EARLY: a pilot study on early diagnosis of atrial fibrillation in a primary healthcare centre

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Received 21 February 2015; accepted after revision 27 April 2015; online publish-ahead-of-print 12 June 2015

Aim
Atrial fibrillation (AF) is associated with high morbidity and mortality. Early diagnosis is likely to improve therapy and prognosis. The study objective was to evaluate the usefulness of a programme for early diagnosis of AF in patients from an urban primary care centre.

Methods and results
Participants were recruited from a randomized sample of patients not diagnosed with AF but having relevant risk factors: age ≥ 65 years, ischaemic and/or valvular heart disease, congestive heart failure, hypertension, and/or diabetes. Patients were randomly assigned to the intervention group (IG) or control group (CG). The intervention included (i) initial visit with clinical history, electrocardiogram, and instruction about pulse palpation and warning signs and (ii) electrocardiogram every 6 months during a 2-year follow-up. The main endpoint of the study was the proportion of new cases diagnosed at 6 months. Secondary endpoints were number of new AF diagnoses and complications associated with the arrhythmia in both groups. A total of 928 patients were included (463 IG and 465 CG). At 6 months, AF was diagnosed in 8 IG patients and 1 CG patient (1.7 vs. 0.2%, respectively, $P = 0.018$). After 2 years of follow-up, 11 IG patients and 6 CG patients had newly diagnosed AF (2.5 vs. 1.3%, respectively, $P = 0.132$). Time to first diagnosis of AF was shorter in IG patients [median (inter-quartile range): 7 (192) days vs. 227 (188.5) days in CG, $P = 0.029$].

Conclusion
The simple screening proposed could be useful for the early detection of AF in primary care.

Keywords
Atrial fibrillation • Early diagnosis • Primary health care

Introduction
Atrial fibrillation (AF) is the most frequent arrhythmia observed in clinical practice, involving 1 to 3% of the population, and its prevalence is growing.1 Both the prevalence and the incidence increase markedly with age.2–4 In addition to advanced age, other factors or diseases that predispose patients to the development of AF have been described. The most frequent co-morbidities associated with AF are hypertension, diabetes, congestive heart failure, ischaemic heart disease, and valvular heart disease.1,2,5–7 Male gender is also a risk factor for developing AF, although the global prevalence is equivalent in both genders due to greater longevity in women.1,2

The clinical presentation of AF varies greatly with regard to both the type and severity of symptoms. These are often related to tachycardia (palpitations, dyspnoea, fatigue, chest pain, and dizziness) and can be related to complications of AF, such as heart failure8 and arterial embolism,2,9 which are the main causes of AF-associated mortality.8 However, symptoms may be non-specific or even absent. As a result, the diagnosis is often delayed until advanced phases of the arrhythmia.10

The morbidity associated with AF may be prevented or effectively controlled with early and adequate treatment of the arrhythmia.11–13 In addition, the earlier a therapeutic action is taken, the greater the probability of reversing the arrhythmia and recovering sinus rhythm, as the arrhythmia itself favours electrical and structural changes in the atrium (atrial remodelling) that perpetuate AF.9,14

The high prevalence of this arrhythmia, the frequent lack of symptoms even in the population at greatest risk, and the importance of early detection to improving patient prognosis suggest the need to establish a screening method for early AF detection. The aim of this study, Early diagnosis of Atrial fibrillation: a Randomized trial in Primary care (EARLY), was to evaluate a screening strategy for early AF diagnosis in an urban primary care centre.
Methods

Study type and population

We performed a randomized, controlled clinical study based on a reference population (30,451 inhabitants) of a primary healthcare centre in an urban area served by a tertiary hospital. Basic demographic and medical data were electronically available in all cases. From the electronic health records for this population, we preselected all patients without a diagnosis of AF but with one or more of the main risk factors for AF: age ≥ 65 years, arterial hypertension, ischaemic heart disease, valvular heart disease, diabetes, and/or congestive heart failure (7498 patients).

