

In this Issue...

1

ISOLATED SYSTOLIC
HYPERTENSION IN THE
ELDERLY

9

CE ASSESSMENT
QUESTIONS

10

NEW MOLECULAR
ENTITIES &
BIOLOGICALS

11

DRUG INFORMATION
AND POISON CENTER
TRAINING—SAUDI
FOOD & DRUG
AUTHORITY

Isolated Systolic Hypertension in the Elderly

Learning Objectives:

1. Characterize isolated systolic hypertension and common co-morbidities.
2. Become familiar with treatment goals in isolated systolic hypertension in the elderly.
3. Understand key issues associated with pharmacologic treatment of isolated systolic hypertension in elderly patients.
4. Become familiar with guidelines related to treatment of isolated systolic hypertension in the elderly.
5. Discuss key studies that form the evidentiary basis of current treatment.

Hypertension, which affects more than one fourth of the world's population, is the leading risk factor for mortality, and a major risk factor for coronary artery disease, diabetes and disability.^{1,2} Even though hypertension affects about one third of the population of the United States, or about 65 million adults, many people remain untreated or under-treated. The National Health and Nutrition Examination Survey (NHANES) from 1999-2000 revealed that only 31% of patients on medications for hypertension reached their target goals, and the control rates were lowest for those over 60 years of age. The NHANES survey from 2001-2002 showed no major change in awareness, treatment or control of hypertension since the earlier survey, and the NHANES survey of 2003-2004 showed that blood pressure (BP) was controlled in only 37% of patients treated for hypertension.^{3,4} Isolated systolic hypertension (ISH) most often occurs in the elderly population, and is the most frequent type of hypertension that is uncontrolled in that group of patients.⁵ Over the years there has been some controversy as to antihypertensive therapy for the elderly, but since the mid-1980s many studies have contributed to the body of evidence supporting treatment of the older population.

Definition and Prevalence

Blood pressure generally refers to arterial pressure. Systolic arterial pressure is the peak arterial pressure, occurring near the start of the cardiac cycle. Diastolic pressure is the lowest pressure and occurs during the cardiac resting phase. Pulse pressure is the difference between systolic and diastolic pressures. Normal BP is considered to be a systolic pressure of less than 120 millimeters of mercury (mm Hg) and diastolic less than 80 mm Hg. This is written as systolic over diastolic, (e.g. 115/75 mm Hg). Prehypertension is considered to be a systolic pressure of 120-139 mm Hg, or a diastolic pressure of 80-89 mm Hg. Isolated systolic hypertension is defined as having systolic BP values of more than or equal to 140 mm Hg and diastolic BP less than or equal to 90 mm Hg, thus there is an increased pulse pressure.^{6,7} Often asymptomatic, ISH is the predominant form of hypertension in the elderly. By 50 years of age, ISH begins to be more prevalent, and by 60 years of age 87% of patients with uncontrolled hypertension have ISH.⁸ Cardiovascular morbidity and mortality are linked closely to systolic blood pressure. From a starting BP of 115/75 mm Hg, the risk of cardiovascular disease doubles with every increase of 20/10 mm Hg.^{4,6}

Pathophysiology

The difference between systolic (maximum) and diastolic (minimum) pressures is the pulse pressure. To understand the implications of increased pulse pressure in ISH, it helps to understand the mechanism of the pulse wave. The pulse wave is created by contraction of the left ventricle, and is then propagated through the vascular bed. This wave is recorded as a nearly symmetric curve in people having normal vasculature. The pulse wave is followed by the “dicrotic notch” which is the result of closure of the aortic valve at the end of systole.⁸ In people with ISH, the pulse wave curve is not symmetrical, but contains a second peak which occurs in late systole and results in an overall increased magnitude of the pulse wave. The second peak is due to reflection of the wave from the arterial bed, and occurs because arterial stiffening causes a more rapid return. In normal vasculature, the reflection is small and occurs in diastole, so that the overall magnitude of the wave is not increased. Both the rapid return and the increased amplitude have an effect on left ventricular function. As the pulse wave is prolonged by the reflection, there is a decrease in time for coronary perfusion during diastole. The increase in amplitude caused by the reflection requires increased left ventricular work during late systole.⁸

The increase in arterial pulse pressure of ISH does not greatly affect systemic circulation to most body tissues, partly because their flow is related to mean pressure, and partly because vasoconstricted arteries and arterioles upstream protect cells. Protection is absent from brain and kidney cells due to the fact that those arterial vessels stay dilated. While mean flow is maintained, the increased arterial pressure affects all sizes of distributing arteries for those organs. In this way, age-related changes in the large arteries have a negative impact on target-organ small artery systems.⁹

BP Measurement and Goals of Therapy

Correct methods and instruments must be used in order to obtain valid BP measurements. Most commonly, a sphygmomanometer is used. Patients should be allowed to sit quietly for 5 minutes or more before taking a reading. A more accurate reading can be taken with the patient seated in a chair, as opposed to on the examination table, with feet on the floor and arm resting approximately level with the heart. Elderly patients should also have BP readings taken while standing, since this group of patients has increased risk of postural hypotension. In order to make a diagnosis of ISH, there must be an elevated BP value based on an average of two or more clinical readings.¹⁰ Two common mistakes made during BP measurement that lead to false high results are using a cuff that is too small, and not allowing the patient to sit quietly.⁶

