Antihypertensive drug therapy in older patients

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Elevated pulse pressure is an important cardiovascular risk factor in the elderly, and it remains to be determined whether this can be reversed. Drug treatment is justified in older patients with isolated systolic hypertension whose systolic blood pressure is 160 mmHg or higher on repeated measurement. Absolute benefit is greater in men, in patients aged 70 years or more, and in those with previous cardiovascular complications or greater pulse pressure. In the recently published comparative trials blood pressure gradients largely accounted for most, if not all, of the differences in outcome. In hypertensive patients, calcium-channel blockers may offer greater protection against stroke than against myocardial infarction, resulting in an overall cardiovascular benefit similar to that provided by older drug classes. The hypothesis that angiotensin-converting enzyme inhibitors or α -blockers might influence outcome over and beyond that expected on the basis of their blood pressure lowering effects still remains to be proved. *Curr Opin Nephrol*

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Abbreviations

ACE	angiotensin-converting enzyme
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
CI	confidence interval
DBP	diastolic blood pressure
SBP	systolic blood pressure

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Introduction

The prevalence of isolated systolic hypertension rises curvilinearly with age. It averages 8% in sexagenarians and exceeds 25% in those who are older than 80 years [1]. Isolated systolic hypertension is a distinct pathophysiological entity that is characterized by stiffening of the large arteries. Recent studies [2^{••},3^{••}] showed that the increased risk is mainly associated with systolic blood pressure (SBP) or pulse pressure.

From 1991 to 1999, three outcome trials in older patients with isolated systolic hypertension [4,5^{••},6] demonstrated that antihypertensive drug treatment is justified when SBP is 160 mmHg or higher on repeated measurement. More recently, several actively controlled trials have been reported [7[•],8,9[•],10^{••}–13^{••},14]. Their objectives were to investigate whether antihypertensive treatment initiated with calcium-channel blockers [7[•],10^{••}–12^{••}], angiotensin-converting enzyme (ACE) inhibitors [8,9[•],10^{••},14] or α -blockers [13^{••}] prevented the cardiovascular complications of hypertension as effectively as did the older therapies starting with diuretics or β -blockers. Two trials [8,15] explored how far blood pressure should be lowered in order to achieve maximal cardiovascular protection. In a few other trials the progression of atherosclerosis and the incidence of events were compared in normotensive and hypertensive high-risk patients who were randomized to placebo or an angiotensin-converting enzyme (ACE) inhibitor [16–18,19^{••}], in hypertensive patients randomized to verapamil or hydrochlorothiazide [20], and in patients with early coronary atherosclerosis randomized to placebo or amlodipine [21[•]].

The present review presents the recent evidence that pulse pressure is a major risk factor in older patients [2^{••},3^{••}]; assesses the placebo-controlled intervention studies in isolated systolic hypertension [3^{••}]; and briefly summarizes the results of some recently published trials, which to a large extent enrolled older hypertensive patients.

Role of pulse pressure as cardiovascular risk factor

We studied 7757 untreated control patients (age 60 years) with isolated systolic hypertension [SBP $\geq$ 160 mmHg and diastolic blood pressure (DBP) <95 mmHg] who were enrolled in three trials on isolated systolic hypertension [4,6,22], and in five other trials which were reported during or before 1991 [23–27]. We evaluated the risks conferred by SBP and DBP at

baseline [3••] with and without correction for regression dilution bias [28,29].

With adjustment for sex, age, smoking and previous cardiovascular complications, total mortality was positively correlated with SBP at entry ($P=0.0001$; Table 1), whereas the association with DBP was negative ($P=0.05$). Using the same adjusted Cox model as for total mortality, the relative hazard rates associated with a 10 mmHg increase in the baseline SBP were 1.12 ($P=0.02$) for stroke, but only 1.04 ($P=0.37$) for coronary events. DBP at baseline tended to be inversely correlated with cardiovascular mortality. The relative hazard rate associated with a 5-mmHg increase was 0.95 ($P=0.08$). However, DBP was not significantly associated with outcome, if fatal and nonfatal events were combined (Table 1). At any given level of SBP, all-cause mortality increased with lower DBP (Fig. 1). These findings highlight the role of pulse pressure as a risk factor.

After correction for regression dilution bias [3••,28], the relative hazard rates associated with a 10-mmHg increase in SBP were 1.26 ($P=0.0001$) for total mortality and 1.22 ($P=0.02$) for stroke, but only 1.07 ($P=0.37$) for coronary events. The correction that we [3••] and other investigators [28] applied for regression dilution bias avoids underestimation of the slope between disease outcomes and patients' blood pressures. However, the correction may also introduce bias because it is based on the blood pressure values of patients with an uneventful 1-year or 2-year follow up.

