Hypertension in the elderly: essentially different

Thiazide-type diuretics and CCBs are recommended as first-line therapy for hypertension in elderly patients, based on the assumption they tend to have low renin essential hypertension and proven efficacy; yet the prevalence of chronic kidney disease and isolated systolic hypertension raises the possibility antihypertensive drugs that act through the renin-angiotensin system or by enhancing endothelial function may also be useful, as **Dr David Bennett-Jones** explains.

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Theoretical support for the decline in plasma renin concentration with age came from studies that claimed to show a progressive reduction of renal mass with increasing age[1,2]. However, as Fliser has pointed out, the early studies into renal size failed to exclude individuals with co-morbidity, which may well have biased the results[3]. Subsequent studies in victims of trauma have shown no such age-associated reduction in renal mass[4]. A study by Alderman in 4,170 untreated hypertensive patients, showed no significant difference in renin levels between patients aged more than, and those less than, 55 years[5]. Nevertheless, essential hypertension in the elderly has been reported to be associated with lower renin levels when compared with younger patients, and this has been shown to have implications for therapy[6]. Beta-blockers and ACE-inhibitors (ACE-Is) were shown to be effective in younger patients, whereas thiazide-type diuretics and calcium channel blockers (CCBs) were more effective in older patients[7].

A form of low renin essential hypertension (LREH), unrelated to older age, is seen most consistently in Afro-Caribbean patients, in whom a genetic basis may be suspected and in whom hypertension is relatively unresponsive to treatment with ACE-I[8]. An analogous observation had previously been made that beta-blockers, which suppress renin levels, were less effective in patients over the age of 60, and in those with a low plasma renin activity[6]. These observations have contributed to a recently outlined theory that there is a distinction between Type 1 (high renin, vasoconstrictor-mediated) and Type 2 (low-renin, volume mediated) hypertension[9]. It is suggested the elderly may have a predilection for Type 2, but the evidence for this is weaker than for Afro-Caribbeans. It is also unclear whether Type 2 hypertension is environmentally or genetically mediated. However, the prevalence of hypertension in older age is only partly explained by the late onset of essential hypertension, whether Type 1 or Type 2. There are two other common causes of hypertension in older patients not characteristic of LREH: the first of these is hypertension with associated renal dysfunction; the second is isolated systolic hypertension (ISH), typically associated with increased vascular stiffness.

Chronic kidney disease (CKD)

There is a very high prevalence of end-stage renal failure in the elderly. The incidence of new patients requiring renal replacement therapy over the age of 65 years is greater than 300 patients per million population (pmp) /year compared with less than 50 pmp/year in patients under the age of 45 years[10]. However, it has also become apparent that cardiovascular mortality rises with the very earliest manifestations of kidney disease, long before the development of symptomatic renal failure, and the need for renal replacement therapy[11] (*Table 1, overleaf*). For these reasons, in order to identify

Table 1. Cardiovascular mortality in patients with CKD[11]

CKD stage	eGFR (ml/min/1.73 m2)	Clinical stage	5-yr probabilityof dialysis (%)	5-yr probabilityof death (%)
1	Renal abnormalities Normal eGFR (>90)	Renal disease without renal impairment		
2	60-90	Mild renal impairment	1.1	19.5
3	30-60	Moderate renal failure	1.3	24.3
4	15-30	Advanced renal failure	17.6	45.7
5	< 15	End-stage renal failure		

patients early in the course of progressive renal failure, at a time when risk factor modification is more likely to be effective, the Joint Specialty Committee on Renal Medicine of the Royal College of Physicians of London and the Renal Association has recommended changes to the methodology for identifying patients with early CKD[12].

Because creatinine is released from somatic muscle, the serum creatinine concentration provides a poor measure of the true level of renal function in older patients. For this reason, the recommended measure of renal function is now a derived estimate of the glomerular filtration rate (eGFR)[12], using a formula based on the patient's serum creatinine, age, gender and racial origin. Using eGFR, CKD is divided into five stages that correspond to distinct phases of clinical management. In reverse order, stage five approximates to patients who need renal replacement therapy; stage four to patients needing preparation for dialysis; and stage three to patients needing monitoring and treatment of complications such as renal anaemia and renal osteodystrophy. A survey in the US has shown that 11 per cent of the non-institutionalised population over the age of 65 years have stage three CKD or worse[13].

