Atrial fibrillation and hypertension

Tonje A. Aksnes[1], Sverre E. Kjeldsen[1,2], Stevo Julius[2]

[1]Cardiovascular and Renal Research Center, Department of Cardiology, Ullevaal University Hospital, Oslo, Norway
[2]Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan, USA

Corresponding author:
Sverre E. Kjeldsen, MD, PhD, FAHA
Department of Cardiology
Ullevaal University Hospital
N-0407 Oslo
Phone: +47 22 11 91 00
Fax: +47 22 11 91 81

A b s t r a c t

Atrial fibrillation (AF) and hypertension often coexist and are both responsible for considerable morbidity and mortality. Aggressive treatment of hypertension, especially with a RAS-blocker, may postpone or prevent AF development and reduce thromboembolic complications. Focus on primary prevention of atrial fibrillation with optimal antihypertensive treatment may reduce morbidity, mortality and health care expenditures.

Key words: atrial fibrillation, hypertension.

Atrial fibrillation (AF) is the most frequent occurring sustained cardiac arrhythmia and is related to many cardiac diseases. Patients with hypertension have an increased risk of developing AF of 42% [1], and patients with AF have increased cardiovascular morbidity and mortality. Due to the high prevalence of hypertension it accounts for more cases of AF than any other risk factor. Hypertension is associated with left ventricular hypertrophy, impaired ventricular filling, slowing of atrial conduction velocity, structural changes and enlargement of the left atria. All these changes in cardiac structure and physiology favour development or AF, and increase the risk of thromboembolic complications. In the following we will review possible mechanisms for the increased risk of AF in hypertensives and look into the effect of different antihypertensive treatment with special focus on blockers of the renin-angiotensin-system (RAS).

Atrial fibrillation is a disease of aging as its prevalence doubles with each decade after 50 years and approaches 10% in those more than 80 years of age [1]. As the general population is aging, the prevalence of AF is expected to rise in the future and methods to prevent or to postpone AF development may be of clinical, prognostic, and economic importance. However, prevention is a new strategy in treatment of AF, as it earlier has been more focus on rate- and rhythm-control and anticoagulation therapy to prevent cardiovascular endpoints [2].

Hypertension is a prevalent, independent, and potentially modifiable risk factor for AF development [1, 3]. The relative risk (RR) of developing AF in patients with hypertension has been calculated to 1.4-2.1, which is modest compared e.g. heart failure and valvular disease which have a relative risk of AF development of 6.1-17.5 and 2.2-8.3, respectively [4]. Increased pulse pressure has recently been recognized as a possible even

more important risk factor. In the Framingham database, increased systolic pressure was associated with AF, but the association was even stronger when low diastolic pressure with a higher pulse pressure effect was added into the statistic model [5]. Other known risk factors for AF is left ventricular hypertrophy, heart failure, valvular (in particular mitral valve) and ischemic heart disease, heart rate, gender, diabetes mellitus, hyperthyroidism, severe infection, pulmonary pathology, stroke, obesity, alcohol abuse, and smoking [6]. Recently new risk factors for AF like sleep apnoea, inflammation, and genetic influence have also been recognized [7].

Lone AF is defined as AF in individuals younger than 60 years without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension [8]. These patients have a favourable prognosis with respect to thromboembolism and mortality [8]. However, underlying hypertension may often not be recognized in these patients diagnosed with lone AF due to inadequate diagnostic investigations or treatment with β-blockers or calcium channel blocker for AF which also have antihypertensive effects [7].

Atrial fibrillation itself produces electrical and structural remodelling of the heart, and may be important for the recurrence or the maintenance of the AF. Angiotensin II have been suggested as one important mechanism for the atrial remodelling and blockers of RAS like angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II-receptor blockers (ARBs) have shown promising results in reducing the incidence of AF in heart failure and hypertension trials [9]. Studies have also shown an additive effect of ARBs and ACEIs on top of that obtained from standard anti-arrhythmic therapy with amiodarone in the prevention of AF recurrence in hypertensive patients [10, 11]. In a meta-analysis

of 11 randomized, controlled human trials by Healey et al. [12], the authors found that treatment with ACEIs or ARBs reduced the relative risk of new AF with 28% (15-40%), but this benefit was limited to patients with systolic left ventricular hypertrophy or dysfunction. Lately the results from the more than 15000 hypertensive patients included in the Valsartan Long-term Use Evaluation (VALUE) trial have been published giving more evidence for a possible preventive effect of RAS blockade [13].