Our findings are in accord with previous reports [30–33,34•,35–39]. The Hypertension Detection and Fol-

low-up Program [30] reported that all-cause mortality rose by 11% per 10-mmHg increment in pulse pressure, but only by 8 and 5% for similar increases in SBP and DBP, respectively. The Framingham Heart Study [32] demonstrated that, in the general population, SBP is a better predictor of cardiovascular risk than DBP, particularly in those over the age of 50 years. More recently, several groups confirmed that pulse pressure both in hypertensive individuals [34•,35–37] and in patients who have suffered a myocardial infarction [38] predicted coronary accidents, and to a lesser extent stroke. These findings were consistent in men and women, and even in treated hypertensive patients, whose DBP was reduced to within the normal range [35–37].

Treatment of isolated systolic hypertension in the elderly

Earlier meta-analyses of the outcome trials in hypertension [40–51] described treatment benefit mainly as a function of the achieved DBP. We computed pooled estimates of relative and absolute benefit of antihypertensive drug treatment with and without stratification for the risk at baseline [3••].

In 15 693 patients enrolled in eight trials [4,6,22–27], the initial blood pressure (mean $\pm$ standard deviation) was 174 ± 12 mmHg for SBP and 83 ± 9 mmHg for DBP. The mean baseline-corrected differences in SBP and DBP between patients assigned control or active treatment were 10.4 [95% confidence interval (CI) 9.8–11.0] mmHg and 4.1 (95% CI 3.8–4.4) mmHg. Among individual trials the blood pressure differences ranged from 6.9 [22] to 18.2 mmHg [25] for SBP and from 2.3 [22] to 8.3 mmHg [24] for DBP.

Table 1. Relative hazard rates associated in 7757 control patients with baseline and usual blood pressures

		Relative hazard rates ^a (95% confidence interval) associated with blood pressure		
Event	Number of events	Measured at baseline	Usual ^b	<i>P</i>
Systolic blood pressure (+10 mmHg) ^c				
All-cause mortality	734	1.14 (1.07–1.21)	1.26 (1.13–1.40)	0.0001
Cardiovascular deaths	392	1.12 (1.03–1.21)	1.22 (1.06–1.40)	0.007
Cardiovascular events	835	1.08 (1.02–1.15)	1.15 (1.04–1.28)	0.01
Stroke	387	1.12 (1.02–1.21)	1.22 (1.04–1.40)	0.02
Coronary events	373	1.04 (0.95–1.14)	1.07 (0.91–1.26)	0.37
Diastolic blood pressure (+5 mmHg) ^c				
All-cause mortality	734	0.96 (0.92–1.00)	0.95 (0.89–1.00)	0.05
Cardiovascular deaths	392	0.95 (0.89–1.01)	0.93 (0.86–1.01)	0.08
Cardiovascular events	835	0.99 (0.95–1.03)	0.98 (0.93–1.04)	0.54
Stroke	387	0.99 (0.93–1.05)	0.98 (0.90–1.06)	0.66
Coronary events	373	1.00 (0.94–1.07)	1.00 (0.91–1.09)	0.99

^aThe Cox regression models were stratified for trial. The relationships between outcome and systolic or diastolic blood pressure were adjusted for each other and for sex and age.

^bCorrection for regression dilution bias [28,29] increased the slopes of the outcomes on systolic and diastolic blood pressures by 90 and 40%, respectively.

^cRelative hazard rates were calculated for increases in systolic or diastolic blood pressure by 10 mmHg or 5 mmHg respectively.

Figure 1. Risk estimates for total mortality

Risk of death in control patients ($n=7757$) with systolic blood pressure (SBP) at baseline and fixed levels of diastolic blood pressure (DBP). The 2-year probability of death was standardized to female sex, mean age (70 years), no previous cardiovascular complications and nonsmoking.

Among 7757 control patients, 734 deaths and 835 major cardiovascular complications occurred; in the 7936 patients who were allocated active treatment, these numbers were 656 and 647, respectively [3•]. Across all trials, active treatment reduced total mortality (Fig. 2) by 13% (95% CI 2–22; $P=0.02$) and cardiovascular deaths by 18% (95% CI 4–29; $P=0.01$). The pooled reduction in fatal combined with nonfatal events (Fig. 3) was 26% (95% CI 17–34; $P<0.0001$) for all cardiovascular complications, 30% (95% CI 18–41; $P<0.0001$) for stroke and 23% (95% CI 10–34; $P=0.001$) for coronary events.

