Atrial Fibrillation in Singapore and Malaysia: Current Trends and Future Prospects

Razali Omar MD FHRS FACC†, Wee Siong Teo MBBS (NUS) FRCP (Edin) FHRS†, David Foo MBBS MRCP (UK) FACC†, Chee Kok Han MBBS MMed FNHAM†, Ahmad Nizar Jamaluddin MD MRCP (UK) FACC (USA)†, Lip Ping Low MBBS FRACP FACC FESC†, Tiong Kiam Ong FRCP FACC FESC†

†Electrophysiology and Pacing Unit, National Heart Institute, Kuala Lumpur, Malaysia
‡Department of Cardiology, National Heart Centre, Singapore
§Department of Cardiology, Tan Tock Seng Hospital, Singapore
¶Faculty of Medicine, Department of Cardiology, University of Malaya, Kuala Lumpur, Malaysia
**Sime Darby Medical Centre, Subang Jaya, Selangor, Malaysia
††Consultant Cardiologist, Low Cardiology Clinic, Mount Elizabeth Medical Centre, Singapore
‡‡Visiting Consultant, National Heart Centre, Singapore
§§Sarawak General Hospital Heart Centre, Kota Samarahan, Sarawak, Malaysia

Atrial fibrillation (AF) imposes substantial burdens of morbidity and impaired health-related quality of life, and significantly increases sufferers’ risk of having a cardiovascular event, in particular a stroke. Prevalence of AF in Asia and the associated healthcare costs are likely to have been underestimated and are expected to increase due to greater awareness, population ageing and increasing prevalence of associated risk factors and comorbidities.

The AF management paradigm is shifting from a conventional focus on achieving heart rate or rhythm control, towards endeavouring to use the safest agents available to reduce patients’ symptoms and improve their quality of life and cardiovascular outcomes. No new anti-AF drugs have been introduced for decades and existing pharmacotherapeutic modalities have potentially serious side effects as well as sub-optimal efficacy in converting to and maintaining normal sinus rhythm and preventing recurrence.

There is an unmet need for better anti-arrhythmic drugs that are well tolerated, efficacious, cost-effective and have a more favourable safety profile than current options. Although the perfect agent remains to be discovered, some promising new anti-arrhythmic drugs have the potential to overcome certain limitations of established approaches to AF management.

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Key words: Anti-arrhythmic, Asia, Control, Dronaderone, Guideline, Management, Rate

Introduction

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterised by uncoordinated electrical activity of the atria. AF is the most common sustained cardiac arrhythmia observed in clinical practice; prevalence increases with age and...
AF may be either idiopathic, or associated with structural heart disease and adverse cardiovascular (CV) outcomes.

The epidemiology of AF and its potential interactions with hypertension, diabetes, congestive heart failure and stroke, rank AF among the top priorities in cardiology and highlight the importance of refining management strategies to control this growing epidemic. To gain insights on AF management in Asian patients, identify unmet needs and recommend practical measures to improve clinical outcomes, experts from Singapore and Malaysia convened to review current practice and discuss emerging opportunities in AF care. This review encapsulates our analysis of existing evidence and collective clinical experience and our consensus view on best practices in AF management. Our intention is not to establish practice standards, but rather to provide useful information that will help doctors in Asia to implement appropriate and effective interventions that will improve outcomes for their AF patients.

Epidemiology and burden of atrial fibrillation

AF is an increasingly important healthcare issue, particularly given the exponential worldwide growth of the elderly population.2) Epidemiological data consistently show that AF affects twice many men as women and is uncommon in people less than 60 years old, but increases markedly in prevalence thereafter and affects approximately 10% of 80 year olds (Figure 1).3) In the Framingham Heart Study, lifetime risk of AF was 25% in adults aged 40 years and above;4) between 1968–70 and 1987–89, age-adjusted prevalence of AF in the Framingham cohort (age 65–84) increased from 3.2% to 9.1% in men and from 2.8% to 4.7% in women;5) the number of AF patients is projected to increase 2.5-fold over the next 40 years.6)

AF has been reported to be slightly less prevalent in Asians than Caucasians. Electrocardiograph (ECG) documented AF prevalence in adults is approximately 1.6% in Japan, 1.5% in Singapore, 0.7% in China, and 1.1% in Taiwan.7–10) Nevertheless, consistent with global trends, AF is the most common significant arrhythmia in Singapore and is increasing rapidly due to population aging. In a study of 1,839 Chinese residents aged 55 years or more, the estimated prevalence of AF was 2.6% in men and 0.6% in women, increasing to 5.8% in adults aged 80 years and above.8) Physicians in Singapore and Malaysia report that AF patient numbers have increased by approximately 10% over the last 3 years,11) with further increases expected due to population aging, increasing prevalence of comorbidities (e.g., diabetes, hypertension), and more frequent referrals as awareness of AF increases.