Blood pressure goal recommendations from the Seventh Report of the Joint National Committee (JNC7) are aimed at reducing cardiovascular and renal morbidity and mortality, and are unrelated to age. Those goals are BP less than 140/90 mm Hg, or less than 130/80 mm Hg for those with diabetes, chronic kidney disease or coronary disease.⁶ Treatment for the elderly, according to the JNC7, is the same as for the general treatment of hypertension, except that starting doses may be lower and titration may be prolonged to reduce the risk of hypotension.¹¹

Lifestyle Modifications

Lifestyle modifications are recommended for prehypertension and hypertension. Even though there have been no long-term trials evaluating lifestyle changes in the older population, healthier lifestyles are recommended by the JNC7 for all age groups.^{1, 11} Lifestyle changes are aimed at reducing cardiovascular risk factors such as hyperlipidemia and insulin resistance, as well as elevated BP, since these risk factors often overlap. Interventions include weight loss if overweight, increased physical activity, smoking cessation, reduced alcohol intake and a healthier diet that is low in total and saturated fats, and rich in fruits and vegetables.¹ Although physical impairment might hinder the very old, an increase in daily physical exercise is recommended if possible.

Pharmacologic Treatment

Many choices of drug treatment for ISH exist today. Those choices include drugs from several different classes, but mainly diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), calcium channel blockers and beta blockers. Combining drugs from different classes is common, since a majority of patients will require treatment with more than one drug to control BP. Treatment must be individualized, and consideration taken for existing target-organ damage and comorbidities. The JNC7 Report observes the following compelling indications that influence choice of drug therapy: heart failure, post myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease and recurrent stroke prevention.¹¹ Because diabetes causes patients to be at very high risk of cardiovascular disease, treatment for those who have both hypertension and diabetes should consist of either an ACE inhibitor or an ARB combined with other agents as needed to reach the BP goal.⁶ Table 1 indicates drug combination treatments for hypertensive patients with compelling indications.¹¹

There has been a long-standing controversy surrounding ISH treatment in elderly patients. One of the concerns has been that of hypotension as a side effect, but this depends on the drug therapy used and can be minimized with low starting doses and careful titration of the drugs. A larger issue has been whether antihyper-

tensive therapy in very elderly patients may reduce the risk of stroke, but increase the risk of death. This concern has persisted, although a meta-analysis published in 1999 found that there was no justification of an age threshold beyond which hypertension should not be treated.¹² That finding has been confirmed by the results of several studies, the most recent of which evaluated indapamide, with or without perindopril, to treat hypertension in patients 80 years old or over.¹³

Key Studies

Several key clinical trials have been conducted to evaluate and support treatment options for ISH. Many of the studies included elderly (over 65 years) to very old patients (over 80 years). The findings of these landmark trials have shaped the progression of treatment of hypertension in elderly patients, starting with the European Working Party on High Blood Pressure in the Elderly (EWPHE) trial which was published in 1985. This trial evaluated the effects of treatment with hydrochlorothiazide plus triamterene as compared with placebo. The investigators found that treated patients had significant reduction in the rate of cardiovascular mortality, and non-significant reductions in cerebrovascular mortality.¹⁴

Another of the early major clinical trials was the Systolic Hypertension in the Elderly Program (SHEP) study that was published in 1991. In this study, investigators showed that, compared with placebo, the benefit of active treatment increased with age, including those patients over 80 years old. In fact, the benefit was at its greatest point in the oldest group of patients.¹⁵

The SHEP study was a randomized, double-blind, placebo-controlled trial of 4736 patients with isolated systolic hypertension (mean age 72 years) who received active treatment (n = 2365) or placebo (n = 2371). The average systolic blood pressure at baseline was 170 mm Hg, while the average diastolic blood pressure was 77 mm Hg. Active treatment included chlorthalidone at a starting dose of 12.5 mg/day or placebo, and was increased to 25 mg/day if the

SBP goal was not met at follow-up visits. If the SBP goal was still not met, atenolol 25 mg/day or placebo was added. If atenolol was contraindicated, reserpine 0.05 mg/day was used. This trial showed that active treatment significantly reduced rates of non-fatal stroke by 36%, coronary heart disease was reduced by 25%, and left ventricular failure was reduced by 53%.¹⁵ The SHEP trial provided evidence that elderly ISH patients benefit from therapy. A fourteen-year follow-up to the SHEP trial was recently published. This follow-up noted that the chlorthalidone-based treatment in the SHEP trial significantly reduced the risk of stroke, but did not significantly lower fatal events. The follow-up analysis found that chlorthalidone-based treatment also significantly reduced the risk of cardiovascular death (CI, 0.76 to 0.98, p = 0.026), and that nearly two thirds of the elderly patients who had ISH and suffered a stroke died within the 14 years.¹⁶

The Systolic Hypertension in Europe (Syst-Eur) trial, published in 1997, provided evidence that antihypertensive therapy in the elderly, including the very old, results in reduced morbidity and mortality. The study included 4695 patients with ISH, 60 years old or older, from 23 countries across western and eastern Europe. The mean (\pm SD) systolic blood pressure at

baseline was 173.8 \pm 9.9 mm Hg in the active treatment group and 173.9 \pm 10.0 mm Hg in the placebo group. Mean diastolic blood pressure was 85.5 \pm 5.8 mm Hg in the active treatment group and 85.5 \pm 5.9 mm Hg in the placebo group. Patients were randomly assigned to nitrendipine (n = 2398) at doses of 10-40 mg/day or placebo. If systolic blood pressure goals were not met, enalapril 5-20 mg/day and hydrochlorothiazide 12.5-25 mg/day, or matching placebos, were added. At a median of two years follow-up, treatment with nitrendipine reduced non-fatal stroke by 44% (p = 0.007), and total stroke by 42% (p = 0.003).¹⁷

A similar trial, the Systolic Hypertension in China (Syst-China) trial was published in 1998. The average age of patients was 66.5 years, and average systolic and diastolic blood pressures at baseline were 170.5 mm Hg

Table 1. Clinical trial and guideline basis for compelling indications for individual drug classes.

