Pharmacological interruption of the renin-angiotensin system (RAS) has emerged over the last few years to be an important therapeutic strategy in the management of hypertension in the presence of compelling indications such as left ventricular hypertrophy (LVH), albuminuria and diabetic nephropathy1-5. The notion that blockade of the RAS provides end-organ protection above and beyond blood pressure reduction is well established although it has been challenged by a recent meta-analysis6. Additional benefits in using angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) include a reduction in new-onset diabetes and more recently, new-onset atrial fibrillation7. These additional metabolic and anti-arrhythmic benefits are likely to result in much greater reduction in cardiovascular morbidity and mortality in the long-term management of hypertension. This article specifically focuses on the effects of ARBs in prevention of new-onset AF.

New-onset atrial fibrillation: clinical trial evidence

Atrial fibrillation (AF) is the commonest arrhythmia observed in clinical practice and hypertension is a major risk factor8. The development of AF in subjects with hypertension significantly increases the risk for stroke and myocardial infarction9. Prevention of new-onset AF in hypertensive individuals is therefore an important intermediate goal in reducing cardiovascular disease. Four important clinical trials using different ARBs have provided some evidence that this class of anti-hypertensive therapy (and ACE inhibitors) may provide additional benefits beyond blood pressure reduction and beyond end-organ protection.

Irbesartan - Madrid et al., 2002

Early evidence came from a Spanish group who studied patients with pre-existent AF (n=154)10. All patients were previously converted to sinus rhythm by cardioversion. Approximately 42% of these individuals had hypertension. These patients were subsequently randomised to amiodarone or amiodarone plus irbesartan (150/300mg titrated against blood pressure). Concomitant medication was similar between groups with the exception that more patients were on beta-blockers in the irbesartan group (15 v 7, P=0.086). Over a period of 254 days (median, range 60-710 days), patients treated with irbesartan had a greater probability of remaining free of AF (79.5% vs 55.9%, P=0.007)11. This study is limited by a relatively small sample size and very wide range of follow up period.

Valsartan - Val-HeFT, 2005

In this study12, the occurrence of AF was evaluated based on adverse event reports in patients (n=4395) with heart failure enrolled into the Val-HeFT study. Over a mean follow up period of 23 months, patients randomised to valsartan therapy had significantly reduced risk (relative risk reduction =37%) in development of AF than those randomised to placebo (5.12% vs 7.95%, P=0.0002). Interestingly, brain natriuretic peptide (BNP) level at baseline was the strongest independent predictor of AF development. Furthermore, the occurrence of AF during follow up significantly worsened the prognosis in patients with heart failure12. One weakness of this study was the fact that the effect of valsartan on incidence of AF was not pre-specified in the study protocol.

Candesartan - CHARM, 2006

In the Candesartan in Heart failure: assessment of Reduction in Mortality and morbidity (CHARM) program, 7601 patients with symptomatic CHF and reduced or preserved left ventricular systolic function were randomised to candesartan (target dose 32 mg once daily, mean dose 24 mg) or placebo13. Unlike Val-HeFT study, the incidence of new AF was a prespecified secondary outcome. There were 6446 patients (84.8%) who did not have AF on their baseline electrocardiogram. Over a median follow-up period of 37.7 months, 392 (6.08%) developed AF, 177 (5.55%) in patients randomised to losartan versus 221 to atenolol (6.8 vs. 10.1 per 1,000 person-years; relative risk 0.67, P < 0.001). These data suggest that candesartan reduced the incidence of new-onset AF in a large population of patients with symptomatic CHF.

Losartan - LIFE, 2005

In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, 9,193 hypertensive patients and patients with electrocardiogram-documented left ventricular hypertrophy were randomised to once-daily losartan- or atenolol-based antihypertensive therapy14. Electrocardiograms were Minnesota coded centrally, and 6,851 patients without AF by electrocardiogram or history, who were thus at risk of developing AF, were followed for 4.8 years. New-onset AF occurred in 150 patients randomised to losartan versus 221 to atenolol (6.8 vs. 10.1 per 1,000 person-years; relative risk 0.67, P < 0.001) despite similar blood pressure reduction. Significantly, patients with new-onset AF had two-, three- and fivefold increased rates, respectively, of cardiovascular events, stroke, and hospitalisation for
heart failure. Thus new-onset AF and associated stroke were significantly reduced by losartan compared to atenolol-based antihypertensive treatment with similar blood pressure reduction. Like the Val-HeFT study, new-onset AF was not a pre-specified endpoint during study design and hence its validity is not as strong as a pre-specified prospective study. Nevertheless, the above study collectively showed that ARBs may have potential anti-arrhythmic properties.

Potential mechanisms

In the LIFE study, patient treated with losartan had significantly greater LVH regression than those on atenolol. This greater LVH regression with losartan may have led to reduced left atrial overload and dilatation, thereby reducing stimuli to new-onset AF. In addition, animal studies have shown that ARB therapy reduces atrial fibrosis, a structural change that predisposes to the development of AF. An important mechanism in AF induced by atrial pacing is shortening of the atrial effective refractory period (AERP). This phenomenon of electrical remodelling increases the inducibility of AF. There is experimental evidence that the ARB, candesartan, prevents AERP shortening during rapid atrial pacing thereby may contribute to the prevention of new-onset AF. Hence, RAS blockade appears to have beneficial effects on both electrical and structural remodelling which leads to prevention of AF.

Future directions

There is now emerging evidence from animal and human studies that ARB therapy prevents new-onset AF. Although results obtained from the few clinical studies were mostly post-hoc analysis, the findings are encouraging and appear to be most beneficial in patients with LVH and heart failure. Future prospective clinical studies and mechanistic studies are required to elucidate the pharmacological mechanisms responsible for such beneficial effects, the optimal doses of therapy required and to define the appropriate patient population who would benefit most from RAS blockade.

References