Antiarrhythmic drugs in patients with recurrent atrial fibrillation: where are we?

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Key words:
Antiarrhythmic drugs; Atrial fibrillation.

In patients with recurrent atrial fibrillation (AF), the hallmark of treatment has long been the use of antiarrhythmic drugs. The following strategies are available: a) any antiarrhythmic treatment; b) out-of-hospital episodic treatment ("pill-in-the-pocket" approach); c) prophylactic antiarrhythmic therapy; and d) hybrid therapy. The following patients with recurrent AF should not undergo any antiarrhythmic therapy: after the first AF episode; patients with rare, hemodynamically well-tolerated and short-lasting (a few hours) AF episodes; patients with perioperative AF, without history of recurrent AF; patients with AF during acute myocardial infarction or other acute diseases, without history of recurrent AF; and "holiday heart" syndrome.

In patients with infrequent AF episodes (< 1 per month) and hemodynamically well-tolerated, but long enough to require emergency room intervention or hospitalization, a good treatment might be the "pill-in-the-pocket" approach, consisting of a single-dose oral ingestion of flecainide or propafenone at the time and place of palpitation onset. A recent Italian study has shown that this treatment is effective and safe. When AF episodes are frequent and/or hemodynamically badly tolerated, the treatment of choice is the prophylactic therapy with antiarrhythmic drugs. When these drugs fail (ineffective or not tolerated) a non-pharmacological treatment or a hybrid therapy may be indicated.

(Ital Heart J 2005; 6 (3): 169-174)

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For the treatment of recurrent atrial fibrillation (AF) several therapeutic options are available: a) any antiarrhythmic treatment; b) pharmacological prophylaxis with antiarrhythmic drugs (rhythm control); c) out-of-hospital episodic treatment ("pill-in-the-pocket" approach); d) transcatheter ablation (ablation of the atrial substrate or "ablate and pace"); e) pacemaker implantation; and f) rate-control strategy. Rhythm-control and rate-control strategies have been widely compared[1-4], whereas the other therapeutic options have been little or not compared. In fact a comparison is not always possible since one treatment is not always indicated for all the clinical situations; as a consequence, there is a large discretionary in the choice of the antiarrhythmic strategy. This paper will address only the pharmacological antiarrhythmic treatment in patients with recurrent AF.

Any antiarrhythmic treatment

Not all the patients with recurrent AF should be treated; in our opinion, the following patients should not undergo any antiarrhythmic treatment[5]:

- after the first AF episode;
- patients with rare, hemodynamically well-tolerated and short-lasting (a few hours) AF episodes;
- patients with perioperative AF, without history of recurrent AF;
- patients with AF during acute myocardial infarction (AMI) or other acute diseases, without history of recurrent AF;
- "holiday heart" syndrome.

After the first atrial fibrillation episode. Up to now, prospective studies did not investigate the natural history of recurrent AF; however, clinical experience teaches us that the course of the tachyarrhythmia can be extremely variable; in fact some patients show relapses in a short time, whereas in many others the first detected episode of AF remains isolated and recurrences may be observed after some years. Therefore, after the first AF episode, patients should be converted to sinus rhythm, but an antiarrhythmic treatment does not appear indicated, as also reported in the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines[6]. Obviously, there may be some exceptions: AF associated with severe

symptoms (heart failure, syncope), presence of mitral stenosis and/or markedly dilated atria, long-lasting episodes (weeks or months).

Patients with rare and short-lasting atrial fibrillation episodes. Some patients show rare, hemodynamically well-tolerated and short-lasting (a few hours) AF episodes. These patients should be reassured without undergoing any antiarrhythmic treatment; in fact neither the pharmacological prophylaxis nor the "pill-in-the-pocket" approach appear indicated.

Patients with perioperative atrial fibrillation. AF is a well-known complication after cardiothoracic surgery and its prevalence ranges from 15 to 40%[7]. Perioperative AF is generally short-lived but is associated with increased morbidity, prolonged hospitalization, and is responsible for increased hospital costs. The incidence of post-discharge AF recurrences has been little investigated. The few available data suggest that relapses are rather frequent during the first month after cardiac surgery (12-34%), thereafter become rare, being observed only in 2-5% of the patients[8-11]. Even if in the absence of therapeutic trials on post-discharge AF, a chronic antiarrhythmic treatment does not appear indicated in patients without preoperative history of AF; it appears indicated only in the first month after discharge.

