

Scientific Update™

Treating systolic hypertension in the elderly: What therapeutic options are available?

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Clinicians are frequently faced with the problem of therapy for systolic hypertension in elderly patients. The criteria for diagnosing hypertension are shown in Table 1.¹ Often, hypertension is discovered to be only systolic in nature and patients are asymptomatic. There is now overwhelming evidence that treatment of these patients prevents important clinical events.^{2,3} The elderly patient is often characterized by high peripheral vascular resistance and low plasma volume.⁴ Treatment of this form of hypertension has largely been empiric and often considered unsuccessful. At the recent American Society of Hypertension Scientific Meeting, data on two studies of the treatment of systolic hypertension were presented: Syst-China and Syst-Eur. While prior studies of isolated systolic hypertension in the elderly have demonstrated the efficacy of both diuretic and beta-blocker therapy, the results of these two studies provide important data towards the safety and efficacy of calcium antagonists in the elderly. Data from prospective, randomized studies such as these — compared to less reliable retrospective

studies — provide clinicians with a better understanding of the safety of these agents. The clinician now has a wider range of treatment options for elderly patients with systolic hypertension.

Significant data published in the literature in the 1990s now allows us to make decisions concerning the therapy of these patients. The Systolic Hypertension in the Elderly Program (SHEP)² was a five-year, multicentered, double-blind, placebo-controlled trial of 4,736 patients with isolated systolic hypertension. A step-wise approach to therapy was utilized. Patients were initially started on chlorthalidone (12.5 to 25 mg/day); step two therapy included atenolol (25 to 50 mg/day) or reserpine (0.05 to 0.1 mg/day). Compared with the placebo-treated group, patients receiving active treatment had 30 fewer cerebral vascular events and 55 fewer cardiovascular events per 1,000 participants studied over the five-year period. Interestingly, the benefit occurred throughout all ranges of systolic blood pressure.

The subsequent Swedish Trial in Old Persons with Hypertension (STOP)³ also demonstrated efficacy of treatment of isolated systolic hypertension. In 1,627 participants, placebo was compared to active treatment consisting of

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Table 1: Classification of blood pressure in adults 18 or older

Category	Systolic	Diastolic
	Pressure (mmHg)	Pressure (mmHg)
Optimal	<120	<80
Normal BP	120-129	80-85
High Normal BP	130-139	85-89
Hypertension		
Stage I	140-159	90-99
Stage II	160-179	100-109
Stage III	>180	≥110

From the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.¹

atenolol, metoprolol, pindolol, or hydrochlorothiazide with amiloride. The combined active treatment resulted in a 40% reduction of total cardiovascular morbidity and mortality and, in addition, a 47% reduction in total fatal and nonfatal strokes. Interestingly, in this study, there was a significant 43% reduction in total mortality.

These two studies demonstrate the benefit of diuretics and beta-blocker therapy in the treatment of elderly patients with isolated systolic hypertension.

Calcium antagonists and systolic hypertension

Many patients presenting with hypertension, particularly those who are elderly, have contraindications to beta-blocker therapy. In addition, they often have concurrent diseases such as peripheral vascular disease, pulmonary disease, diabetes mellitus, and angina pectoris. As a result, additional therapeutic options are often considered by the physician.

Two recent studies of the treatment of systolic hypertension were presented at the American Society of Hypertension in May, 1998. In 1988, the Syst-China Collaborative Group initiated a placebo-controlled trial to investigate whether

Table 2: Syst-China demographics (at entry)

	Placebo	Nitrendipine
n	1141	1253
Age (yrs)	71	71
Cholesterol	5.1	5.1
Female %	36	35
BP (mmHg)	171/86	171/86
CHD (%)	9.4	9.4

CHD = known coronary heart disease

anti-hypertensive drug therapy would reduce the incidence of stroke in elderly Chinese patients with isolated systolic hypertension, defined as systolic blood pressure ≥ 160 mmHg and a diastolic blood pressure < 95 mmHg. These investigators randomized 2,394 patients to active treatment consisting of nitrendipine (10-40 mg/day), with the possible addition of captopril (12.5-50 mg/day) or hydrochlorothiazide (12.5-25 mg/day) to either the nitrendipine or placebo group. These therapies were utilized to reduce systolic blood pressure by > 20 mmHg, or a target of < 150 mmHg. Patient clinical characteristics of this population are outlined in Table 2.

Patients were enrolled from both northern and southern China and 42% of screened patients were enrolled. Patients were excluded if they had had major complications such as stroke or myocardial infarction (MI) one year prior to enrollment. All patients had to have a standing systolic blood pressure > 140 mmHg.

Of the 1,253 patients receiving active therapy:

- 98% received nitrendipine at a mean dose of 23 mg
- 24% received captopril at a mean dose of 30 mg
- 5.9% received hydrochlorothiazide at a mean dose of 25 mg.

The median follow-up was 3 years. The nitrendipine group had a significant reduction of blood pressure of 8.2/2.8 mmHg (95% CI, 7.4-9.0/2.0-3.6 mmHg). All endpoints were evaluated by a blinded independent committee

Table 3: Endpoints of the Syst-China trial

	Placebo	Nitrendipine	Relative Risk	P
Stroke	6.9	2.9	↓58%	0.02
Cardiac				
MI	1.0	1.4		
SD	5.5	3.1		
CV	15.2	9.4	↓39%	0.03

CV = all cardiovascular events
MI = myocardial infarction
SD = sudden death

and the primary endpoint of the trial was stroke reduction. Additional identified events were cardiac events consisting of MI and sudden death. These findings are summarized in Table 3.

