Treatment of Elderly Hypertensive Patients with Angiotensin Receptor Blockers

Dr. G Neil Thomas1, Prof. Brian Tomlinson2

1Department of Community Medicine, The University of Hong Kong, Hong Kong; 2Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong.

Hypertension in the elderly

In most developed populations, hypertension is common and the prevalence increases with age so that in people over 65 years usually at least two thirds will have hypertension, and it is a major independent risk factor for vascular disease. The relationship between increasing systolic blood pressure and the relative risk of stroke, particularly haemorrhagic stroke, is steeper than that for coronary events. A recent meta-analysis of data from one million (40-89 years) adults showed that at all ages, usual blood pressure is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg.

Although trials in the elderly have shown that antihypertensive therapy can reduce the risk of vascular events, there has been continued debate over which type of antihypertensive agent is most appropriate for first line therapy. However, the realisation that most patients will require combination therapy and the recent recommendation that if the blood pressure is >160/100 mm Hg or >20/10 mm Hg above the goal, then therapy should be initiated with a combination of two agents [1] makes the choice of combinations just as important as single drug first line therapy. Furthermore, the elderly represent a special group because of a higher frequency of concomitant conditions and organ damage related to hypertension and a greater requirement for multiple drug therapies that increase the risk for adverse drug reactions and problems with drug compliance.

The renin-angiotensin-aldosterone system (RAAS) is integrally involved in maintaining normal haemodynamic status, and angiotensin II contributes to atherogenesis and end-organ damage. Blockade of the RAAS with angiotensin-converting enzyme inhibitors (ACEIs) has proved useful in the treatment of hypertension and related vascular disorders. However, limitations, have been found with these agents, particularly the high incidence of cough, due in part to bradykinin or prostaglandin accumulation, and in rare cases, angio-oedema. The angiotensin receptor blockers (ARBs) act at the final step of the pathway selectively inhibiting the angiotensin II type 1 receptor subtype. The role of the ARBs in treating high blood pressure and end-organ damage in older patients is summarised briefly below. A more detailed summary can be found in the review by Thomas et al.

Relative blood pressure lowering efficacy amongst ARBs

Comparisons between different ARBs have generally been small short term studies with inconsistent findings. Meta-analyses of randomised, placebo-controlled trials involving over 12,000 patients treated with losartan, valsartan, irbesartan and candesartan found a mean absolute reduction of systolic/diastolic blood pressure of 10.4-11.8/8.2-8.9 mm Hg and there was no significant difference in blood pressure-lowering efficacy between any of these agents when used as monotherapy. Despite the reduced activation of the circulating RAAS in the elderly, overall reductions in blood pressure with ARBs are similar to those with other classes of antihypertensive agent in both young and elderly patients. When the hypertensive effect of these agents is not sufficient, the addition of a low dose of a thiazide diuretic will have an additive or possibly synergistic effect reducing blood pressure by 16.1-20.6/9.9-13.6 mm Hg.

ARB trials in the elderly

Few studies have evaluated the effect of ARB on elderly subjects. The Study on Cognition and Prognosis in the Elderly (SCOPE) examined the double-blind effects of the ARB, candesartan, compared to placebo in 4,964 patients, aged 70 to 89 years, who also received open-label antihypertensive therapy, predominantly thiazide diuretics to help control blood pressure. Candesartan insignificantly (p=0.19) reduced first vascular events by 10.9%, but did not reduce myocardial infarction and cardiovascular mortality, nor did the treatment reduce significant cognitive decline or developed dementia. However, candesartan reduced non-fatal stroke by 27.8% and all stroke by 23.6% (p=0.056). Similar observations were recorded in a subgroup analysis in those patients with isolated systolic hypertension, with a significant reduction in stroke events, but not other vascular disease events. This beneficial effect in stroke reduction observed in the SCOPE study is likely to be due to differences in blood pressure reduction (in favour of the ARB arm). Hence it remains unclear from this trial whether ARBs have a class effect in CVD protection.

In the Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) secondary prevention study of 1405 patients
Clinical trials in type 2 diabetic patients with albuminuria

The prevalence of diabetes is rapidly increasing worldwide, particularly in the elderly. Furthermore, approximately 50% of diabetics from the general population have hypertension, with rates increasing in the elderly, for whom renal disease is a major cause of morbidity and mortality. The benefits of ACEIs in the treatment of Type 1 diabetic patients with albuminuria have been recognised for some time, and more recently studies have highlighted the renoprotective effect of the ARBs, which have influenced recent guidelines. The European Society of Hypertension/European Society of Cardiology (ESH/ESC) recommend that ARBs should be used as a first line therapy for hypertension in those patients with Type 2 diabetes and proteinuria who may be controlled with monotherapy or they should be included as a component of combination therapies. Similarly, the JNC-7 guidelines state that albuminuria is a compelling indication for the use of ARBs. Overall, it has been recommended that ARBs should be added in patients with continued hypertension or proteinuria despite ACEI therapy in diabetic and non-diabetic renal disease.

ARBs and new-onset diabetes mellitus

Hypertensive patients are at increased risk of developing diabetes. Inhibition of the RAAS appears to reduce the risk of developing diabetes. This has been seen in a number of trials using ACEIs and with ARBs and may represent an additional benefit which would only be seen with trials extending over a longer period than is usual in studies comparing antihypertensive drugs. This issue is particularly relevant in the elderly who are at increased risk of developing diabetes as the function of pancreatic beta-cells declines with age.

