Commentary

Rate or Rhythm Control of Atrial Fibrillation – Pearls for the Internist

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Abstract

Atrial fibrillation is an epidemic in Asia that is increasingly prevalent. Apart from stroke risk stratification and management of anticoagulation, physicians managing this group of patients also need to determine an optimal strategy in terms of rate or rhythm control. With new techniques of catheter ablation to maintain patients in sinus rhythm, patients with atrial fibrillation now have more options for treatment, on top of pharmacological methods. This paper aims to review the current evidence for rate and rhythm control in both general patients and subgroups of interest commonly encountered in clinical practices such as obesity, heart failure and thyroid disease.

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Introduction

Atrial fibrillation (AF) is the most commonly sustained cardiac arrhythmia. The prevalence rate of AF in the adult population is 1% in most Asian countries, with an estimated 72 million patients in Asia affected by 2050.[1]

Stroke Prevention in Atrial Fibrillation

Risk stratification systems like the CHA_2DS_2-VASc score help determine annual stroke risk to aid understanding and discussion of anticoagulants in non-valvular AF. This risk scoring system is not applicable to patients with rheumatic mitral stenosis and conditions like hypertrophic cardiomyopathy where AF confers elevated stroke risks regardless of CHA_2DS_2-VASc score and when anticoagulation should be commenced. Aspirin alone should not be offered for stroke risk prevention in AF.[2,3]

Current options of anticoagulation for non-valvular AF include warfarin and non-vitamin K antagonist oral anticoagulants (NOACs); only dabigatran, rivaroxaban and apixaban are currently available in Singapore.

Warfarin is effective if good quality anticoagulation control—defined by the time in therapeutic range (TTR) of over 70%—is achieved. However, achieving a good TTR can be difficult, particularly in Asian populations.[4] Hence, NOACs offer a therapeutic alternative. A meta analysis[5] of 4 landmark NOAC trials revealed a significant 19% stroke risk reduction, driven by the reduction in haemorrhagic stroke, and a 10% reduction in all-cause mortality relative to warfarin, at the expense of a slight increase in gastrointestinal bleeding. The efficacy and safety of NOACs over warfarin seem to be even greater in East Asians compared with non-Asians.[6]

Percutaneous left atrial appendage occlusion might be an alternative for patients who are at high risk but have contraindications to oral anticoagulants; this should be considered a secondary option and patients still require dual antiplatelets for at least 6 weeks after the procedure.

Symptom Management: The Controversy of Rate or Rhythm Control

The 2 main treatment strategies for symptom management are rate and rhythm control. These 2 strategies are not exclusive; rate control is central to AF management, even for patients who ultimately require rhythm control.

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Several large clinical trials have been performed to compare the risks and benefits of rate versus pharmacological rhythm control strategies in patients with AF,[7-9] and rate control was not shown to be inferior to rhythm control in terms of cardiovascular mortality and morbidity. The lack of superiority of rhythm control in these trials may be due to the modest ability to maintain sinus rhythm using pharmacological rhythm when compared to rate control agents, with sinus rhythm ranging from 26% to 63% in the rhythm control arm; a more effective rhythm control therapy might have resulted in greater benefit.

Rate Control

Ventricular rate control in AF can help reduce symptoms and enable exercise. However, the target ventricular rates for AF are unclear. Few trials look at this issue in AF. In the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation: a comparison between Lenient and Strict Rate Control II) study,[9] comparing lenient rate control of <110 beats per minute (mean heart rate in study 93 ± 9 beats/minute) versus strict rate control of less than 80 beats per minute, there was no difference in the composite clinical outcome of cardiovascular mortality and morbidity and also no differences in patient reported outcomes. The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (SENIORS) study in elderly AF patients with preserved ejection fraction and subanalysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) also failed to demonstrate better outcomes with stricter heart rate control of less than 80 beats per minute.[10,11]

Lenient rate control is easier to accomplish for both physician and patient, with significantly fewer hospital visits and lower dosages of drugs necessary to achieve the target heart rate. Drugs commonly used for rate control and their characteristics are summarised in Table 1.

