Follow-up of atrial fibrillation:

The initial experience of the Canadian Registry of Atrial Fibrillation

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Previous reports of the follow-up of patients with atrial fibrillation have been confusing because of the variety of clinical presentations, heterogeneity of underlying pathology, and the initiation of follow-up at various stages of the patient's disease. The Canadian Registry of Atrial Fibrillation (CARAF) is a non-interventional, follow-up study of patients enrolled at the time of their initial diagnosis with atrial fibrillation at seven Canadian centres. At baseline, a comprehensive database recorded clinical, laboratory, and echocardiographic variables. No specific intervention was initiated and care was left to the attending physicians. Follow-up was performed at 3 months, 1 year, then annually. Echocardiograms were repeated every 2 years. Recurrence of atrial fibrillation, medical intervention, stroke, death, and other significant events have been specifically recorded. To date, 967 patients have been enrolled. Seven hundred and sixty-seven patients have been followed for 1 year, 468 for 2 years, and 217 for 3 years.

Several studies have been undertaken on these patients. One study compared the variables of patients who were symptomatic with those who were asymptomatic. This study demonstrated that symptoms were more likely to occur if the patient were younger, had high blood pressure and high ventricular response during atrial fibrillation, and were female. These all achieve statistical significance and a formula was developed to predict the probability of symptoms in different subgroups of patients.

Antiarrhythmic drug use was evaluated. Sotalol and propafenone were the most commonly used drugs and their use increased when atrial fibrillation was recurrent. Many patients initially received no antiarrhythmic drugs. Trends suggest that therapy is more aggressive with recurrence of the arrhythmia.

The prevalence of thyroid abnormalities was investigated utilizing sensitive TSH measurements. This showed that overt hyperthyroidism is rare (1%) but laboratory abnormalities and history of thyroid dysfunction occurred more frequently, in 19% of patients.

Another study evaluated antithrombotic therapy. Factors known to increase stroke risk, including congestive heart failure, previous stroke, and large left atrium all increased the use of anticoagulants. Anticoagulants were used more frequently in patients over the age of 65 and in patients with recurrent or chronic atrial fibrillation. There was concern that hypertension, shown to be a high predictor of stroke, did not result in a significant use of warfarin. Aspirin use was common in patients not placed on anticoagulants.

Further studies are being undertaken with the ultimate goal to utilize baseline data to predict clinical outcomes.

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Key Words: Atrial fibrillation, thyroid function, antiarrrhythmic drugs.

Introduction

Atrial fibrillation is the commonest sustained arrhythmia, the prevalence of which increases progressively with age[1]. In addition to frequent disabling symptoms, studies have demonstrated significant, morbidity and mortality[2-3].

Valid data on the follow-up of atrial fibrillation from the time of initial diagnosis are lacking. Many follow-up studies are hampered by entry of patients at various times during their disease process, inconsistent baseline data collection, and sporadic patient follow-up[4,5].

The Canadian Registry of Atrial Fibrillation is a multicentre registry of patients presenting at their first diagnosis of electrocardiographically documented atrial fibrillation. This registry provides a unique opportunity for gaining insight into characteristics at the time of
initial presentation as well as into predictors of long-term outcome.

**Methods**

CARAF enrols patients at the time of initial diagnosis of atrial fibrillation, the diagnosis of which is confirmed by electrocardiogram. It is a follow-up study that does not predicate any specific intervention. Enrolment occurs at seven Canadian centres in six cities.

Patients are recruited from offices of family practitioners and specialists, emergency rooms, cardiology laboratories, and during hospitalization for other disorders. Extensive baseline data are collected by a research nurse. A comprehensive history is recorded and basic laboratory tests are performed, including measurements of thyroid function (sensitive thyroid stimulating hormone (TSH) and serum T4 (T4) level). Echocardiograms are performed to assess atrial and ventricular dimension and function, presence of hypertrophy, and presence of valvular disease.

Patients are followed at 3 months, 1 year, and then annually with echocardiograms being obtained every 2 years. To date, 967 patients have been enrolled and 923 have been followed for 3 months, 767 for 1 year, 468 for 2 years, 217 for 3 years, and 17 for 4 years. All data and laboratory tests are performed locally. The data are encoded and registered in the central database at the University of British Columbia in Vancouver.

**Goals of CARAF**

The long-term goals of CARAF will be to enrol 3000–5000 patients and provide 20 000 to 30 000 patient years of follow-up. During this follow-up, baseline data will be utilized to provide predictors for various outcomes including: recurrent atrial fibrillation, progression to chronic atrial fibrillation, occurrence of thromboembolic events and stroke, and mortality. Changes in atrial and ventricular function will be evaluated.

Patterns of practice will be monitored including the use of antiarrhythmic drugs, use of antithrombotic agents, and utilization of methodology to control rate response. A specific subgroup will evaluate the follow-up of patients developing atrial fibrillation following open heart surgery and establish the predictors for recurrence of arrhythmia in this patient population.

