

Managing atrial fibrillation — redrawing a line in the sand

The findings of two major trials show that rhythm control is not necessarily superior to rate control

THERE ARE TWO BROAD STRATEGIC OPTIONS in managing recurrent or persistent atrial fibrillation (AF). They are:

- **Rhythm control**, in which treatment is directed toward restoring and maintaining sinus rhythm; and
- **Rate control**, in which AF is allowed to continue or recur unimpeded, and medications are given to control ventricular rate.¹

It has been a widely held and natural assumption that rate control is inferior to rhythm control. Theoretically, the advantages of maintaining sinus rhythm should include fewer thromboembolic complications, reduced need for anticoagulation, and less cardiac failure. In short, fewer deaths and fewer symptoms.

However, antiarrhythmic medications have only modest efficacy for preventing AF recurrences, both symptomatic and asymptomatic, so rate-controlling and anticoagulant drugs must also be used in many patients being treated primarily for rhythm control. Also, antiarrhythmic medications can have serious side effects, including life-threatening proarrhythmia and, in the case of the commonly used drug amiodarone, pulmonary fibrosis, thyroid dysfunction and hepatic toxicity. Until recently, few randomised trial data have been available to gauge the extent to which these practical deficiencies offset the potential benefits of rhythm control.² Now, two major trials comparing the two treatment strategies have been published.^{3,4}

The larger AFFIRM trial was conducted in North America, with all-cause mortality its primary endpoint.³ The smaller trial was conducted in the Netherlands, and had a composite primary endpoint which included heart failure, thromboembolism, bleeding, need for pacemaker implantation, death from cardiovascular causes, and other severe adverse effects of drugs.⁴

The primary finding in both trials was that rate control was not inferior to rhythm control, and that there were some trends towards superiority of rate control. In the AFFIRM trial, 5-year mortality was 21.3% for rate control versus 23.8% for rhythm control ($P=0.08$). In the Dutch trial, the primary endpoint occurred in 17.2% (rate control) versus 22.6% (rhythm control), also narrowly failing to reach conventional significance. For the patient populations studied (minimally symptomatic; mean age, 69 ± 9 years; most with at least one prior episode of AF), these findings indicate that the benefits of the rhythm-control strategy do not, in general, outweigh the risks.

What drugs were used? In AFFIRM, by physicians' choice, amiodarone was used in 38% of patients being treated for rhythm control initially, and in 63% at some time in the trial. Sotalol was used in 31% initially, and 41% at some time. Other drugs, including propafenone, procainamide, quinidine, flecainide, disopyramide, moricizine and dofetilide were each used in less than 10% of patients. In the Dutch trial, sotalol was used initially, but replaced (if AF recurred within six months) by propafenone or flecainide, and then, if

necessary, by amiodarone. Warfarin treatment could be stopped at the physician's discretion when sinus rhythm had apparently been maintained for four weeks after cardioversion.

The detailed outcomes quantify the impact of shortcomings of these antiarrhythmic agents. Sinus rhythm was present in 62.6% (AFFIRM) and 39% (Dutch), respectively, of patients being treated for rhythm control at the conclusion of the trials. The proportion of patients taking warfarin remained above 70% in the AFFIRM study, and above 86% in the Dutch trial. Most disappointingly, the strategy failed to reduce the rates of stroke, other thromboembolic complications, or haemorrhages compared with rate control (see Box). Of the 80 ischaemic strokes incurred in the AFFIRM trial's rhythm-control arm, 55% occurred after discontinuation of warfarin. A further 21% occurred during warfarin treatment, while patients' international normalised ratios (INR) were < 2.0 . Only 31% had AF at the time of their stroke.

These findings suggest that it may be unsafe to stop anticoagulation for AF patients treated with a rhythm-control strategy, unless there are no other risk factors for stroke (age > 60 , previous stroke or transient ischaemic attack, hypertension, rheumatic valve disease, diabetes, cardiomyopathy, planned or recent cardioversion) and/or maintenance of sinus rhythm has been demonstrated not only by lack of symptoms, but also by appropriate ambulatory ("Holter") monitoring.^{1,5,6}

The rate-control arms had significantly lower rates of severe adverse effects attributable to medications — effects such as torsade de pointes, resuscitated cardiac arrest due to bradycardia or pulseless electrical activity, and various non-cardiac adverse events (see Box). The incidence of congestive cardiac failure was non-significantly lower in the rate-control arms in both trials.