Notably there was marked 58% reduction of stroke and an overall 39% reduction for all other cardiovascular events. There was no significant difference in cancer rate. The results show that if 1,000 elderly patients with isolated systolic hypertension were treated for five years, 55 deaths would be prevented and there would be 39 fewer strokes or 59 major CV endpoints.

Syst-Eur — Subgroup and per protocol analysis

In a previous issue of *Cardiology Scientific Update*, the overall results of the Systolic Hypertension in Europe Trial (Syst-Eur) have been reported. At the recent American Society of Hypertension Scientific Meeting, further analysis of these data became available. Its purpose was to describe the efficacy of therapy in subgroups and in patients who conformed to the trial protocol during the blinded portion of the study. This analysis was termed “Per-Protocol (PP) Analysis.”

Of 8,926 elderly patients screened with suspected isolated systolic hypertension, 72% entered a three-month run-in phase. A total of 4,695, or 53% of these patients, were

Table 4: Syst-Eur demographics at entry

	Placebo	Nitrendipine
n	2297	2398
age (yrs)	70.2	70.3
BP (mmHg)	174/85	174/85
Female (%)	66	68
Prior cardiac events	30	29

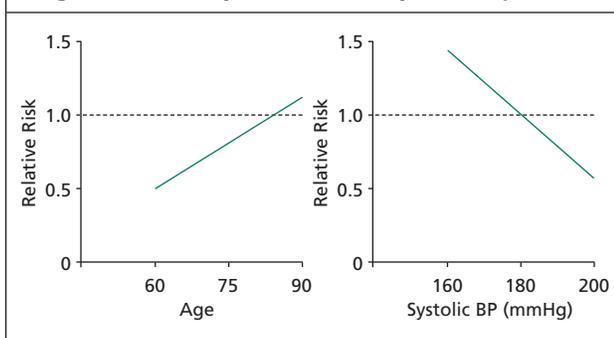
randomized to receive nitrendipine (10-40 mg/day) or placebo, with the possible addition of enalapril (5-20 mg/day) and/or hydrochlorothiazide (12.5-25 mg/day) to either group. These medications were titrated or combined to reduce the sitting systolic blood pressure ≥ 20 mmHg to <150 mmHg. Patients were randomized and stratified by centre, gender, and prior complications. Treatment was continued for 5-7 years. The nitrendipine or placebo and enalapril were administered at night and hydrochlorothiazide in the morning. The per protocol analysis includes endpoints that occurred only during the double-blind therapy phase of the protocol.

The demographics are shown in Table 4. Of the patient population, 55% were enrolled in Western Europe and 45% in Eastern Europe.

Nitrendipine was administered to 89% of subjects, enalapril to 36%, and hydrochlorothiazide to 24%. The mean dose of nitrendipine was 25 mg/day, enalapril 14 mg/day, and hydrochlorothiazide 21 mg/day.

Overall cardiovascular events were reduced with nitrendipine by 30% ($P=0.05$). Nitrendipine also reduced the incidence of stroke by 44% ($p=0.004$) and nonfatal stroke by 48% ($p=0.005$). There was no significant difference in rates of bleeding, cancer, or intercurrent disease. The cardiovascular events included transient ischemic attacks (TIA), angina, and arterial disease. The benefits of active treatment were not influenced by gender, previous cardiovascular disease, or origin of patient population. The per protocol analysis demonstrated that treating 1,000 patients for five years

Figure 1: Mortality — Reduction by nitrendipine



would prevent 24 deaths, 54 major cardiovascular endpoints including 29 strokes, and 25 cardiac endpoints.

An interesting subgroup analysis demonstrated an interaction of therapy with both age and degree of systolic hypertension. The relative risk varies as shown in figure 1.

Note that with increasing age, there is relatively less risk reduction, particularly as patients approach age 90. However, in this age group, there was significant prevention of nonfatal vascular events. As systolic blood pressure rose, the relative reduction of mortality increased. For mortality benefit, the effects of treatment appear to be greater if patient age is <80 or if systolic blood pressure is >180 mmHg.

Summary of the results

These two studies provide strong evidence that treating systolic hypertension in elderly patients prevents cardiovascular events, including stroke and sudden death. The rates of stroke are much higher than the rates for MI, particularly in the Chinese population. Both studies are consistent in demonstrating a reduction of events throughout all age groups, but mortality appears to be significantly improved in younger patients. There was no difference in efficacy throughout the ranges of blood pressure in the Chinese study, but a significant interaction with the level of hypertension and mortality reduction was observed in the European patients. The Syst-China study evaluated the data according to an "intention-to-treat" protocol; the Syst-Eur

assessed the patients while in the placebo-controlled blinded portion of the study, but the conclusions are similar to the intention-to-treat analysis.

Conclusion

Prior studies of isolated systolic hypertension in the elderly have demonstrated the efficacy of both diuretic and beta-blocker therapy. The two important studies discussed here demonstrate the efficacy of the long-acting calcium antagonist nitrendipine. Although nitrendipine is not available in North America, the JNC VI has recommended that other long-acting dihydropyridines are an appropriate alternative in these patients.¹

These two studies also contribute important experience towards the safety of calcium antagonists. Prospective data from these randomized trials did not reveal any increase in MI, GI bleeding, or cancer that have been suggested in less reliable retrospective studies. These randomized trials support the safety of calcium antagonists in hypertensive patients. Initial therapy with nitrendipine for systolic hypertension, followed by a step-wise approach to allow the addition of ACE inhibitor therapy or diuretic therapy, is very effective in preventing stroke and cardiac events in the elderly. Thus, the clinician now has a wide range of options for the treatment of our elderly patients with systolic hypertension.

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