ORIGINAL ARTICLE

Outpatient Treatment of Recent-Onset Atrial Fibrillation with the "Pill-in-the-Pocket" Approach

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ABSTRACT

BACKGROUND

In-hospital administration of flecainide and propafenone in a single oral loading dose has been shown to be effective and superior to placebo in terminating atrial fibrillation. We evaluated the feasibility and the safety of self-administered oral loading of flecainide and propafenone in terminating atrial fibrillation of recent onset outside the hospital.

METHODS

We administered either flecainide or propafenone orally to restore sinus rhythm in 268 patients with mild heart disease or none who came to the emergency room with atrial fibrillation of recent onset that was hemodynamically well tolerated. Of these patients, 58 (22 percent) were excluded from the study because of treatment failure or side effects. Out-of-hospital self-administration of flecainide or propafenone — the "pill-in-the-pocket" approach — after the onset of heart palpitations was evaluated in the remaining 210 patients (mean age [±SD], 59±11 years).

RESULTS

During a mean follow-up of 15±5 months, 165 patients (79 percent) had a total of 618 episodes of arrhythmia; of those episodes, 569 (92 percent) were treated 36±93 minutes after the onset of symptoms. Treatment was successful in 534 episodes (94 percent); the time to resolution of symptoms was 113±84 minutes. Among the 165 patients with recurrences, the drug was effective during all the arrhythmic episodes in 139 patients (84 percent). Adverse effects were reported during one or more arrhythmic episodes by 12 patients (7 percent), including atrial flutter at a rapid ventricular rate in 1 patient and noncardiac side effects in 11 patients. The numbers of monthly visits to the emergency room and hospitalizations were significantly lower during follow-up than during the year before the target episode ($P<0.001$ for both comparisons).

CONCLUSIONS

In a selected, risk-stratified population of patients with recurrent atrial fibrillation, pill-in-the-pocket treatment is feasible and safe, with a high rate of compliance by patients, a low rate of adverse events, and a marked reduction in emergency room visits and hospital admissions.

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In patients with recurrent atrial fibrillation, long-term oral prophylaxis with antiarrhythmic drugs has long been used to prevent recurrences. However, both the need for daily administration of antiarrhythmic agents and the risk of adverse effects are recognized as disadvantages of long-term prophylaxis.[1-5] In addition, relapses are frequent. During the past few years, radiofrequency catheter ablation of pulmonary veins has been introduced into clinical practice.[6] However, in all studies, the procedure has been used only in patients who have frequent arrhythmic episodes despite long-term oral prophylaxis.[7] Some patients with recurrent atrial fibrillation may present with episodes that are not frequent and are well tolerated but that are long enough in duration that they require either emergency room intervention or hospitalization.

Oral prophylaxis or catheter ablation may not be the most appropriate first-line treatment for such patients. An alternative treatment is the "pill-in-the-pocket" approach, in which the patient takes a single oral dose of an antiarrhythmic drug at the time of the onset of palpitations. This type of treatment has already been investigated in studies carried out in hospitalized patients with atrial fibrillation of recent onset. The oral drugs that have been used to convert atrial fibrillation of recent onset to sinus rhythm are class IA, class IC, and class III antiarrhythmic agents.[8-22] The class IC agents flecainide and propafenone have the advantage of acting rapidly, and their efficacy in converting atrial fibrillation of recent onset to sinus rhythm has been documented in several placebo-controlled trials.[8,13,15,16,18,20,22,23] The two drugs had similar efficacy in the studies, and the success rates ranged from 58 to 95 percent.[8-13,15-20,23] In all controlled studies, a low incidence of adverse effects has been reported.[8-13,15-20,22,23] The most serious side effect appears to be a transient atrial flutter with a rapid ventricular rate owing to an atrioventricular conduction ratio of 1:1 (in about 1 percent of patients).

We conducted a study to assess the feasibility and safety of treatment with either flecainide or propafenone administered as a single oral dose outside the hospital to terminate atrial fibrillation of recent onset in patients without severe heart disease who have infrequent, well-tolerated arrhythmic episodes. The primary end points were the rate of success with this treatment and the rate of adverse events. The secondary end points were the rates of emergency room visits and hospital admissions as compared with those in the year preceding enrollment in the study.

