Indapamide SR Versus Candesartan and Amlodipine in Hypertension: The X-CELLENT Study

Gerard London, Rolland Schmieder, Carlos Calvo, and Rolland Asmar

Background: Reducing systolic blood pressure (BP) is of major benefit to patients with isolated systolic hypertension, but lowering normal diastolic BP may be harmful in terms of cardiovascular risk. Effects of different drugs on systolic BP, diastolic BP, and pulse pressure are therefore of interest.

Methods: The NatriliX SR versus CandEsartan and amLodipine in the reduction of systoLic blood prEssure in hyperteNsive patienTs study (X-CELLENT) was a randomized, double-blind, placebo-controlled study comparing the effects of three drugs on these BP components. Patients with systolic–diastolic or isolated systolic hypertension (n = 1758) received indapamide (1.5 mg) sustained release (SR), candesartan (8 mg), amlodipine (5 mg), or placebo once daily for 12 weeks.

Results: Compared to placebo all active treatments reduced all BP components significantly ($P < .001$). For the patients with isolated systolic hypertension (n = 388), the three treatments significantly reduced systolic BP, but only indapamide SR did not change diastolic BP and thus reduced pulse pressure significantly relative to placebo (P = .005). In an ancillary study using ambulatory BP monitoring (n = 576), all three treatments significantly reduced BP components during 24 h relative to placebo. Changes in systolic BP and pulse pressure were similar with the three treatments, but the reduction in diastolic BP was significantly smaller, and therefore more favorable, with indapamide SR compared with candesartan (P = .039). In patients with isolated systolic hypertension (n = 106), indapamide SR reduced 24-h systolic BP significantly more than amlodipine (P = .037), and only indapamide SR reduced 24-h pulse pressure significantly relative to placebo (P = .03). All three drugs were well tolerated.

Conclusions: This distinctive BP-lowering profile of indapamide SR seems highly beneficial when compared to the either of candesartan or amlodipine. Am J Hypertens 2006;19:113–121 © 2006 American Journal of Hypertension, Ltd.

Key Words: Indapamide SR, candesartan, amlodipine, hypertension.

Hypertension is well established as an important risk factor for cardiovascular disease,[1] and reducing blood pressure (BP) has been shown to reduce the risk of cardiac events and strokes.[2,3] The relationship between BP and cardiovascular risk has been described as continuous and independent.[4] However, the relationships between risk and the different components of BP, including systolic BP and diastolic BP and pulse pressure (PP), have been the subject of much research interest. Traditionally, only diastolic BP was considered a risk factor, but recent work has highlighted the importance of systolic BP,[5,6] and PP has emerged as an independent cardiovascular risk factor[7,8] in both hypertensive and normotensive subjects.[9]

The roles of the different BP components have become clearer with an improved appreciation of their evolution with aging. Systolic BP generally increases linearly throughout adult life. Diastolic BP shows an early increase and late decrease, with a transition at 50 to 60 years.[10,11] Pulse pressure thus increases markedly in later life, and isolated systolic hypertension (ISH) becomes the predominant form of hypertension at more than 60 years of age.[12] These changes are accompanied by an age-related shift from diastolic to systolic hypertension, and finally to high PP as key predictors of coronary heart disease (CHD) risk.[13] Importantly, from age 60 years, diastolic BP is negatively related to CHD risk. In middle-aged and elderly subjects, for any given level of systolic BP, those with lower diastolic BP have greater CHD and mortality risk.[7,14] In a meta-analysis of outcome trials in patients with ISH, the benefit of treatment was overwhelmingly due to the reduc-

Received February 18, 2005. First decision May 19, 2005. Accepted June 16, 2005.

From Service de Néphrologie et d'Hémodialyse, Centre Hospitalier F.H. Manhès, Ste Geneviève des Bois 91712, France (GL), Medizinische Klinik Erlangen, 91054 Germany (RS), Hospital General de Galicia, Unidad HTA, Santiago de Compostela 15705, Spain (CC) and Cardiovascular Institute, 75016 Paris, France (RA).

Address correspondence and reprint requests to Dr. Gerard London, Centre Hospitalier Gerard Manhes, Nephrology, 8 rue Roger Clavier, Fleury Merogis, 91712 Saint Genevieve des Bois, France; e-mail: glondon@club-internet.fr

0895-7061/06/$30.00
doi:10.1016/j.amjhyper.2005.06.027

tion in systolic BP rather than diastolic BP.[1,14] Furthermore, in the Systolic Hypertension in the Elderly Program (SHEP), a decrease of 5 mm Hg in diastolic BP was associated with significantly increased risk of stroke and cardiovascular disease.[15] Furthermore, clinical trials and epidemiologic studies have shown that control of systolic BP is more difficult to achieve than control of diastolic BP.[16]

Antihypertensive agents may have different effects on the various components of BP. Agents that target systolic BP could be of particular interest in improving the rates of BP control, and in reducing morbidity and mortality attributed to systolic hypertension.[17]

The X-CELLENT study (NatriliX SR versus CandEsartan and amLodipine in the reduction of systoLic blood prEssure in hyperteNsive patienTs) compared the effects of the thiazide-type diuretic, indapamide (1.5 mg) sustained release (Natrilix SR, Servier, France) on systolic BP, diastolic BP, and PP with those of candesartan, an angiotensin II receptor blocker, and amlodipine, a long-acting dihydropyridine calcium channel blocker, in patients with either combined systolic–diastolic hypertension or ISH. The results of X-CELLENT are reported in this article.