New-onset atrial fibrillation in hypertension trials using RAS-blocker

There has never been any prospective hypertension trial investigating effect of RAS blockade on development of AF as a primary endpoint, but there are several secondary analyzes of large randomized trials as shown in Table I. However, there are limitations in the evaluation of new-onset AF in these trials which were not designed to investigate this as the primary endpoint, especially as the definitions and evaluations of AF differ between the trials. Annual electrocardiogram (ECG) recordings may underestimate the prevalence of AF (although equal between the treatment groups); in recent ongoing trials new-onset AF is a pre-specified endpoint and trans-telephonic ECG monitoring is included to recognize also asymptomatic AF. There have been a couple of hypertension trials using ACEIs reporting the effect on AF, but these trials were not designed to investigate AF and must be looked upon more as chance findings, and no significant effects of RAS-blockade were found [14, 15].

In placebo-controlled trials it is not known if an effect on AF is a result of the blood pressure reduction per se or the effect is specific for blocking of RAS. In the Losartan Intervention for Endpoint Reduction in hypertension (LIFE) study more

Table I. Large hypertension trials reporting new-onset AF and use of ACEI or ARB

Study	N	Study drug	Definition of AF	Effect of RAS-blockade on new-onset AF [RR]
CAPPP [14]	10985	ACEI (captopril) vs. D/BB (conventional)	• Not stated	NS [RR 0.87 (0.68-1.11)]
LIFE [17]	9193	ARB (losartan) vs. BB	• Secondary analysis, planned before study termination • Yearly ECG, one single ECG core centre	33% (P<0.001) [RR 0.67 (0.55-0.83)]
STOP-H2 [15]	6614	ACEI (enalapril) vs. D/BB (conventional)	• Yearly ECG and when symptoms	NS [RR 1.15 (0.94-1.41)]
VALUE [13]	15245	ARB (valsartan) vs. CCB	• Pre-specified secondary endpoint • ECG every year, centrally analyzed	16% (P=0.0455) [RR 0.84 (0.713-0.997)]

AF – atrial fibrillation, BB – β-blockers, CCB – calcium channel blocker, D – diuretics, HT – hypertension, n – number of patients, NS – non significant, P – P-value, RR – relative risk, y – years

than 9000 hypertensive patients with signs of left ventricular hypertrophy in their electrocardiogram (ECG) were randomized to atenolol (β-blocker)- or losartan (ARB)-based antihypertensive treatment with similar blood pressure reduction between the two treatment groups [16]. 8851 patients with no previous history of AF and in sinus rhythm at baseline were included in the analyzes of AF [17]. New-onset AF was identified in 371 of these patients from annual in-study ECGs analysed at one single centre, during the mean 4.8 years of follow-up; 221 of the atenolol-treated and 150 of the losartan-treated patients [17]. This indicates a relative risk reduction of 33% of new-onset AF between the two treatment groups independent of other risk factors (P-value <0.001) [17]. Patients with new-onset AF had a twofold increased risk of cardiovascular events, a threefold risk of fatal and non-fatal stroke, and fivefold increased rate of hospitalization for heart failure [17].

In the VALUE trial more than 15000 high-risk hypertensive patients were treated with amlodipine (calcium channel blocker) or valsartan (ARB) and new-onset AF was a secondary pre-specified endpoint and ECG recording were obtained every year and centrally analyzed [13]. During the average 4.2 years of the trial the incidence of at least one ECG-documented episode of new-onset AF was 3.67% in the valsartan-treated and 4.34% in the amlodipine-treated patients resulting in a hazard ratio of 0.84 (0.713-0.997, P-value =0.0455) [13]. When taking potential confounding covariates into account (age, history of coronary artery disease, left ventricular hypertrophy) the incidence of AF reduction with ARB-treatment remained significant [13].