METHODS

STUDY POPULATION

The inclusion criteria were an age of 18 to 75 years, emergency room intervention for an episode of electrocardiographically documented atrial fibrillation of recent onset (<48 hours earlier), a mean heart rate of more than 70 beats per minute, and a systolic pressure of 100 mm Hg or more. Additional criteria for inclusion in the study were a history of palpitations with an abrupt onset that were hemodynamically well tolerated (i.e., without symptoms such as dyspnea, presyncope, or syncope), at least 1 but fewer than 12 episodes of atrial fibrillation (excluding the target episode) in the previous year, and no cardiac symptoms apart from the episodes of arrhythmia.

Patients were excluded if they had one or more of the following findings: electrocardiographic evidence of ventricular pre-excitation or bundle-branch block (QRS interval, >120 msec), a previous episode of atrial fibrillation lasting seven days or more, ischemic heart disease, dilated or hypertrophic cardiomyopathy, a history of heart failure, severe valvular heart disease, chronic cor pulmonale, left ventricular dysfunction (ejection fraction, <50 percent), a long QT interval or the Brugada syndrome, the bradycardia–tachycardia syndrome (resting heart rate, ≤50 beats per minute, or repetitive sinoatrial blocks during waking hours), documentation of previous episodes of second- or third-degree atrioventricular block, previous thromboembolic episodes, acute disease, very severe chronic diseases (e.g., muscular dystrophies or systemic collagen diseases), renal or hepatic insufficiency, previous hypokalemia (potassium level, <3 mmol per liter), suspected or known pregnancy, a known intolerance of flecainide or current propafenone, or current prophylactic antiarrhythmic treatment.

We obtained a medical history for all patients and performed a physical examination, electrocardiography, routine biochemical laboratory tests (including an assay of thyroid hormones), and two-dimensional echocardiography. Other investigations, such as exercise stress testing, were performed when clinically indicated. Patients were recruited from

September 1, 2001, to February 28, 2003; follow-up was terminated September 30, 2003.

The study was approved by the local ethics committee, and written informed consent was obtained from all participants. A committee monitored the progress of the study. At two of the study sites (Como and Taranto), all the patients requiring emergency room intervention for atrial fibrillation of recent onset were monitored in order to determine the percentage of patients who were considered candidates for out-of-hospital treatment.

IN-HOSPITAL ANTIARRHYTHMIC TREATMENT

The patients were treated either in the emergency room or in the cardiology ward. Each hospital used its own criteria for admission, which were the same during the study period as they were in the year preceding enrollment. The researchers at each center used the drug (either flecainide or propafenone) with which they were more familiar.

For conversion of atrial fibrillation to sinus rhythm, oral flecainide or propafenone was administered in a single dose according to the weight of the patient. The dose of flecainide was 300 mg if the patient weighed 70 kg or more and was 200 mg otherwise; the dose of propafenone was 600 mg if the patient weighed 70 kg or more and was 450 mg otherwise. After administration of the drug, heart rhythm was monitored for at least 8 hours, blood pressure was measured every 30 minutes with the use of a cuff, and a 12-lead electrocardiogram was recorded every hour. The treatment was considered successful if the interval between administration of the drug and conversion to sinus rhythm was six hours or less and there were no observable side effects, such as symptomatic hypotension (systolic blood pressure, ≤80 mm Hg), symptomatic bradycardia after restoration of sinus rhythm, dyspnea, presyncope, syncope, conversion to atrial flutter or atrial tachycardia, or episodes of sustained or unsustained ventricular tachycardia.

OUT-OF-HOSPITAL EPISODIC TREATMENT

Patients were recruited for in-hospital treatment if all the inclusion criteria were fulfilled and no exclusion criteria were documented after the medical history had been obtained and physical examination and electrocardiographic studies performed. Patients were selected for out-of-hospital treatment from among those who were treated successfully in the hospital and were not excluded during subsequent examination.

Before discharge, all patients who had been treated successfully in the hospital were instructed to take the drug five minutes after any subsequent onset of palpitations. After the ingestion of the drug, a resting state (in a supine or sitting position) was recommended until the palpitations had stopped or at least four hours had passed. Patients were also given a form and asked to record the number of arrhythmic episodes they had; the exact times of onset of palpitations, drug ingestion, and termination of symptoms; and any adverse effects.

