Review Paper

Hypertension and the Elderly: More Than Just Blood Pressure Control

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Hypertension is a major risk factor for cardiovascular disease in both young and elderly persons; therefore, good blood pressure control is at the center of improved cardiovascular health. The recently issued seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the European Society of Hypertension/European Society of Cardiology 2003 guidelines for hypertension management emphasize the importance of treatment efficacy rather than age in treating elderly persons with hypertension. Most hypertension clinical trials have been carried out with younger hypertensives, but this is changing with trials such as the Systolic Hypertension in the Elderly Program, the first Swedish Trial of Old Patients With Hypertension, and the Systolic Hypertension in Europe trial. These trials have clearly demonstrated the benefits of good blood pressure control in reducing the risk of stroke in elderly persons. With many safe and effective antihypertensive drugs on the market, the question becomes how elderly persons should be treated. Elderly patients often have isolated systolic hypertension, which is related to loss of arterial elasticity or compliance with aging and is more recalcitrant to treatment than essential hypertension. In addition, with advancing age there is the likelihood that other disease states are present in addition to hypertension. The newer antihypertensive drugs that interfere with the renin angiotensin system, such as angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, have the potential of improving cardiovascular outcomes in elderly persons in addition to offering effective blood pressure reduction. Their use should be considered within a comprehensive risk assessment that includes individualized risk–benefit considerations. (J Clin Hypertens. 2004;6:249–255) ©2004 *Le Jacq Communications, Inc.*

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Guidelines on hypertension management usually designate elderly persons as a separate group of patients to treat because the pathophysiology of hypertension and age-related comorbidities distinguishes the elderly from other groups of hypertensives. Landmark clinical trials such as the Systolic Hypertension in the Elderly Program (SHEP) and Systolic Hypertension in Europe (Syst-Eur) have helped introduce a paradigm shift in the general perception that increasing blood pressure (BP) with advancing age is harmless as long as it remains asymptomatic.[1,2] Hypertension in elderly persons is most often isolated systolic hypertension (ISH), which is a rise in systolic blood pressure (SBP) in the presence of normal diastolic blood pressure (DBP). Because the therapeutic goal in the treatment of hypertension previously emphasized the control of the diastolic component of BP to <90 mm Hg without a strict target for SBP, it is possible that ISH might have been underdiagnosed.[3–5] Evidence from clinical trials has shown that reducing SBP results in lower rates of stroke, myocardial infarction, and other cardiac events in elderly persons. SBP is now recognized as a better predictor of cardiovascular disease (CVD) than DBP.[3,6,7]

Hypertension is a major risk factor for CVD, which is the primary cause of death for people aged ≥75 years.[8] Consequently, good BP control is at the center of improved cardiovascular health, although lack of awareness and adequate treatment can hinder this. Data from the National Health and Nutrition Examination Survey 1999–2000 showed that 59% of all persons with hypertension in the United States were receiving treatment at the time the survey was conducted and only 34% were controlled to

recommended goal BP.[9] A survey of Americans older than age 50 years found that lack of awareness about ISH was a greater barrier to BP control than the cost of medications.[10] The Society of Geriatric Cardiology, in its position paper "Treatment of High Blood Pressure in the Elderly,"[11] estimates that fewer than 25% of people aged >65 years with hypertension are being treated. Missed opportunities to control hypertension will result in an increase in adverse cardiovascular events, higher health care costs, and a decrease in the quality of life for the elderly. This review discusses current issues in treating elderly patients with hypertension and looks to the future regarding treatments for hypertension and the prevention of CVD.

IS THERE AN AGE TO BE OLD?

There is no standard age at which one becomes "elderly," although age 60 years is most frequently used in guideline documents to distinguish middle age from elderly age (Table I). In the Global Risk Assessment Scoring Chart, developed from Framingham Study data, the relative weight of age as a risk factor for coronary heart disease increases steadily for every 5 years of life.[17] From age 45 years, age in women is correlated with higher risk points than for men, although this difference begins to plateau at 60 years of age.

