Effective management of hypertension can substantially reduce the risk of complications. The angiotensin receptor blockers are one of the latest anti-hypertensive agents to be developed. In this article, Dr Simon Croxson focuses on the data that guides the use of these agents in the treatment of hypertension in the elderly and explores other areas where these drugs have potential benefit in elderly people.

The renin-angiotensin-aldosterone system (RAAS) plays an important role in the pathophysiology of hypertension (Figure 1). Angiotensin II acting on the AT1 receptor is a potent vasoconstrictor, increasing peripheral resistance and consequently blood pressure. Most of the known adverse effects of angiotensin II are mediated via the AT1 receptor, whereas effects on the AT2 receptor can be beneficial.

The RAAS pathway is targeted mainly by two classes of anti-hypertensive agents – ACE inhibitors and ARBs. ACE inhibitors target the synthesis of angiotensin II by ACE, but the production of angiotensin II via non-ACE pathways may increase during long-term ACE inhibitor therapy – a compensatory mechanism known as ‘ACE escape’. In contrast, ARBs inhibit the binding of angiotensin II to AT1 receptors, targeting the effects of angiotensin II rather than its production. ARBs are competitive antagonists, with a much greater affinity for the AT1 receptor (which mediates the clinical effects) than the AT2 receptor.

ARBs have different binding affinity for the AT1 receptor and different specificity for the AT1 versus AT2 receptor, although it is difficult to find all the data for all the ARBs; however, trough:peak ratios (Table 1) show the duration of clinical effect, with ratios close to one suggesting better 24-hour control. Most ARBs are usually administered once daily, improving compliance.

Hypertension in the elderly

Hypertension is an increasingly common condition among the growing elderly population, and is a major vascular risk factor, which, if left undiagnosed or inadequately treated, may lead to ischaemic heart disease, left ventricular hypertrophy, heart failure, cerebrovascular disease and dementia. However, effective management can substantially reduce the risk of these complications.

Traditionally, beta-blockers with thiazide-type diuretics have been the first-line combination for treating hypertension, despite the 1992 Medical Research Council (MRC) trial showing a significant reduction of stroke and coronary events with hydrochlorothiazide (HCTZ) but no similar benefit from atenolol. Both agents caused similar blood pressure reduction, demonstrating that hard outcome data are vitally important, rather than considering blood pressure reduction alone.

Recent studies such as the LIFE (Losartan Intervention For Endpoint study) and the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) showed that modern treatment options are more effective than beta-blockers, reducing vascular events and new diabetes. Following these studies, the 2006 National Institute for Health and Clinical Excellence (NICE) hypertension guidelines removed beta-blockers from the first-line agents, mainly due to their diabetogenic potential. The
new guidelines recommend that people over the age of 55 years (or black of any age) are given a thiazide-type diuretic or a calcium channel blocker (CCB) as first-line therapy. The second step (if patients are not controlled on monotherapy) is to add in an ACE inhibitor or ARB if the patient is ACE inhibitor intolerant. The third step is to add in a CCB or thiazide-diuretic (depending on what was given as first-line therapy). If the patient is still not controlled, NICE recommend adding further diuretic therapy, an alpha or beta blocker and seeking specialist advice.

When considering treatment options for elderly hypertensive people, it is important to balance guidelines (that are mostly based on evidence from younger patients) and current clinical evidence for elderly patients with other key issues such as compliance, polypharmacy, cognitive impairment and co-morbidities.

**Clinical evidence**

Although the World Health Organisation has specific definitions of ‘elderly’ (aged 60–79 years) and ‘old’ (aged ≥80 years) people, clinical studies in older people use varying age groups of subjects, which can make direct comparisons between studies difficult. Although the elderly population continues to increase, few trials have focused specifically on the effect of ARBs in elderly hypertensive patients. Trial design has also altered, with comparisons between active drugs replacing placebo-controlled trials. Finally, hard outcome trials examining stroke and other cardiovascular outcomes provide gold standard evidence, but many trials report only blood pressure reduction.

Four ARBs have been investigated in the elderly (aged 60 years and over). Most of these trials were randomised, double-blind studies, comparing the efficacy of an ARB against placebo, a thiazide diuretic, an ACE-inhibitor or a CCB. Compared with placebo, candesartan and eprosartan both reduced blood pressure in elderly patients (p<0.001 and p<0.0001, respectively). Compared with an ACE inhibitor or a CCB, eprosartan, telmisartan and valsartan reduced blood pressure in elderly patients to a similar extent. Thus ARBs are as effective as established anti-hypertensives at reducing blood pressure.

