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HYPERTENSION AND ATRIAL FIBRILLATION WITH EMPHASIS ON PREVENTION

Sverre E. Kjeldsen[1], Tonje A. Aksnes[1], Roland E. Schmieder[2]
[1]Department of Cardiology, Oslo University Hospital, Ullevaal, Norway
[2]Department of Nephrology, University Hospital, Erlangen, Germany

Why discuss atrial fibrillation in hypertension?

Atrial fibrillation (AF) is the most frequently occurring sustained cardiac arrhythmia and is related to many cardiac diseases. Its prevalence doubles with each decade after 50 years and approaches 10% in those more than 80 years of age [1]. In men and women, respectively, hypertensive patients have a 1.4- and 1.5-fold risk of developing AF [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 [1]. 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 of AF, and increase the risk of thromboembolic complications. In the following, we will review possible mechanisms for increased risk of AF in hypertensives and look into the effect of different antihypertensive treatments.

Hypertension is a prevalent, independent, and potentially modifiable risk factor for AF development [1]. The relative risk (RR) of developing AF in patients with hypertension has been calculated at 1.4–2.1, which is modest compared to *e.g.* heart failure and valvular disease, which have relative risks of AF development of 6.1––17.5 and 2.2–8.3, respectively [2]. However, due to the high prevalence of hypertension, it is the most important risk factor. 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 statistical model [3]. Other known risk factors for AF are left ventricular hypertrophy, left atrial size, heart failure, valvular (in particular mitral valve) and ischaemic heart disease, heart rate, gender, diabetes mellitus, hyperthyroidism, severe infection, pulmonary pathology, stroke, obesity, alcohol abuse, and smoking [4]. Recently new risk factors for AF, such as sleep apnoea, inflammation, and genetic influence, have also been recognized [5].

Lone AF is defined as AF in individuals younger than 60 years without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension [6]. These patients have a favourable prognosis with respect to thromboembolism and mortality [6]. However, underlying hypertension often may not be recognized in these patients diagnosed with lone AF due to inadequate diagnostic investigations (*e.g.* no 24-hour ambulatory blood pressure measurement) or treatment with beta-blockers or calcium channel blockers for AF, which also have antihypertensive effects [5].

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 has been suggested as one important mechanism for the atrial remodelling, and blockers of RAS, such as 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 [7].

New-onset AF in hypertension trials using RAS-blocker

As yet, no prospective hypertension trial is available investigating the effect of RAS blockade on the development of AF as a primary endpoint, but there are several secondary analyses of large randomized trials. 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 ECG recordings may underestimate the prevalence of AF (although equal between the treatment groups); in recent ongoing trials, new-onset AF is a prespecified endpoint and trans-telephonic ECG monitoring is also included to recognize asymptomatic AF. There have been several hypertension trials with 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 [8, 9].

In the LIFE study, more than 9000 hypertensive patients with signs of left ventricular hypertrophy in their electrocardiogram (ECG) were randomized to atenolol (beta-blocker)- or losartan (ARB)-based antihypertensive treatment with similar blood pressure reduction between the two treatment groups [10]. Included in the analyzes of AF [11] were 8851 patients with no previous history of AF and in sinus rhythm at baseline. New-onset AF was identified in 371 of these patients from annual in-study ECGs analysed at a single centre, during the mean 4.8 years of follow-up: 221 of the atenolol--treated and 150 of the losartan-treated patients [11]. This indicates that randomization to ARB-treatment was associated with a relative risk reduction of 33% of new-onset AF, independent of other risk factors ($P < 0.001$) [11]. Patients with new-onset AF had an approximately twofold increase in risk of cardiovascular events, a threefold increase in risk of stroke, and fivefold increase in rate of hospitalization for heart failure, even after adjustment for covariates [11].

In the VALUE trial, more than 15,000 high-risk hypertensive patients were treated with amlodipine (calcium channel blocker [CCB]) or valsartan (ARB), and new-onset AF was a secondary prespecified endpoint; ECGs were obtained every year and centrally analyzed [12]. 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, $P = 0.0455$) [12]. The incidence of persistent AF was 1.35% with valsartan-treatment and 1.97% with amlodipine-treatment, resulting in an unadjusted hazard ratio of 0.68 (0.525–0.889, $P = 0.0046$). 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 [12].

In a study comparing various antihypertensive agents on AF recurrence, 369 mild hypertensive patients in sinus rhythm (but with at least two episodes of AF during the last six months) were randomized double-blindly into treatment with ARB (valsartan), ACEI (ramipril), or CCB (amlodipine) for one year [13]. AF recurrence was reduced significantly after treatment with RAS-blockade (ARB and ACEI) compared with treatment with CCB, despite a similar blood pressure lowering effect [13]. Consistently, in the ONTARGET trial 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 and ARB in cases of new-onset AF [14].

Several smaller studies have analyzed the effect of RAS blockade in combination with amiodarone after electrical cardioversion in patients with AF. In a study of 154 patients randomized to open-label treatment with the ARB irbesartan, the time until recurrence and the probability of remaining free of AF were greater after treatment with irbesartan and amiodarone than after treatment with amiodarone alone (80% *vs.* 56%, $P = 0.007$) [15]. In the hypertensive subgroup (< 50%) there was a trend for irbesartan plus amiodarone to be superior to amiodarone alone in reducing AF recurrence, with a relative risk reduction (RR) of 0.49 (0.11–2.06) [15]. Use of ARB was the only significant variable related to the maintenance of sinus rhythm after cardioversion in a multivariate analysis [15]. In another study by Ueng et al. [16], the addition of ACEI enalapril to amiodarone facilitated subsequent long-term maintenance of sinus rhythm.