The presence of hypertension is also an independent risk factor for CVD events. However, the relationship between age, hypertension, and overall CVD risk is not as straightforward as might be expected. A Japanese study of elderly patients aged 60–79 years showed that stages 1–3 hypertension in elderly Japanese persons was associated with an increased rate of CVD when compared with elderly persons of the same age with optimal or normotensive BP. This increase in risk did not rise linearly with age; after age 80 years, the correlation between the presence of hypertension and increased CVD risk was only observed for stage 3 hypertension.[18] Thus, in Japanese elderly persons, age 80 years seemed to be an important turning point with implications for treatment recommendations where the risk–benefit ratio would require careful consideration before determining treatment strategies.[19] A recent meta-analysis of 61 prospective observational studies on hypertension and mortality also found that increases in BP above 115/75 mm Hg in the 80–89-years age group was less strongly correlated with death rates from ischemic heart disease or other vascular causes compared with younger age groups.[20]

Evidence-based medicine for treating elderly persons for hypertension generally extends to the 60–79-years age group. A meta-analysis of hypertension trials was conducted to explore the potential clinical benefits of treatment for patients over age 80 years.[21] According to this analysis, actively treated elderly patients had a 34% reduction in stroke, 22% reduction in the rate of major cardiovascular events, and a 39% reduction in the rate of heart failure. However, no treatment benefit was found for cardiovascular death, and a nonsignificant relative excess of 6% of death from all causes was noted in the treatment group.[21] Although the findings on mortality contrast with the benefit of treatment for nonfatal events, the authors of the meta-analysis state that these results do not argue for setting an age threshold beyond which hypertension should not be treated. However, because of the potentially wide divergences seen in the health of octogenarians, the beneficial effects of treatment escape generalization in this group of patients. A frail octogenarian might be harmed by treatment, whereas a healthy patient might benefit from treatment.[22]

The ongoing Hypertension in the Very Elderly Trial (HYVET) is the first morbidity and mortality trial investigating the association between BP reduction and cardiovascular mortality in very elderly persons (>80 years) with hypertension. This 2100-patient study, which will randomize patients to a diuretic plus angiotensin-converting enzyme (ACE) inhibitor treatment strategy vs. no treatment, is powered to detect a 35% difference in stroke events between the placebo and active treatment groups; secondary end points include total and cardiovascular mortality.[23] The results of this trial will provide additional information with respect to the risk–benefit assessment in treating hypertension in very elderly persons.

In the absence of conclusive findings from prospective randomized trials demonstrating mortality benefits from treatment of hypertension in very elderly persons, a number of current hypertension guidelines recommend that treatment should be individualized. Recently issued guideline documents from the seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and the European Society of Hypertension/European Society of Cardiology (ESH/ESC) have adopted a pragmatic approach regarding hypertension treatment in elderly persons (Table I): BP level and associated cardiovascular risk factors rather than age should determine treatment.[9,13] As a result, the emphasis shifted from age to efficacy of treatment. That elderly persons respond similarly to antihypertensive therapy compared with younger persons with hypertension has recently been corroborated in a study of patients whose BP was not controlled using monotherapy.[24] This study compared the safety and efficacy of fixed combinations of valsartan and hydrochlorothiazide (HCTZ) vs. valsartan monotherapy.

After 4 weeks of 160 mg valsartan q.d. monotherapy, nonresponders were given either 12.5 or 25 mg HCTZ in addition to valsartan. Both the elderly (≥65 years) persons and the nonelderly persons responded similarly to combination therapy, with responder rates increasing with increasing doses of HCTZ. For the combination of 160 mg valsartan plus 25 mg HCTZ, the response rates in the nonelderly and elderly groups were comparable at 67.3% and 70.7%, respectively.

ISOLATED SYSTOLIC HYPERTENSION

ISH, which is defined as SBP ≥140 mm Hg in the presence of DBP ≤90 mm Hg,[13] is the result of the loss of arterial elasticity or compliance with aging.[3] This increase in aortic stiffness leads to a rise in SBP and a reduction in aortic volume, which in turn causes a decline in diastolic run-off and a reduction in DBP. The increase in pulse pressure caused by large artery stiffness, when taken as a surrogate measure, has been associated with damage to the heart, brain, and kidneys in elderly patients with ISH compared with persons of the same age with the same level of SBP in essential hypertension, that is, with elevated DBP.[25] It is now recognized that SBP is a better indicator of increased cardiovascular risk in elderly persons and more reliable than DBP alone.[4,5,26–29]

SHEP was the first placebo-controlled hypertension trial in the elderly where men and women aged >60 years with ISH were randomized to treatment with a diuretic and an add-on β blocker.[1] The study showed that active treatment of ISH reduced total stroke risk by 36% (Table II). ISH is more recalcitrant to treatment with antihypertensive agents than essential hypertension, as corroborated in the Hypertension Optimal Treatment (HOT) trial, where the achieved DBP was successfully controlled to below the defined study targets of ≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg.[32] The final mean SBP achieved in each of the DBP target groups was 143.7 mm Hg, 141.4 mm Hg, and 139.7 mm Hg, respectively, despite the use of combination therapy with a calcium antagonist, ACE inhibitor, and β blocker. In an Australian study comparing the efficacy of ACE inhibitors, β blockers, calcium channel blockers (CCBs), and diuretics for the control of ISH, only 6%–15% of patients reached target SBP <140 mm Hg through monotherapy.[33] Lack of adequate SBP control is also the reason for the poor rates of overall control to goal BP in a cohort of Framingham Heart Study participants from the years 1990–1995.[6]