Stages one and two — the earliest stages of CKD — comprise those patients with renal abnormalities, such as microalbuminuria, proteinuria or haematuria, and either normal renal function (stage one) or mild renal impairment (eGFR 90–60 ml/min/1.73m2 — stage two). Traditionally, these findings in an elderly patient have received little attention beyond a possible urology referral to exclude renal tract neoplasia in patients with haematuria. However, patients who fall into these two stages of CKD are numerous, comprising approximately six per cent of the whole population, and a very much higher proportion of the elderly population. It has become clear they are at high risk of cardiovascular events. Even screening-detected microalbuminuria, which represents the earliest stage of renal dysfunction in a non-diabetic hypertensive patient, is associated with increased vascular morbidity and mortality[14]. Although a more rapid fall in renal function has been shown in hypertensive patients with microalbuminuria compared to those without, the rate of decline of eGFR is nonetheless generally slow. Importantly, it is the early incidence of cardiovascular disease, rather than the rapid development of kidney failure that threatens these patients. For example, 19.5 per cent of patients with stage two CKD will die, usually of a vascular event, over the following five years, compared with just 1.1 per cent that will require dialysis[11]. It is preferable, therefore, to think of stage one and two CKD as pointing to widespread disease of the systemic vasculature, rather than simply as a risk factor for renal failure.

Should the finding of stage one or two CKD in an elderly patient influence the therapeutic approach to treatment of hypertension? Elderly patients, including those with renal impairment, may respond well to sodium loss, which can be attempted by dietary restriction before initiating therapy with a thiazide-type diuretic. Second-line antihypertensive therapy will then often be required. Comparative trials, which have been summarised in guidance from the National Collaborating Centre for Chronic Conditions, on behalf of the National Institute for Health and Clincal Excellence (NICE)[15] suggest that CCBs, ACE-Is and angiotensin II receptor blockers (ARBs) have similar efficacy in the elderly. Despite this evidence, only CCBs and thiazide-type diuretics are recommended as initial therapy in patients >55 years in preference to ACE-Is and ARBs, partly based on an analysis of cost effectiveness.

The danger of worsening renal failure through the use of drugs that block the renin-angiotensin system (RAS) may be overstated in published guidelines[12]. Haemodynamically critical

atherosclerotic renal artery stenosis of both kidneys, or of a single functioning kidney, does occur and caution is needed in patients with evidence of atherosclerosis elsewhere, but it is relatively unusual. Renal function should be monitored in all patients, however, and a rise in the plasma creatinine of greater than 30 per cent above the baseline, or a fall in eGFR of greater than 20 per cent following the introduction of an ACE-I or ARB, should prompt referral to a renal specialist[12]. A rise of less than this, providing it stabilises, probably reflects a corresponding fall in the glomerular capillary pressure that is likely to have a long-term beneficial effect on reducing further renal damage. In effect, it is preferable to resist the temptation to discontinue these drugs when there is a moderate rise in the serum creatinine, since such a rise is no more than an indication the drug is having the desired pharmacological effect. Even so, there is still a paucity of published data on optimum treatment for cardiovascular protection in patients with CKD[16]. The rationale for treating hypertension in patients with minor renal abnormalities is not to prevent them developing renal failure, but for treatment of systemic vascular disease. Nevertheless, the presence of CKD may support the use of a drug that acts through the RAS.