Patients were advised to contact the emergency room if their palpitations had not ceased six to eight hours after the ingestion of the drug, if they had symptoms that had not occurred during previous arrhythmic episodes (e.g., dyspnea, presyncope, or syncope), or if they felt a marked increase in heart rate after ingestion of the drug. Finally, patients were advised not to take more than one oral dose during a 24-hour period. After discharge, patients were seen in the outpatient clinic every four months.

STATISTICAL ANALYSIS

All the investigators had full access to the data and performed the data analysis. Data are expressed as means ±SD. Continuous variables were compared by using Student's t-test for independent samples. A two-tailed chi-square test was used to determine the statistical significance of associations in two-by-two tables. The efficacy of the oral drug was provided as a crude estimate. However, because calculation of drug efficacy may be biased if individual patients have multiple treated episodes, an adjusted estimate of efficacy was obtained by using the generalized estimating equation with an exchangeable correlation structure.[24] This method controls for multiple responses from one patient by assuming a common correlation between any two responses. A P value of less than 0.05 by two-sided test was considered to indicate statistical significance.

RESULTS

IN-HOSPITAL TREATMENT

A total of 268 consecutive patients with atrial fibrillation of recent onset received an in-hospital oral dose of flecainide (mean dose, 263±54 mg) or propafenone (mean dose, 555±81 mg). Of those patients, 138 were treated in the emergency room and 130 in the cardiology ward. Of the 268 patients who were treated, 58 were not given out-of-hospital treatment for the following reasons (Fig. 1): ex-