COMPELLING INDICATION*	RECOMMENDED DRUGS					
	DIURETIC	BB	ACEI	ARB	CCB	ALDO ANT
Heart failure	•	•	•	•		•
Postmyocardial infarction		•	•			•
High coronary disease risk	•	•	•		•	
Diabetes	•	•	•	•	•	
Chronic kidney disease			•	•		
Recurrent stroke prevention	•		•			

* Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the BP.

† Conditions for which clinical trials demonstrate the benefit of specific classes of antihypertensive drugs used as part of an antihypertensive regimen to achieve BP goal to test outcomes.

Adapted from Chobanian AV, Bakris GL, Black HR, et al: National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560-2572. (IDIS Article Number 499778)


Table 2. Summary of key studies in elderly patients or elderly patients with isolated systolic hypertension

Study	No. Pts	Mean Age (Yrs)	Median Follow-up (Yrs)	Mean Start SBP/DBP (mm Hg)	Treatment(s)	Outcomes	Results- Comparison between groups
EWPHÉ ¹⁴ 1985	840	72	4.6	183/101	<ul style="list-style-type: none"> HCTZ+thiamterene with methyldopa add-on placebo 	<ul style="list-style-type: none"> event / rate per 1000 pt-yrs active vs. placebo all cardiovascular mortality 34 vs. 47 cardiac mortality 15 vs. 24 all cause mortality 69 vs. 76 	RRR (95% CI) 27 (1 to 46) 38 (1 to 61) 9 (+15 to 28)
SHEP ¹⁵ 1991	4736	71.6	4.5	170/77	<ul style="list-style-type: none"> Chlorthalidone, atenolol or reserpine add-on goal SBP < 160 or reduce by 20 mm Hg placebo 	<ul style="list-style-type: none"> event / 5-year incidence % active vs. placebo stroke 5.2 % vs. 8.2% all CHD events 5.9% vs. 7.7% all cardiovascular events 12.2% vs. 17.5% 	RR (95% CI) 0.64 (0.50 to 0.82) 0.75 (0.60 to 0.94) 0.68 (0.58 to 0.79)
Syst-Eur ¹⁷ 1997	4695	70.3	2.0	174/86	<ul style="list-style-type: none"> nifedipine combine or replace by enalapril +/- HCTZ to reach goal SBP < 150 placebo 	<ul style="list-style-type: none"> event / rate per 1000 pt-yrs active vs. placebo stroke 7.9 vs. 13.7 all mortality 20.5 vs. 24.0 cardiovascular events 23.3 vs. 33.9 	RRR (95% CI) 42% (17 to 60) 14% (+9 to 33) 31% (14 to 45)
Syst-China ¹⁸ 1998	2394	66.4	3.0	171/86	<ul style="list-style-type: none"> nitrendipine +captopril +/-HCTZ to reach goal SBP < 150 placebo 	<ul style="list-style-type: none"> event / rate per 1000 pt-yrs active vs. placebo stroke 13.0 vs. 20.8 all mortality 17.4 vs. 28.4 cardiovascular mortality 9.4 vs. 15.2 	RRR (95% CI) 38% (9 to 58) 39% (16 to 57) 39% (4 to 61)
STOP-2 ²⁴ 1999	6614	76.0	4.0	194/98 (supine)	<ul style="list-style-type: none"> conventional (atenolol, metoprolol, pindolol or HCTZ, or combined β-blocker/diuretic) newer (enalapril, lisinopril, felodipine, or isradipine) add-on diuretic or ACE or β-blocker; target <160/95 	<ul style="list-style-type: none"> event / rate per 1000 patient-yrs combined (fatal stroke, fatal MI, fatal CVD) / 19.8 for newer or conventional treatment combined all cardiovascular or cerebrovascular events / ~43 for each all mortality / ~33 for each <p>Blood pressure was reduced by ~35/17 in all groups</p>	RR (95% CI) conventional/newer 0.99 (0.84 to 1.16) 0.96 (0.86 to 1.08) 1.01 (0.89 to 1.14)
ALLHAT ¹⁹ 2002	33,357	66.9	4.9	146/84	<ul style="list-style-type: none"> chlorthalidone amlodipine lisinopril add-on drugs as needed for goal BP <140/90 	<ul style="list-style-type: none"> Event/ 6-year rate per 100 persons Combined fatal CHD or non-fatal MI/ chlorthalidone 11.5 amlodipine 11.3 lisinopril 11.4 	RR (95% CI) amlodipine vs. chlorthalidone 0.98 (0.90 to 1.07) lisinopril vs. chlorthalidone 0.99 (0.91 to 1.08)
LIFE ²¹ 2002 Substudy	1326	70	4.7	174/83	<ul style="list-style-type: none"> losartan atenolol with HCTZ add-on and then other drugs to reach goal SBP 140 	<ul style="list-style-type: none"> event / rate per 1000 patient-yrs Composite CVD death, stroke or MI/ 25.1 with losartan vs. 35.4 with atenolol Total mortality/ 21.2 with losartan vs. 30.2 with atenolol 	RR (95% CI) losartan/atenolol 0.75 (0.56 to 1.01) 0.72 (0.53 to 1.00)
SCOPE ²³ 2003	4964	76.4	3.7	166/90	<ul style="list-style-type: none"> candesartan placebo double dose, then add-on open-label therapy for either group for goal BP <160/90 	<ul style="list-style-type: none"> Event/ rate per 1000 pt years cardiovascular death, MI or stroke/ 26.7 in candesartan vs. 30.0 in control total mortality/ 27.9 in candesartan vs. 29.0 in control non-fatal stroke/ 7.4 in candesartan vs. 10.3 in control 	RRR (95% CI) candesartan/control 10.9% (-6.0 to 25.1) 3.7% (CI not reported) 27.8% (1.3 to 47.2) Note: BP during trial in candesartan group 145/80 vs. placebo 148/82