The patients were subdivided into lower risk and higher risk groups on the basis of the following baseline characteristics: sex, age, SBP, pulse pressure, the presence of previous cardiovascular complications and current smoking. Relative benefit was similar across these strata. However, in terms of absolute benefit, active treatment was particularly effective in men, older persons and patients with previous cardiovascular complications. To prevent one major fatal or nonfatal cardiovascular event, the number of patients needed to treat for 5 years was 18 in men versus 38 in women, 19 in patients aged 70 years or older versus 39 in those aged 60–69 years, and 16 in patients with previous cardiovascular complications versus 37 in those without such complications. The number of patients needed to treat in order to prevent one cardiovascular death was 63 if pulse pressure at baseline was 90 mmHg or greater as compared with 119 for patients with smaller pulse

Figure 2. Effects of treatment on total and cardiovascular mortality

Solid squares represent the treatment–control odds ratios in trials, and their size is proportional to the number of events. The 95% confidence intervals for individual trials are denoted by lines and those for the pooled odds ratios by diamonds. Odds ratios are presented for three smaller trials [23–25] in systolic and diastolic hypertension (TSDH), the Medical Research Council (MRC) trials in mild hypertension [27] and in older adults [26], the Systolic Hypertension in the Elderly Program (SHEP) [4], the Systolic Hypertension in Europe trial (Syst-Eur) [6] and the Systolic Hypertension in China trial (Syst-China) [22]. Pooled estimates exclude [All randomized controlled trials (RCTs)] or include (All) the Syst-China results. Reproduced with permission from [3•].

pressure. Finally, the number of patients needed to treat for 5 years to prevent one major fatal or nonfatal cardiovascular event was similar in smokers and non-smokers (30 versus 26, respectively), because of opposite trends for stroke (85 versus 45) and coronary events (43 versus 72).

Actively controlled outcome trials in hypertension

We reviewed outcome trials in which older and newer classes of antihypertensive drugs were compared with regard to the prevention of cardiovascular complications [7•,8,9•,10••–12••]. We calculated pooled odds ratios for

Figure 3. Effects of treatment on fatal and nonfatal cardiovascular complications, stroke and coronary events

Solid squares represent the treatment-control odds ratios in trials, and their size is proportional to the number of events. The 95% confidence intervals for individual trials are denoted by lines and those for the pooled odds ratios by diamonds. Odds ratios are presented for three smaller trials [23–25] in systolic and diastolic hypertension (TSDH), the Medical Research Council (MRC) trials in mild hypertension [27] and in older adults [26], the Systolic Hypertension in the Elderly Program (SHEP) [4], the Systolic Hypertension in Europe trial (Syst-Eur) [6] and the Systolic Hypertension in China trial (Syst-China) [22]. Pooled estimates exclude [All randomized controlled trials (RCTs)] or include (All) the Syst-China results. Reproduced with permission from [3**].

the newer drugs (calcium-channel blockers and ACE inhibitors) versus the older antihypertensive agents (diuretics and β -blockers), using established statistical methods [3**] and the summary statistics published in each paper [7*,8,9*,10**–12**]. We excluded the Japanese National Intervention Cooperative Study in Elderly Hypertensives trial [7*] from our analysis because of the small number of cardiovascular complications.

Fatal end-points in our quantitative review were cardiovascular mortality and deaths from stroke, myocardial infarction, and myocardial infarction combined with sudden death. The pooled odds ratios across five trials and 30 269 randomized patients [8,9*,10**–12**] were 1.03 (95% CI 0.91–1.16; $P=0.66$) for cardiovascular mortality, 0.94 (95% CI 0.73–1.22; $P=0.70$) for fatal stroke, 1.08 (95% CI 0.86–1.35; $P=0.53$) for fatal myocardial infarction, and 1.02 (95% CI 0.86–1.22; $P=0.85$) for fatal myocardial infarction combined with sudden death. For each of these end-points, Zelen's test of heterogeneity ($P>0.10$) confirmed the hypothesis of a common odds ratio across the five trials.

We also computed pooled statistics for fatal and nonfatal end-points combined, including all cardiovascular complications as defined in each article, stroke, myocardial infarction and congestive heart failure. The pooled odds ratios across the five trials [8,9*,10**–12**] were 1.02 (95% CI 0.95–1.09; $P=0.64$) for all cardiovascular end-points, 0.95 (95% CI 0.86–1.06; $P=0.39$) for stroke, 1.10 (95% CI 0.99–1.24; $P=0.09$) for myocardial infarction, and 1.07 (95% CI 0.92–1.24; $P=0.39$) for congestive heart failure. Zelen's test showed slight heterogeneity among the trials ($P<0.03$) because, in comparison with the older drugs (diuretics and/or β -blockers), calcium-channel blockers were slightly less effective in preventing myocardial infarction (pooled odds ratio versus older drugs 1.20, 95% CI 1.04–1.39; $P=0.01$), but were more effective in preventing strokes (0.85, 95% CI 0.74–0.91, $P=0.02$). Thus, the overall cardiovascular benefit associated with their use (1.09, 95% CI 0.93–1.09; $P=0.75$) was similar to that of the older agents.

