalent
Major bleeding	Equivalent	Superior	Superior	Equivalent

2 RATE CONTROL

The aim of a rate control strategy for AF is to:

- Reduce symptoms (palpitations, light headedness, dyspnoea) by controlling ventricular rate.
- Preserve left ventricular function (i.e. avoid tachycardia-related cardiomyopathy).
- Allow the patient to remain in AF without restoration of sinus rhythm.

Rate control is also important for patients prescribed rhythm control in case of breakthrough AF.

Rate control can be achieved pharmacologically with beta blockers, calcium channel blockers (verapamil, diltiazem) or digoxin. Nonpharmacological methods include implantation of a pacemaker with atrioventricular (AV) node ablation about 4-6 weeks later, making the patient completely pacemaker dependent in exchange for absolute rate control.

Lenient vs strict rate control

What is the appropriate heart rate target for AF patients? How hard should we try to achieve this target? The RACE II trial answered some of these questions.[9] Patients with permanent AF > 80 bpm were randomised to either lenient or strict rate control. The lenient group received rate control drugs aiming at a resting heart rate below 110 bpm. The strict control group was treated with negative dromotropic drugs in order to achieve two targets: a resting heart rate below 80 bpm, and a heart rate below 110 bpm during moderate exercise, which was defined as the heart rate at 25% duration of the maximal exercise time.

The rate control target was achieved in 98% of the lenient rate control group versus 67% of the strict rate control group. Furthermore, the number of visits necessary to achieve the heart rate target was lower in the lenient group; 0.2 versus 2.3 visits. Rate control medication was used more often in the strict rate control patients; 10% of the patients in the lenient group did not need any medication versus 1% in the strict group.

So the bottom line is we don't really need to try that hard to achieve rate control in AF patients – aiming for a heart rate of less than 110 bpm is satisfactory. However, lower target resting heart rates are more appropriate for some patients, such as those with heart failure or those with symptoms on exertion due to high heart rate.

AV junction ablation

The main benefits of AV node ablation include improved quality of life in patients who cannot achieve rate control with medications. However, AV junction ablation is irreversible, controls symptoms only, may be associated with pacing issues and anticoagulation requirements remain unchanged.

Rate or rhythm control?

The AFFIRM trial showed that pharmacological rhythm control is not superior to rate control for AF.[10] Further analysis suggested that, because anti-arrhythmic drugs are not associated with improved survival, any beneficial antiarrhythmic effects may be offset by their adverse effects.[11] If an alternative method for maintaining sinus rhythm with fewer adverse effects were available, it might be beneficial. Dr Stiles suggested that such an effective method might be ablation.

3 RHYTHM CONTROL

In New Zealand, pharmacological agents available for rhythm control include flecainide (or propafenone), sotalol and amiodarone. Non-pharmacological methods include cardioversion and ablation. Points to note are that flecainide is only suitable for those with a structurally-normal heart, sotalol increases the QT interval, particularly in women and those with renal impairment, and amiodarone needs monitoring (for thyroid, liver, lung, eye, and skin disorders).

How successful is AF ablation?

A number of studies have examined the effect of ablation compared to anti-arrhythmic drugs. For maintenance of sinus rhythm, data strongly favour catheter ablation whether for paroxysmal AF or persistent AF.[12] Ablation is also associated with improvement in symptoms, exercise capacity and QOL.[13]

A meta-analysis showed that one year after a single ablation procedure for paroxysmal AF, two thirds of patients had no AF with no anti-arrhythmic drugs. One year after a single ablation procedure for non-paroxysmal AF, just over half of patients had no AF with no anti-arrhythmic drugs.[14] However, it is not uncommon to need more than one procedure. Late multi-procedure success was seen in approximately 80% of patients, whether they had paroxysmal or non-paroxysmal AF.

The only evidence in favour of ablation is that it improves quality of life and left ventricular ejection fraction. There is no evidence yet to support AF ablation for reduction in stroke risk, improvement in survival or for patients who wish to come off warfarin or NOACs.

Radiofrequency ablation or cryoablation

Catheter-based pulmonary vein isolation using radiofrequency current has become a standard treatment for drug-resistant and symptomatic paroxysmal AF. In recent years, the cryoballoon-based technique is increasingly used as a promising alternative.

The FIRE AND ICE trial showed that cryoballoon ablation was non-inferior to radiofrequency ablation with respect to efficacy for the treatment of patients with drug-refractory paroxysmal AF, and there was no significant difference between the two methods with regard to overall safety.[15]

Who should have AF ablation?