AF causes multiple electrophysiological changes, such as electrical, contractile, and structural remodelling of the atria.12) Patients with AF have a significantly higher prevalence of comorbidities and concomitant CV risk factors than matched controls, in particular, hypertension, dyslipidemia, coronary heart disease, heart failure and diabes.13,14) AF doubles the risk of dying,15) increases the likelihood of hospitalisation two- to threefold,16) and increases the risk of stroke by up to five times.17) Stroke associated with AF is typically more severe than that due to other causes18) and even patients with less severely symptomatic or asymptomatic AF are at increased risk. Survival rates for complicated AF are worse than those of common cancers. Moreover, AF adversely affects quality of life.19)
Consequently, AF imposes a heavy burden on healthcare systems worldwide. In the USA, hospitalisations resulting from AF rose two- to three-fold from 1985 to 1999. AF accounted for 2.8% of 1,435 acute admissions to Kuala Lumpur General Hospital, Malaysia, over 4-weeks from May to June 2000. Similarly, almost 3% of 11,531 admissions to the National Heart Centre, Singapore, from 1999 to 2001 were due to AF.

Current practice and emerging trends in the management of atrial fibrillation

Guidelines and terminology

In a cross-sectional survey of cardiologists, electrophysiologists and internal medicine specialists from Singapore and Malaysia with experience of diagnosing and managing AF patients, most cited guidelines from the American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC) as the chief influences on their treatment approach. Accordingly, AF is usually classified as paroxysmal, persistent, or permanent, depending on its pattern of onset/recurrence and duration. Paroxysmal AF denotes intermittent, self-terminating episodes, usually lasting less than 7 days, and affects approximately a quarter of AF patients in Singapore and Malaysia. Sustained AF episodes (usually 1 week to 6 months) that do not revert to sinus rhythm without medical intervention are termed persistent and account for approximately 18% of the AF population in Singapore and 34% in Malaysia. AF lasting for more than 1 year is classified as permanent and comprises the majority of diagnoses in Singapore (56%) and Malaysia (40%).

Rate and rhythm control agents

The primary concern in AF management has conventionally been choosing between rate-control and rhythm-control strategies. Rate-control aims to normalise the rapid ventricular rate in AF, without attempting to restore or maintain sinus rhythm. Optimum rate control usually requires ventricular rate reduction both at rest and during activity. Rates of 60 to 80 beats per minute (bpm) at rest and 90 to 115 bpm during ‘moderate’ exercise have been proposed as adequate. Rate control is usually accomplished by pharmacotherapy (Table 1), with non-pharmacological therapy reserved for pa-
Patients who are intolerant to rate-control medications or in whom pharmacological measures fail.\textsuperscript{13} Rate control has advantages of low risk of drug-induced pro-arrhythmia and lower cost, while limitations include impaired haemodynamics and the need for long-term anticoagulation.\textsuperscript{29}

Rhythm-control attempts to restore and/or maintain normal sinus rhythm with anti-arrhythmic drugs or non-pharmacological treatment (Table 1).\textsuperscript{1,28} Advantages of anti-arrhythmic therapy include low initial cost and high efficacy in terms of symptomatic and haemodynamic improvement, at least initially; however, these benefits are often offset by high recurrence rates, high long-term costs, and side effects such as pro-arrhythmia (e.g., torsades de pointes), congestive heart failure, organ toxicities (including neuronal, pulmonary, hepatic, optic neuropathy, and thyroid abnormalities), and increased mortality in patients with structurally abnormal hearts.\textsuperscript{30,31}

Priorities of physicians in Singapore and Malaysia have hitherto been rate control for permanent AF and rhythm control for paroxysmal AF.\textsuperscript{11} Anti-arrhythmic monotherapy is widely prescribed, with amiodarone preferred in paroxysmal and persistent AF patients and used more often than flecainide and propafenone due to their potential pro-arrhythmic effects, especially in patients with underlying heart disease. Sotalol and atenolol are also commonly prescribed for rate/rhythm control in paroxysmal and persistent AF patients, while in permanent AF patients, bisoprolol is also used. A minority of patients in each AF subclass in Singapore (25–30\%) and Malaysia (<20\%) progress from first- to second-line treatment, with 10\% or fewer receiving third-line treatment and a similarly low proportion referred for ablation and other invasive procedures.\textsuperscript{11}

Paradigm-shift in AF management

Patient safety and well-being are paramount concerns in AF management. Consequently, key treatment goals should extend beyond normalising the ECG pattern and preventing recurrence to include reducing symptoms, decreasing the risk of CV and stroke-related morbidity and mortality, and improving quality of life. These goals necessitate early detection and treatment of the underlying causes of AF, for example, thyrotoxicosis, alcohol consumption, or tachycardia-induced AF.