Study	No. Pts	Mean Age (Yrs)	Median Follow-up (Yrs)	Mean Start SBP/DBP (mm Hg)	Treatment(s)	Outcomes	Results- Comparison between groups
SHELL ²² 2003	1882	72	2.7	178/87	<ul style="list-style-type: none"> lacidipine chlorthalidone add-on ACE inhibitor if needed for goal SBP ≤160	<ul style="list-style-type: none"> Composite of cardiovascular and cerebrovascular events (overall incidence 9.3%) All cause mortality (overall incidence 14.2%) 	HR (95% CI) lacidipine/chlorthalidone 1.01 (0.75 to 1.36) 1.23 (0.97 to 1.57)
Val-Syst ²⁵ 2003	421	69	0.5	170/84	<ul style="list-style-type: none"> valsartan 80mg daily amlodipine 5 mg daily double dose then add-on low dose HCTZ if needed	Mean sitting systolic blood pressure goal < 140 mm Hg	Mean end BP 139/78 Difference in SBP change -1.53 (95% CI - 4.01 to 0.94)
INSIGHT ²⁶ 2004 subanalysis	6321 (total) 1498 (ISH subanalysis)	Range 55-80	3.0	173/88	<ul style="list-style-type: none"> nifedipine GITS HCTZ + amloride (co-amilozide) add-on atenolol or enalapril, then add third drug for either group	Composite of cardiovascular or cerebrovascular death, MI, heart failure or stroke	The incidence of an outcome was 6.0% with nifedipine and 6.6% with co-amilozide. This difference was not statistically significant. The incidence rates were similar in subjects with ISH and those without ISH.
HYVET ¹³ 2008	3845	83.6	1.8* * stopped early; reduced mortality	173/90	<ul style="list-style-type: none"> sustained release indapamide- add on perindopril if needed to reach goal BP 150/80 Placebo 	<ul style="list-style-type: none"> Fatal or non-fatal stroke Death- any cause Heart Failure 	HR (95% CI) active/placebo 0.70 (0.49-1.01) 0.79 (0.65-0.95) 0.36 (0.22-0.58)

HYVET= Hypertension in the Very Elderly Trial; INSIGHT = International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment; Val-Syst = Valsartan and amlodipine in the treatment of isolated Systolic hypertension in elderly patients ;SHELL= Systolic Hypertension in the Elderly Long-term Lacidipine; SCOPE = Study on Cognition and Prognosis in the Elderly; LIFE = Losartan Intervention for Endpoint; ALLHAT = Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack ; PRESERVE = Prospective Randomized Enalapril Study Evaluation regression of Ventricular Enlargement; STOP-2 = Swedish Trial in Old Patients with hypertension-2 ; Syst-China = Systolic Hypertension in China; Syst-Eur = Systolic Hypertension in Europe; SHEP = Systolic Hypertension in the Elderly Program; EWPHE = European Working Party on High blood pressure in the Elderly

CHD= coronary heart disease; CI = confidence interval; CVD=cardiovascular disease; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; HR = hazards ratio; ISH = isolated systolic hypertension; LV=left ventricular; pt-yrs= patient-years; RR = relative risk; RRR = relative risk reduction; SBP = systolic blood pressure;



Dr. Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and (Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the *IDIS* database, overseeing the Drug vocabulary and contributing articles for the *World of Drug Information* newsletter.

and 86.0 mm Hg respectively. Patients were randomized to the active treatment group (n = 1253) or placebo (n = 1141). Active treatment consisted of nitrendipine at doses of 10-40 mg/day, with additional captopril at 12.5-50 mg/day or hydrochlorothiazide at 12.5-50 mg/day, or both, if needed. Active treatment was found to reduce total stroke by 38% (p = 0.01), all-cause mortality by 39% (p = 0.003), cardiovascular mortality by 39% (p = 0.03), and stroke mortality by 58% (p = 0.02).¹⁸

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) Trial, published in 2002, was important in finding that thiazide diuretics are unsurpassed in reducing morbidity and mortality in hypertension.

The objective of this study was to find whether treatment with a calcium channel blocker or an ACE inhibitor reduces the incidence of coronary heart disease or other cardiovascular disease events as compared with treatment with a diuretic. The study showed instead that there was no difference in the primary outcome among the treatment groups.