Patients who have the greatest freedom from AF after ablation are patients with symptomatic AF with no (or mild) structural heart disease. Patients without structural heart disease have better outcomes, but those with structural heart disease may have the most to gain (e.g. patients with hypertrophic cardiomyopathy are often highly symptomatic of AF). Ablation outcomes are better in patients with paroxysmal AF versus persistent AF. Paroxysmal AF is defined as >30s to <7 consecutive days of AF, while persistent AF is defined as ≥7 consecutive days of AF. Ablation may particularly benefit younger patients with lone AF; this group are frequently symptomatic and very-long-term anti-arrhythmic and anticoagulation poses cumulative risks and lifestyle costs.

Who should not have AF ablation?

Most patients with longstanding persistent AF (>1 year continuous AF) should not have ablation although there are exceptions. Asymptomatic or minimally symptomatic AF patients may also benefit from ablation and sinus rhythm in the long term; however, until further clinical data are available it is difficult to justify an invasive procedure to a patient who may not be aware that they have a problem.

AF ablation – who and when to refer

- Refer your younger (<75 years), symptomatic paroxysmal AF patients early.
- Refer persistent AF patients with clear symptomatic improvement in sinus rhythm, or low ejection fraction.
- Preferably have failed at least one rhythm control drug.
- Inform the patient early about a possible second procedure.
- Note that some patients may require ongoing anti-arrhythmic drugs.
- Control risk factors for recurrence (e.g. BP, obstructive sleep apnoea, obesity).

4 LIFESTYLE MODIFICATION

AF is a progressive disease - most patients progress from paroxysmal to persistent and then permanent AF. Recent data suggest that this progression may be related to associated cardiovascular risk factors. With increasing risk factors the chance of more persistent forms of AF increases proportionately.

Risk factors for AF

Age, hypertension, heart failure, diabetes and structural heart disease have been conventionally associated with increased risk for AF (Table 2). More recently, obesity and sleep apnoea have been shown to be important risk factors for AF. These risk factors result in structural and electrical remodeling predisposing to AF.

In a study involving 40 patients with obstructive sleep apnoea, the disorder was associated with significant atrial remodelling characterised by atrial enlargement, reduction in voltage, site-specific and widespread conduction abnormalities, and longer sinus node recovery. These features may in part explain the association between obstructive sleep apnoea and AF.[16]

In the ARIC study, each component of metabolic syndrome was associated with risk of AF. The risk of AF increased significantly with each additional component of metabolic syndrome with a 67% overall increase in the risk of AF among individuals with metabolic syndrome.[17]

Table 2. Risk factors for AF

Established risk factors
Ageing
Hypertension
Heart failure
Diabetes
Valvular heart disease
Ischaemic heart disease
Congenital heart disease
Infiltrative heart disease
Novel risk factors
Obesity
Sleep apnoea
Pre-hypertension and aortic stiffness
Familial AF

There have been several population based studies that have provided the epidemiological link between obesity and AF. Data from the Women's Health Study demonstrated the dynamic relationship between weight and AF.[18] Women who gained weight during the first 5 years of the study had a greater risk of developing new AF, while women that dropped their BMI to below 30 reduced their risk. While this link between obesity and AF has been observed, until recently there was only limited information on the atrial abnormalities that result from obesity to predispose to AF. In a sheep model, obesity resulted in electrophysiological, electroanatomical, and structural remodelling of the atria, all of which resulted in a greater inducibility of AF.[19] Fibrosis represents the cornerstone of the structural remodelling. Obese sheep demonstrated increased fibrosis compared to the controls. The most important finding was that with weight reduction there was regression of atrial fibrosis to levels seen in the control animals.