Syst-Eur and its follow-up, Syst-Eur 2, studied the long-term safety and impact of BP lowering using a dihydropyridine CCB, with the addition of an ACE inhibitor and a diuretic, in elderly patients with ISH.[2,34] Patients in the active treatment group in Syst-Eur experienced a 42% reduction of risk of total stroke compared with placebo (Table II). CCBs are currently the most prescribed antihypertensive agents, and it has been claimed that amlodipine monotherapy is effective in reducing SBP and should be considered in the management of patients with ISH.[35]

ANGIOTENSIN-RECEPTOR BLOCKERS

Newer antihypertensives, such as angiotensin-receptor blockers (ARBs), when used in combination with a diuretic, are as effective as CCBs in reducing SBP. Since the mid-1990s, ARBs have been on the market and extensively studied. Through the selective blockade of the angiotensin II type 1 receptor, ARBs prevent the pathophysiologic effects mediated by this receptor when angiotensin II (Ang II) binds to it, such as vasoconstriction, sodium absorption, aldosterone release, and vascular smooth muscle remodeling. Ang II is the main effector molecule of the renin-angiotensin-aldosterone system (RAAS), and in addition to its volume-regulating effects, Ang II has been shown to also stimulate collagen synthesis by vascular smooth muscle cells in culture,[36] thus implicating the RAAS in the mechanism of ISH. Preclinical studies have shown that treatment with valsartan in spontaneously hypertensive rats lowered BP, prevented aortic collagen accumulation, and decreased carotid stiffness in parallel with diminished wall stress in the presence of a low-sodium diet.[37]

ARBs have been studied in the elderly population, where they have been shown to be well tolerated and effective.[19,38,39] Two studies evaluating the efficacy of losartan and valsartan in the treatment of ISH in elderly persons have reported comparable favorable results with respect to SBP lowering. The CDSP-944 Study Group reported the noninferiority of losartan treatment compared with amlodipine in elderly patients (N=857) with ISH, treated for 18 weeks.[39] Losartan and amlodipine treatments reduced BP by comparable amounts, although fewer patients experienced adverse effects on losartan than amlodipine. No conclusions regarding the equivalence of treatments could be made because the trial design was not symmetrical; losartan-treated patients could receive add-on HCTZ at Week 6 of the study, whereas amlodipine-treated patients could receive add-on HCTZ only at Week 12.

The Valsartan and Amlodipine for the Treatment of Isolated Systolic Hypertension in the Elderly (Val-Syst) trial[40] compared valsartan treatment with amlodipine treatment in elderly patients (aged 60–80 years) with ISH (N=421). It was a multicenter, double-blind, randomized, parallel-group study, with the possibility for dose titration with both study drugs, as

Table I. Guidelines and Hypertension Management in the Elderly

Guidelines	Criteria	Recommended Treatment
JNC 7[9]	Target BP <140/90 mm Hg	Diagnosis of hypertension class based on values of SBP and/or DBP Treatment recommendations same as for younger hypertensives
ESH/ESC 2003[12]	Target BP <140/90 mm Hg	Anithypertensive treatment in the elderly to follow general treatment guidelines, but gradual approach recommended, especially for frail persons
World Health Organization/ International Society of Hypertension 1999[13]	Age given as a risk factor for CVD: men >55 years and women >65 years ISH defined as SBP ≥140 mm Hg and DBP ≤90 mm Hg	Recommend treatment for hypertension up to age 80 years Advise caution in the treatment of very elderly, in the absence of sufficient data for those ≥80 years
2001 Canadian Hypertension Recommendations[14]	Elderly >60 but <84 years[15] Target BP <140/90 mm Hg	Thiazide diuretics, ARBs, or long-acting dihydropyridine CCBs recommended as initial therapy for ISH without other compelling indications For very elderly, treatment should be cautious and individualized[15]
Scottish Intercollegiate Guidelines Network[16]	Blood pressure check recommended for patients >75 years Need for identification of at-risk patients in 60–75 years age group Full assessment of cardiovascular risk Target BP: <140/90 mm Hg	Lifestyle changes Low-dose thiazide diuretics, β blockers, ACE inhibitor (no renal artery stenosis present), CCBs (avoid short acting) indicated as first line therapy ARB as alternative to ACE inhibitor if cough is present as adverse effect