Novel anti-arrhythmic agents with an approved indication for AF have been recently introduced and may potentially enhance patient outcomes compared to conventional pharmacotherapies. ‘Upstream’ ap-

**Table 1** Pharmacological and non-pharmacological interventions to control rate and rhythm and prevent stroke and atrial remodelling in atrial fibrillation

<table>
<thead>
<tr>
<th>Therapeutic Strategy</th>
<th>Pharmacological</th>
<th>Non-pharmacological</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rate control</strong>\textsuperscript{a}</td>
<td>Calcium channel blocker (verapamil, diltiazem)</td>
<td>Atroventricular node ablation plus ventricular pacing</td>
</tr>
<tr>
<td></td>
<td>β-blocker</td>
<td></td>
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<tr>
<td></td>
<td>Digoxin</td>
<td></td>
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<tr>
<td></td>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td><strong>Rhythm control</strong>\textsuperscript{a}</td>
<td>Class 1A (quinidine, disopyramide)</td>
<td>Catheter ablation</td>
</tr>
<tr>
<td></td>
<td>Class 1C (propafenone, flecainide)</td>
<td>Pacing</td>
</tr>
<tr>
<td></td>
<td>Class III (sotalol, amiodarone)</td>
<td>Surgery (Maze procedure, pulmonary vein isolation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Implantable atrial defibrillator</td>
</tr>
<tr>
<td><strong>Prevent stroke</strong>\textsuperscript{a}</td>
<td>Warfarin</td>
<td>Left atrial appendage removal/isolation</td>
</tr>
<tr>
<td></td>
<td>Thrombin inhibitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td><strong>Prevent atrial remodelling</strong>\textsuperscript{a}</td>
<td>Calcium channel blocker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angiotensin conversion]</td>
<td></td>
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<tr>
<td></td>
<td>enzyme inhibitor</td>
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<td></td>
<td>Angiotensin receptor blocker</td>
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</tbody>
</table>

\textsuperscript{a} Decide most appropriate therapy based on patient’s profile

\textsuperscript{1} Recommended for all patients

Adapted from American Journal of Cardiology, Vol 85, Prystowsky EN: Management of atrial fibrillation: therapeutic options and clinical decisions, 3D–11D, \textcopyright 2000, with permission from Elsevier.
Table 2  General characteristics of patients with atrial fibrillation and rhythm-control vs. rate-control outcomes in major trials[^44]

<table>
<thead>
<tr>
<th>Trial name</th>
<th>N</th>
<th>Mean age (years)</th>
<th>Mean follow-up (years)</th>
<th>Inclusion criteria</th>
<th>Primary endpoint(s)</th>
<th>Proportion of patients reaching primary endpoint</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rate control</td>
<td>Rhythm control</td>
</tr>
<tr>
<td>Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM)</td>
<td>4060</td>
<td>69.7</td>
<td>3.5</td>
<td>Paroxysmal or persistent AF, age ≥65 years, or risk of stroke or death</td>
<td>All-cause mortality</td>
<td>25.9%</td>
<td>26.7%</td>
</tr>
<tr>
<td>Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE)</td>
<td>522</td>
<td>68.0</td>
<td>2.3</td>
<td>Persistent AF or flutter for &lt;1 year, 1 or 2 cardioversions over 2 years and oral anticoagulation</td>
<td>Composite: CV death/CHF/severe bleeding/pacemaker implantation/thromboembolic events/severe adverse effects of anti-arrhythmic drugs</td>
<td>17.2%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Pharmacological Intervention in Atrial Fibrillation (PIAF)</td>
<td>252</td>
<td>61.0</td>
<td>1.0</td>
<td>Persistent AF (&gt;7 &amp; &lt;360 days)</td>
<td>Symptom improvement</td>
<td>60.8%</td>
<td>55.1%</td>
</tr>
<tr>
<td>Strategies of Treatment of Atrial Fibrillation (STAF)</td>
<td>200</td>
<td>66.0</td>
<td>1.6</td>
<td>Persistent AF (&gt;4 weeks &amp; &lt;2 years), left atrium &gt;45 mm, CHF NYHA class II–IV, LVEF &lt;45%</td>
<td>Composite: overall mortality/cerebrovascular complications/cardiopulmonary resuscitation/embolic events</td>
<td>10.0%</td>
<td>9.0%</td>
</tr>
<tr>
<td>How to Treat Chronic Atrial Fibrillation (HOT CAFE)</td>
<td>205</td>
<td>60.8</td>
<td>1.7</td>
<td>First clinically overt episode of persistent AF (&gt;7 days, &lt;2 years), age 50–75 years</td>
<td>Composite: death/thromboembolic complications/intracranial or other major haemorrhage</td>
<td>1.0%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

approaches intended to prevent or attenuate AF-induced myocardial remodelling are also emerging as potential treatment modalities.\textsuperscript{1,2,5,32}

**Stroke prevention**

Stroke in AF mainly results from thromboembolism as a consequence of blood stagnating in the left atrial appendage.\textsuperscript{33} Most AF patients require appropriate thromboprophylaxis, irrespective of whether a rate- or rhythm-control strategy is used,\textsuperscript{26} and generally receive antiplatelet or anticoagulant medications (Table 1). These agents are recommended for long-term use in patients at high risk for thromboembolism or in those with risk factors for AF recurrence, for example, underlying structural heart disease or high CHADS\(_2\) (cardiac failure, hypertension, age, diabetes, stroke [doubled]) score.\textsuperscript{1,32} Warfarin remains the predominant anticoagulant used in Singapore and Malaysia;\textsuperscript{11} newer agents, for example dabigatran, were only approved very recently. Left atrial appendage removal/isolation is a non-pharmacological alternative for stroke prevention.\textsuperscript{1}