In a study of 213 patients with mild hypertension and paroxysmal AF treated with amiodarone, additional treatment with the ARB losartan for one year yielded a significantly lower recurrence rate of AF compared with patients treated with the CCB amlodipine: 13 patients versus 39 patients, respectively ($P < 0.01$) [17]. Treatment with ARB alone, without adjunct anti-arrhythmic therapy be-

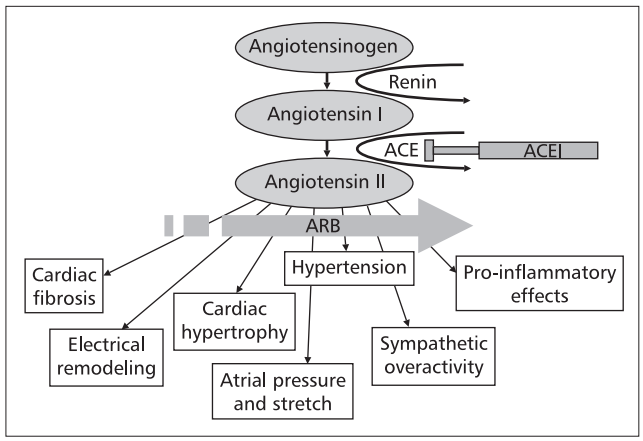

Figure 1. Possible mechanisms of how RAS-blockade may reduce new-onset AF and AF recurrence (reproduced with permission from Seminars in Cardiology [19])

fore electrical cardioversion for AF, was tested in the CAPRAF study [18]. 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 [18]. Therefore, the effect of RAS-blockade on AF recurrence without hypertension and anti-arrhythmic treatment is not known for sure. In a most recent trial (GISSI-AF) secondary prevention with ARB was also not successful to prevent recurrent AF [19].

Possible mechanisms for the AF-reducing effects of RAS blockers are summarized in Figure 1. These can be non-haemodynamic or haemodynamic effects *e.g.* by reducing blood pressure *per se* [20]. Reduction of left ventricular hypertrophy by blockers of RAS may improve left ventricular haemodynamics 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 activity [7]. Blockade of RAS may also have potassium-sparing effects that may reduce the risk of tachyarrhythmia, and a direct anti-arrhythmic effect of the drugs has 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 can also be overcome by a rise in renin during antihypertensive treatment. The above observations provide no definitive indication for the use of RAS blockade to prevent AF but their use in patients with recurrent AF has been suggested, particularly if there are other indications such as hypertension, heart failure, or diabetes mellitus [21].

New-onset AF in trials using other antihypertensive treatment regimens

Lately, the use of beta-blockers as first-line therapy for hypertension has been questioned [21]. However, beta-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 [22, 23]. In a meta-analysis including almost 12,000 patients with systolic heart failure (about 90% received RAS-blockade), beta-blockers significantly reduced the incidence of onset of AF with a relative risk reduction of 27% (RR 0.61–0.86, $P < 0.001$) [22]. The non-selective beta-blocker sotalol is effective in maintaining sinus rhythm but has pro-arrhythmic effects and is not recommended for antihypertensive treatment. Possible mechanisms of action of the plain beta-blockers to reduce risk of AF may be prevention of adverse remodelling and ischaemia, reduced sympathetic drive, or counteract of the beta-adrenergic shortening of action potential which could otherwise contribute to perpetuation of AF [22].

Calcium channel blockers are a heterogeneous group of drugs with antihypertensive properties. Non-dihydropyridines, such as diltiazem and verapamil, are used to slow the ventricular response in AF, and verapamil has been investigated for its effectiveness in maintaining sinus rhythm after cardioversion. Calcium lowering drugs could hypothetically attenuate the Ca^{2+} overload in tachycardia-induced electrical remodelling of the atria [24]. However, studies have shown variable results, and in the VALUE trial the ARB valsartan was more effective than the CCB amlodipine in preventing new-onset AF [12].

Diuretics are often included in antihypertensive treatment regimens, but, to our knowledge, the effect on new-onset AF has 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 [25, 26]. Left ventricular mass and left atrial size are both known AF risk factors, but the effect on new-onset AF is not known.

Conclusions

AF and hypertension are two prevalent and often coexistent conditions, and both are responsible for considerable morbidity and mortality. 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 the treatment of AF 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 and a 2.5-fold increase in the number of patients with AF is expected during the next 50 years [27], a focus on primary prevention with optimal antihypertensive treatment may be important to reduce morbidity, mortality, and health care expenditure 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. 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.
3. Mitchell GF, Vasan RS, Keyes MJ, et al. Pulse pressure and risk of new-onset atrial fibrillation. JAMA 2007; 297: 709–715.
4. 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: 840–844.
5. 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: 668–673.
6. 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.
7. 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.
8. 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: 1751–1756.
9. 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: 611–616.
10. Dahlöf B, Devereux RB, Kjeldsen SE, et al. 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.
11. 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: 712–719.
12. 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: 403–411.
13. 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: 1034–1039.
14. 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: 1547–1559.
15. 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: 331–336.
16. 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: 2090–2098.
17. 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.
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. GISSI-AF Investigators, Disertori M, Latini R, Barlera S, et al. Valsartan for prevention of recurrent atrial fibrillation. N Engl J Med 2009; 360: 1606–1617.
20. Aksnes TA, Strand AH, Flaa A, Kjeldsen SE. Prevention of new-onset atrial fibrillation with blockade of the renin-angiotensin system. Seminars in Cardiology 2006; 12: 125–135.
21. 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: 1105–1187.
22. 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: 457–462.
23. 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 (2 Suppl): 39S–47S.
24. Van Noord T, Van Gelder I, 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: 766–769.
25. 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: 2007–2014.
26. 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: 140–148.
27. 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: 2370–2375.