Patients with atrial fibrillation during acute myocardial infarction. In the thrombolytic era the prevalence of AF during AMI is about 8-10% and about half of the patients do not have a previous history of AF[12,13]. AF during AMI is associated with more severe cardiac involvement, i.e. a higher Killip class, poor left ventricular function, previous AMI, hypertension, and diabetes. Among patients with AMI, AF seems to represent an independent predictor of in-hospital and long-term mortality. Unlikely, the incidence of recurrences after discharge in patients with AF during AMI has never been investigated. However, clinical experience teaches us that the course of AF can be extremely variable; in fact in some patients relapses appear in the first months after discharge, whereas in others recurrences are not observed. Therefore, common sense suggests that patients with AF during AMI, without history of AF, should be discharged in sinus rhythm without prescribing any antiarrhythmic treatment; this can be started if relapses appear during the follow-up.

Holiday heart syndrome. Cardiac arrhythmias following acute alcohol consumption have been well documented. Ettinger et al.[14] reported that cardiac arrhythmias, mostly observed during weekends or holidays ("holiday heart" syndrome), were induced by heavy recent alcohol consumption or binge drinking. Other studies have shown that heavy drinking or binge drinking is associated with increased risk of AF[15]. Obviously, patients who develop AF in association with alcohol abuse should not undergo prophylactic antiarrhythmic treatment, but should be recommended to avoid alcohol abuse.

Out-of-hospital treatment with the "pill-in-the-pocket" approach

In the clinical setting, several patients with recurrent AF present with episodes that are not frequent (< 1 per month) and are hemodynamically well-tolerated, but which are long enough to require emergency room (ER) intervention or hospitalization. These patients need a treatment, but long-term oral prophylaxis or catheter ablation may not be the most appropriate first-line treatment. Rather, a good treatment in this group of patients might be the "pill-in-the-pocket" approach, consisting of a single-dose oral ingestion at the time and place of palpitation onset. This type of treatment has already been investigated in studies carried out in hospital, in patients with recent-onset AF. The oral drugs that have been used to convert recent-onset AF to sinus rhythm are class IA, class IC and class III antiarrhythmic agents[16-22]. The class IC agents flecainide and propafenone have the advantage of being conveniently administered in a single oral dose that acts rapidly and causes minimal side effects[16,21,23-31]. The efficacy of single oral loading dose of flecainide and propafenone in converting recent-onset AF to sinus rhythm has been documented by several placebo-controlled trials[16,21,23,24,26,28,31]. Both drugs showed similar efficacy, and their success rate varied from 58 to 95%[16,21,23-28], depending on the duration of AF and the observation period after drug administration. In all controlled studies, a low incidence of adverse effects has been reported[16-21,23-28,30,31]. The most serious side effect seems to be the appearance of a transient atrial flutter with high ventricular rate owing to 1:1 atrioventricular (AV) conduction (in about 1% of patients).

Very recently, the out-of-hospital treatment with the "pill-in-the-pocket" approach has been investigated in an Italian multicenter study[32]. Inclusion criteria were as follows: patients aged between 18 and 75 years requiring ER intervention for recent-onset AF (< 48 hours); history of palpitation with abrupt onset, hemodynamically well-tolerated (absence of symptoms such as dyspnea, presyncope or syncope); number of episodes in the last year < 1 per month; absence of cardiological symptoms apart from the arrhythmic episodes. Patients with contraindications to class IC agents were excluded. The patients could be treated either in the ER or in the cardiological ward. For AF conversion, oral propafenone and flecainide were administered in a single dose according to the patient's weight: flecainide 300 mg if the patient weighed ≥ 70 kg, or 200 mg otherwise; propafenone, 600 mg if the patient weighed ≥ 70 Kg, or 450 mg otherwise. The drug treatment was

considered "successful" if the conversion time to sinus rhythm was < 6 hours after drug administration, without severe side effects.