Hypertension

ISH, a particularly common form of hypertension in the elderly, provides an equally important marker of widespread vascular as well as endothelial dysfunction. It is well recognised that systolic blood pressure rises with increasing age, while diastolic pressure falls, resulting in ISH. This distinctive form of hypertension has its origin in increased vascular stiffness of major blood vessels, resulting in loss of the Windkessel effect (compliant stretching of the aorta, which buffers smaller arteries from too rapid a rise and fall of arterial pressure during ventricular systole) and augmentation of the systolic pressure due to reflection of the pulse wave back to the aorta. ISH is associated with increased cardiovascular morbidity and it has been shown in large placebo-controlled trials SHEP[17], syst-EUR[18] and SCOPE[19] that treatment with thiazide-type diuretics, CCBs, or ARBs is beneficial. Recommendations from NICE suggest ISH should be treated in the same way as essential hypertension, favouring the use of diuretics and CCBs in the elderly[15]. However, there have recently been a number of direct comparisons between ARBs and CCBs in ISH, comparing losartan, valsartan and telmisartan with amlodipine[20,21,22]. These three studies convincingly demonstrated that losartan, valsartan and telmisartan respectively, are as effective as amlodipine for reducing systolic blood pressure, generally with fewer side effects.

However, because the pathogenesis of ISH is believed to be different to essential hypertension, it is possible that different approaches might also be considered. Vascular endothelium produces a number of chemical mediators including an endothelium derived relaxing factor, which has been identified as nitric oxide (NO). Studies have shown endothelial dysfunction results in reduced NO production — associated with increased arterial stiffness and consequent ISH[23]. These findings therefore raise the possibility of treating ISH either with exogenous NO sources, such as pharmacological nitrate preparations, or by enhancing endothelial NO production by other pharmacological means. The former approach has been investigated and found it is possible to reduce systolic pressure, without causing an excessive reduction in diastolic pressure, using oral nitrate preparations[24,25]. Other approaches shown to decrease arterial stiffness include aerobic exercise, decreased sodium intake, omega-3 fatty acids, oestrogen therapy and ACE-Is[26]. Drugs acting through the RAS have also been shown to have a beneficial effect on the pulse pressure[27]. The mechanism of action of all these various approaches is not known. Beta-blockers, for example, which lower blood pressure by both renin-dependent and renin-independent effects, have not generally been effective in reducing arterial stiffness. A meta-analysis of beta-blockers by Messerli, suggests poorer cardiovascular outcomes when they are used as first-line for the treatment of hypertension in the elderly[28]. Although beta-blockers are now no longer recommended as first-line treatment by NICE, the guidance acknowledges that much of the published data relates to atenolol[15]. However, different beta-blockers have many distinguishing characteristics such as beta-1 selectivity, lipophilicity, alpha-agonist action and intrinsic sympathomimetic activity that makes it difficult to generalise. Nebivolol, for example, in addition to marked beta-1 selectivity, has been found to cause vasodilation, and reduce arterial stiffness by increasing endothelium-dependent NO production[22]. This may have significant implications for the future use of this beta-blocker in the treatment of ISH.

Implications for therapy

What conclusions can be drawn therefore about the

Key points

- Hypertension in the elderly is commonly associated with chronic kidney disease, and these patients have a particularly high mortality.
- Drugs acting through the renin/angiotensin system may be indicated for patients with chronic kidney disease.
- Isolated systolic hypertension, which is characteristic of essential hypertension in the elderly, is associated with endothelial dysfunction.
- Drugs that increase circulating nitric oxide may be beneficial for patients with isolated systolic hypertension.

pharmacological approach to hypertension in the elderly? The key message at the beginning of this article continues to be valid, that elderly patients have been shown to respond well to thiazide-type diuretics and CCBs. However, it is perhaps no longer the case that diuretics and CCBs should be considered the favoured antihypertensive agents for hypertension in the elderly. Drugs acting through the RAS have an important role in the treatment of hypertension to reduce cardiovascular risk factors in elderly patients with stage one or two CKD. ARBs are also shown to be effective for the treatment of ISH. Nitrates could also be considered for ISH in appropriate cases, although their use is not licensed for this indication. Beta-blockers may currently be out of favour for older patients, but some agents in this class may find a therapeutic role in specific situations. Further studies are needed into the role of ACE-Is and ARBs in the control of hypertension in elderly patients with CKD, and whether there are differences between beta-blockers in the treatment of ISH.

Conflict of interest: Dr Bennett-Jones has undertaken consultancy work for Boehringer Ingelheim and AstraZeneca, and has received speaker fees from Boehringer Ingelheim, AstraZeneca, MSD, BMS, Pfizer and GSK.

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