JNC=Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; BP=blood pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure; ESH/ESC=European Society of Hypertension/European Society of Cardiology; CVD=cardiovascular disease; ARB=angiotensin receptor blocker; CCB=calcium channel blocker; ISH=isolated systolic hypertension; ACE=angiotensin-converting enzyme

Table II. Blood Pressure Reduction and Stroke

	SBP at End Point				
Trial	Active (mm Hg)	Placebo (mm Hg)	SBP at Baseline (mm Hg)	Active Treatment	Stroke Reduction (%)
SHEP[1]	143	155	160–219	Diuretic+β blocker vs. placebo	36
STOP-1[30]	167	186	195	Diuretic or β blocker vs. placebo	47
Syst-Eur[2]	150	160	174	CCB+ACE inhibitor+HCTZ vs. placebo	42
Syst-China[31]	151	160	170	CCB+ACE inhibitor+HCTZ vs. placebo	42

CCB=calcium channel blocker; ACE=angiotensin-converting enzyme; HCTZ=hydrochlorothiazide; STOP-1=first Swedish Trial in Old Patients With Hypertension; Syst-China=Systolic Hypertension in China; other trial names are expanded in text

well as add-on of HCTZ. Both valsartan and amlodipine effectively reduced SBP by 33.4 mm Hg and 33.5 mm Hg, respectively. Both treatments resulted in excellent control rates, with 74.7% of valsartan-treated patients and 73.0% of amlodipine-treated patients controlled to SBP <140 mm Hg. Despite similarity in treatment effects between valsartan and amlodipine, valsartan was associated with fewer adverse events. In this study, 26.8% of participants in the amlodipine group experienced peripheral edema compared with 4.8% of participants in the valsartan group. Val-Syst showed that valsartan and amlodipine were equally effective in reducing BP, but amlodipine was associated with dose-related adverse effects.[40]

PREVENTION RATHER THAN TREATMENT: THE ROLE OF RAAS MODULATION

The additional benefits of antihypertensive agents beyond blood pressure lowering can be viewed from the perspective of the cardiovascular continuum, a concept developed by Dzau and Braunwald.[41] The cardiovascular continuum highlights the importance of the RAAS in heart failure and its central role in regulating homeostasis between heart, kidney, and vasculature. This model is the basis for understanding the underlying pathophysiology of diseases in which the RAAS is implicated, including heart failure, vascular disease, and nephropathy. Because elderly patients often have concomitant cardiovascular diseases, the

choice of antihypertensive treatment agent should ideally offer protection across the entire cardiovascular continuum in addition to reducing BP.

Approximately 60% of elderly persons with diabetes will develop hypertension after age 75 years.[42] Tight BP control in diabetic patients is associated with clinically significant benefits. Diabetic patients in the UK Prospective Diabetes Study Group (UKPDS 38) were randomized to a tight BP control (SBP/DBP <150/85 mm Hg) and less-tight control (SBP/DBP <180/105 mm Hg) group. Patients in the tight control group experienced a clinically important reduction in the risk of deaths related to diabetes, complications related to diabetes, progression of diabetic retinopathy, and deterioration in visual acuity compared with the less-tight control group.[42] For the nonprimary end point of combined myocardial infarction (MI), stroke, and peripheral vascular disease, the group with tighter BP control had a 34% reduction in risk compared with the group with less-tight control (p=0.019).

The Heart Outcomes Prevention Evaluation (HOPE) study opened the door to the possibility that antihypertensive agents could confer CV protection beyond BP lowering.[43] HOPE randomized 9297 patients aged ≥55 years at high risk of cardiovascular events to receive either ramipril or placebo in addition to concomitant antihypertensive therapy.[44] Nearly 50% of the patient population was diagnosed with hypertension at baseline, but because they were receiving antihypertensive treatment already, their BP was adequately controlled at baseline. In HOPE, BP lowering was modest at 3–4 mm Hg SBP and 1–2 mm Hg DBP with the ACE inhibitor ramipril. Despite this mild reduction in BP, participants in the active treatment group experienced a reduction in the rate of stroke (32%), MI (20%), and death from cardiovascular causes (26%).