A simple random sample of 4000 candidates was preselected from the reference population. Patients were then randomized, with a 1:1 allocation ratio, and consecutively assigned to either the intervention group (IG) or the control group (CG), until the required sample was achieved. The sample size calculation was based on previous data, assuming that the intervention protocol would increase the diagnosis of AF by 2% per year compared with controls (4 vs. 2% per year) and accounting for up to a 5% loss to follow-up. With 458 patients per group (918 total) followed for 2 years, the study had 80% statistical power in a standard design with a standard level of significance set at \( P = 0.05 \). The identification of all risk factors was based on the medical history recorded by each patient’s physician, with some added conditions required for inclusion: (i) patients with a diagnosis of arterial hypertension or diabetes were included only if they received the corresponding treatment, (ii) valvular heart disease diagnosis had to be confirmed by an echocardiogram, (iii) ischaemic heart disease diagnosis had to be confirmed by an electrocardiogram, stress test, catheterization, or computed tomography angiogram, and (iv) heart failure diagnosis had to be confirmed by chronic treatment, an echocardiogram or an acute episode that required emergency care and/or hospital admission.

Patients unable to come to the healthcare centre to participate in the study were excluded. Patients who had a pacemaker, could not be contacted by telephone, or declined to participate in the study were also excluded. Inclusion and exclusion criteria for each patient were confirmed by two independent investigators who reviewed individual medical records no more than 7 days prior to study inclusion. The inclusion date was considered time 0.

All participants were treated according to the criteria of their general practitioners, who were blinded to the IG or CG randomization. The study was approved by the Research Ethics Committee of Hospital Clinic, Barcelona (2006/3441).

Intervention

Patients in the intervention group were invited by telephone call to participate in the study. If a patient did not answer, the call was repeated up to three different times and/or days.

A 2-year programme for early detection of AF was carried out in the IG, with an office visit every 6 months that involved an electrocardiogram (ECG), physical examination, and a complete medical history including anamnesis related to symptoms indicating the possible presence of AF (palpitations, chest pain, dyspnoea, fatigue, and dizziness). Chronic medication (at least 3 months) was also recorded. On the first visit, a nurse instructed the participants on warning signs, taught them to take their own pulse in a resting position, and requested they do so once a month. If the patient observed an arrhythmic pulse or other warning signs, the instruction was to visit the healthcare centre as soon as possible. If outside of working hours, the patient was instructed to go to the nearest medical centre or, if the symptoms were incapacitating, to call the emergency medical services. In a pilot proof, the median time invested by the nurse was 11 min for the first visit and 6 min for each subsequent visit.

No specific action was taken in the CG. The clinical history was reviewed using the electronic medical records system at the end of the study period (2 years after inclusion); patients were contacted by telephone as needed to obtain complete information.

Recording data

The primary endpoint was the proportion of patients with newly diagnosed AF at 6 months. Secondary endpoints were the following: (i) number of patients diagnosed with AF during the 2-year follow-up; (ii) complications related to AF (heart failure, stroke or systemic embolism, symptomatic bradycardia requiring pacemaker, and severe haemodynamic angina) or to its treatment (malignant arrhythmia or symptomatic bradycardia requiring pacemaker in patients on antiarrhythmic treatment, bleeding in patients on anticoagulant therapy); (iii) origin of the initial AF diagnosis (early detection programme, family physician, cardiology consultation, emergency department, and hospital admission); and (iv) means of AF diagnosis (early detection programme, casual diagnosis during consultation for any other reason, or presence of AF-related complications).

Statistical methods

To address the study aim, the survival function for the main outcome variable (proportion of patients with newly diagnosed AF at 6 months) was analysed using the Kaplan–Meier method, and study groups were compared with the log-rank test. A truncated analysis was performed at 6, 12, and 18 months and at the end of the 2-year follow-up.

The IG and CG were compared using the Student t-test for continuous variables if applicable, and otherwise with the Mann–Whitney test. Chi-square or Fisher exact test was applied for the remaining binary variables as appropriate.

The level of significance for a two-tailed test was established at 5%. Simple random sampling and randomization was done using SAS version 9.1.3 (SAS Institute Inc., Cary, NC, USA) and analysis with SPSS version 18.0 (SPSS, Inc., 2009, Chicago, IL, USA).

Results

The recruitment period was from January 2008 to October 2010. The intention-to-treat population set consisted of 463 patients in the IG arm and 465 in the CG arm (Figure 1).