Two hundred and sixty-eight patients with recent-onset AF received an in-hospital oral loading dose of flecainide and propafenone. Of these, 58 were excluded from the out-of-hospital treatment: in 3 (1%) exclusion criteria emerged during echocardiographic recording, in 41 (14%) the drug was not effective in restoring sinus rhythm within 6 hours, and in 14 (6%) the drug induced side effects (transient hypotension in 4, atrial flutter in 7, one of which with 1:1 AV conduction, and slightly symptomatic bradycardia in 3). The remaining 210 patients (mean age 59 ± 11 years) were discharged on flecainide or propafenone for the "pill-in-the-pocket" treatment of recurrent AF. One hundred and eighteen patients had no signs of heart disease and the remaining 92 (43%) had a mild heart disease. The mean follow-up was 15 ± 5 months; 4 patients were lost just after enrolment. Of the remaining 206 patients, 41 (20%) did not experience any arrhythmic recurrences during the follow-up period and 165 reported 618 episodes of palpitation with abrupt onset, 569 of whom were treated with flecainide (n = 64) or propafenone (n = 101). The drug was effective in 534 out of 569 arrhythmic episodes (94%). Similar results on the efficacy of class IC drugs were recently reported by Capucci et al.[31], who investigated in hospital the reproducibility of efficacy of oral loading dose of propafenone in restoring sinus rhythm in patients with recurrent AF. Efficacy was evaluated by electrocardiographic monitoring and it was reproducible in 93% of the patients. In the Italian multicenter study, time-to-symptom resolution after drug ingestion was 113 ± 84 min (median 98 min). Sixteen arrhythmic episodes were interrupted in a time > 6 hours without the patients contacting the ER. Twenty-six episodes (5%) required ER intervention, 10 of which (2%) also needed hospitalization. Out of the 618 episodes, 49 were not treated, mainly because of drug unavailability and 5 (10%) of these required ER intervention. Therefore, during the follow-up period, the number of ER contacts among the treated and untreated arrhythmic episodes was 31 (5%), and 10 of them also needed hospitalization. Out of the 31 calls for ER intervention, 19 were due to AF lasting > 6 hours, one to acceleration of heart rate after drug ingestion (atrial flutter with 1:1 AV conduction), and 11 to anxiety (request for ER intervention although palpitation had ceased).

During follow-up, the number of calls for ER intervention per month was significantly lower compared with that in the year before the target episode (4.9 vs 45.6, $p < 0.001$). Even the number of hospitalization per month during the follow-up period was significantly lower (1.6 vs 15, $p < 0.001$). Adverse effects during one or more arrhythmic episodes were reported in 12 out of the 165 patients (7%) who utilized the drug during the follow-up. One (0.7%) felt a marked acceleration of heart rate after drug ingestion and contacted the ER; the electrocardiogram showed atrial flutter with 1:1 AV conduction. This means that successful in-hospital treatment does not completely prevent the appearance of atrial flutter at high rate during follow-up. The remaining 11 patients reported non-cardiac side effects such as nausea, asthenia or vertigo.

These results show that the out-of-hospital treatment of recurrent AF with the "pill-in-the-pocket" approach is feasible and safe, in view of the high rate of patient's compliance and the very low incidence of adverse effects. Data from the Italian study show that the "pill-in-the-pocket" strategy with flecainide or propafenone is effective in over 90% of the arrhythmic episodes, after patient selection on clinical grounds and on the basis of the results of in-hospital treatment. Episodic treatment minimizes the need for ER and hospital admission during the acute event. It is noteworthy that about one third of ER contacts were due to anxiety. Therefore, a psychological management of these patients (particularly reassurance) could further reduce calls for ER intervention. The marked reduction in ER and hospital admissions, besides avoiding prophylactic treatment, will help to reduce the economic impact of AF, although in a rather small group of patients with this tachyarrhythmia. The safety of this approach without previous evaluation of in-hospital treatment remains to be investigated; therefore, at present, oral flecainide or propafenone must be tested once in hospital before the prescription for out-of-hospital treatment.

Prophylactic treatment with antiarrhythmic drugs

In patients with frequent and/or hemodynamically badly tolerated AF episodes, the "pill-in-the-pocket" strategy does not appear adequate and a prophylactic treatment is indicated. In these patients the hallmark of the treatment has long been the use of antiarrhythmic drugs.