**Summary of projects completed or in progress**

The following are summaries of projects that have either been completed or reached a point where initial data can be provided.

1. **Anti-arrhythmic drug use**

   The use of antiarrhythmic drugs was evaluated in patients who had not undergone open heart surgery. They were divided into patients considered chronic after the first 3 months and those who were considered paroxysmal. The classification of paroxysmal required the documentation of sinus rhythm following the initial ECG recording of atrial fibrillation.

   - **(a) Chronic atrial fibrillation**
     
     A total of 139 patients were considered to have chronic atrial fibrillation and the use of atioventricular nodal blocking drugs and other antiarrhythmic drugs were evaluated.

     The use of drugs is shown in Table 1. Nearly 70% were taking digoxin whereas 19% were utilizing a beta-blocker and 18% a calcium channel blocker. Thirty-five percent were on another antiarrhythmic drug, most of which had been started prior to the chronicity of the arrhythmia and which may have contributed to rate control, (for instance propafenone, sotalol, or amiodarone). Fifteen percent were on no antiarrhythmic drug and 56% were on a combination of medications, the vast majority on digoxin plus another agent.

     The adequacy of rate control was unknown in this population.

   - **(b) Antiarrhythmic drug use in patients with paroxysmal atrial fibrillation**
     
     Four hundred and thirty-eight patients had paroxysmal atrial fibrillation. Their drug use was evaluated at 1 year. A subgroup of 194 patients with documented recurrent atrial fibrillation was evaluated. The drug use in these patient populations is shown in Table 2. In the total population, 56% of patients received no antiarrhythmic drugs, probably because for the majority this was their first episode of atrial fibrillation. Sotalol (25%) and propafenone (12%) were the most commonly used antiarrhythmic drugs. In the subgroup with recurrent atrial fibrillation, not surprisingly, the number of patients with no antiarrhythmic drug fell to 45%, whereas the use of other antiarrhythmic drugs rose, with sotalol increasing to 33-5% and propafenone to 17-5%.

     The number of patients on more than one antiarrhythmic drug increased from 6-3% to 12-4%

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**Table 1** AV nodal blocking drugs in patients with chronic atrial fibrillation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percentage of patients</th>
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<tbody>
<tr>
<td>Beta-blockers</td>
<td>19-4%</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>11-5%</td>
</tr>
<tr>
<td>Verapamil</td>
<td>6-4%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>69-1%</td>
</tr>
<tr>
<td>Other agents</td>
<td>35-1%</td>
</tr>
<tr>
<td>No drug</td>
<td>15-2%</td>
</tr>
<tr>
<td>1+ Drugs</td>
<td>56-3%</td>
</tr>
</tbody>
</table>
in the patients with recurrent atrial fibrillation. Amiodarone was used in only 3% of both groups.

(2) Thyroid function in patients presenting with atrial fibrillation

Thyroid function was evaluated in all patients by sensitive TSH and T4 measurements. The significance of laboratory tests was considered as follows. If the TSH was <0.1 mU L⁻¹ patients were considered hyperthyroid. For patients in whom the TSH was >0.1 mU L⁻¹ but less than laboratory normals, the tests were considered non-diagnostic and the T4 was utilized to determine if the patient was hyperthyroid. Endocrinology consultation was obtained if the diagnosis was unclear.

In 19 of 287 patients at the time of initial evaluation, the TSH was < laboratory normals, but in only two of these patients, who were considered clinically hyperthyroid, was the TSH <0.1 mU L⁻¹. A further patient had a high T4 and was felt to be clinically hyperthyroid. In the other 16, the T4 values were normal and they were deemed clinically euthyroid. Thus, only three patients had definite hyperthyroidism.

TSH was > laboratory normal in 32 patients, and T4 levels were low in two patients who were considered hypothyroid. Of the other patients, previous hypothyroidism had occurred in five and all were taking thyroid replacement. Others had mild elevation in TSH and were considered clinically euthyroid. Another six patients had previous thyroid disease but had normal laboratory values. Three of these had been hypothyroid and were taking thyroxine, whereas three were hypothyroid and had been treated. Therefore, abnormal thyroid function or a history of thyroid disease is common in patients with atrial fibrillation, occurring in 57 of 287 patients (19%). In the majority of patients, these abnormalities were not felt to be the cause of atrial fibrillation. Overt hyperthyroidism is a rare cause of atrial fibrillation, occurring in three of 287 patients (1%).

(3) Patterns of anticoagulant use

The study permitted evaluation of the patterns of anticoagulant use in the context of the results of multiple clinical trials of anticoagulant use.

Three hundred and twenty-seven patients were evaluated at 3 months, 22% of whom were taking warfarin only, 54% aspirin only, and 4% both agents; 19% were on no therapy. At 12 months the number of patients taking warfarin did not change substantially.