**Evidence-based management of atrial fibrillation**

**Rate-control versus rhythm-control**

Studies comparing rate-control and rhythm-control show no difference in survival and quality of life outcomes among AF patients (Table 2).\textsuperscript{34} Meta-analysis of five trials (n = 5,239), detected no significant difference in all-cause mortality between rate- and rhythm-control groups (13% vs. 14.6%; \(P = 0.09\)) and rate-control plus anticoagulation appeared at least equivalent to maintaining sinus rhythm with anti-arrhythmic agents in reducing the rate of ischaemic stroke (3.5% vs. 3.9%; \(P = 0.30\)).\textsuperscript{35} Therefore, decisions on the most appropriate approach to AF therapy should be individualised based on patient circumstances and preferences.

**Pharmacological rate control**

Rate control alone may be suitable for patients who are asymptomatic or have relatively few symptoms, and is a preferred option in patients with AF of longer than 12 months duration, left atrial diameter greater than six centimetres, or those at greater risk of pro-arrhythmia.\textsuperscript{1} The efficacy of rate control pharmacotherapy is approximately 80%.\textsuperscript{36} Non-dihydropyridine calcium channel blockers (CCBs) are effective for acute and chronic rate control in AF. During chronic treatment, beta-blockers have also been shown to be effective and safe compared to placebo and digoxin.\textsuperscript{32} The United Kingdom National Institute for Health and Clinical Excellence (NICE) guidelines on the management of AF (2006), recommend beta-blockers or rate-limiting CCBs as preferred initial monotherapy for pharmacological rate control in all patients.\textsuperscript{26} Although digoxin monotherapy reduces heart rate by approximately 4–21 bpm versus placebo at rest, it is not effective during exercise,\textsuperscript{1,37} and should therefore only be considered as monotherapy in sedentary patients. NICE recommends using CCBs plus digoxin if additional rate control at rest or during exercise is needed and in cases where rate control with combination therapy is inadequate, to use other drugs such as amiodarone or refer for specialist investigation.\textsuperscript{26}

**Dronaderone**

A new rate-control agent for AF is dronaderone (sanofi-aventis), which is a non-iodinated amiodarone-derived multichannel blocker that has an electrophysiological profile similar to its precursor and has both rate-control and rhythm control activities. In the Efficacy and Safety of Dronedarone for the Control of Ventricular Rate During AF (ERATO) trial, 14 days of treatment with dronedarone added to standard therapy (including thromboprophylaxis) significantly reduced mean 24-hour ventricular rate by 11.7 bpm versus placebo in patients with permanent AF (\(P < 0.0001\)), which was sustained through 6-months.\textsuperscript{38}

**Pharmacological rhythm control**

Pharmacological or electrical cardioversion is performed as part of a rhythm-control strategy and should be attempted in patients with significant AF symptoms despite rate control, reasonable potential for maintaining sinus rhythm, acute haemodynamic compromise, or recurrent thromboembolism despite anticoagulation.\textsuperscript{13} Pharmacological or electrical cardioversion is effective in up to 90% of AF patients.\textsuperscript{39} NICE recommends using a Class IC anti-arrhythmic (e.g., propafenone or flecainide) for pharmacological cardioversion in patients without structural heart disease, but amiodarone if structural heart disease is present.\textsuperscript{26} Continuous use of anti-arrhythmic drugs in paroxysmal AF with infrequent (once per year to every few months) recurrences may not be justified relative to their toxicity. In such cases, especially in the absence of structural heart disease, outpatient pulse treatment with oral propafenone or flecainide may be attempted.\textsuperscript{32} In a study of recent-onset AF patients with no or minimal heart disease, self-administration of propafenone or flecainide successfully controlled over 90% of episodes within 2 hours;\textsuperscript{40} however, 7% of patients reported adverse
effects during one or more arrhythmic episodes, including a case of atrial flutter with rapid conduction, indicating that close monitoring is necessary, especially following the first treatment.

Maintenance of sinus rhythm is necessary after cardioversion and may contribute to reduced mortality and morbidity. In the AF Follow-up Investigation of Rhythm Management (AFFIRM) study, which compared rate-control and rhythm-control pharmacotherapies, patients in sinus rhythm at the end of the study across the different treatment arms had 47% reduced risk of mortality compared to those in AF.\(^{41}\) Overall, use of anti-arrhythmic drugs approximately doubles the likelihood of maintaining sinus rhythm.\(^{42}\) Meta-analysis of 44 randomised controlled trials, suggests that anti-arrhythmic agents significantly reduce the rate of recurrent AF compared to placebo or no treatment, with annual number needed to treat (NNT) between two and nine. However, withdrawal due to side effects was frequent and Class IA anti-arrhythmic agents were associated with increased mortality.\(^{43}\)

