Clinical Medicine Insights: Cardiology

METHODOLOGY

An Observational, Prospective Survey Assessing the Control of Atrial Fibrillation in Asia Pacific: Rationale and Design of the RecordAF-AP Registry

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Abstract:

Background: The literature suggests that the prevalence of atrial fibrillation (AF) may be lower in Asian countries than in Western countries. Nevertheless, AF remains a significant public health problem in the region. The burden of AF, the experiences of previous trials and the lack of data on AF and its management in Asia Pacific highlight the need for a comprehensive prospective study of AF management.

Methods: The REgistry on Cardiac rhythm disORDers assessing the control of Atrial Fibrillation Asia Pacific (RecordAF-AP) is a prospective, observational survey of the management of recently diagnosed AF patients with 1-year follow-up in 8 countries across Asia Pacific. Eligible patients presenting with AF, treated or not, will be included in the registry and data will be recorded prospectively during follow-up visits at 6 and 12 months.

Results: RecordAF-AP will recruit more than 3000 patients. Study recruitment commenced in April 2009 and the final results anticipated at the end of 2011.

Conclusions: RecordAF-AP will assess the real-life management of AF patients in Asia Pacific, including a comparison of clinical outcomes in rhythm versus rate control strategies, providing much needed insight into the costs, treatment choices and clinical outcomes of AF patients in this region.

Keywords: atrial fibrillation, sinus arrhythmia, rate-control, rhythm-control, cardiac glycosides, RecordAF

Clinical Medicine Insights: Cardiology 2011:5 1–6

doi: 10.4137/CMC.S6289

This article is available from http://www.la-press.com.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia; its prevalence increases with age such that 70% of cases occur in patients aged 65 years and older.[1] AF is a progressive disease that often worsens over time and is both a contributory factor to and an indicator of progressive cardiovascular disease. For example, AF increases the risk of stroke by 5-fold[2] and the risk of heart failure by 3-fold.[3] AF causes considerable morbidity and mortality, negatively impacts quality of life and well-being and imposes significant burden on health care systems.[4] Aging populations, increasing prevalence of comorbidities and more effective treatment of cardiovascular diseases are all contributing to the increasing incidence of AF and its associated health care burden.[5] As a result, the societal impact of AF is expected to double over the next three decades.[6]

Literature regarding the clinical epidemiology of AF in non-white populations is limited.[7] Data from the US indicates that AF is more common in white versus black patients who are aged 60 years or older.[8] Available data suggests that the prevalence of AF may be lower in Asian countries (Singapore,[9] Korea,[10] Malaysia[7] and mainland China[11]) than in Western countries, although it should be borne in mind that differences in diagnosis and population characteristics across these studies could have had some impact on the results obtained. Nevertheless, AF remains a significant public health problem.[11]

Management of AF involves two key objectives—prevention of thromboembolism and symptom management. Initial symptom management, according to current guidelines, involves either the restoration of and maintenance of sinus rhythm (rhythm control) or the control of ventricular response (rate control).[12] Non-pharmacological and pharmacological therapies are used in both strategies. No significant differences between rate and rhythm control with respect to mortality, major bleeding and thromboembolic events have been demonstrated.[13–19]

Several antiarrhythmic drugs are available and have been demonstrated to be effective in reducing the recurrence of AF after conversion to sinus rhythm but are limited by adverse events.[20] Given these limitations, chronic management of AF remains difficult for both patient and physician. Advances in available medical treatments, in particular dronedarone and dabigatran, offer the possibility of changes in treatment paradigms and a greater emphasis on reducing hospitalizations and improvement in long-term outcomes.[5] Despite these therapeutic advances, there remains a need to investigate further the real-life management of AF.

Prospective data from the Euro Heart Survey shows divergence between guidelines and day to day clinical practice,[21] with under-treatment being associated with a significantly higher chance of thromboembolism.[22] The **Re**gistry on **C**ardiac rhythm dis**ord**ers assessing the control of **A**trial **F**ibrillation (RecordAF) is the first worldwide, 1-year observational, longitudinal study of the management of paroxysmal/persistent atrial fibrillation in recently diagnosed patients (n = 5604). The results of this study will provide a global perspective on current treatment strategies for AF. The design and baseline data from 532 sites in 21 countries across Europe, America and Asia have recently been published.[23] Patient data have been contributed from Australia, South Korea, Philippines and Thailand, but they account for only 12.3% (n = 715) of the total population studied. The burden of AF, the experiences of previous trials and the lack of data on AF and its management in Asia Pacific highlight the need for a comprehensive prospective study of AF management in day to day practice. In this paper we discuss the methodology of an extension of the RecordAF study, RecordAF-AP, the intent of which is to produce a large-scale prospective Asia Pacific database on the management of AF.

Patients and Methods

RecordAF-AP is a prospective, observational survey of the management of recently diagnosed AF patients with a 1-year follow-up. The primary objective of the study is to prospectively assess AF control over 1 year in patients attending clinical or specialized practices in order to compare clinical outcomes in rhythm versus rate control strategies. The study will also describe the key demographics and treatment modalities of AF patients across the Asia Pacific region, determine any associations between the pharmacological treatment of AF and AF control, determine any associations between control of AF and clinical outcomes and collect information on suspected adverse events to the treatment prescribed for AF.