In general, antiarrhythmic drugs should only be used in patients with symptomatic AF in whom sinus rhythm needs to be maintained. When considering antiarrhythmic drugs for the management of AF, the risks and benefits of these drugs should be weighed in each individual patient. The decision to use antiarrhythmic drugs should be based on the associated underlying heart disease and the potential side effects of the drug. By careful characterization of the patient profile, the risk of antiarrhythmic drugs can be reduced.

The most effective drug available for AF prevention is amiodarone. In the CTAF trial[33] the efficacy of amiodarone or propafenone/sotalol for the prevention of AF was evaluated in patients with many different underlying pathologies. It was found that after a follow-up period of 16 months, 35% of patients using amiodarone vs 63% of patients on propafenone/sotalol experienced a relapse of AF. Although it was concluded that amio-

darone should be used as first-line therapy, it should be noted that the follow-up was relatively short and the relative safety of amiodarone as observed in this study may be different when patients are treated for a longer period.

Prevention of atrial fibrillation in patients with mild or no underlying heart disease. In a minority of patients with AF, no underlying heart disease is found ("lone AF"). Especially in the young, the presence of AF in the absence of structural atrial abnormalities suggests that triggers may be crucial for initiating and maintaining the arrhythmia. In these patients beta-blockers may help to reduce AF recurrences, but other drugs such as class I and sotalol can be equally effective. In patients with adrenergically-driven AF, beta-blockers are the drug of choice. In "vagal AF" disopyramide and flecainide can be considered.

Congestive heart failure. AF is often seen in patients with congestive heart failure. At present, dofetilide, azimilide and amiodarone are the drugs considered for AF prevention in the setting of ventricular dysfunction, but the only agent available in Europe is amiodarone. In the STAT-CHF study[34], it was found that amiodarone reduced the incidence of AF over 4 years from 8% (placebo) to 4% in patients with heart failure. In addition, in patients who had preexisting AF amiodarone was more effective than placebo in restoring sinus rhythm. Of note, amiodarone had a neutral effect on mortality. Class I drugs are not indicated. Mortality rates in the SPAF II study were the highest in patients with heart failure treated with class I antiarrhythmics[35].

Prevention of atrial fibrillation in patients with hypertension. It has recently become clear that hypertension is an important risk factor for the development of AF. In this respect it becomes clear that controlling the blood pressure is crucial in preventing AF in hypertensive patients. When using antiarrhythmic drugs in patients with hypertension and severe ventricular hypertrophy, the use of QT-prolonging drugs should be avoided; in fact left ventricular hypertrophy is a risk factor for the development of potential lethal torsade de pointes arrhythmias. An exception is amiodarone, that, although it prolongs the QT interval, it does not cause torsade de pointes. In the absence of severe left ventricular hypertrophy, beta-blockers, sotalol and class IC agents are the drugs of choice.

Coronary artery disease. Studies, such as the CAST, have demonstrated that class I antiarrhythmic drugs

Table I. Prophylactic antiarrhythmic treatment of atrial fibrillation (AF): choice of the antiarrhythmic agent.

	Drug
Patients with no or mild structural heart disease	Beta-blocker, sotalol or class IA or IC drugs
Patients with hypertension (without severe left ventricular hypertrophy)	Beta-blocker, sotalol or class IA or IC drugs
Patients with high resting sinus rate	Beta-blocker or sotalol
Patients with severe left ventricular hypertrophy	Amiodarone
Patients with valvular heart disease	Amiodarone
Patients with ischemic heart disease	Sotalol or amiodarone
Patients with left ventricular dysfunction (with or without heart failure)	Amiodarone
Patients with vagally-mediated AF	Flecainide or disopyramide
Patients with adrenergically-mediated AF	Beta-blocker

Table II. Indications for the various treatments on the basis of the frequency of atrial fibrillation (AF) episodes and the severity of the underlying heart disease.