In a study by Madrid et al. [10], 154 patients were randomized to open-label treatment with amiodarone or amiodarone plus irbesartan (ARB) before electrical cardioversion for chronic AF. Time to recurrence and the probability of remaining free of AF were greater in the group treated with irbesartan (80 vs. 56%, P-value =0.007). At baseline 38% of the patients treated with amiodarone alone and 46% of the patients treated with amiodarone plus irbesartan were hypertensive and there was a trend for irbesartan plus amiodarone to be superior to amiodarone alone in patients with hypertension [RR 0.49 (0.11-2.06)]. Use of ARB was the only significant variable related to the maintenance of sinus rhythm after cardioversion in a multivariate analysis [10]. In another study by Ueng et al. [19], the addition of the ACEI enalapril to amiodarone in patients scheduled for external cardioversion (about 30% hypertensives) decreased the rate of immediate and sub-acute arrhythmia recurrences and facilitated subsequent long-term maintenance of sinus rhythm after cardioversion. However, one limitation with these studies is that the effect of RAS-blockade alone was not tested.

In a study by Fogari et al. [11], 213 patients with mild hypertension and paroxysmal AF treated with amiodarone were randomized to additional treatment with amlodipine (calcium channel blocker) or losartan (ARB). During the 1-year follow up, at least one ECG-documented episode of AF was reported in 13 of the 107 patients treated with losartan and in 39 of the 106 the patients treated with amlodipine, with a significant lower recurrence rate in the ARB-treated patients (P<0.01) [11]. Treatment with ARB alone without adjunct anti-arrhythmic therapy 3-6 weeks before electrical cardioversion for AF was tested in the Candesartan in the Prevention of Relapsing Atrial Fibrillation (CAPRAF) study [19]. In this study only 25-35% of the patients were hypertensive and no statistically significant difference in AF recurrence was found between the two treatment regimens [19]. Therefore an effect on AF recurrence of RAS- blockade alone without anti-arrhythmic treatment is not known for sure.

In another recent published trial by Fogari et al. [20], 369 mild hypertensive patients [systolic blood pressure (SBP): 140-160 and/or diastolic blood pressure (DBP): 90-110 mm Hg] in sinus rhythm, but with at least two episodes of AF during the last 6 months, were randomized double-blindly into treatment with three different drug regimens for one year [ARB (valsartan), ACEI (ramipril) or calcium channel blocker (amlodipine)]. Atrial fibrillation recurrence was reduced significantly with ARB and ACEI compared with calcium channel blocker (CCB) despite similar blood pressure lowering effect [20]. Although, different mechanisms of drug action and possible more AF-reduction seen in hypertension trials using ARBs than ACEIs, no significant difference between ACEI and ARB treatment was found in this study by Fogari and in the ONTARGET-trial [20, 21]. In ONTARGET about 69% of the patients were hypertensive and no significant difference was seen between the ACEI ramipril, the ARB telmisartan or the combination of both (ACEI + ARB) in case of new-onset AF [21]. On the other side in the Val-HeFT (heart failure) study the ARB valsartan even showed an effect on top of another blocker of RAS (92.5% also used ACEI) [22].