The use of anticoagulants was evaluated on the basis of six clinical and echocardiographic variables demonstrated to increase the likelihood of embolic events: congestive heart failure; previous transient ischaemic episode or stroke; hypertension; left atrial dimension ≥47 mm; documented recurrent atrial fibrillation (either chronic or paroxysmal); age ≥65 years. Univariate analysis of warfarin use based on these predictors is shown in Table 3. All of these factors except hypertension led to an increased use of warfarin compared to the population as a whole. As the number of predictors increases, the percentage of patients receiving warfarin progressively increased. Therefore, there appears to be an appropriate recognition of the risk factors for stroke and an increasing use of warfarin in this patient population. The exception to this is hypertension which, although repeatedly shown to be an increased risk factor for embolic events, did not result in an increased use of warfarin.

(4) Predictors of symptoms in patients with atrial fibrillation

Of 674 patients presenting with atrial fibrillation 532 were symptomatic at the time of diagnosis and 142 were asymptomatic. Symptoms included palpitations, chest pain, fatigue, lightheadedness or syncope, dyspnoea, anxiety, and nausea.

A large number of variables were evaluated to assess their ability to predict symptoms and five were found to be statistically significant. Symptoms were more likely to occur at a younger age and in women. Symptoms were more likely to occur with progressively

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**Table 2 Antiarrhythmic drug use in patients with paroxysmal atrial fibrillation (AF)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>All patients (438 patients)</th>
<th>Patients with recurrent AF (194 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>3.2%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>0.9%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Flecainide</td>
<td>0.7%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Procanamide</td>
<td>1.6%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Propafenone</td>
<td>12.3%</td>
<td>17.3%</td>
</tr>
<tr>
<td>Sotalol</td>
<td>25.1%</td>
<td>33.3%</td>
</tr>
<tr>
<td>Quinidine</td>
<td>6.6%</td>
<td>9.3%</td>
</tr>
<tr>
<td>No AA drug</td>
<td>55.9%</td>
<td>45.4%</td>
</tr>
<tr>
<td>1+ AA drugs</td>
<td>6.3%</td>
<td>12.4%</td>
</tr>
</tbody>
</table>

**Table 3 Univariate predictors of warfarin use**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>n</th>
<th>Warfarin use (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>54</td>
<td>26 (48)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>27</td>
<td>15 (56)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LA &gt; 47 mm</td>
<td>66</td>
<td>32 (48)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Age ≥ 65</td>
<td>68</td>
<td>59 (35)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HTN</td>
<td>122</td>
<td>39 (32)</td>
<td>ns</td>
</tr>
<tr>
<td>Rec/Chronic AF</td>
<td>96</td>
<td>49 (51)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total</td>
<td>327</td>
<td>87 (27)</td>
<td></td>
</tr>
</tbody>
</table>

CHF = congestive heart failure; TIA = transient ischaemic attack; LA = left atrium; HTN = hypertension; Rec = recurrent; AF = atrial fibrillation.
increasing blood pressure and heart rate and in patients with no previous history of myocardial infarction. A complex logarithmic equation was developed that could predict the presence of symptoms. Each symptom was evaluated and individual predictors of each symptom were evaluated. Thus, a profile of patients who may develop symptoms can be derived.

**Discussion**

The Canadian Registry of Atrial Fibrillation provides a valuable tool for assessing the clinical status of patients at the time of their initial presentation of atrial fibrillation and is beginning to provide data on the follow-up of patients. Furthermore, there is considerable data being collected evaluating the patterns of practise and comparing those patterns to the results of clinical trials.

To date, the registry has demonstrated that antiarrhythmic drug use in Canada favours the use of sotalol and propafenone, a considerable change in the pattern antiarrhythmic drug use over the last decade. This pattern reflects recent clinical studies in which these agents show equal efficacy to, but fewer adverse effects than, other type Ia drugs. Amiodarone is used rarely, compared to its frequent use in other countries.

This study has demonstrated that overt hyperthyroidism is a rare cause of atrial fibrillation, and was a probable cause in approximately 1% of patients, when evaluated at the time of their initial presentation. Previous studies have shown markedly divergent estimates of incidence of hyperthyroidism, but were hampered by different drug tests, different patient populations, and assessment at various stages of their disease process.

Anticoagulant use in a relatively informed physician population appears to follow the pattern suggested by the large, multicentre clinical trials. The one exception is the use of warfarin in patients with hypertension. This underscores the need to consider hypertension as a risk factor for the development of embolic events and the potential use of warfarin in patients whose hypertension is adequately controlled.

The presence and variety of symptoms during atrial fibrillation is fascinating but the causes of these symptoms have been enigmatic. A detailed study has been completed regarding the predictor of symptoms. This has been submitted for publication and details the various clinical variables that may predict a variety of symptoms that may occur during atrial fibrillation.

Ultimately, the long-term follow-up with additional patients will permit the study of the predictors of clinical outcomes in patients at the time of their initial presentation with atrial fibrillation.

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**References**