	Treatment
Patients with rare, hemodynamically well-tolerated and short-lasting (a few hours) AF episodes	Any antiarrhythmic treatment
Patients with infrequent AF episodes (< 1 per month), in the setting of a normal heart or only mild heart disease, highly symptomatic for palpitation with abrupt onset, hemodynamically well-tolerated, but long enough to require emergency room intervention	Out-of-hospital "pill-in-the-pocket" treatment
Patients with frequent and/or hemodynamically badly tolerated AF episodes	Prophylactic pharmacological antiarrhythmic treatment
Patients with frequent and/or hemodynamically badly tolerated AF episodes, refractory to pharmacological antiarrhythmic treatment and with markedly impaired quality of life	Non-pharmacological treatment or hybrid therapy

such as flecainide, but probably also propafenone increase mortality in patients with coronary artery disease[36]. Therefore, class I drugs should not be given in patients with coronary artery disease. In these patients the drugs of choice appear to be sotalol and amiodarone.

The indications for the several antiarrhythmic drugs in the different clinical situations are summarized in table I.

In patients with frequent and/or hemodynamically badly tolerated AF episodes, refractory to prophylactic antiarrhythmic drugs, and with markedly impaired quality of life, a non-pharmacological treatment (ablation of the atrial substrate, "ablate and pace") or hybrid therapy are indicated. In table II, indications for the various treatments on the basis of the frequency of the AF episodes and the severity of underlying heart disease are reported.

References

1. Hohnloser SH, Kuck HH, Lilienthal J. Rhythm or rate control in atrial fibrillation - Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. Lancet 2000; 356: 1789-94.
2. Wyse DG, Waldo AL, DiMarco JP, et al, for the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002; 347: 1825-33.
3. Van Gelder IC, Hagens VE, Bosker HA, et al, for the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002; 347: 1834-40.
4. Carlsson J, Miketic S, Windeler J, et al. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation. The Strategies of Treatment of Atrial Fibrillation (STAF) study. J Am Coll Cardiol 2003; 41: 1690-6.
5. Alboni P. When not to prescribe chronic treatment to the patient with atrial fibrillation. G Ital Cardiol 1999; 29: 824-7.
6. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to develop guidelines for the management of patients with atrial fibrillation) developed in collaboration with the North American Society of Pacing and Electrophysiology. Eur Heart J 2001; 22: 1852-923.
7. Omnen SR, Odell JA, Stanton MS. Atrial arrhythmias after cardiothoracic surgery. N Engl J Med 1997; 336: 1429-34.
8. Beggs VL, Birkemeyer NJ, Nugent WC, Dacey LJ, O'Connor GT. Factors related to rehospitalization within thirty days of discharge after coronary artery bypass grafting. Best Pract Benchmarking Healthc 1996; 1: 180-6.
9. Cioffi G, Cemin C, Russo TE, Pellegrini A, Terrasi F, Ferrario G. Post-discharge recurrences of new-onset atrial fibrillation following cardiac surgery: impact of low-dose amiodarone and beta-blocker prophylaxis. Ital Heart J 2000; 1: 691-7.
10. Cioffi G, Mureddu G, Cemin C, et al. Characterization of post-discharge atrial fibrillation following open-heart surgery in uncomplicated patients referred to an early rehabilitation program. Ital Heart J 2001; 2: 519-28.
11. Antonelli D, Peres P, Freedberg NA, Feldman A, Rosenfeld C. Incidence of postdischarge symptomatic paroxysmal atrial fibrillation in patients who underwent coronary artery bypass graft: long-term follow-up. Pacing Clin Electrophysiol 2004; 27: 365-7.
12. Behar S, Zahavi Z, Goldourt U, Reicher-Reiss H. Long-term prognosis of patients with paroxysmal atrial fibrillation complicating acute myocardial infarction. SPRINT Study Group. Eur Heart J 1992; 13: 45-50.
13. Eldar M, Canetti M, Rotstein Z, et al. Significance of paroxysmal atrial fibrillation complicating acute myocardial infarction in the thrombolytic era. SPRINT and Thrombolytic Survey Groups. Circulation 1998; 97: 965-70.
14. Ettinger PO, Wu CF, De La Cruz C Jr, Weisse AB, Ahmed SS, Regan TJ. Arrhythmias and the "holiday heart": alcohol-associated cardiac rhythm disorders. Am Heart J 1978; 95: 555-62.
15. Kostinen P, Kupari M, Leinonen H. Role of alcohol in recurrences of atrial fibrillation in persons less than 65 years of age. Am J Cardiol 1990; 66: 954-8.
16. Villani GQ, Rosi A, Piepoli M, et al. The efficacy of oral treatment with flecainide for paroxysmal atrial fibrillation: correlation with plasma concentration. G Ital Cardiol 1990; 20: 564-68.
17. Capucci A, Lenzi T, Boriani G, et al. Effectiveness of loading oral flecainide for converting recent-onset atrial fibrillation to sinus rhythm in patients without organic heart disease or with only systemic hypertension. Am J Cardiol 1992; 70: 69-72.
18. Botto GL, Bonini W, Broffoni T, et al. Regular ventricular rhythms before conversion of recent onset atrial fibrillation to sinus rhythm. Pacing Clin Electrophysiol 1994; 17 (Part 2): 2114-7.
19. Capucci A, Boriani G, Botto GL, et al. Conversion of recent-onset atrial fibrillation by a single oral loading dose of propafenone or flecainide. Am J Cardiol 1994; 74: 503-5.
20. Capucci A, Boriani G, Rubino I, Della Casa S, Sanguinetti M, Magnani B. A controlled study on oral propafenone versus digoxin plus quinidine in converting recent-onset atrial fibrillation to sinus rhythm. Int J Cardiol 1994; 43: 305-13.
21. Boriani G, Capucci A, Lenzi T, Sanguinetti M, Magnani B. Propafenone for conversion of recent-onset atrial fibrillation. A controlled comparison between oral loading dose and intravenous administration. Chest 1995; 108: 355-8.
22. Halinen MO, Huttunen M, Paakkinen S, Tarssanen L. Comparison of sotalol with digoxin-quinidine for conversion of acute atrial fibrillation to sinus rhythm (the Sotalol-Digoxin-Quinidine Trial). Am J Cardiol 1995; 76: 495-8.
23. Botto GL, Bonini W, Broffoni T, et al. Conversion of recent onset atrial fibrillation with single loading oral dose of propafenone: is in-hospital admission absolutely necessary? Pacing Clin Electrophysiol 1996; 19 (Part 2): 1939-43.
24. Azpitarte J, Alvarez M, Baun O, et al. Value of single oral loading dose of propafenone in converting recent-onset atrial fibrillation: results of a randomized, double-blind, controlled study. Eur Heart J 1997; 18: 1649-54.
25. Boriani G, Biffi M, Capucci A, et al. Oral propafenone to convert recent-onset atrial fibrillation in patients with and without underlying heart disease: a randomized, controlled trial. Ann Intern Med 1997; 126: 621-5.
26. Botto GL, Capucci A, Bonini W, et al. Conversion of recent onset atrial fibrillation to sinus rhythm using a single oral loading dose of propafenone: comparison of two regimens. Int J Cardiol 1997; 58: 55-61.
27. Botto GL, Bonini W, Broffoni T, et al. Randomized, cross-

