HYPERTENSION AND ATRIAL FIBRILLATION WITH EMPHASIS ON PREVENTION

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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.

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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 block- ade in combination with a beta-blocker or a non-dihydropyridine CCB 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-
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-arhythmic treatment is not known for sure. In a most recent trial (GISSI-AF) secondary prevention with ARB was also not successful to prevent AF recurrence [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 has been suggested for RAS 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 anti-arrhythmic treatment. The above observations provide no definitive indication for the use of RAS-blockade to prevent or to reduce AF in patients with 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 Ca2+ 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 postulate a role in prevention and recurrence of AF. Calcium channel blockers are known to prevent AF onset and recurrence but have not been studied in trials. Aggressive treatment of hypertension, especially with a RAS-blocker, may 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 2.5–3.5-fold increase in the number of patients with AF is expected during the next 50 years [27], AF prophylaxis in hypertension with antihypertensive treatment may be important to reduce morbidity, mortality, and health care expenditure in the future.