This randomized trial, with a mean follow-up of 4.9 years, included 33,357 hypertensive patients 55 years of age or older (mean = 66.9 yrs). Mean untreated systolic blood pressure at baseline was 156 mm Hg and mean untreated diastolic blood pressure was 89 mm Hg. Patients were randomly assigned to chlorthalidone 12.5-25 mg/day (n = 15,255); amlodipine 2.5-10 mg/day (n = 9,048); or lisinopril 10-40 mg/day (n = 9054). The primary outcome, combined fatal coronary heart disease or non-fatal myocardial infarction, occurred in 2956 patients and was not different between the groups. All-cause mortality was also not different between the treatment groups. However, the 5-year systolic blood pressures were significantly higher in the amlodipine group (0.8 mm Hg, p = 0.03) and in the lisinopril group (2 mm Hg, p < 0.001) compared with the chlorthalidone group. Diastolic blood pressure was significantly lower in the amlodipine group (0.8 mm Hg, p < 0.001). The investigators concluded that thiazide diuretics should be the first step in treating hypertension.¹⁹

Results from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study were also published in 2002. This was a 5-6 year, randomized, double-blind trial of 9193 hypertensive patients 55-80 years of age, with systolic blood pressures of 160-200 mm Hg and diastolic blood pressures of 95-115 mm Hg.²⁰

A subset of this population (n = 1326) with ISH was also studied. These patients were 55-80 years old and had systolic blood pressures between 160-200 mm Hg, and diastolic blood pressures less than 90 mm Hg. These patients were randomized to losartan 50-100 mg/day (n = 660) or atenolol 50-100 mg/day (n = 666) with

hydrochlorothiazide 12.5-25 mg/day as add-on to both groups. The primary outcome measure was a composite end point of cardiovascular death, stroke or myocardial infarction. Mean follow-up was 4.7 years. Results of this study showed that BP was reduced by 28/9 mm Hg in both groups, however, the main outcome was reduced 25% in the losartan group compared with atenolol, with 25.1 events per 1000 patient-years in the losartan group and 35.4 events per 1000 patients years in the atenolol group, (95% CI 0.53-0.95; p = 0.02). The losartan group also had reductions in cardiovascular mortality (95% CI 0.34-0.87; p = 0.01); non-fatal and fatal stroke (95% CI 0.38-0.92; p = 0.02); new onset diabetes (95% CI 0.40-0.97; p = 0.04); and total mortality (95% CI 0.53-1.00; p = 0.046). Left ventricular hypertrophy, as measured by electrocardiography, was reduced in the losartan group compared to atenolol (p < 0.001).²¹

Lacidipine and chlorthalidone were compared for treatment of ISH in the elderly in the Systolic Hypertension in the Elderly: Lacidipine Long-term (SHELL) study, published in 2003. The purpose of this study was to conduct a trial comparing treatments that had been shown to protect against complications of ISH. A total of 1882 male and female patients with ISH, aged \geq 60 years, were randomized to receive oral doses of chlorthalidone 12.5-25 mg/day (n = 940) or oral lacidipine 4-6 mg/day (n = 942), with fosinopril add-on if necessary. At baseline, patients had systolic BP of \geq 160 mm Hg, and diastolic BP of \leq 95 mm Hg. Median length of treatment was 32 months and the primary endpoint was a composite of cardiovascular and cerebrovascular events.

Both study drugs were shown to significantly reduce SBP and DBP (95% CI 30-33; p < 0.001 for both) though the SBP was reduced to a greater extent. The mean reduction was 36.8/8.1 mm Hg in the chlorthalidone group, and 38.4/7.9 mm Hg in the lacidipine group. There was no significant difference between the two groups as to the overall incidence of cardiovascular and cerebrovascular events, or total mortality. This study showed no significant difference between treatment with the thiazide diuretic or the calcium channel blocker.²²

The Study on Cognition and Prognosis in the Elderly (SCOPE) trial was conducted from 1997-2002 and was published in 2003. This double-blind, randomized trial evaluated whether candesartan use in elderly patients with mild to moderate hypertension could achieve a reduction in cardiovascular events, cognitive decline and dementia. The study included 4937 patients who were from 15 countries, were 70-89 years of age, and had SBP 160-179 mm Hg and/or DBP 90-99 mm Hg. Patients had Mini Mental State Examination (MMSE) scores \geq 24. Patients were randomized to receive candesartan orally at doses of 8-16 mg/day (n = 2477) or

placebo (n = 2460), with hydrochlorothiazide added if needed. The treatment period was 3-5 years, and the primary endpoint measured was a composite of cardiovascular death, non-fatal stroke and non-fatal myocardial infarction.

Investigators found that BP was lowered by 21.7/10.8 mm Hg in the candesartan group and by 18.5/9.2 mm Hg in the control group. Regarding the primary endpoints, there were 242 occurrences of a first major cardiovascular event in the candesartan group and 268 occurrences in the control group (95% CI -6.0-25.1; p = 0.19). Candesartan reduced non-fatal stroke by 27.8% (95% CI 1.3-47.2; p = 0.04), and all stroke by 23.6% (95% CI -0.7-42.1; p = 0.056). No significant differences were seen in myocardial infarction and cardiovascular mortality. The mean MMSE score was lowered in the candesartan group from 28.5 to 28.0 and in the control group from 28.5 to 27.9 (p = 0.20).

In elderly patients with mild to moderate hypertension, compared to control, candesartan showed slightly more reduction of BP, a reduction (though statistically non-significant) in major cardiovascular events, and a significant reduction in non-fatal strokes. Both study groups maintained cognitive function.²³

The most recently published study, the Hypertension in the Very Elderly Trial (HYVET), included 3845 patients over 80 years old from Europe, China, Australasia and Tunisia. This trial also showed that there is no upper age limit for treating patients with hypertension.