Available data suggest that amiodarone (NNT = 3) is more effective than either flecainide and propafenone (NNT = 4), sotalol (NNT = 8), or placebo in long-term maintenance of sinus rhythm in patients with paroxysmal or persistent AF.\(^{43-47}\) In the Sotalol Amiodarone AF Efficacy Trial (SAFE-T), amiodarone was significantly superior to sotalol in maintaining sinus rhythm, but both drugs showed similar efficacy in patients with ischaemic heart disease.\(^{48}\) Post-hoc analysis of AFFIRM patients treated with rhythm-control, showed amiodarone to be significantly more effective than either sotalol or Class IA agents in achieving sinus rhythm at 1 year (P ≤ 0.002).\(^{45}\) In a prospective multicenter trial, low-dose amiodarone was more efficacious than sotalol or propafenone in maintaining sinus rhythm, with an AF recurrence rate of 35% versus 63% after mean follow-up of 16 months; however, cardiac and non-cardiac adverse events requiring discontinuation of therapy occurred in 18% of patients receiving amiodarone compared to 11% treated with sotalol or propafenone.\(^{44}\) Another post-hoc analysis of AFFIRM showed that mortality and CV hospitalisation were significantly more frequent in those who received amiodarone as the primary therapy than among rate-control patients (P < 0.0001).\(^{49}\)

In light of such findings, the latest thinking in anti-arrhythmic therapy for recurrent AF advocates a stepwise, safety-first approach, in which safer but possibly less efficacious medications are tried before resorting to more potent but less-safe drugs if initial therapy fails. For this reason, amiodarone is often reserved for second-line or third-line therapy (Figure 2),\(^{25}\) because despite being more potent and effective than other current anti-arrhythmic agents, it is associated with a relatively high incidence of potentially severe cardiac and extracardiac adverse effects.

**Dronedarone**

In randomised placebo-controlled trials, dronedarone was significantly more effective in maintaining sinus rhythm and controlling ventricular rate during recurrences of AF.\(^{50}\) In the context of rhythm control, dronedarone has been shown to significantly reduce CV mortality, arrhythmic death, stroke and hospitalisation relative to placebo,\(^{51,52}\) and is the first anti-arrhythmic drug shown to reduce CV hospitalisations and the risk of stroke in AF patients. There are no comparative data on the relative impact of other anti-arrhythmic agents on similar AF outcomes.

In a placebo-controlled, double-blind, parallel arm trial to assess the efficacy of dronedarone (ATHENA) in 4,628 patients with paroxysmal or persistent AF, adding dronedarone to standard therapy (including rate control, and/or antithrombotic therapy and/or other CV agents) significantly decreased the risk of hospitalisation due to CV events or death from any cause by 24% versus placebo (Figure 3a). Death from CV causes occurred in 29% fewer patients in the dronedarone arm (63) compared to placebo (90) (Figure 3b).\(^{51}\) Post-hoc analysis also suggested a significant decrease in the risk of stroke with dronedarone versus placebo (P = 0.027).\(^{52}\) Based on such data, the United States Food and Drug Administration approved dronedarone for treating AF.\(^{53}\)

In ATHENA, adverse events occurring significantly more frequently with dronedarone than placebo included bradycardia, QT-interval prolongation, diarrhoea, nausea, rash, and increased serum creatinine level; no significant increases in the rates of thyroid or pulmonary disorders were observed. These observations indicate that dronedarone has a much safer and more benign side-effect profile than amiodarone. Preliminary data from a trial of efficacy and safety of dronedarone versus amiodarone for maintaining of sinus rhythm in patients with AF (DIONYSOS)\(^{54}\) and an indirect meta-analysis comparing amiodarone with dronedarone\(^{55}\) show that although amiodarone is more effective than dronedarone in maintaining sinus rhythm, dronedarone is associated with fewer adverse effects and premature study-drug discontinuations. This unique safety and efficacy profile suggests an important role for dronedarone as a first-line AF therapy.\(^{32}\)
Non-pharmacological therapy for atrial fibrillation

**Healthier lifestyle**

Recent research shows that avoiding unhealthy behaviours and adopting a healthier lifestyle to minimise the adverse effects of CV risk factors such as hypertension, smoking, diabetes and excess body-weight, could potentially more than halve the burden of AF.⁵⁶)

**Electrical cardioversion**

In certain circumstances, for example, younger patients without structural heart disease and tachycardia-induced cardiomyopathy associated with AF, non-pharmacological approaches may be preferred to life-long drug therapy. Electrical cardioversion, for instance, may be used either alone or in combination with pharmacotherapy and has an 80% to 90% conversion rate; however, it requires

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**Figure 3** (a) ATHENA: Cumulative incidence of cardiovascular hospitalisation or death from any cause (primary endpoint). (b) ATHENA: Cumulative incidence of cardiovascular mortality (secondary endpoint) bid: twice-daily administration

*Standard therapy may have included rate control agents (beta-blockers, and/or Calcium channel antagonist and/or digoxin) and/or anti-thrombotic therapy (vitamin K antagonists and/or aspirin and other antiplatelet therapies) and/or other cardiovascular agents such as angiotensin conversion enzyme inhibitors, angiotensin receptor blockers and statins.