In the IG arm, 626 (31.3%) patients did not answer the calls, 425 (21.2%) did not consent to participate, 78 (3.9%) were no longer assigned to the health centre (address change), and 3 (0.15%) had died before the study began. A further 234 patients (11.7%) met clinical exclusion criteria: 46 had known AF, 15 had no AF risk factors, 30 had a pacemaker, and 62 had a disability that prevented them from coming to the health centre.

In the CG arm, 42 (2.1%) patients were no longer assigned to the health centre, 6 (0.3%) had died before the study began, and 38 (1.9%) patients met clinical exclusion criteria: 3 had known AF, 11 had no AF diagnoses.
risk factors, 10 had a pacemaker, and 14 had a disability that precluded visiting the centre.

Mean age (standard deviation, SD) was 69 (10) years, and 469 patients (50.3%) were women. Mean (SD) follow-up was 670.7 (149.9) days. The types and number of risk factors were similar in both groups (Table 1).

At 6 months, more patients in the IG were diagnosed with AF (8 IG patients vs. 1 CG patient; respective cumulative proportion, 1.7 vs. 0.2%, \( P = 0.018 \)) (Figure 2); at 2 years, 17 patients had been diagnosed (11 IG and 6 CG, 2.5 vs. 1.3%, \( P = 0.132 \) (Figure 2)). Time to diagnosis was shorter in the IG [median (inter-quartile range): 7.0 (192) vs. 277.0 (188.25) days in CG, \( P = 0.029 \); Figure 3].

In both groups, a higher proportion of patients with more than two risk factors was diagnosed with AF, compared with patients with two risk factors or less (\( P < 0.001 \)). Comparing the two groups, no single risk factor or combination of risk factors was associated with greater AF detection in the IG at 2-year follow-up. The only difference between the study groups in the cumulative proportion of AF detection was observed in men: 4.0% in the IG vs. 1.3% in the CG (\( P = 0.041 \)).

In the IG, 179 patients (38.7%) had symptoms that could be attributable to AF, the most frequent being palpitations (104 patients, 22.4%). No association was found between previous symptoms attributable to AF and the AF diagnosis. In the IG, only one (1.3%) of
the 78 patients taking beta-blockers developed the arrhythmia, compared with 2.6% of those taking angiotensin-converting enzyme inhibitors and 3% of those taking statins. No association between chronic medication and AF diagnosis was found.

The characteristics of patients diagnosed with AF were similar between the study groups (Table 2). Of the 11 IG patients with AF, 10 (91%) were diagnosed by the early AF detection programme (5 were asymptomatic, 3 consulted the programme’s nurse because of AF-related symptoms, and 2 patients consulted a family physician because of symptoms and irregular pulse palpation, respectively). One IG patient was diagnosed with AF because of a hospital emergency room visit for urinary sepsis. In the CG, one patient was
diagnosed by a private cardiologist when consulting for chest pain, four patients were diagnosed incidentally in the hospital, and another in the emergency room due to a complication of AF (heart failure).

At the end of follow-up, no other patient had developed complications associated with the diagnosis of AF. All IG patients but one (with a CHA2DS2-VASc score of 0) were started on anticoagulation therapy, as were two patients in the CG. Two patients had developed mild complications related to treatment: one IG patient had cutaneous haematomas related to anticoagulation, and one CG patient developed bradycardia associated with amiodarone.

Seven IG patients (1.5%) and 8 CG patients (1.7%) died during the study period. In total, 54 patients (5.8%) were lost to follow-up, 45 in the IG and 9 in the CG (Table 3).

Discussion

In the present pilot study, a low-cost early detection programme applied to patients at risk of developing AF led to earlier diagnosis of the arrhythmia, compared with a control group that received no intervention. These results were obtained in an actual patient population using a simple, non-invasive programme applicable to the daily reality of the primary care practice. Full implementation of the programme would suppose an absolute increase in diagnosed patients of 1.7% at 6 months; i.e. of 60 patients included, one patient would benefit from early AF diagnosis and a likely sparing of future events derived from early diagnosis and appropriate management. However, our study was not powered or designed to translate this finding into cost–benefit estimation. As a gross estimation limited to stroke as a complication of untreated AF (raising the annual stroke risk from 1 to 5%), and taking into account the results at 6 months, a programme like our pilot would need to include 1471 patients to avoid one stroke in the following year, at a cost of 11 128€, derived from the nursing time associated with the detection programme. By comparison, the cost of a first stroke is estimated as US$30 865 at 2 years and US$130 576 lifetime (28 502€ and 120 580€, respectively).