In subgroup analyses of the AFFIRM trial, rate control had lower risk of death for patients older than 64 years, those without pre-existing congestive cardiac failure, and those with coronary artery disease. A trend in favour of rate control in patients with hypertension in the AFFIRM trial is supported by superiority (primary endpoint 17.3% v 30.8% for rhythm control) in the corresponding subgroup analysis of the Dutch study.

These two trials do not spell the end for electrical cardioversions and antiarrhythmic medications in the management of AF. They concentrated on older, high-risk patients, excluding or under-representing some subgroups of patients who experience AF, for example:

- patients considered unsuitable for one of the strategies (eg, those with hypertrophic cardiomyopathy, those too symptomatic in rate-controlled AF, or those at unacceptably high risk of bleeding with anticoagulation); and
- patients under 65 years of age and with no other risk factors for stroke or death.

Summary of the findings of two major studies examining rate control and rhythm control in atrial fibrillation

Event	AFFIRM ³			Dutch study ⁴		
	Rate	Rhythm	Difference significant? (P)	Rate	Rhythm	Difference significant?
Number of participants		4060			522	
Mean duration of follow-up		3.5 years			2.3 years	
Mean age at baseline		70 years			68 years	
Females		39%			36%	
Primary endpoint*	21.3%	23.8%	No (0.08)	17.2%	22.6%	No
Congestive heart failure	2.1%	2.7%	No (0.58)	3.5%	4.5%	No
Thromboembolism				5.5%	7.9%	No
Cerebral	5.5%	7.1%	No (0.79)			
Other systemic	0.5%	0.4%	No (0.62)			
Pulmonary	0.1%	0.5%	No (0.16)			
Haemorrhage				4.7%	3.4%	No
Primary intracerebral	1.1%	1.3%	No (0.73)			
Subdural or subarachnoid	0.8%	0.8%	No (0.68)			
Non-central nervous system	7.7%	6.9%	No (0.44)			
Severe adverse effects of drugs (other than anticoagulants)				0.8%	4.5%	Yes
Torsade de pointes	0.2%	0.8%	Yes (0.007)			
Resuscitated cardiac arrest due to bradycardia or pulseless electrical activity	< 0.1%	0.6%	Yes (0.01)			
Pulmonary events [†]	1.7%	7.3%	Yes (< 0.001)			
Gastrointestinal events [†]	2.1%	8.0%	Yes (< 0.001)			
Bradycardia [†]	4.2%	6.0%	Yes (0.001)			
Prolongation of corrected QT interval (> 520 ms) [†]	0.3%	1.9%	Yes (< 0.001)			
Other adverse events [†]	14.0%	25.4%	Yes (< 0.001)			

* All-cause mortality for the AFFIRM trial,³ and a composite primary endpoint which included heart failure, thromboembolism, bleeding, need for pacemaker implantation, death from cardiovascular causes, and other severe adverse effects of drugs for the Dutch trial.⁴ † Prompting discontinuation of a drug.

For many such patients, and for most patients' first episode of persistent AF, it remains appropriate to cardiovert once, with a level of anticoagulation appropriate to the patient's risk-benefit profile for some weeks or months, meanwhile treating any concomitant predisposing conditions (congestive heart failure, lung disease, etc), and then review. Many issues need to be considered when deciding and revising optimal treatment in an individual patient. In selected individuals, potentially curative non-pharmacological treatments (eg, pacing,⁷ catheter ablation,^{8,9} or maze operation¹⁰) may be appropriate.

However, for patients represented in the AFFIRM and Dutch trials, a line in the sand has been redrawn. Rate control is safe and should not be considered inferior to rhythm control for minimally symptomatic patients in whom AF is considered likely to recur after cardioversion, particularly if they are older than 64, or have coronary artery disease or hypertension. Healthcare professionals should make assiduous efforts to help patients maintain their INR between 2.0 and 3.0 continuously, and to achieve adequate rate control (defined for the AFFIRM trial as resting rate \leq 80 beats per minute, and either a 6-minute walk test with a rate \leq 110, or a 24-hour Holter recording with average rate \leq 100 and no individual rate more than 110% of the predicted maximum).¹¹

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