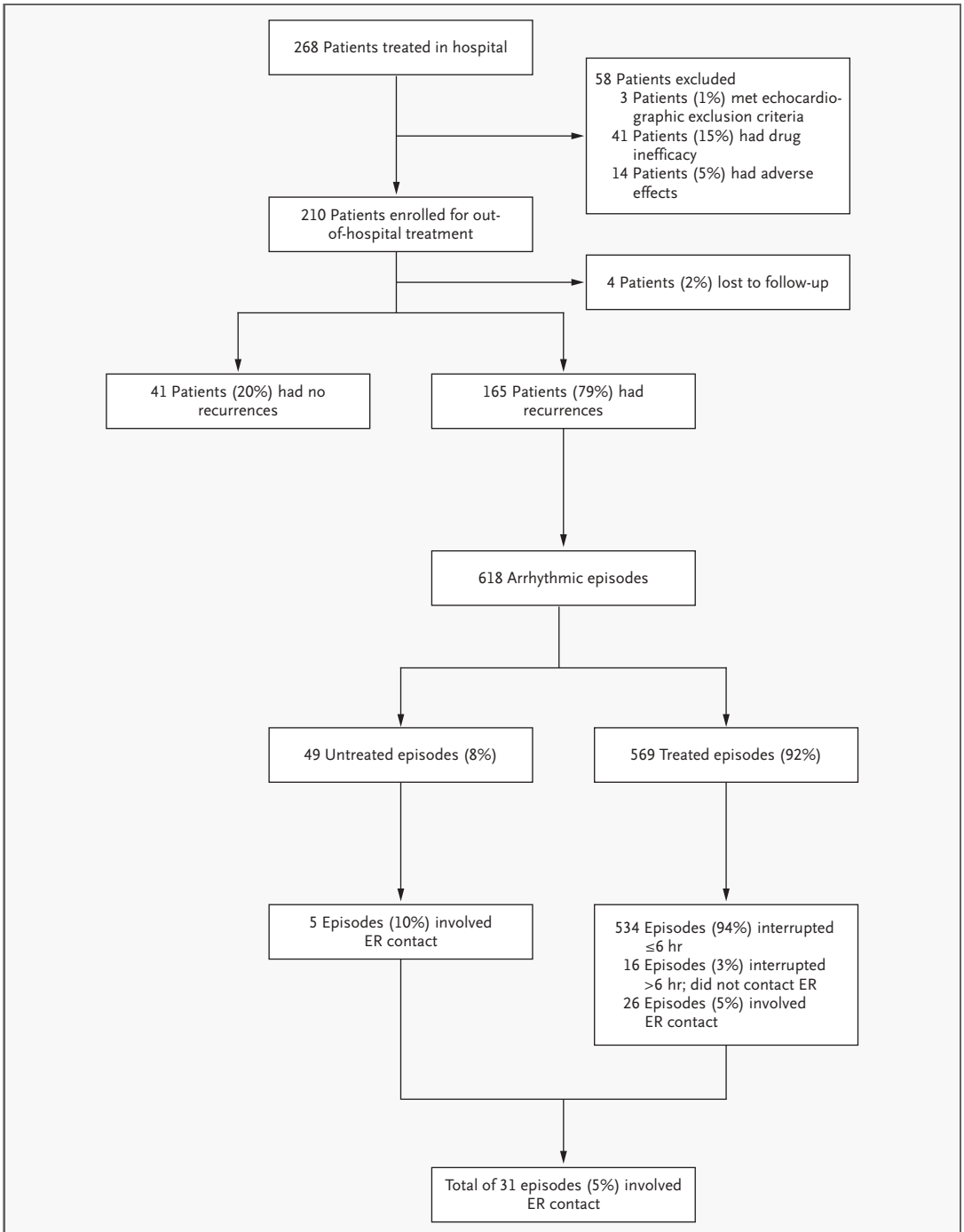

Figure 1. Enrollment and Treated and Untreated Episodes of Atrial Fibrillation.

Among the 569 treated episodes, 26 that required emergency room (ER) intervention included 7 in which the episode was interrupted in less than six hours but the patient sought help for anxiety.

clusion criteria were identified during echocardiographic recording in 3 (1 percent), the drug was not effective in restoring sinus rhythm within six hours in 41 (15 percent), and the drug induced side effects in 14 (5 percent), including transient hypotension (4), transient atrial flutter (7), and slightly symptomatic bradycardia (3). Of the seven patients who had transient atrial flutter after drug administration, one had an atrioventricular conduction ratio of 1:1 and six had an atrioventricular conduction ratio of 2:1 or more. The mean heart rate was more than 150 beats per minute in one patient (230 beats per minute); none of the patients had syncope, presyncope, or hypotension or needed electrical cardioversion. The remaining 210 patients were discharged and given flecainide (74) or propafenone (136) for pill-in-the-pocket treatment of recurrent atrial fibrillation. In these patients, the mean duration of atrial fibrillation before in-hospital treatment was 280±368 minutes (median, 120), and the mean time to conversion to sinus rhythm was 135±79 minutes (median, 120).

In Como and Taranto, where all patients with atrial fibrillation of recent onset who came to the emergency room were monitored during the recruiting period, the total number of patients was 541 and the number of patients who were candidates for out-of-hospital treatment was 65 (12 percent).

Table 1. Clinical Characteristics of 210 Patients Enrolled for Out-of-Hospital Treatment of Recurrent Atrial Fibrillation.

Characteristic	Value*
Age — yr	59±11
Male sex — no. (%)	122 (58)
Mild heart disease — no. (%)	92 (44)
History of atrial fibrillation — yr	
Mean	4±5
Median	3
Symptomatic episodes of atrial fibrillation in previous year — no./patient†	3.3±2.6
Emergency room contacts in previous year — no./patient†	2.7±2.3
Hospitalizations in previous year — no./patient†	0.9±1.1
Duration of target episode before in-hospital treatment — min	
Mean	280±368
Median	120
Previous prophylactic treatment — no. of patients (%)	72 (34)
Left ventricular ejection fraction — %	59±5
Left atrial diameter — mm	39±5

* Plus–minus values are means ±SD.
† Data do not include the target episode.

CLINICAL CHARACTERISTICS

The clinical characteristics of the 210 patients who were discharged and given flecainide or propafenone are reported in Table 1. A total of 118 patients had no signs of organic heart disease, and the remaining 92 (44 percent) had mild heart disease (hypertension in 76, valvular heart disease without ventricular hypertrophy or dilatation in 12, and other conditions in 4).

OUT-OF-HOSPITAL TREATMENT

The mean follow-up period was 15±5 months (range, 7 to 19) (Fig. 1). Four patients (2 percent) were lost to follow-up. Of the remaining 206 patients, 41 (20 percent) did not have any arrhythmic recurrences during the follow-up period, and 165 reported a total of 618 episodes of palpitations with an abrupt onset, 569 (92 percent) of which were treated with either flecainide (in 64 patients) or propafenone (in 101 patients). As compared with the patients who had recurrences, those without recurrences were younger ($P=0.008$) and had had fewer emergency room interventions ($P<0.001$) and hospitalizations ($P=0.01$) during the previous year.