conscious sedation or anaesthesia as well as anti-coagulation for 4 weeks pre- and post-treatment in AF episodes longer than 48 hours.\(^{32}\) In case of concern about successfully restoring sinus rhythm (such as previous failure to cardiovert or early recurrence of AF), concomitant anti-arrhythmic agents may increase the success of electrical cardioversion.\(^1\) Between 1997 and 1999, the National Heart Centre in Singapore performed 55 cardioversions for persistent AF; 80% were successful in restoring sinus rhythm and 5% achieved transient restoration. Successfully cardioverted patients had significantly lower left atrial size than those in whom cardioversion was unsuccessful (42 ± 11 mm vs. 51 ± 11 mm; \(P = 0.05\)), and 70% remained in sinus rhythm during follow-up.\(^{39}\)

**Pacing therapy**

Pacing with atrioventricular (AV) node ablation may benefit patients with poorly-tolerated AF that is refractory to drug treatment. Achieving rate-control requires AV junction ablation; hence, permanent anti-bradycardia pacing is necessary.\(^{57}\) Pacing devices may also help to maintain sinus rhythm and have been shown to be effective mainly in bradycardia-induced AF, including sick-sinus syndrome and its brady-tachy variant. Techniques proposed for suppressing AF include: standard atrial pacing; alternative single-site atrial pacing; multi-site atrial pacing; algorithms to increase the frequency of atrial pacing; anti-tachycardia atrial pacing for termination of organised AF or atrial flutter; inter-atrial septal or Bachmann bundle pacing; combined prevention and termination algorithms; ventricular and biventricular pacing; and hybrid approaches (pacing devices with medications or ablation).\(^{58}\)

Emerging evidence indicates that excessive right ventricular pacing is deleterious and increases AF, heart failure, and possibly mortality. Therefore, physiological pacing with minimisation of right ventricular pacing is desirable.\(^{59}\) Trials suggest that in patients with symptomatic bradycardia, the risk of AF is lower with atrial than ventricular pacing.\(^{60}\) In patients with sinus node dysfunction and normal AV conduction, data support atrial or dual-chamber pacing rather than ventricular pacing for preventing or delaying progression of AF.\(^{61,62}\) Studies comparing single-site with dual-site or multi-site atrial pacing in recurrent paroxysmal AF show modest and non-significant benefit of dual/multi-site pacing in time to first AF and frequency of AF.\(^{63,64}\) However, additional benefits may be obtained by using particular pacing sites, specific pacing algorithms designed to target potential AF triggers, and pace-termination of atrial tachycardia. Investigations are currently underway to determine whether minimising the detrimental effects of right ventricular apical pacing could further enhance the benefits of AV synchronous pacing.\(^{65}\)

**Implantable atrial debrillators**

The success of implantable ventricular defibrillators in relieving recurrent ventricular tachycardia prompted the development of implantable atrial debrillators that provide reproducible detection and termination of AF with low-energy shocks,\(^{66}\) with the aim of achieving internal cardioversion of AF. In preliminary studies, implantable atrial defibrillators have been both effective and safe for terminating AF in patients without significant structural heart disease.\(^{67-69}\) Nevertheless, frequent arrhythmia recurrences and patient intolerance to repeated cardioversion shocks remain major limitations of these devices.\(^{70}\)

**Catheter ablation**

Radiofrequency catheter ablation of the AV node along with ventricular pacemaker implantation can improve cardiac performance in AF patients with suboptimal pharmacological rate control. Alternatively, catheter-based radiofrequency modification of AV node conduction properties may reduce ventricular rate and AF-related symptoms without any requirement for permanent pacing;\(^1\) however, this procedure is associated with recurrence and AV node ablation and pacemaker implantation appear more effective. In a study of 44 patients with drug-resistant chronic AF, complete AV block was achieved in all patients undergoing AV node ablation with permanent ventricular pacemaker implantation (n = 22), while only 32% of patients undergoing AV node modification had permanent slowing of the ventricular rate. Patients undergoing AV node ablation with pacemaker implantation also experienced a significant improvement in ejection fraction (P < 0.01) and quality of life scores (P < 0.01) post-ablation relative to baseline. In contrast, there was no significant change in ejection fraction or quality of life with AV node modification.\(^{71}\)