Possible mechanisms for the AF-reducing effects of RAS blockers are summarized in Figure 1 and may be haemodynamic effects by reducing blood pressure *per se*. Reduction of left ventricular hypertrophy by blockers of RAS may improve left ventricular haemodynamic and the risk of developing AF. Other anti-arrhythmic effects beyond blood pressure lowering have also been suggested e.g. ion-channel function, reduction of P-wave dispersion, cardiac fibrosis, atrial stretch and left atrial dilatation, and modulation of sympathetic
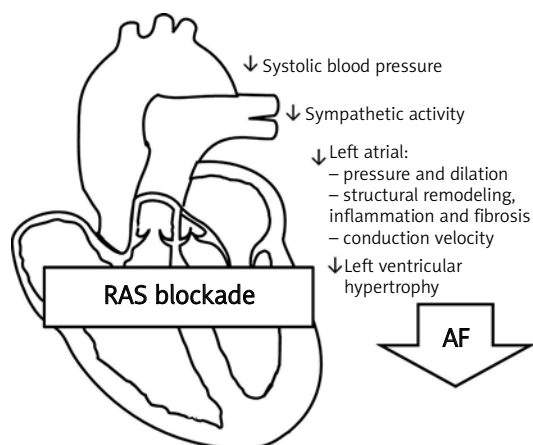
Figure 1. Possible mechanisms for reduced new-onset AF seen in patients using RAS blockers (ACEIs and ARBs)

activity. Blockade of RAS also has potassium-sparing effects that may reduce the risk of tachyarrhythmia and a direct anti-arrhythmic effect of the drugs has also been suggested. ARBs are effective in both non-ACE and ACE-dependent production of angiotensin II by giving a direct blockade at the receptor site, while an ACEI is only a competitive inhibitor of ACE that also can be overcome by a rise in renin during antihypertensive treatment. The angiotensin II-producing chimase (non-ACE dependent angiotensin II-production) seems to be more active in the left atrium than in the other cardiac chambers [23, 24], and this may be involved in a possible precedence of ARBs compared to ACEIs in reducing new-onset AF. However, more research is needed and there are ongoing prospective trials that will explore the effect of RAS blocking [25-29]. Until then none of the above observations provides a definitive indication for the use of RAS blockade to prevent AF, but have been suggested to be used in patients with recurrent AF, particularly if there are other indications such as hypertension, heart failure, or diabetes mellitus. Recent guidelines of hypertension [30] and AF [8] have also included treatment with ACEIs or ARBs for prevention of AF in hypertension due to their safety profile and a possible additional benefit of reduction of AF.

New-onset atrial fibrillation in trials using other antihypertensive treatment

The efficiency of antihypertensive treatment in reducing blood pressure is not necessarily predicting reduction in AF e.g. its capacity to reduce myocardial fibrosis. It is also difficult to draw conclusions from the results of trials comparing two or more active antihypertensive treatment regimens, due to uncertainty whether the observed effects may represent a detrimental effect of one regiment or a beneficial effect of the other or vice versa.

The use of β-blockers as first-line therapy for hypertension has lately been questioned [30, 31], but β-blockers have known effects in AF rate-control and a possible effect in maintaining sinus rhythm, especially in heart failure and in cardiac postoperative settings [32-34]. In a systematic review including almost 12000 patients with systolic heart failure (about 90% received RAS-blockade), the incidence of new-onset AF was significantly lower in the patients treated with β-blockers compared with those assigned to placebo with a relative risk reduction of 27% (14-38%, P-value <0.001) [34]. The non-selective β-blocker sotalol is effective in maintaining sinus rhythm, but has pro-arrhythmic effects and is not recommended as antihypertensive treatment. Possible mechanisms of action of the plain β-blockers to reduce risk of AF may be prevention of adverse remodelling and ischemia, reduced sympathetic drive or counteract of the β-adrenergic shortening of action potential which otherwise could contribute to perpetuation of AF [32, 34].

Calcium channel blockers are a heterogeneous group of drugs with antihypertensive properties. Non-dihydropyridines like diltiazem and verapamil are used to slow the ventricular response in AF, and verapamil has also been investigated for its effectiveness in maintaining sinus rhythm after cardioversion. Calcium channel blockers could hypothetically attenuate the Ca^{2+} overload in tachycardia-induced electrical remodelling of the atria [35]. However, studies have shown variable results and in the VALUE trial the ARB valsartan was more effective than the calcium channel blocker amlodipine in preventing new-onset AF [13].