The mean time from the onset of symptoms to the ingestion of the drug was 36±93 minutes (median, 10). The drug was effective (i.e., palpitations were interrupted within six hours) in 534 of 569 arrhythmic episodes (94 percent; corrected efficacy, 93 percent; 95 percent confidence interval, 90 to 95). The mean time to the resolution of symptoms after the ingestion of the drug was 113±84 minutes (median, 98). Flecainide was effective in 239 of 254 episodes (94 percent), and propafenone in 295 of 315 (94 percent).

Sixteen arrhythmic episodes (3 percent) were interrupted after more than 6 hours (range, 390 to 890 minutes) without the patients' contacting the emergency room. Twenty-six episodes (5 percent) required emergency room intervention, 10 of which (2 percent) also required hospitalization. Of the total of 618 episodes of palpitations, 49 were not treated, either because the patient felt that the arrhythmic attack was mild or because the drug was unavailable, and 5 of these episodes (10 percent) required emergency room intervention. Thus, during the follow-up period, a total of 31 treated or untreated arrhythmic episodes (5 percent) resulted in emergency room visits, and 10 of these episodes required

hospitalization. Of the 31 emergency room visits, 19 were due to episodes of atrial fibrillation that lasted for more than six hours, 1 to acceleration of the heart rate after drug ingestion, and 11 to anxiety. (Among the calls that were attributed to anxiety, seven involved a request for emergency room intervention even though the atrial fibrillation had lasted for less than six hours and was well tolerated and four involved a request for an electrocardiogram although palpitations had ceased.)

Among the 165 patients with recurrences, the drug was effective during all the arrhythmic episodes in 139 (84 percent). Of the 27 patients who had at least one episode that lasted for more than six hours after the ingestion of the drug, 9 (5 percent) did not request emergency room intervention, whereas 18 (11 percent) did. During the follow-up period, 31 patients took atrioventricular nodal blockers for treatment of hypertension (beta-blockers in 24 and verapamil in 7).

COMPARISON WITH THE YEAR BEFORE ENROLLMENT

Among the 210 patients enrolled, the mean number of symptomatic episodes per month for the group was 59.8 in the year before enrollment (excluding the target episode) and 54.5 during the follow-up period, not a significant difference. During follow-up, the number of calls for emergency room intervention was 4.9 per month, which was significantly lower than the number per month in the year before the target episode (45.6, $P<0.001$). The number of hospitalizations per month during the follow-up period was also significantly lower (1.6 vs. 15.0, $P<0.001$).

ADVERSE EFFECTS

Adverse effects during one or more arrhythmic episodes were reported in 12 of the 165 patients who used the drug during follow-up (7 percent). One patient (0.6 percent) felt a marked acceleration of heart rate after ingestion of the drug and contacted the emergency room; the electrocardiogram showed atrial flutter, with an atrioventricular conduction ratio of 1:1 and a ventricular rate of 210 beats per minute. The remaining 11 patients reported noncardiac side effects such as nausea, asthenia, and vertigo.

Twenty-seven of the 210 patients (13 percent) dropped out of the study after a mean of 7±3 months: 13 (6 percent) because the drug was ineffective, 7 (3 percent) because of multiple episodes requiring antiarrhythmic prophylactic treatment, 2 (1 percent) because of adverse effects (atrial flutter at a rapid ventricular rate in 1 and nausea in 1), and 5 (2 percent) because of psychological problems or noncompliance.

DISCUSSION

Several controlled studies carried out in hospitalized patients have shown that oral flecainide and propafenone, in the first three to eight hours after administration, have a similar efficacy and are more effective than placebo and other oral antiarrhythmic agents such as amiodarone and quinidine plus digoxin.[8-13,15-20] Our study focused on out-of-hospital treatment for atrial fibrillation of recent onset. The main finding is that self-administration of a single oral loading dose of flecainide or propafenone is feasible and safe and appears to be effective.

During the in-hospital phase, treatment with flecainide or propafenone was successful in about 80 percent of patients. We chose resolution of palpitations within six hours after ingestion of the drug as the criterion of efficacy because after six hours, the rate of success of oral class IC agents is similar to that of placebo; moreover, a period of six hours is reasonable from the clinical point of view. The dose we used had previously been demonstrated to be the most suitable for oral treatment.[8,16,18,22,25]

After the exclusion of patients who had a conversion to sinus rhythm after more than six hours or adverse effects during in-hospital treatment, we found that oral flecainide and propafenone interrupted 94 percent of the out-of-hospital arrhythmic episodes, and in 84 percent of the patients, the treatment was effective for all the arrhythmic episodes, with a mean conversion time of about two hours. In the remaining patients, failure occurred during one or more episodes because the drug was ineffective or unavailable. However, despite efficacy, about 5 percent of the patients dropped out of the study because of multiple recurrences, side effects (especially nausea), or anxiety.