Rate control in every patient requires consideration of their activity level and symptoms, the type of AF (paroxysmal, persistent and permanent), age, underlying disorders, the presence of heart failure, and previous attempts at medical management. However, if one condition remains symptomatic despite initial lenient rate control measures, stepping up on rate control needs to be balanced with risks of symptomatic bradycardia and pauses. Alternatively, pharmacological rhythm control or AF ablation can be considered. In cases of drug refractory

Table 1. Common Rate Control Agents Used in Atrial Fibrillation

Type of Agent	Example of Medications	Benefits	Side Effects	Comments
Beta blockers	Metoprolol, bisoprolol, nebivolol, carvedilol, esmolol	Widely available and safe to use in patients with low LVEF. Intravenous formulation available for metoprolol and esmolol (convenient when patients are fasted). Esmolol has minimal effect on blood pressure with rapid half-life.	Most common adverse symptoms are lethargy, headache, peripheral oedema, upper respiratory tract symptoms, gastrointestinal upset and dizziness. More serious adverse effects include bradycardia, atrioventricular block and hypotension.	Beta 1 selective agents are preferred, especially in the setting of bronchospasm and severe asthma. Carvedilol should be avoided in such circumstances.
Calcium channel blockers	Verapamil, diltiazem	Consistent atrioventricular nodal blockade. Both are available in intravenous forms. Safe to use in reactive airway disease.	Adverse effects include heart block, hypotension and myocardial depression. Use in patients with low LVEF suggestive of increased death, re-infarction and heart failure.	Use with caution in Wolfe-Parkinson-White syndrome. Need to be careful when in combination with beta blockers. Reduce dose with hepatic impairment and tart with smaller dose in renal impairment.
Cardiac glycosides*	Digoxin	Available in intravenous and oral forms. Systematic review suggests no increase in mortality in concomitant heart failure and AF. Can be used in combination with beta blockers and calcium channel blockers.	Gastrointestinal upset, dizziness, blurred vision, headache and rash. In toxic states (serum levels >2 ng/mL), digoxin is pro-arrhythmic and can aggravate heart failure, particularly with coexistent hypokalaemia.	Contra-indicated in patients with accessory pathways, ventricular tachycardia and hypertrophic cardiomyopathy with outflow obstruction. Need to monitor digoxin level and use with caution in patients with renal impairment; higher risk of toxicity.

AF: Atrial fibrillation; LVEF: Left ventricular ejection fraction
*Na+/K+ pump inhibitor, increases intracellular calcium.

symptomatic-persistent AF, physicians may need to consider atrioventricular nodal ablation with implantation of a permanent pacemaker to provide better ventricular rate control.

Rhythm Control

Catheter Ablation of AF

Catheter ablation is an invasive procedure which isolates the pulmonary veins and eliminates triggers for AF. A review of 7 studies directly comparing catheter ablation and drugs confirmed that sinus rhythm is better maintained following catheter ablation,[12] with improved patient reported outcomes over anti-arrhythmic drugs (AADs). The profile of patients enrolled in these studies tends to be younger with symptomatic paroxysmal AF and this partly contributes to better sinus rhythm maintenance postablation.

Cardioversion

Termination of AF can be achieved by direct current or pharmacological cardioversion. For electrical cardioversion, pretreatment with AAD increases the probability of restoring sinus rhythm. Anterior posterior electrode placement has also been shown to be more effective than the anterolateral placement in clinical trials. Otherwise, pharmacological cardioversion with bolus administration of AAD can be attempted with success rate of approximately 50% within 15 to 120 minutes. Examples of common drugs used for pharmacological cardioversion are: intravenous flecainide, propafenone, ibutilide and amiodarone.

Other drugs used for maintenance of sinus rhythm besides those listed are summarised in Table 2. Drug selection for patients largely depends on the presence of any structural heart disease such as coronary artery disease, congestive cardiac failure or left ventricular ejection fraction of less than 35%, left ventricular hypertrophy >1.4 cm.