Other recent trials

In the Hypertension Optimal Treatment study [15], a total of 18 790 hypertensive patients from 26 countries (mean age 61.5 years) were randomized to reach one of three target levels of DBP (≤ 90 , ≤ 85 or ≤ 80 mmHg). The calcium-channel blocker felodipine served as the mainstay of treatment (5–10 mg/day), with the possible addition of ACE inhibitors or β -blockers. The actual blood pressure levels attained in the three groups were 143.7/85.2, 141.4/83.2 and 139.7/81.1 mmHg, respectively. In the study population as a whole, these small 2-mmHg differences in mean DBP did not influence the incidence of end-points, with the exception of myocardial infarction ($P=0.05$). In contrast, the diabetic subgroup (8%) fared particularly well on having their DBP tightly controlled by felodipine as the main component of the therapeutic regimen. Indeed, the risk of cardiovascular events and cardiovascular mortality was two to three times higher in the patients whose target DBP was 90 mmHg, as compared with those randomized to attain 80 mmHg.

In the UK Prospective Diabetes Study, type 2 diabetic patients with hypertension were randomized to tight or less tight blood pressure control [8] to be achieved by randomly allocated first-line treatment starting with atenolol or captopril [52•]. Mean blood pressure during follow up was significantly more reduced in the group assigned tight control (144/82 mmHg versus 157/87 mmHg). Risk reductions in the group randomized to tight blood pressure control were 24% for diabetes-related end-points, 32% for deaths related to diabetes, 44% for strokes and 37% for microvascular end-points [8]. Atenolol and captopril were equally effective, reducing blood pressure to a mean of 143/81 and 144/83 mmHg, respectively [52•]. Both first-line drugs were equally effective in reducing the incidence of macrovascular and microvascular end-points [52•].

In the placebo-controlled Heart Outcomes Prevention Evaluation trial [19•,53•], approximately 90% of patients had previous cardiovascular complications. Treatment with ramipril reduced cardiovascular mortality and the incidence of stroke, myocardial infarction and congestive heart failure [19•]. There was a 3/1 mmHg difference in blood pressure between the ramipril and placebo groups [19•]. The investigators hypothesized that the endothelial actions of ramipril [53•] might stabilize atherosclerotic plaques in large arteries [54]. ACE inhibitors have proven benefit in patients with heart failure [55] or dysfunction of the left ventricle [56]. However, the results of other large trials of ACE inhibitors in hypertensive patients [9•,10•] did not suggest a consistent benefit that could not be explained by blood pressure.

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [13•], patients randomized to doxazosin experienced higher rates of stroke and congestive heart failure than those allocated chlorthalidone. The ALLHAT investigators suggested that the observed blood pressure differences were sufficient to explain the higher incidence of stroke on doxazosin, but only a 10–20% increase in the occurrence of heart failure, rather than a doubling of the rate. However, this interpretation may be too simple. Before randomization, 90% of the ALLHAT patients were on antihypertensive drugs, presumably diuretics in many instances. Thus, the ALLHAT trial not only tested doxazosin versus chlorthalidone, but also stopping versus not stopping diuretic treatment in a group of hypertensive patients, of whom a considerable proportion must have been at high risk for heart failure. This probably explains why the Kaplan–Meier curves for heart failure started to diverge immediately after randomization [13•].

Conclusion

Elevated pulse pressure is an important cardiovascular risk factor in the elderly, and it remains to be determined

whether this can be reversed [2•,3•]. In older patients with isolated systolic hypertension, drug treatment is justified if systolic blood pressure is 160 mmHg or higher on repeated measurement. Absolute benefit is greater in men, in older patients and in those with previous cardiovascular complications or greater pulse pressure [3•]. In the recently published comparative trials, blood pressure gradients largely account for most, if not all, of the differences in outcome. In hypertensive patients, calcium-channel blockers may offer greater protection against stroke than against myocardial infarction, resulting in an overall cardiovascular benefit similar to that provided by the older drug classes. The hypothesis that ACE inhibitors or β -blockers might influence outcome over and beyond their blood pressure lowering effects remains to be proved.

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