The Irbesartan Diabetic Nephropathy Trial (IDNT)[45] and the Reduction in Endpoints in Patients with non–Insulin-dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL)[46] study demonstrated the renoprotective effect of ARBs in patients with type 2 diabetes, independent of BP reduction. These studies extended the proven renoprotective effect of RAAS modulators beyond ACE inhibitors and type 1 diabetes seen in the Captopril-Diabetic Nephropathy Study.[44]

As the results of the HOPE, RENAAL, and IDNT trials suggest, therapeutic agents that interfere with the RAAS could have cardio- and renoprotective benefits. Similar results were found for the ARB losartan in the Losartan Intervention for Endpoint reduction (LIFE) trial. Participants in LIFE randomized to losartan experienced a 13% reduction for the composite end point of cardiovascular death, stroke, or MI, compared with atenolol. In this study, both study agents lowered BP by similar amounts, but losartan was associated with additional benefits beyond BP lowering. How compounds that interact with the RAAS protect against stroke is unclear at this time, but ARBs may provide beneficial effects on endothelial function.[48,49] The cardioprotective effect of agents that modulate the RAAS was further supported by the lower event rate in the ACE inhibitor arm of the Second Australian National Blood Pressure Study (ANBP2).[50] The added cardioprotective effect of RAAS modulators, based on the results of studies such as ANBP2, HOPE, and LIFE, is not accepted by all. Two large meta-analyses demonstrated that BP reduction largely accounted for the reduction in cardiovascular events independent of the antihypertensive agent.[51,52]

Results from the ongoing Valsartan Anti hypertensive Long-Term Use (VALUE) trial will further clarify whether or not stroke protection benefits exist for the ARB class beyond BP reduction.[53] VALUE is comparing two effective antihypertensives, valsartan and amlodipine, for the primary end point of cardiac mortality and morbidity in a high-risk hypertensive population.

Currently, ACE inhibitors are recommended for the treatment of a variety of disease states across the cardiovascular continuum, including heart failure and post-MI. Because these benefits derive from the inhibition of the RAAS by ACE inhibitors, the more complete blockade of the RAAS by ARBs, alone or in combination with ACE inhibitors, could potentially be more beneficial. The Valsartan in Acute Myocardial Infarction Trial (VALIANT) compared the efficacy and safety of long-term treatment with valsartan, captopril, and their combination in high-risk patients after MI. VALIANT demonstrated that RAAS blockade with an ARB in the post-MI setting appeared equal to an ACE inhibitor; the combination of an ARB and an ACE inhibitor did not offer any added benefit when compared to monotherapy. The results of VALIANT differed from those of the Optimal Trial in Myocardial Infarction with the angiotensin II Antagonist Losartan (OPTIMAAL) trial, where monotherapy with an ACE inhibitor appeared to be more effective than an ARB. The difference observed with respect to the efficacy of ARBs in these two post-MI trials could potentially be explained by the higher target dose of the ARB in VALIANT (valsartan 160 mg b.i.d.) than in OPTIMAAL (losartan 50 mg q.d.).

CURRENT PERSPECTIVE

International and national guidelines (Table I) for hypertension specifically address hypertension in elderly persons and concur on a target BP of <140/90 mm Hg. Two recently issued guideline documents, the JNC 7 and ESH/ESC 2003, have adopted a pragmatic and straightforward approach to the treatment of hypertension in elderly persons that is focused on overall CVD risk as opposed to age.

The goals of treatment of hypertension in elderly persons, a group at high risk of cardiovascular events, extend beyond BP reduction. Therefore, therapies that target multiple aspects of the cardiovascular continuum are attractive. ACE inhibitors and ARBs, due to their inhibition and blockade, respectively, of the RAAS, have been shown to confer cardiovascular benefits beyond their BP-lowering effects. For a similar degree of BP lowering and target organ protection across the cardiovascular continuum, ARBs are clearly better tolerated than ACE inhibitors, with a placebo-like tolerability profile.

Results from ongoing trials with ARBs will help clarify the role of this class of antihypertensive agents for treatment and prevention of CVD in elderly persons. VALUE will provide more insight into the relationship between BP lowering and reduction in cardiovascular morbidity and mortality. VALUE will also investigate whether the stroke reduction achieved in patients treated with losartan in LIFE was due to a specific class effect of ARBs or the potential negative effects of the β blocker atenolol.[53]

Adequately controlling BP in elderly persons confers clear benefits in cardiovascular outcomes, particularly stroke. There is consensus that BP in elderly persons should be lowered to SBP/DBP <140/90 mm Hg for the age group 60–79 years. Reaching this goal will depend not only on the efficacy of agents but also on their tolerability, which will affect compliance and overall success of treatment. Effective and safe therapies for BP reduction in elderly persons exist, but the best therapy might be early prevention of CVD through tight BP control before old age.

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