Catheter ablation aimed at permanently curing AF has become increasingly common and is recommended in highly symptomatic young patients with focal AF without severe heart disease. Techniques include: catheter ablation of the triggering focus; three-dimensional guided left atrial circumferential ablation with pulmonary vein isolation; lasso-guided ostial electrical disconnection of pulmonary veins;
ablation guided by three-dimensional non-contact electroanatomical mapping; catheter ablation targeting complex fractionated atrial electrograms; and a combination of two or more strategies in the same individual.72) No specific technique appears to be superior and the specific technique depends on the type of AF and underlying heart disease. In a heterogenous patient population (n = 16,309) undergoing treatment at electrophysiology laboratories worldwide, with different techniques and varying investigator experience, catheter ablation was curative in an average of 70% of patients without concomitant anti-arrhythmic agents and in a further 10% with the use of (formerly ineffective) anti-arrhythmic agents after 18 months follow-up. The overall incidence of major complications (including death, stroke, transient ischaemic attacks, pericardial tamponade, pulmonary vein stenosis, atrio-oesophageal fistula, and atypical atrial flutter) was approximately 4.5%.72) Catheter ablation of AF is a rapidly evolving technique, and these results suggest an increase in the success rate of catheter ablation therapy coupled with a reduction in major complications compared to similar studies conducted in the past.73) Meta-analyses of studies performed mostly in patients with paroxysmal AF, that compared anti-arrhythmic medication and catheter ablation, have demonstrated superior rhythm control following catheter ablation.74,75) However, most such studies included patients already resistant to anti-arrhythmic drug treatment and had relatively short follow-up periods. Long-term follow-up studies indicate that while sinus rhythm is better preserved compared to anti-arrhythmic drugs, late recurrences of AF are not uncommon with catheter ablation.76) Considerable operator experience and technical skill are needed for ablation of AF, and this should be considered when contemplating a complex ablation procedure in a patient with symptomatic AF.

**Surgical ablation**

Surgery for AF has played an important role in selected symptomatic AF patients, especially as an adjunct to coronary bypass or valve repair surgery. Surgical procedures for AF include the conventional ‘cut-and-sew’ Maze procedure, pulmonary vein isolation, and left atrial linear ablation. Maze III, has become the gold standard to which other surgical procedures for AF are compared.77) A 10-year outcome analysis of AF patients (n = 335) undergoing the standard Maze procedure at experienced surgical centres, indicated that, at last follow-up (mean, 42 ± 6 months), 88% of the patients were AF-free.78)

Surgical pulmonary vein isolation is effective in restoring sinus rhythm in permanent AF associated with mitral valve disease. In a case series (n = 50) of box isolations of all four pulmonary veins using epicardial microwave energy performed totally endoscopically on the beating heart, 79.5% of patients were in normal sinus rhythm at last follow-up (mean, 7.6 months).79)

Due to the complexity and technical difficulty of the Maze procedure, attempts have been made to simplify the operation by replacing the traditional ‘cut-and-sew’ incisions with linear lines of ablation created using a variety of energy sources.80) Excellent results have been reported with radiofrequency ablation-assisted Maze procedures, with over 90% of patients remaining symptom free after one year of treatment.81,82)

The advent of ablation technology has simplified the surgical treatment of AF by allowing it to be performed through limited access incisions. While few patients have been candidates for a stand-alone surgical procedure to cure AF, minimally-invasive approaches in development could expand the indications for stand-alone surgery for AF in the future.

**Prevention of thromboembolism**

Pooled analyses from randomised trials demonstrate that oral anticoagulation therapy with vitamin K antagonists (e.g., warfarin) reduces the risk of stroke by 68% compared to 21% with aspirin.83) The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study showed that vitamin K antagonism reduced the occurrence of fatal or disabling stroke, intracranial haemorrhage, and clinically significant arterial embolism by 52% compared to aspirin 75 mg daily; there was no difference in the risk of serious bleeding complications.84) In the Warfarin versus Aspirin for Stroke Prevention in Octogenarians with AF (WASPO) trial, significantly more adverse events, including serious bleeding, were observed with aspirin than with warfarin (33% vs. 6%; P = 0.002).85) In the AF Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-Warfarin arm (ACTIVE-W) trial, anticoagulation therapy was superior to the combination of clopidogrel and aspirin, with no difference in bleeding events between treatment arms.86) Thus, current evidence supports the use of warfarin in patients with AF who are at risk of stroke; however, the narrow therapeutic index and a high risk/benefit ratio of warfarin necessitate close and long-term monitoring. Guidelines in the US87) and UK88) recommend a target international normalised ratio (INR) range of two to three for warfarin therapy;
however, Japanese and Chinese data indicate that Asians may require lower INR values than Caucasians (e.g., 1.5 to 2.5) for anticoagulation.\(^{89,90}\) Combination therapy with warfarin and antiplatelet agents has been evaluated; however, no beneficial effect with regard to ischaemic stroke or vascular events was observed, on the contrary, additional bleeding was evident.\(^{1}\)

**Non-pharmacological approaches to thromboprophylaxis**

Removal or closure of the left atrial appendage, which is considered to be the main site of atrial thrombogenesis, is performed to reduce the development of atrial thrombi and stroke in AF patients with contraindications to long-term anticoagulation therapy. In a trial comparing the efficacy and safety of percutaneous closure of the left atrial appendage for prevention of stroke with warfarin treatment in AF patients (\(n = 707\)), the primary composite efficacy endpoint of stroke, CV death, and systemic embolism was non-inferior to that of warfarin.\(^{91}\) There was a higher rate of adverse events in the intervention group than in control subjects, due mainly to procedural complications. In addition to direct surgical amputation or truncation of the left atrial appendage, several methods are under development to achieve this via intravascular catheters or transpericardial approaches.\(^{92}\)

**Upstream therapies in atrial fibrillation**

Upstream modulation of certain AF risk factors to produce downstream effects including reduced likelihood of subsequent development of AF has been investigated with agents including angiotensin conversion enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, HMG-CoA reductase inhibitors (statins), corticosteroids and n-3 polyunsaturated fatty acids. However, evidence for prevention of atrial remodelling from early phase trials remains equivocal and further large-scale investigations with adequately defined endpoints are needed.\(^{1}\)

**Management of atrial fibrillation—Evidence gaps**

Our review of the management of AF suggests that significant evidence gaps exist, particularly in Asian populations; comprehensive epidemiological data from Asian countries, including Singapore and Malaysia, are lacking. Although the extent of AF in these countries is uncertain, it is likely to have been underestimated. More robust data are needed to support the case that AF is a serious public health problem and for including AF metrics (e.g., ECG screening) in national health surveys.