Diuretics are often included in antihypertensive treatment regimens, but the effect on new-onset AF has to our knowledge seldom been investigated. In the Veteran Affairs Cooperative Study on Single-Drug Therapy in Mild-Moderate Hypertension comparing different antihypertensive agents, hydrochlorothiazide was associated with a significant reduction in left ventricular mass and a greater overall reduction in left atrial size than the other agents [36, 37]. Left ventricular mass and left atrial size are both known AF risk factors, but it has been suggested that the reduction of left ventricular mass with diuretics is mainly due to reduction of ventricular diameter and volume and not wall thickness or hypertrophy and the effect on new-onset AF is not known [37].

Conclusion

Atrial fibrillation and hypertension are two prevalent and often coexistent conditions, and both are responsible for considerable morbidity and mortality. The incidence of stroke in patients with

AF is strongly related to age and risk factors like hypertension, diabetes mellitus and heart failure [38, 39]. Aggressive treatment of hypertension, especially with a RAS-blocker, may reverse structural changes in the heart and may postpone or prevent AF development and recurrence and reduce thromboembolic complications. Primary prevention is a new strategy in treatment of AF (e.g. not discussed in guidelines), as it has previously been more common to focus on prevention of adverse outcome and rate- and rhythm-control of the final condition. However, as our population is aging, the number of patients with AF is expected to rise by a 2.5-fold during the next 50 years [40], a focus on primary prevention with optimal antihypertensive treatment may be important to reduce morbidity, mortality and health care expenditures in the future.

References

1. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998; 82: 2N-9N.
2. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002; 347: 1825-33.
3. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation 1997; 96: 2455-61.
4. Healey JS, Connolly SJ. Atrial fibrillation: hypertension as a causative agent, risk factor for complications, and potential therapeutic target. Am J Cardiol 2003; 91: 9G-14G.
5. Mitchell GF, Vasan RS, Keyes MJ, et al. Pulse pressure and risk of new-onset atrial fibrillation. JAMA 2007; 297: 709-15.
6. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994; 271: 840-4.
7. Schoonderwoerd BA, Smit MD, Pen L, Van Gelder, IC. New risk factors for atrial fibrillation: causes of 'not-so-lone atrial fibrillation. Europace 2008; 10: 668-73.
8. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation – executive summary: 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 (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol 2006; 48: 854-906.
9. Aksnes TA, Flaa A, Strand A, Kjeldsen SE. Prevention of new-onset atrial fibrillation and its predictors with angiotensin II-receptor blockers in the treatment of hypertension and heart failure. J Hypertens 2007; 25: 15-23.
10. Madrid AH, Bueno MG, Rebollo JM, et al. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: a prospective and randomized study. Circulation 2002; 106: 331-6.
11. Fogari R, Mugellini A, Destro M, et al. Losartan and prevention of atrial fibrillation recurrence in hypertensive patients. J Cardiovasc Pharmacol 2006; 47: 46-50.
12. Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol 2005; 45: 1832-9.
13. Schmieder RE, Kjeldsen SE, Julius S, McInnes GT, Zanchetti A, Hua TA. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. J Hypertens 2008; 26: 403-11.
14. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999; 353: 611-6.
15. Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999; 354: 1751-6.
16. Dahlöf B, Devereux RB, Kjeldsen SE, et al.; LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359: 995-1003.
17. Wachtell K, Lehto M, Gerdts E, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol 2005; 45: 712-9.
18. Tveit A, Grundvold I, Olufsen M, et al. Candesartan in the prevention of relapsing atrial fibrillation. Int J Cardiol 2007; 120: 85-91.
19. Ueng KC, Tsai TP, Yu WC, et al. Use of enalapril to facilitate sinus rhythm maintenance after external cardioversion of long-standing persistent atrial fibrillation. Results of a prospective and controlled study. Eur Heart J 2003; 24: 2090-8.
20. Fogari R, Derosa G, Ferrari I, et al. Effect of valsartan and ramipril on atrial fibrillation recurrence and P-wave dispersion in hypertensive patients with recurrent symptomatic lone atrial fibrillation. Am J Hypertens 2008; 21: 1034-9.
21. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008; 358: 1547-59.
22. Maggioni AP, Latini R, Carson PE, et al.; Val-HeFT Investigators. Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J 2005; 149: 548-57.
23. Nakashima H, Kumagai K, Urata H, Gondo N, Ideishi M, Arakawa K. Angiotensin II antagonist prevents electrical remodeling in atrial fibrillation. Circulation 2000; 101: 2612-7.
24. Celik T, Iyisoy A, Kursaklioglu H, et al. The comparative effects of telmisartan and ramipril on P-wave dispersion in hypertensive patients: a randomized clinical study. Clin Cardiol 2005; 28: 298-302.
25. The Active Steering Committee; ACTIVE Investigators, Connolly S, Yusuf S, Budaj A, Rationale and design of ACTIVE: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. Am Heart J 2006; 151: 1187-93.
26. Goette A, Breithardt G, Fetsch T, et al. Angiotensin II antagonist in paroxysmal atrial fibrillation (ANTIPAF) trial: rationale and study design. Clin Drug Investig 2007; 27: 697-705.