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is an important independent predictor for vascular disease and the prevalence increases dramatically with age. A meta-analysis of treatment effects on LVH found that left ventricular mass index (LVMI) decreased by 13% with ARBs, 11% with calcium antagonists, 10% with ACEIs, 8% with diuretics, and 6% with beta-blockers. The effects of beta-blockers were significantly less than ARBs, ACEIs and calcium antagonists. In the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) trial in patients with essential hypertension and LVH, losartan-based therapy induced greater reduction in LVMI than atenolol-based treatment and this was thought to contribute to the better clinical outcome particularly with regard to stroke with the ARB-based therapy. In a subgroup of the LIFE study with isolated systolic hypertension with a mean age of 70 years, losartan similarly significantly reduced cardiovascular and cerebrovascular mortality more than in those receiving atenolol. Additionally, in a subgroup of diabetic patients with LVH and nephropathy, with a mean age of 60 years, losartan was found to have reduced mortality levels to those inpatients without LVH.

ARBs in heart failure

Heart failure is a common consequence of hypertension in elderly patients. Activation of the RAAS and sympathetic nervous system are important in the pathogenesis of progression of chronic congestive heart failure. In patients with heart failure who are not taking ACEIs, treatment with ARBs improves mortality and morbidity. Most patients with moderate or severe heart failure do not have hypertension but in patients with both conditions, ACEIs are the preferred treatment because of their well established efficacy. The use of ARBs in addition to ACEIs is also supported in some studies. For instance, in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) patients with chronic heart failure on ACEIs (CHARM-Added) also showed a significant (p=0.021) reduction of 16% in cardiovascular death with candesartan compared to placebo, but this benefit was not seen with the combination of valsartan and captopril in patients with left ventricular dysfunction after acute myocardial infarction.

Adverse effects of ARBs

The rate of adverse events with ARBs is similar to that seen in the placebo groups and significantly lower than in those groups receiving ACEIs and this may result in improved compliance. Common side effects include headache, dizziness or fatigue and the dry cough found with ACEIs, which seems more common in some Asian populations, is no more frequent with ARBs than with placebo. The side effects of most concern involve renal function deterioration, hyperkalaemia and hypotension. With both ARBs and ACEIs slight increases in plasma creatinine up to 20% can be expected; but greater increases may be indicative of volume depletion or renal artery stenosis. ARBs have been used without adverse effect in renovascular hypertension secondary to unilateral renal artery stenosis but ARBs should be avoided in patients with bilateral renal artery stenosis. It is always advisable to check the renal function and serum potassium soon after starting ARBs treatment, particularly in the elderly to check for deterioration in renal function or changes in plasma potassium. The ARBs may be less likely than ACEIs to cause an acute reduction in glomerular filtration because ARBs appear to increase renal blood flow more than ACEIs in hypertensive patients.
Despite the finding that most of the ARBs show somewhat higher plasma concentrations in the elderly compared to younger people, the ARBs generally do not require a dose-adjustment for elderly patients per se, partly because the elderly are slightly less responsive to drugs which inhibit the RAAS. However, in patients with moderate hepatic impairment generally all the ARBs except irbesartan and eprosartan require a reduction or limitation in dose, and in patients with severe renal impairment olmesartan should be used at a maximum dosage of 20 mg but the dosage of other ARBs does not have to be reduced.

Very few drug interactions of clinical significance have been seen with the ARBs, but telmisartan increases median trough digoxin levels by 20% so digoxin doses may have to be adjusted.17 Concomitant use of ACEIs, spironolactone, the other potassium-sparing diuretics, or potassium supplements may lead to increases in serum potassium, especially in the presence of declining renal function in the elderly. Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors decrease the antihypertensive effects of ACEIs and ARBs and may interact resulting in renal insufficiency and hyperkalaemia. The risk of this may be less with ARBs than with ACEIs but this combination should be used with caution.

**Drug selection considerations**

The ARBs represent one of the classes of drugs which can be used to treat hypertension in the elderly as either monotherapy or in combination with other classes of anti-hypertensive drugs.2,3,6,12-18 Some guidelines suggest diuretics or calcium channel blockers may have advantages in the elderly because of their efficacy in reducing systolic blood pressure and the evidence that they improve cardiovascular outcomes.2,3 In patients with hypertension and concomitant heart failure, ACEIs are still considered the first line therapy and ARBs are still considered as first line therapy or as part of a combination in diabetics with microalbuminuria or overt nephropathy.1,12 ARBs should also be considered for elderly patients with hypertension and LVH as they have been shown to be superior to beta-blocker based regimens in such high risk subjects and are especially useful in preventing stroke. Their excellent tolerability with few side effects and effectiveness in once daily dosing, offer distinct advantages over many of the older drugs and should improve compliance. This is particularly useful in elderly patients who are more likely to have concomitant diseases or be taking other drug treatments.

The ARBs appear to be a useful treatment for both uncomplicated hypertension and when hypertension is associated with complications in older patients, particularly those who have side effects when taking ACEIs. Although, the higher cost of the ARBs is a disadvantage, this may be offset when the costs related to side effects and non-compliance are taken into account.

**References**