SCOPE (The Study on Cognition and Prognosis in the Elderly) is the only study to examine vascular outcomes of ARBs in the elderly and old. Initially, patients were randomised to receive candesartan or placebo, but it was subsequently thought that having an untreated arm was unethical. Consequently, additional anti-hypertensive medication was added after up-titration of candesartan/placebo to achieve target blood pressure (<160/85mmHg). Overall, 4,937 patients were randomised (approximately 21 per cent aged ≥80 years) and followed up for a mean of 44.6 months. Although the risk of a first major cardiovascular event (primary endpoint) was not significantly reduced in SCOPE, candesartan significantly reduced the risk of non-fatal stroke (a secondary endpoint) by 27.8 per cent (p=0.04). This finding is particularly important to elderly people, who wish to avoid non-fatal disabling complications that diminish quality of life.

In addition, cognitive function may also be improved by treatment with an ARB. A combination of telmisartan and HCTZ resulted in significantly improved scores in three of six cognitive function tests (word-list memory score, word-list recall score, and Trails B score [p<0.05]) after only 12 weeks of treatment, which was not seen in the group receiving lisinopril and HCTZ. However, this effect was not seen in SCOPE.
although cognition was assessed by the Mini Mental State Examination. Generally at least five years of anti-hypertensive treatment is required to reduce the incidence of dementia, so this is rarely seen in blood pressure trials (PROGRESS and Syst-Eur being the notable exceptions).

Data from other ARB studies, although not focusing solely on elderly patients, may also have implications for the treatment of the elderly. The ACCESS (Acute Candesartan Cilexetil Therapy in Stroke Survivors) study (patients aged 18–85 years) suggests that candesartan is a suitable agent for the early treatment of hypertension in acute ischaemic stroke if systolic blood pressure is ≥180 mmHg. Early candesartan initiation versus delayed initiation significantly improved cardiovascular morbidity and mortality, with no adverse events (AEs) due to hypotension. At present, due to a lack of available evidence, it is not known if this is a class effect.

**Other potential benefits of ARBs**

From these data, treatment of hypertension in older people with an ARB would be expected to reduce vascular events and associated disability, medical/social care and costs. However, ARBs have other beneficial effects, and may be useful in heart failure and microalbuminuria and hyperuricaemia.

The ELITE-I, Val-HeFT and CHARM heart failure studies showed that treatment with an ARB led to reductions in all cause mortality and significantly fewer hospitalisations. ELITE I compared losartan 50mg od to captopril 50mg tds: death and/or hospital admission for heart failure occurred in 9.4 per cent of losartan and 13.2 per cent of captopril patients (risk reduction 32 per cent), primarily due to a decrease in all-cause mortality (4.8 per cent versus 8.7 per cent; risk reduction 46 per cent).

The CHARM programme demonstrated that candesartan treatment provided cardiovascular benefits when added to various heart failure treatments, including ACE inhibitor, beta-blocker or aldosterone antagonist (or all three agents), when used in subjects intolerant of ACE inhibitor, and when used in subjects with presumed diastolic dysfunction. These benefits are particularly relevant for elderly patients, in whom hypertension and heart failure often co-exist. ELITE-II

<table>
<thead>
<tr>
<th>ARB</th>
<th>Trough: peak ratio*</th>
<th>Recommended doses**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>0.9–1.1 (DBP)</td>
<td>Starting dose: 8 mg od Maximum: 32 mg od</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>0.65–0.8 (DBP)</td>
<td>Starting dose: 300 mg od Maximum: 800 mg od</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>0.6–0.7 (SBP &amp; DBP)</td>
<td>Starting dose: 75 mg od Maximum: 300 mg od</td>
</tr>
<tr>
<td>Losartan</td>
<td>0.7 (DBP)</td>
<td>Starting dose: 25 mg od Maximum: 100 mg od</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>0.6–0.8 (SBP &amp; DBP)</td>
<td>Starting dose: 10 mg od Maximum: 20 mg od***</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>0.85 (SBP)- 0.61 (DBP)</td>
<td>Starting dose: 40 mg od Maximum: 80 mg od</td>
</tr>
<tr>
<td>Valsartan</td>
<td>0.66 (SBP &amp; DBP)</td>
<td>Starting dose: 40 mg od Maximum: 160 mg od</td>
</tr>
</tbody>
</table>

* Trough-peak ratio is the ratio of whatever one is measuring (such as systolic blood pressure) at the trough of effect (ie, just before the next dose is due) and the peak of effect (generally at a few hours post dose) These figures were calculated from trough and peak effects reported at predefined time periods for trough and peak drug plasma levels within a 24-hour period.