During out-of-hospital treatment, the incidence of adverse effects was low. Only one patient (0.6 percent) felt a marked acceleration of the heart rate after the ingestion of flecainide, and the electrocardiogram recorded in the emergency room showed atrial flutter with a rapid ventricular rate. This finding indicates that successful in-hospital treatment does not rule out an atrial flutter at a high rate during subsequent treatment out of the hospital.

The pill-in-the-pocket strategy markedly reduced

emergency room visits and hospital admissions. The reduction in hospitalizations paralleled the reduction in emergency room visits. These data are of clinical significance because emergency room visits and hospital admissions often represent the most important concern for patients with recurrent atrial fibrillation. However, among the patients in our study who contacted the emergency room during the recruitment period, only a small group (12 percent) were candidates for out-of-hospital treatment. A not-unexpected finding was that the clinical course may deteriorate in some patients; this was the case in 7 of the 210 patients in the study (3 percent), who were switched from pill-in-the-pocket treatment to prophylactic antiarrhythmic therapy owing to the occurrence of more frequent arrhythmic episodes.

In evaluating the out-of-hospital efficacy of class IC drugs in recurrent atrial fibrillation, we did not perform a randomized comparison of these drugs with placebo because several in-hospital trials had already demonstrated the superiority of oral flecainide and propafenone over placebo during observation periods of four to eight hours. The purpose of our study was to investigate the feasibility and safety of the pill-in-the-pocket approach. During the follow-up period, arrhythmic episodes and concomitant drug treatment were assessed on the basis of the patients' symptoms. We cannot exclude the possibility that some episodes of palpitations were the result of arrhythmias other than atrial fibrillation. The use of patient-activated transmission of cardiac data by telephone in choosing the arrhythmic episodes to be treated would have enabled us to evaluate more precisely the efficacy of flecainide and propafenone in terminating recurrent episodes of atrial fibrillation. However, this approach would not have allowed us to investigate the safety of the pill-in-the-pocket strategy in the real world.

The pill-in-the-pocket approach appears to be feasible and safe, in view of the high rate of patient compliance and the very low incidence of adverse effects. Data from our study show that the pill-in-the-pocket strategy with flecainide and propafenone is effective for all the arrhythmic episodes in more than 80 percent of patients with recurrent atrial fibrillation, after selection of patients on the basis of clinical features and the results of in-hospital treatment. Out-of-hospital treatment minimizes the need for subsequent emergency room visits and hospitalization, which should reduce the costs associated with atrial fibrillation, albeit in a small group of patients who have this tachyarrhythmia. The safety of this approach without previous evaluation of in-hospital treatment remains to be investigated.

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APPENDIX

The members of the steering committee of the study (with their locations in Italy) were P. Alboni (Cento), N. Baldi (Taranto), G. Boriani (Bologna), G.L. Botto (Como), M. Brignole (Lavagna), A. Capucci (Piacenza), A. Del Rosso (Fucecchio), A. De Simone (Maddaloni), G. Inama (Crema), G. Marinoni (Pavia), C. Menozzi (Reggio Emilia), and A. Raviele (Mestre–Venezia). Participating centers and investigators included Ospedale Civile, Cento, L. Gianfranchi; Ospedale S. Anna, Como, M. Luzi; Ospedale SS. Annunziata, Taranto, V. Russo; Ospedale del Delta, Lagosanto, P. Marchi; Arcispedale Santa Maria Nuova, Reggio Emilia, M. Calzolari; Ospedali Riuniti, Lavagna, A. Solano; Ospedale Galmarini, Tradate, R. Baroffio; Ospedale Civile, Sampierdarena, G. Gaggioli; Ospedale Renzetti, Lanciano, D. Tullio; Policlinico S. Orsola, Bologna, G. Boriani; Ospedale Ceccarini, Riccione, N. Candiotti; Ospedale Ferrari, Casarano, A. Marzo; Ospedale S.C. di Gesù, Gallipoli, L. Stella; Ospedale Civile, Sassuolo, F. Melandri.

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