The study will recruit more than 3000 patients from 8 countries across Asia Pacific (Australia [20 sites], China [20 sites], Hong Kong [3 sites], Korea [20 sites], Malaysia [5 sites], Philippines [4 sites], Taiwan [15 sites] and Thailand [30 sites]). Participating investigators have been randomly selected and are representative of cardiologists who manage AF patients based upon the expertise and healthcare structure of each participating country. The study will be conducted in accordance with the Declaration of Helsinki (as amended in 2004),[24] guidelines for Good Epidemiological Practice[25] and local regulations. Ethics approval has been sought and provided locally by each participating country.

Patient inclusion and exclusion criteria are the same as have been previously described for the RecordAF study[23] and are summarized in Table 1. Eligible patients are to be included irrespective of the reason for their visit to the participating cardiologist. Data will be collected at baseline (visit 1) and during routine follow-up visits at 6 ± 2 months (visit 2) and 12 ± 3 months (visit 3). During the 12 months from recruitment to end of study (visit 3), treatment including the choice of medication, dosage and titration will be conducted at the doctor's discretion.

Table 1. Patient selection criteria.

Inclusion criteria	• Male or female aged ≥18 years

	• Presenting with one of the following:
	  • History of AF diagnosed ≤1 year by standard ECG or by ECG-Holter monitoring (patient may be either treated or not treated at inclusion visit)
	  • New AF diagnosed standard ECG or by ECG-Holter monitoring at inclusion visit

	• Eligible for pharmacological treatment of AF (by rhythm or rate control agents)
	• Willing and able to sign data release consent form
Exclusion criteria	• AF due to transient cause
	• Post cardiac surgery AF (≤3 months)
	• Life expectancy of <1 year due to severe disease
	• Unable to understand or sign the written informed consent due to mental disability
	• Unable to comply with follow-up visits
	• Has a pacemaker or implantable cardioverter defribrilator*
	• Scheduled for pulmonary vein isolation, atrioventricular node/His bundle ablation or pacemaker implantation*
	• Participation in an AF clinical trial in the previous 3 months
	• Pregnant or lactating

Note: *These patients are excluded because of the difficulties in interpreting their rhythm/rate-control strategies.

The co-primary endpoints at 12 months' follow up are the rate of therapeutic success and the incidence of clinical outcomes in rhythm versus rate control strategies. Therapeutic success, for a given patient at 12 ± 3 months follow-up, will be defined as either the presence of sinus rhythm (for patients with a rhythm-control strategy at baseline) or a resting heart rate in the target range of ≤80 beats/min (for patients with a rate-control strategy at baseline) with no incidence of clinical outcomes and no cross-over between rhythm and rate control strategies during the follow-up period. Clinical outcomes are cardiovascular death, hospitalization for transient ischemic attack, myocardial infarction, hospitalization or prolongation of hospitalization for arrhythmic or proarrhythmic events, other cardiovascular events or major complications of ablative procedure. The secondary objectives, at 12 months follow-up, are assessment of treatment effectiveness (proportion of patients in sinus rhythm or at rate control target, depending on the baseline strategy, with no symptoms of AF, still taking baseline medication, with no reports of treatment related adverse events, clinical outcomes, cardioversion or ablation) and success rate according to the pharmacological treatment class, evaluation of the impact of cardiovascular risk factors on the occurrence of clinical events (cardiovascular death, myocardial infarction, ischemic stroke, other arrhythmia, hospitalization for myocardial infarction, congestive heart failure episode, ischemic stroke or other arrhythmia), collation of information on suspected adverse reactions to prescribed AF treatments. A summary of the primary and secondary objectives is provided in Table 2.

Statistical analysis will be based on all patients enrolled into the study; only patients with a baseline and a post-baseline assessment will be included in the analysis. Patients will be stratified to rate or rhythm control based on the therapeutic strategy selected at the inclusion visit. Descriptive data will be summarized using mean and standard deviation and categorical data as number counts and percentages. The rate of patients in sinus rhythm or at rate control target will be provided with a 95% confidence interval (CI) and

Table 2. Record AF-AP registry objectives.

Primary	• Prospectively assess, over 1 year, disease control in AF patients in daily practice • Report clinical outcomes of rhythm-control and rate-control strategies
Secondary	• Describe key demographics and treatment features of AF patients followed by cardiologists in various countries in Asia Pacific • Determine the association between pharmacological treatments of AF and AF control • Determine the association between control of AF and clinical outcomes • Evaluate health status and resource utilisation • Gather information on suspected adverse events

logistic regression models will be used for analysis of the cardiovascular event rate. Health related quality of life will be assessed at baseline and 12 months using the EQ-5D questionnaire.[26] The EQ-5D is a self-administered descriptive system comprising five items (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) which provides a simple profile and an overall numeric estimate of health related quality of life.