AADs have significant drug-related toxicities. Amiodarone, the most effective AAD, has up to 6% risk of adverse events, including hepatic toxicity, peripheral neuropathy, hyper- and hypo-thyroidism and pulmonary toxicity. Overall complication rate for AF ablation also approximates 6%, and the most feared complication of

Table 2. Common Pharmacological Rhythm Control Agents Used in Atrial Fibrillation

Type of Agent	Example of Medications	Benefits	Side Effects	Comments
Class Ia*	Procainamide, quinidine, disopyramide	Procainamide is available in intravenous dosing, and is useful in patients with Wolfe-Parkinson-White syndrome with AF and normal LVEF.	Can cause QT prolongation and arrhythmia. Procainamide and quinidine have frequent gastrointestinal side effects and procainamide can cause a lupus-like syndrome and hypotension.	Dosage of procainamide and disopyramide need to reduce dose for patients with hepatic and renal impairment; metabolism is via CYP3A4 and hence, there is a need to be aware of possible drug interactions.
Class Ic†	Flecainide, propafenone	Available in oral and intravenous dosing and can be used for acute pharmacological conversion of AF.	Adverse effects include hypotension, atrial flutter with 1:1 conduction, QRS prolongation. Will need concomitant beta blockade. Avoid use in ischaemic and structural heart diseases.	Flecainide used in patients post myocardial infarction increases mortality. Propafenone can precipitate decompensated heart failure, particularly in CYP 2D6 slow-metabolisers.
Class III‡	Amiodarone, dronedarone, dofetilide, ibutilide, sotalol	Amiodarone, dofetilide and ibutilide can be used for pharmacological conversion of AF. Amiodarone and dofetilide can be used in structural heart disease.	QT prolongation with increased risk of ventricular arrhythmias. Amiodarone can worsen sinus node dysfunction and cause hepatotoxicity, hypo/hyperthyroidism and pulmonary fibrosis. Dronedarone is associated with increased mortality In patients with heart failure.	Sotalol and dofetilide need to be used with caution in patients with renal impairment; latter is contraindicated if CrCl <20 ml/min. Dofetilide requires inpatient stay for loading due to risk of torsades.

AF: Atrial fibrillation; CrCI: Creatinine clearance rate; LVEF: Left ventricular ejection fraction
*Prolong conduction, slow repolarisation and block fast inward Na+ channels.
†Block myocardial Na+ channels.
‡Potassium channel blockers and prolong phase 3 of action potential.

catheter ablation—atrio-oesophageal fistula often leading to fulminant sepsis and death—is estimated to be 0.03%-1.5%.

With current evidence, for patients with few or no symptoms attributable to their AF, the risks of currently available AAD or catheter ablation outweigh the modest effectiveness of these agents in the maintenance of sinus rhythm. However, rhythm control still holds value for symptomatic patients despite optimal rate control therapy.

Special Conditions: Obesity

In the Framingham Heart Study, every unit increase in body mass index correlated with a 4%-5% increase in AF risk.[13] Obesity and related obstructive sleep apnoea are the few modifiable risk factors for AF that have been identified. Weight loss modifies AF substrate including diastolic function, inflammation, and pericardial fat,[14] which are important players of AF mechanism in obesity.

Significant weight reduction reduces AF burden and symptom severity, and has shown to decrease interventricular septal thickness and left atrial area.[15] This suggests that cardiac remodelling with sustained weight potentially benefits obese patients with difficult-to-control, symptomatic AF, on top of pharmacological and ablation therapies.

Hyperthyroidism

AF is a common arrhythmia in the thyrotoxic state. The prevalence of AF in this disease ranges between 2% and 20%. Successful treatment with either radioiodine or thioureas is associated with a reversion to sinus rhythm in a majority of patients within 2 to 3 months. First line treatment for AF in thyroid disease is beta-adrenergic blockade. Digitalis may be less effective due to the increased rate of digitalis clearance as well as the decreased sensitivity of the heart in hyperthyroid state.[16] Treatment with calcium channel blockers, especially when administered parenterally, should be avoided because of the potential unwanted effects of blood pressure reduction through effects on the smooth muscle cells of the resistance arterioles as hyperthyroid patients may already be in a vasodilated state. Amiodarone, which is iodine-rich, should also be used with caution in a thyrotoxic state due to potential iodine organification and iodine-induced exacerbation of thyrotoxicosis.