Despite more AF diagnoses in the IG after 2 years, compared with controls, the difference was less than that observed early in the study. This was an expected result, because the probability of any patient having consulted a doctor because of symptoms or any other reason increases over time.

Few studies have demonstrated the usefulness of primary early detection in patients who have risk factors for developing AF but have not yet presented with symptoms or complications. The detection methods used in these studies were pulse palpation and/or ECG. The intervention used in our study was unique, because it also trained patients to take their own pulse, recognize warning signs, and know what to do should they appear. This training can be easily implemented during normal clinical practice by the family physician or, in most cases in the present study, by a nurse, given that nurses have an increasingly recognized role in improving treatment and prognosis of cardiovascular diseases, and early detection of AF.

Our study also differs from previous studies in the prospective follow-up of IG patients; together with the training, this directly led to half of the AF diagnoses made. As anticipated, a higher number of IG compared with CG patients had received AF diagnoses after 6 months; however, AF incidence in both groups was much lower than in previous studies, likely because many of the patients had only one risk factor, and having more than two risk factors was associated with greater detection of AF in both study groups. Few studies directed towards early diagnosis of AF have specifically included patients with risk factors other than age, and none of them were prospective and randomized. The present study design more accurately reflects the population of patients with AF because, in our work and other studies, most patients diagnosed with AF has at least one of these ‘other’ risk factors. The design of our study did not take male gender into account as a risk factor, because the greater longevity of women results in a similar global prevalence of AF. However, in view of the results obtained, this factor should probably be considered in attempting early detection of arrhythmias.

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**Table 2** Clinical characteristics of patients with atrial fibrillation

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Intervention group (n = 11)</th>
<th>Control group (n = 6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (females)</td>
<td>2 (18.2)</td>
<td>3 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Age ≥ 65</td>
<td>10 (90.1%)</td>
<td>6 (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (63.6%)</td>
<td>3 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>4 (36.4%)</td>
<td>3 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>4 (36.4%)</td>
<td>1 (16.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>1 (9.1%)</td>
<td>1 (16.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (9.1%)</td>
<td>1 (16.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (9.1%)</td>
<td>2 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4 (36.4%)</td>
<td>1 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 (54.5%)</td>
<td>2 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0 (0%)</td>
<td>1 (16.7%)</td>
<td></td>
</tr>
</tbody>
</table>

NS, non-significant.

**Table 3** Losses to follow-up

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention group</td>
<td>45 (9.7)</td>
</tr>
<tr>
<td>Not located/did not attend visits</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td>Work</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Mobility problems (physical or social limitation)</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td>Do not see the need</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td>Dependent (requiring home care)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Residence outside area/change in residence</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td>Hospital admission/incapacitating disease</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
</tr>
<tr>
<td>Residence outside area/change in residence</td>
<td>9 (1.9)</td>
</tr>
</tbody>
</table>
A limitation of the study was the possibility that patients with paroxysmal AF may not have been detected with this programme if the episode was of short duration; we attempted to reduce this limitation by training IG participants to take their pulse and advising them to go to the nearest health centre as soon as possible in case of palpitations or arrhythmic pulse. Another limitation was the unexpectedly high number of post-randomization losses, which could diminish the value of the randomization carried out at an early phase of the study. Finally, although the overall losses to follow-up came close to the expected rate, losses were greater in the IG than in the CG. The difference between groups is easy to understand, as patients in the CG had no study-specific visits to the health centre and were only lost if they had a change in residence. The difficulty of IG participant retention, also observed in other studies, could diminish or even disappear if the study were done by the patient’s usual nurse and/or doctor rather than an external investigator.

In conclusion, the EARLY study demonstrated a simple and useful method for the primary early detection of AF in primary care that decreased the time to diagnosis of AF by 7.1 months.

Acknowledgements
We thank Elaine Lilly, PhD, for careful English language revision of the manuscript.

Conflict of interest: none declared.

Funding
This study was supported by a grant from the FIS (Fondo de Investigación Sanitaria). Record PI07/0278.

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