HYVET was a randomized, placebo-controlled trial in which the mean patient age was 83.6 years, and mean BP was 173/90 mm Hg (sitting). Active treatment was 1.5 mg sustained release indapamide (a thiazide-like diuretic) with the ACE inhibitor perindopril 2 or 4 mg (or placebo) added if needed to reach target BP goals. There were 1933 patients in the active treatment group and 1912 patients in the placebo group. The primary endpoint was fatal or nonfatal stroke.

After a mean follow-up of 1.8 years, there was a 30% reduction of fatal or nonfatal stroke (95% CI, -1 to 51; p = 0.06), and the reduction in rate of fatal stroke was 39% (95% CI, 1 to 62; p = 0.05) in the active treatment group. The reduction in rate of any cause death was 21% (95% CI, 4 to 35; p = 0.02), the rate of cardiovascular related death showed a reduction of 23% (95% CI, -1 to 40; p = 0.06), and reduction in rate of heart failure was 64% (95% CI, 42 to 78; p < 0.001). Active treatment was very well tolerated with fewer adverse events reported in that group than in the placebo group. Investigators concluded that it is beneficial to treat hypertensive patients over 80 years old with the sustained release diuretic, indapamide, with or without perindopril.¹³

Conclusion

Evidence in support of treating older and very old patients with ISH has been mounting steadily since the mid-1980s. Several landmark studies have indicated the effectiveness of thiazide diuretics, either alone as the first-step treatment for ISH, or in combination with other antihypertensive medications. The importance of reaching target BP goals cannot be overstated, especially in patients who also have compelling indications, to prevent target-organ damage. The AHA guidelines for hypertension, the European guidelines for hypertension and the JNC7 all recommend treating hypertension regardless of age.^{1,10,11} More caution in titration may be needed at the outset, depending on the patient and the regimen, to avoid undue side effects, but there should now be no doubt that treating hypertension in the elderly population shows clear benefits in reducing cardiovascular morbidity and mortality. With the body of evidence now available supporting intervention, the next few years should show an increase in the percentage of elderly hypertensive patients who are successfully treated.

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ACCREDITATION INFORMATION

The University of Iowa College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider for continuing pharmacy education. The ACPE program number is 107-999-08-067-H01-P. The University of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.

To earn continuing education credit, complete the assessment exercise, CE registration form and program evaluation on page 9, and return to Kristen K. Dearden, The Collaborative Education Institute, 8515 Douglas Avenue, Suite 16, Des Moines, IA 50322, with a \$7.50 check for the processing fee, made out to the College of Pharmacy. A certificate will be awarded upon achieving a passing grade of 70% or better. Please allow up to 4 weeks for processing. Pharmacists must complete this program by July 19, 2011 to receive credit.



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CE REGISTRATION

ACPE# 107-999-08-067-H01-P (0.1 CEU/1 Hr.)

Volume: 19 Issue: 2 JUNE 2008

Title of Educational Activity

Isolated Systolic Hypertension in the Elderly

Name _____

Address _____

City _____ State _____ Zip _____

Social Security Number (optional) _____

Pharmacy License Number(s) _____

I hereby certify that I have taken this test:

Signature/Date _____

(circle the correct answer)

1. Isolated systolic hypertension is defined as:
 - a. 120-129/80-89 mm Hg
 - b. $\geq 140/\leq 90$ mm Hg
 - c. $\geq 130/\leq 80$ mm Hg
 - d. $> 140/< 80$ mm Hg
2. When treating isolated systolic hypertension, unless contraindicated, the first line of drug therapy should be:
 - a. a beta-adrenergic blocker
 - b. an ACE inhibitor
 - c. a combination of diuretic and beta-adrenergic blocker
 - d. a thiazide diuretic
3. JNC7 blood pressure goal recommendations are:
 - a. slightly higher for people over 60 years old
 - b. lower for people with diabetes
 - c. unrelated to comorbidities
 - d. slightly lower for people over 60 years old
4. Lifestyle modifications:
 - a. are usually not possible for very elderly patients
 - b. do not include increased physical exercise for very elderly patients
 - c. are recommended for prehypertension and hypertension
 - d. are recommended based on long-term trials in elderly patients
5. Of the following, the most appropriate treatment of isolated systolic hypertension in a patient with diabetes consists of:
 - a. a combination of a diuretic and a beta blocker
 - b. a combination of a diuretic and an ACE inhibitor
 - c. a combination of a diuretic and a calcium channel blocker
 - d. a combination of a diuretic and an aldosterone antagonist
6. The ALLHAT trial was important in showing that when treating hypertension:
 - a. a calcium channel blocker is slightly more effective than an ACE inhibitor
 - b. chlorthalidone is slightly more effective than a calcium channel blocker
 - c. chlorthalidone is as effective as either an ACE inhibitor or a calcium channel blocker
 - d. combination therapy with chlorthalidone and lisinopril should be the first-step therapy
7. A serious concern associated with treating isolated systolic hypertension in the elderly has been that drug therapy would:
 - a. reduce the risk of stroke but increase the risk of death
 - b. reduce the risk of stroke but

- increase the risk of left ventricular failure
- c. increase the risk of non-fatal stroke
- d. reduce the risk of death but increase the risk of non-fatal stroke