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study was an important landmark study comparing rhythm and rate control strategies in terms of clinical outcomes. The AFFIRM sub-study of first anti-arrhythmic drug, performed in patients randomized to rhythm control, compared different antiarrhythmic drugs by randomly assigning the first drug treatment to amiodarone, sotalol or a class I drug.[27] The primary end point was the proportion of patients alive, in sinus rhythm, with no additional cardioversions and still taking the assigned drug at one year. At one year, this primary endpoint was achieved in 62% of patients treated with amiodarone, compared with 23% taking class I agents ($P < 0.001$), 60% of patients treated with amiodarone, compared with 38% taking sotalol ($P = 0.002$) and 34% of patients treated with sotalol, compared with 23% taking class I agents ($P = 0.488$). Additionally, in the AFFIRM trial, after 5 years follow-up, 35% of patients (with AF and a high risk for stroke or death) allocated to rate control strategy were in sinus rhythm (58% at 1 year) and 80% were at heart rate target. Among patients allocated to rhythm control strategy, 82% were in sinus rhythm at 1 year follow-up (decreasing to 63% at 5 years). Based on these data, the overall therapeutic success rate in the Record-AFAP study was assumed to be 50% at 1 year.

Sample size calculation has determined that data from 384 evaluable patients in each geographic unit of interest are required to be able to estimate a therapeutic success rate of 50% at 1 year with a precision of 5% for the 95% CI. Five regions of interest have been identified for this study: Australia, Korea, Taiwan, Thailand and other Asian countries (Malaysia, Hong Kong and Philippines). With a maximum expected lost to follow up rate of 25%, a total of 1,920 evaluable patients and 2,560 enrolled patients are needed.

Discussion

Available data from the global RecordAF study have already provided some insight into the management of AF. Prior to the initiation of the RecordAF study, one cardiologist from each of the 583 sites in 6 regions completed a pre-study questionnaire in order that theoretical approaches to rhythm and rate control could be investigated.[28] The results indicate some divergence from the American College of Cardiology (ACC)/ American Heart Association (AHA)/ European Society of Cardiology (ESC) guidelines for the management of AF with regard to first-line drug selection in patients with AF and associated structural heart disease (SHD), AF and congestive heart failure (CHF) or lone AF. For AF patients with SHD, in all regions amiodarone was first choice amongst rhythm control agents and β blockers were the first choice amongst rate control agents. For AF patients with CHF, in all regions amiodarone was the first choice amongst rhythm control agents. There was, however, some variation with regard to first choice amongst rate control agents; β blockers were first choice in the US, Eastern Europe and North Western Europe whereas cardiac glycosides were first choice in Asia, South Western Europe and South/Central America. Finally, for patients with lone AF, β blockers were the first choice amongst rate control agents in all regions. With regard to choice of rhythm control agents, across all regions, propafenone (30.6%), flecainide (24.1%), and amiodarone (21.7%) were the most common choices. There was again some variance by specific

region; in Asia amiodarone was the clear first choice whilst in Western Europe it was flecainide and in the US, Eastern Europe and South/Central America it was propafenone.

The recently published baseline data from RecordAF indicates that, in concert with AF treatment guidelines, rhythm-control strategies are more likely to be used in younger patients, with recently diagnosed AF or paroxysmal AF than are rate-control strategies.[23] Rhythm-control patients were more likely to be receiving β blockers and class III agents whilst β blockers and cardiac glycosides are more likely to be used in rate-control patients.

The RecordAF-AP study will enable assessment of the real-life success rate of rhythm and rate control strategies with the various medical treatments currently used in the Asia Pacific region. It will provide a specific and focused assessment of AF management in the Asia Pacific region as compared with the global perspective provided by the RecordAF study.[23] The study will characterize current management approaches for AF, including their costs and clinical outcomes, and provide insight into inherent differences in patient characteristics and population demographics across the region.

Conclusion

Study recruitment for RecordAF-AP commenced in April 2009; baseline results are expected to be available by late 2010 and the final results by the end of 2011. The results are anticipated to yield further understanding of the rationale for selecting rhythm or rate control strategies, the rationale for drug selection, titration and switch and drop-out rates. An important aspect of the study will be to document the correlation between hard clinical endpoints and success rates of therapies, as in the AFFIRM study,[29] and assess the benefits of sinus rhythm maintenance. As such, this study will facilitate rational and informed choices regarding AF treatment strategies amongst healthcare professionals in the Asia Pacific region.

Acknowledgements and Disclosures

This paper is unique, is not under consideration by any other publication and has not been published elsewhere. The authors confirm that they have permission to reproduce any copyrighted material. The RecordAF-AP registry is being funded by Sanofi-Aventis Asia Pacific. This work has been carried out with financial support from Sanofi-Aventis Asia Pacific. Editorial support was provided by Hazel Palmer (Scius Solutions Pty Ltd, Sydney) and funded by Sanofi-Aventis Australia Pty Ltd (Sydney, Australia). This manuscript has been read and approved by all authors.

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