Although clinical trial data on various AF treatment strategies are promising, it remains to be determined how the results will translate into real-life practice and whether or not there may be differences in outcomes between Caucasians and other racial groups. Most current evidence on strategies to treat AF derives from Caucasians aged 65 years and above who were enrolled into clinical studies according to strict inclusion and exclusion criteria. Evidence of benefits of pharmacological therapy in patient populations outside of clinical trials, for example, younger patients with minimal or no underlying heart disease, who are more likely to benefit from surgery, is lacking.

**Addressing challenges and unmet needs**

AF imposes a significant burden on healthcare systems and societies and is too prevalent to ignore. There is an urgent need to engage key stakeholders, including healthcare funding authorities, policymakers, patients as well as primary care physicians, cardiologists, and internists in the AF care cycle. The biggest stakeholders are the primary care physicians and general physicians at the forefront of screening, diagnosis, risk stratification, counselling and referral of AF patients to specialist centres.

As the AF management paradigm shifts from a traditional focus on rate and rhythm control to normalise ECG patterns and prevent recurrence, towards prioritising symptom reduction, health-related quality of life, and reducing CV and cerebrovascular morbidity and mortality, the greatest challenge is to realign physicians’ mindset with this new thinking. AF is not a single disease, is complex to treat and requires individualised therapy according to patients’ symptoms and risk profiles. Lack of awareness of the impact and consequences of AF among physicians, particularly in the primary care setting, is common, leading to low detection rates (as AF is frequently asymptomatic).

Early detection, including that of asymptomatic disease and treatment of AF is important because of the risk of serious complications, especially stroke. Stroke prevention is the biggest issue in AF, as stroke rather than AF itself is the main cause of mortality; however, stroke risk is seldom addressed in primary care. For this reason, there is an urgent need to raise awareness among physicians that AF increases the risk of stroke irrespective of symptom severity, and for continuing medical education on the importance
of stroke prophylaxis based on proper risk stratification (e.g., CHADS$_2$ and CHA$_2$DS$_2$VASc scores) and use of anticoagulation therapy. Oral anticoagulant therapy remains underused in AF. Foremost regarding the underuse of warfarin is the lack of physician (and patient) awareness about its risk/benefit profile. Convincing physicians to start warfarin therapy and achieving a recommended therapeutic INR range are important obstacles to meeting current challenges in AF management.

Lack of patient education in primary care is also an important issue. Improving patient awareness and proactive provision of information to patients need to be targeted through concerted efforts by both the physician community and wider society. Treatment compliance is also an important aspect of AF care, as all AF patients are at increased risk of thrombotic events. Therefore, educating patients that they are at increased risk of stroke and CV events, even though they may not feel unwell, and ensuring compliance with warfarin therapy are imperative to reducing AF-associated morbidity and mortality.

**An ideal anti-atrial fibrillation drug?**

Enhancing the capability to revert to and maintain sinus rhythm may benefit highly symptomatic patients. Currently, rhythm-control is limited by the drugs available. In the survey of specialists from Singapore and Malaysia, a majority expressed concerns about the limitations of current medications, including low efficacy (e.g., with regard to conversion to sinus rhythm, sinus rhythm maintenance, and prevention of recurrence), adverse side effects (e.g., pro-arrhythmia), toxicity, and drug interactions. However, most respondents were aware of new anti-arrhythmic drugs and anticipated reduced usage of amiodarone in the future due to the availability of safer alternatives.

In principle, an ideal anti-AF drug should be well-tolerated, efficacious (i.e., should provide relief of AF symptoms and reduce morbidity, mortality, and healthcare utilisation), cost-effective with once-daily administration (to improve compliance), and have a favourable safety profile relative to the current options (e.g., no serious side effects and minimal drug interactions). The perfect anti-arrhythmic agent is not yet available and the search for new therapies with better safety and efficacy profiles continues.

**Conclusions**

A paradigm shift in the management of AF, from a focus on rate and rhythm control towards improving quality of life and reducing adverse CV and cerebrovascular outcomes, is needed, with patient safety assuming overriding priority. Emerging therapies have the potential to overcome certain limitations of established approaches to AF management. It is our hope that this review of the absolute and relative benefits and risks of alternative therapeutic strategies will provide helpful insights that help fellow physicians to better understand current standards and gaps in patient care and thereby enhance the effectiveness of care and address unmet needs to improve patient outcomes.

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