8. The SHEP study provided evidence that, compared with placebo, active treatment:
 - a. did not cause hypotension in older patients
 - b. reached its maximum benefit in patients 80 years and older
 - c. should be comprised of at least two drugs to treat older patients
 - d. provided equal benefit to all age groups
9. The JNC7 recommended that treatment of isolated systolic hypertension in the elderly should be the same as general treatment for hypertension except:
 - a. combinations of more than two drugs should not be used
 - b. goals of therapy should not be as stringent as those for younger patients
 - c. lower starting doses may be used
 - d. beta blockers should be the first step of therapy
10. Beginning at 115/75 mmHg, risk of cardiovascular disease doubles with what increase?
 - a. every 5/10 mm Hg
 - b. every 10/10 mm Hg
 - c. every 15/10 mm Hg
 - d. every 20/10 mm Hg

Please Note: The CE processing fee is \$7.50 USD. Forms should be mailed to:

Kristen K. Dearden
 Collaborative Education Institute,
 8515 Douglas Avenue, Suite 16
 Des Moines, IA 50322
 Phone 515-270-0713
 Fax: 515-270-2979

PROGRAM EVALUATION

	Excellent		Poor		
	5	4	3	2	1
Overall quality	5	4	3	2	1
Relevance to practice	5	4	3	2	1
Value of content	5	4	3	2	1
	Agree		Disagree		
	5	4	3	2	1
Important to pharmacists	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Achieved stated objectives	5	4	3	2	1
Was educational and not promotional	5	4	3	2	1

It took me _____ hours and _____ minutes to read this article and complete the assessment questions.

New Molecular Entities & Biologicals

FDA Approvals
February 2008 – May 2008

An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. Additional information on these newly approved drugs will be available in the FDA Approval Package (an official United States Food and Drug Administration [FDA] document) that is compiled for new drugs following approval. The FDA Approval Package includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the *IDIS* database as they become available. Use the descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the *IDIS* database.

Generic Name Trade Name (Review Classification)	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number (<i>IDIS</i> Citations)	Indication/Use Dosage Form	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
Alvimopan <i>Entereg</i> (S)	GlaxoSmith-Kline (May 20, 2008)	ALVIMOPAN 28100010 (23 citations)	Accelerate restoration of normal bowel function after partial large or small bowel resection surgery. Oral Capsule	Paralytic Ileus 560.1
Bendamustine Hydrochloride <i>Treanda</i> (OP)	Cephalon (Mar. 20, 2008)	BENDAMUSTINE 10040418 (7 citations)	Chronic lymphocytic leukemia (CML). Injection	Leukemia, Lymphoid, Chronic 204.1
Certolizumab Pegol <i>Cimzia</i> (BIOL)	UCB Inc. (Apr. 22, 2008)	CERTOLIZUMAB PEGOL 82000496 (17 citations)	Crohn's Disease. Injection	Enteritis, Regional 555.
Methylnaltrexone Bromide <i>Relistor</i> (S)	Progenics Pharma (Apr. 24, 2008)	METHYLNALTREXONE 28100011 (17 citations)	Opioid-induced constipation. Subcutaneous Inject	Constipation 564.0 TX/AE-Drug/Chemical E999.
Regadenoson <i>Lexiscan</i> (S)	CV Therapeutics, Inc. (Apr. 10, 2008)	REGADENOSON 24120076 (5 citations)	Pharmacologic stress agent in radionuclide myocardial perfusion imaging. Injection	Diag Test-Stress, Cardiac 89.4

Review Classification:

S = Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs

AA = Accelerated Approval

FT = Fast Track

P = Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease

BIOL = Biological

O = Orphan drug

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Association of Faculties of Pharmacy of Canada
(AACP/AFPC)*

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Pharmacy and Pharmaceutical Sciences World Congress (FIP)
Congress Center Basel
Basel, Switzerland
August 29 - September 4, 2008*

*43rd ASHP American Society of Health-System Pharmacists
Midyear Clinical Meeting and Exhibits (ASHP)
Orange County Convention Center
Orlando, Florida
December 7-11, 2008*

Selected Bibliography

Alvimopan

Wolff BG, Michelassi F, Gerkin TM, et al. A novel, peripherally acting mu opioid antagonist: results of a multi-center, randomized, double-blind, placebo-controlled Phase III trial of major abdominal surgery and postoperative ileus. *Annals of Surgery*. 2004; 240:728-735. (IDIS Article Number 522619)

This study included 469 patients scheduled for bowel resection (n = 451) or radical hysterectomy (n = 18) who were randomized (1 : 1 : 1) to receive either 6 mg or 12 mg of alvimopan or placebo orally at 2 or more hours prior to surgery, then twice daily until discharge from the hospital or for up to 7 days. In the 6 mg alvimopan group, time to recovery of gastrointestinal function was accelerated (hazard ratio [HR] = 1.28; p < 0.05), and accelerated in the 12 mg alvimopan group (HR = 1.54; p < 0.001) with mean differences of 15 and 22 hours, respectively, compared with placebo. The study drug was found to be effective and well tolerated at both doses.

Certolizumab Pegol

Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med*. 2007; 357:228-238. (IDIS Article Number 579035)

Efficacy of certolizumab pegol was evaluated in this randomized, double-blind, placebo-controlled trial involving 662 patients with moderate to severe Crohn's disease. Patients received certolizumab 400 mg subcutaneously, or placebo, at weeks 0, 2 and 4, and then every 6 weeks for 26 weeks. At 6 weeks, response rates were 35% in the study drug group and 27% in the placebo group (p = 0.02). Reported serious adverse events were 10% in the certolizumab group and 7% in the placebo group. Investigators concluded that, compared to placebo, certolizumab provided moderate improvement in response rates, but no significant improvement in remission rates.