Heart Failure

Although subgroup data suggests that sinus rhythm is associated with improved outcomes in patients with AF (including all-cause survival), clinical trials have failed to demonstrate superiority of either a rate or rhythm control strategy. There are several reasons why rhythm control has failed to improve survival in clinical trials, including limited efficacy and adverse effects of available treatments such as AAD (in which choices are further limited in the setting of heart failure), or delayed intervention such that the cumulative effects of AF are already unable to be reversed. Sinus rhythm can be difficult to achieve and maintain, particularly in patients with heart failure. For example, recurrence of AF after successful cardioversion is a frequent problem (>50% at 6 months), particularly in patients with heart failure.

While the older studies mainly used AAD to maintain patients in sinus rhythm, recent trials that used catheter ablation seemed to have more promising outcomes[17-19] (Table 3). Larger and more definitive trials are underway

Table 3. Randomised Controlled Trials Comparing Rhythm and Rate Control in Heart Failure

Trial	Year	n	Type of AF	Rhythm Control Method	Outcome	Follow-up
AF CHF*	2008	1376	Permanent/ paroxysmal AF with LVEF <35%	DC cardioversion and anti-arrhythmic therapy	No difference in cardiovascular mortality (hazard ratio in the rhythm-control group, 1.06; 95% confidence interval, 0.86 to 1.30; $P = 0.59$ by the log-rank test). No significant difference in secondary composite outcome of death from cardiovascular causes, stroke, or worsening heart failure.	37 months
CAFÉ-II	2009	61	Permanent	DC cardioversion and amiodarone	NYHA class ($P = 0.424$) and 6MWT distance ($P = 0.342$) were similar between groups. Patients assigned to rhythm control had improved LV function ($P = 0.014$), NT-proBNP concentration ($P = 0.046$) and QOL ($P = 0.019$) compared with those assigned to rate control.	12 months

AF: Atrial fibrillation; DC: Direct current; EF: Ejection fraction; LVEF: Left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; QOL: Quality of life; 6MWT: Six-minute walk test

*Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358:2667-77.

†Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. J Am Coll Cardiol 2013;61:1894-903.

‡Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol 2014;7:31-8.

Table 3. Randomised Controlled Trials Comparing Rhythm and Rate Control in Heart Failure (Cont'd)

Trial	Year	n	Type of AF	Rhythm Control Method	Outcome	Follow-up
MacDonald, et al	2011	41	Persistent AF, LVEF <35%	Pulmonary vein isolation ± linear and focal complex fractionated atrial electrogram ablation	Fifty percent AF-free survival in the ablation group at 6 months; no significant increase in LVEF, functional capacity, and QOL between ablation and rate control group. However, patient who remained in sinus rhythm had significant increase in LVEF.	6 – 14 months
ARC-HF†	2013	52	Persistent AF, LVEF <35%	Pulmonary vein isolation ± linear and focal complex fractionated atrial electrogram ablation	Eighty-eight percent AF-free survival in ablation group at 12 months; peak oxygen consumption significantly increased in the ablation arm compared with rate control (difference +3.07 ml/kg/min, $P = 0.018$). Significant improvements in Minnesota Score ($P = 0.019$) and B-type natriuretic peptide ($P = 0.045$), and trend towards improvement in EF ($P = 0.055$).	12 months
CAMTAF‡	2014	50	Persistent AF, LVEF <50%	Pulmonary vein isolation ± linear and focal complex fractionated atrial electrogram ablation	LVEF in ablation group was 40 ± 12% compared with 31 ± 13% in the rate control group ($P = 0.015$). Significantly improved peak oxygen consumption (22 ± 6 versus 18 ± 6 mL/kg per minute; $P = 0.014$) and Minnesota living with Heart Failure Questionnaire Score (24 ± 22 vs 47 ± 22; $P = 0.001$) compared with rate control.	6 months

AF: Atrial fibrillation; DC: Direct current; EF: Ejection fraction; LVEF: Left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; QOL: Quality of life; 6MWT: Six-minute walk test

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to help clarify whether ablation leads to improved cardiovascular outcomes in patients with AF and heart failure.

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