27. Disertori M, Latini R, Maggioni AP, et al.; GISSI-AF Investigators. Rationale and design of the GISSI-Atrial Fibrillation Trial: a randomized, prospective, multicentre study on the use of valsartan, an angiotensin II AT1-receptor blocker, in the prevention of atrial fibrillation recurrence. J Cardiovasc Med 2006; 7: 29-38.

28. Yamashita T, Ogawa S, Aizawa Y, et al.; J-RHYTHM II Investigators. Randomized study of angiotensin II type 1 receptor blocker vs dihydropiridine calcium antagonist for the treatment of paroxysmal atrial fibrillation in patients with hypertension. Circ J 2006; 70: 1318-21.

29. Tardif JC, Talajic M. Perindopril and prevention of atrial fibrillation. Eur Heart J Suppl 2007; 9: E25-E29.

30. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; 25: 1105-87.

31. National Institute for Health and Clinical Excellence (NICE) website. NICE/BHS hypertension guidelines. Available at CE's website and accessed 2006: http://www.nice.org.uk/guidance/index.jsp?action=download&o=30114.

32. Kühlkamp V, Schirdewan A, Stangl K, Homberg M, Ploch M, Beck OA. Use of metoprolol CR/XL to maintain sinus rhythm after conversion from persistent atrial fibrillation: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol 2000; 36: 139-46.

33. Bradley D, Creswell LL, Hogue CW Jr, Epstein AE, Prystowsky EN, Daoud EG. Pharmacologic prophylaxis: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest 2005; 128: 39S-47S.

34. Nasr IA, Bouzamondo A, Hulot JS, Dubourg O, Le Heuzey JY, Lechat P. Prevention of atrial fibrillation onset by beta-blocker treatment in heart failure: a meta-analysis. Eur Heart J 2007; 28: 457-62.

35. Van Noord T, Van Gelder IC Tieleman RG, et al. VERDICT: the Verapamil versus Digoxin Cardioversion Trial: A randomized study on the role of calcium lowering for maintenance of sinus rhythm after cardioversion of persistent atrial fibrillation. J Cardiovasc Electrophysiol 2001; 12: 766-9.

36. Gottdiener JS, Reda DJ, Williams DW, Materson BJ, Cushman W, Anderson RJ. Effect of single-drug therapy on reduction of left atrial size in mild to moderate hypertension: comparison of six antihypertensive agents. Circulation 1998; 98: 140-8.

37. Gottdiener JS, Reda DJ, Massie BM, Materson BJ, Williams DW, Anderson RJ. Effect of single-drug therapy on reduction of left ventricular mass in mild to moderate hypertension: comparison of six antihypertensive agents. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Circulation 1997; 95: 2007-14.

38. Jahangir A, Lee V, Friedman PA, et al. Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. Circulation 2007; 115: 3050-6.

39. Kopecky SL, Gersh BJ, McGoon MD, et al. Lone atrial fibrillation in elderly persons: a marker for cardiovascular risk. Arch Intern Med 1999; 159: 1118-22.

40. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285: 2370-5.