Methylnaltrexone Bromide

Yuan CS, Foss JF, O'Connor M, et al. Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial. *JAMA*. 2000; 283:367-372. (IDIS Article Number 438597)

A total of 22 subjects, participating in a methadone maintenance program and experiencing methadone-induced constipation, were randomized to intravenous methylnaltrexone (n = 11) at doses of 0.015, 0.05, 0.1, and 0.2 mg/kg in 4 syringes, up to 0.365mg/kg, or placebo. All 11 subjects who received the study drug experienced laxation response (p < 0.001). At baseline, the average oral-cecal transit times were 132.3 minutes in the methylnaltrexone group and 126.8 minutes in the placebo group. Average (SD) oral-cecal transit time change in the methylnaltrexone group was -77.7(32.2) minutes, and in the placebo group was -1.4(12.0) minutes (p < 0.001). There were no serious adverse effects and no subject experienced opioid withdrawal.

Regadenoson

Hendel RC, Bateman TM, Cerqueira MD, et al. Initial clinical experience with regadenoson, a novel selective A2A agonist for pharmacologic stress single-photon emission computed tomography myocardial perfusion imaging. *Journal of the American College of Cardiology*. 2005; 46:2069-2075. (IDIS Article Number 544715)

Thirty-six patients with ischemia that had been shown on 6-minute adenosine SPECT imaging within the previous 2-46 days were included in this non-randomized, Phase II, multicenter open-label trial. Regadenoson was given intravenously as a rapid bolus dose of 400 µg (n = 18) or 500 µg (n = 18), and the radiopharmaceutical was given within one minute. Standard SPECT imaging was performed and uniformly processed and then adenosine and regadenoson studies were randomly presented and interpreted by three observers, and a quantitative analysis with 4D-MSPECT software (University of Michigan, Ann Arbor, Michigan) was also performed. Overall agreement was 86% for the presence of reversible hypoperfusion. Investigators found that regadenoson was as effective as adenosine for detecting and quantifying hypoperfusion, and was well tolerated, as well as having simplicity of administration as a bolus.

Nicola Sarrazin, R.Ph., Pharm.D.
Staff Pharmacist II-Academic Research

Drug Information and Poison Center Training Saudi Food & Drug Authority

Mohammed Barasain and Omar Al-Burikan are pharmacists from Riyadh, Saudi Arabia and work in the newly created National Drug and Poison Information Center. They came to Iowa for two weeks to receive training in how to set up and operate a national drug information center. The Division of Drug Information Service (DDIS) was able to play a role in providing training for these two young pharmacists in the Saudi Food and Drug Authority (SFDA). The SFDA is in the process of developing a regulatory body that is committed to a high level of protection and improvement in public health in the Kingdom of Saudi Arabia. The SFDA Drug sector has 8 important tasks: (1) licensing of the manufacture, import, export, distribution, promotion and advertising of medications; (2) assessing the safety, efficacy and quality of medications, and issuing marketing authorization; (3) inspecting and surveillance of manufacturers, importers, wholesalers and dispensers of medications; (4) controlling and monitoring the quality of medications on the market; (5) controlling promotion and advertising of medications; (6) monitoring adverse reactions to medications; (7) providing independent information on medications to professionals and the public and (8) assuring cosmetic product safety.

The training was tailored to meet the specific goals of the trainees. Part of the time focused on reviewing the administrative aspects of operating an information center including how to document and record center activities. Time was spent examining how to use a systematic approach to respond to information requests. We examined how a database could be designed and document templates used to facilitate this standard approach. Essential resources that should be in the center were discussed and then reviewed by each trainee to ensure that they were comfortable using those resources. Time was also devoted to reviewing some of the key principles for how to evaluate primary and tertiary drug literature. The SFDA is a subscriber to *IDIS/Web* so sufficient time was devoted to ensure that both pharmacists could efficiently use *IDIS/Web* and could go back and train their fellow colleagues in the Drug and Poison Information Center how to use *IDIS/Web*.

The SFDA will also provide poison information to medical professionals and to the public in Kingdom of Saudi Arabia, approximately 26 million people. As a result, two days of the training were at the Iowa Statewide Poison Control Center in Sioux City. The trainees were exposed to a busy poison call center that handles over 30,000 calls per year from residents and professionals around the state of Iowa.

Mohammed and Omar, since returning to the SFDA, have been the operating Drug and Poison Center on a limited basis with a full scale opening scheduled for 2009. They said the training was invaluable in shaping the direction that our National Drug Information and Poison Center will take as it begins to become a reality.

Further information regarding our customized drug information training program is available at: <http://www.uiowa.edu/~idis/education.htm>.



Ron Herman, IDIN Director, Omar Al Burikan, Mohammed Barasain, and Kevin Moores, DDIS Director



Pat Gunia, a poison control specialist, demonstrates to Omar and Mohammed the system for recording poison calls.

DDIS
Division of Drug Information Service

The University of Iowa
100 Oakdale Campus N330 OH
Iowa City, IA 52242-5000 USA

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IDIS

Iowa Drug Information Service

Telephone: 319-335-4800
US Toll-Free: 800-525-IDIS
Fax: 319-335-4440
E-mail: IDIS@uiowa.edu
Web Site: <http://www.uiowa.edu/~idis>

IDIN

Iowa Drug Information Network

Telephone: 319-335-4800
US Toll-Free: 800-525-4347
Fax: 319-335-4440
E-mail: IDIN@uiowa.edu
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