over, controlled comparison of oral loading versus intravenous infusion of propafenone in recent-onset atrial fibrillation. Pacing Clin Electrophysiol 1998; 21 (Part 2): 2480-4.
28. Blanc JJ, Voinov C, Maarek M, for the PARSIFAL Study Group. Comparison of oral loading dose of propafenone and amiodarone for converting recent-onset atrial fibrillation. Am J Cardiol 1999; 84: 1029-32.
29. Kishikawa T, Maruyoma T, Kaji Y, et al. Effects of oral repetitive loading of disopyramide on acute-onset atrial fibrillation with concurrent monitoring of serum drug concentration. Int J Cardiol 1999; 68: 57-62.
30. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. J Am Coll Cardiol 2001; 37: 542-7.
31. Capucci A, Villani GQ, Piepoli MF. Reproducible efficacy of loading oral propafenone in restoring sinus rhythm in patients with paroxysmal atrial fibrillation. Am J Cardiol 2003; 92: 1345-7.
32. Alboni P, Botto GL, Baldi N, et al. Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. N Engl J Med 2004; 351: 2384-91.
33. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. N Engl J Med 2000; 342: 913-20.
34. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmias. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. N Engl J Med 1995; 333: 77-82.
35. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. Lancet 1994; 343: 687-91.
36. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991; 324: 781-8.