** British National Formulary 48, March 2004

*** Maximum dose of olmesartan in non-elderly patients is 40mg
confirmed that ARB treatment is well tolerated in heart failure, with significantly fewer patients discontinuing due to AEs in the losartan group compared with captopril-treated patients; and CHARM-Alternative showed candesartan tolerability equivalent to placebo in a group previously intolerant of ACE inhibitor (72 per cent cough, 13 per cent symptomatic hypotension, 12 per cent renal dysfunction).

Microalbuminuria is associated with increased mortality in the elderly patient. While most ARBs have been shown to reduce both microalbuminuria and the rate of decline of creatinine levels, the effect on microalbuminuria-associated mortality in the elderly has not been reported and has not been examined in a significant number of elderly patients. However, the risk of cardiovascular death is likely to be greater than the risk of developing end stage renal failure in older people.

Losartan has two interesting properties not reported with other ARBs. Losartan reduces urate levels by around 50µmol/L, this slight reduction might be useful in the treatment of hypertensive patients with gout. Losartan also improves non-alcoholic steatohepatitis (fatty liver), a possible precursor of cryptogenic cirrhosis.

Safety and tolerability
Safety and tolerability are important. Generally, ARBs are well tolerated by elderly patients (although the doses for some ARBs are reduced in the elderly) and clinical trials demonstrate a similar overall AE profile in ARB-treated patients and those given placebo. In particular, safety data from SCOPE confirmed that candesartan is well tolerated, with a safety profile comparable with placebo in elderly patients. Trial data (where available) show compliance rates of at least 90 per cent during treatment with ARBs, suggesting that the once-daily dosing, and low risk of AEs, encourages compliance in elderly patients.

As one would expect, compared with an ARB, patients treated with HCTZ alone were more likely to develop hypokalaemia and hyperuricaemia; those treated with enalapril were considerably more likely to report a cough, and CCB-treated elderly patients were significantly more likely to experience peripheral oedema. Although coughing and peripheral oedema are not life-threatening, they may have an impact on the elderly patient’s quality of life, especially if treatment is long-term, and may lead to drug withdrawal.

Key points

- Treatments for elderly patients must also consider compliance, polypharmacy, cognitive impairment and co-morbidities.
- Simple, once-daily dosing regimens encourage patient compliance.
- Therapies should decrease patient morbidity and enhance quality of life.
- Essential hypertension and heart failure often co-exist in the elderly.
- ARBs are well tolerated effective antihypertensive agents.

Practical aspects
The multiple co-morbidities and polypharmacy in older people are a challenge to compliance. This may be aided by once-daily dosing and fixed drug combinations such as the ARB combinations with thiazides (losartan + HCTZ, valsartan + HCTZ, irbesartan + HCTZ, olmesartan + HCTZ, telmisartan + HCTZ) and with CCB (valsartan + amlodipine). Often the extra agent added to the ARB does not add to the cost of the ARB.

Conclusion
The ARBs are a valuable group of drugs whose members differ in terms of pharmacokinetics, cost and evidence base of hard outcomes. Studies have shown that ARBs have proven efficacy in the treatment of hypertension in elderly patients. In addition, the potential benefits of ARBs in avoiding non-fatal stroke, preserving cognitive function and use in heart failure, coupled with their favourable safety and tolerability profile and high compliance rates, may make these agents particularly suited to this population.

Conflict of interest: Dr Croxson received an unconditional grant (donated to Help the Aged) from Takeda UK Ltd (makers of candesartan) to research and write this manuscript.

The author would like to thank Nia Jones for invaluable assistance.
References


8. Punzi HA, Punzi CF. Once-daily selective AT1 receptor antagonist, compared with enalapril in elderly patients with primary hypertension. TEES Study Group. J Hypertens 1999; 17: 293–302