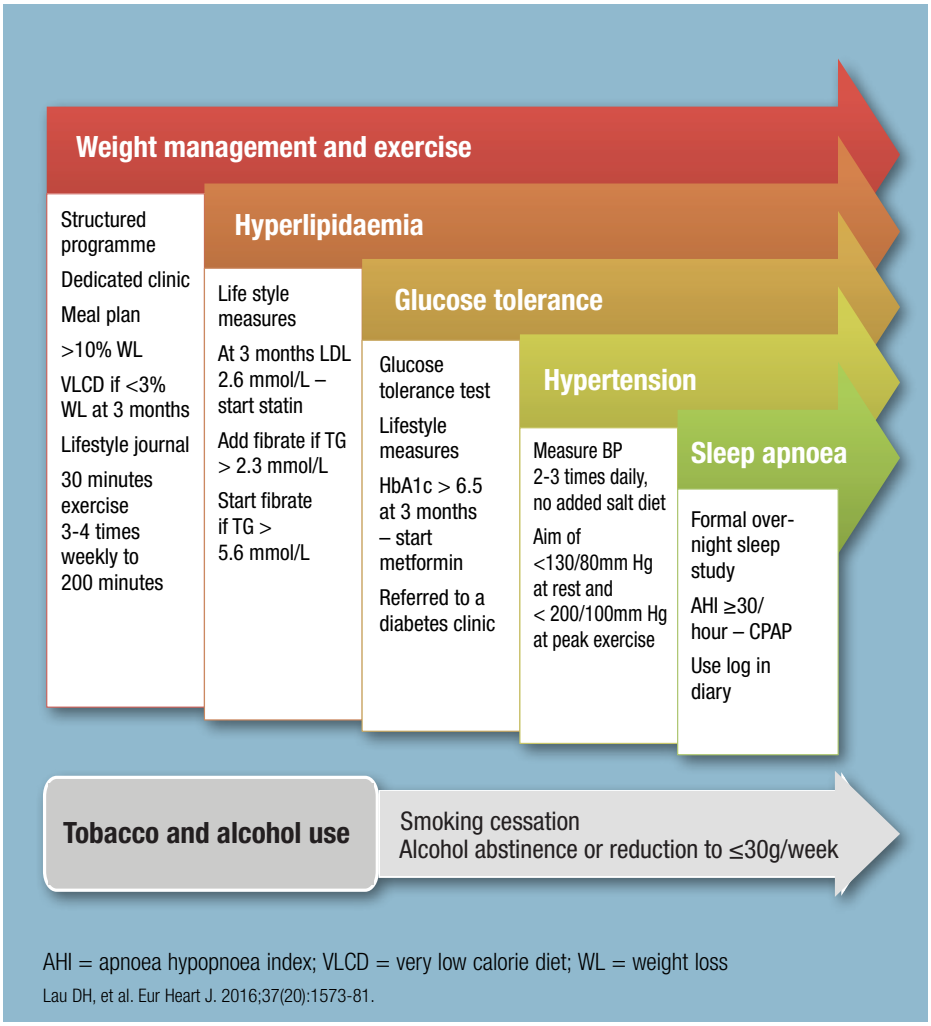
Is increase in AF risk reversible?

Considering the established epidemiological link, these comorbidities could be a potential target for intervention to stem the expanding epidemic of AF.

Results from a randomised controlled trial demonstrated that short term weight loss in obese patients with AF resulted in a reduction in AF burden. It is noteworthy that, as early as 3 months, the AF frequency, duration and symptom severity scores started to separate between the weight loss and non-weight loss groups. At final follow up these scores were significantly less in the weight loss group compared to control.[20] In another study, obese patients with AF who had long-term sustained weight loss had a significant reduction of AF burden and maintenance of sinus rhythm.[21] A study evaluating the impact of risk factor and weight management on AF ablation outcomes found that aggressive risk factor management greatly improved the long-term success of AF ablation.[22]

Risk factor management

A multi-disciplinary integrated care approach involving aggressive risk factor management as shown in the figure below has shown great promise in improving cardiovascular outcomes of patients with AF.[23] The structured programme involves three-monthly clinic visits to achieve weight loss, frequent moderate intensity exercise, lipid management, glycaemic and BP control, sleep apnoea control, complete smoking cessation, and reduced alcohol consumption.



AHI = apnoea hypopnoea index; VLCD = very low calorie diet; WL = weight loss

Lau DH, et al. Eur Heart J. 2016;37(20):1573-81.

Risk factors and AF key points

- Modifiable risk factors contribute to the increased burden of AF.
- Therapy directed at the primary causes of AF is associated with reduction in symptom burden and reversal of atrial remodelling.
- Treatment of risk factors improves outcome from rhythm control strategies.
- Treating risk factors should be an essential component of AF management.

THE FOUR PILLARS OF AF MANAGEMENT: TAKE HOME MESSAGES

Adapted from ESC Guidelines 2016

Anticoagulation

- Anticoagulation should be considered in patients with a CHA_2DS_2VASc score = 1 (unless the score of 1 is for being female)
- Anticoagulation should be offered to patients with a CHA_2DS_2VASc score ≥ 2
- NOACs are more convenient than warfarin with comparable or better efficacy and safety
- Reversal is now possible for dabigatran

Rate control

- Aim for resting HR <110 bpm (100 if congestive heart failure). However, lower target resting heart rates are more appropriate for some patients, such as those with heart failure or those with symptoms on exertion due to high heart rate
- Achievable with drugs, pacemaker or ablation
- No mortality difference in rate vs rhythm control

Rhythm control

- Indicated for symptomatic AF patients
- Drugs are usually first line
- Ablation for second line or patient preference
- Better outcomes in paroxysmal AF vs persistent AF

Lifestyle modification

- Complete programme of weight loss, exercise, alcohol reduction, smoking cessation
- Reduces symptoms and AF burden

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