Methods

Patients

Patients were male and female outpatients, 40 to 80 years old, with essential hypertension, having either systolic BP ≥150 to <180 mm Hg and diastolic BP ≥95 to <110 mm Hg or systolic BP ≥160 to <180 mm Hg and diastolic BP <90 mm Hg. Patients had no major cardiovascular complications related to hypertension at inclusion. In particular, patients with a history of coronary artery disease, heart failure, stroke or transient ischemic attack, left ventricular hypertrophy, diabetes mellitus (type 1 or type 2), and renal failure were not included in the study.

Lipid-lowering and uricosuric agents, and low-dose (<350 mg/d) aspirin were permitted; other treatments that might affect BP were not allowed.

Study Design

This was a multicenter, multinational, randomized, double-blind, placebo-controlled study with four parallel treatment arms. After a 4-week selection and run-in placebo period, patients were randomized to receive either placebo, indapamide (1.5 mg) SR (sustained release), candesartan (8 mg), or amlodipine (5 mg), all given once daily in the morning. As the dosage of indapamide cannot be increased, neither dose titration nor combination were allowed during the study, and patients with uncontrolled BP (diastolic BP or systolic BP >109/179 mm Hg) or poor treatment tolerance had to be withdrawn from the study. The dosage of candesartan and amlodipine were chosen according to respective monograph for the start of antihypertensive treatment in this type of hypertensive patients. The treatment period was 12 weeks, with visits, including BP measurements, at randomization (week 0 [W0]), W4, and W12).

Efficacy was evaluated by office BP measurements using a validated automatic device, the Omron 705CP.[18,19] Blood pressure was measured in the supine position after a rest of 10 min, using an appropriate cuff size, in the morning before drug intake (ie, at trough of drug activity). Measurements were made in triplicate at 1-min intervals and the mean value considered for analysis. For each patient, measurements were taken using the same equipment on the same arm, and by the same investigator.

Safety and acceptability were assessed by adverse events reported at each visit, and by clinical signs and examinations, including body weight, heart rate, and laboratory tests (comprehensive at W0 and W12, simplified at W4). Compliance to treatment was evaluated by direct questioning and tablet and capsule count at each visit.

A group of patients participated in an ambulatory BP monitoring (ABPM) ancillary study. The ABPM was performed during 25 h, 4 (±3) days before the W0 and W12 visits and according to the European Society of Hypertension recommendations.[4]

The study protocol was approved by the responsible Ethics Committees in each country and written informed consent was obtained from each study participant.

Statistical Analysis

The main efficacy criterion was change in systolic BP measured in the clinic by the Omron device. Secondary efficacy criteria included changes in diastolic BP and PP. A further secondary criterion was the number of responders, defined as patients with BP <140/90 mm Hg or a reduction in systolic BP ≥20 mm Hg or in diastolic BP ≥10 mm Hg in the main population. All BP changes were measured as changes from baseline (W0) to the final value (W12 or last value obtained). Analyses were performed in the intention-to-treat population, which consisted of all randomized patients who received at least one dose of study drug and for whom a baseline systolic BP value was available. A prespecified subset analysis was performed in the group of patients with ISH (systolic BP >140 mm Hg and diastolic BP <90 mm Hg) at baseline. The safety set consisted of all patients who received at least one dose of study drug.

The main statistical analysis was the comparison of indapamide SR versus candesartan and amlodipine on systolic BP, analyzed by one-way analysis of covariance with treatment as a fixed factor and baseline value as a covariate. Pairwise comparisons were performed using Dunnett's test, with indapamide SR as the control. As a secondary analysis, the three active treatments were compared versus placebo using the same methodology, with placebo as the control in the pairwise comparisons. The α threshold was 5% for all analyses (two-sided). The sample size had the power of $\beta =$ 83% to detect a difference of 3 mm Hg.

Table 1a. Demographics and Clinical Characteristics of the Intention-to-Treat Population in the X-CELLENT Study.*

	Indapamide SR	Candesartan	Amlodipine	Placebo
Main study population (*N* = 1758)				
	***n* = 440**	***n* = 435**	***n* = 444**	***n* = 439**
Age, years	58.4 ± 10.3	59.4 ± 10.3	58.9 ± 9.9	59.0 ± 10.1
Male, *n* (%)	219 (49.8)	224 (51.5)	230 (51.8)	217 (49.4)
Caucasian, *n* (%)	429 (97.5)	425 (97.7)	431 (97.1)	435 (99.1)
Body mass index, kg/m^2	27.0 ± 3.1	27.1 ± 3.2	26.8 ± 3.2	26.8 ± 3.1
Current smokers, *n* (%)	70 (15.9)	58 (13.3)	62 (14.0)	62 (14.1)
Duration of hypertension, months	66.0 ± 75.1	58.5 ± 67.4	66.4 ± 72.3	61.8 ± 69.3
Previous antihypertensive medication, *n* (%)	263 (59.8)	264 (60.7)	279 (62.8)	259 (59.0)
Patients with isolated systolic hypertension (*N* = 388)				
	***n* = 96**	***n* = 94**	***n* = 100**	***n* = 98**
Age, years	63.5 ± 10.0	64.0 ± 9.9	64.4 ± 9.0	63.9 ± 9.7
Male, *n* (%)	42 (43.8)	40 (42.6)	48 (48.0)	34 (34.7)
Caucasian, *n* (%)	93 (96.9)	93 (98.9)	100 (100)	98 (100)

* Values are mean ± SD, unless otherwise indicated.

Results

Main Study

The study was conducted at 392 centers in three countries. A total of 1762 patients (50.7% men) were randomized, with a mean age of 58.9 ± 10.1 years. The intention-to-treat population consisted of 1758 patients, whose characteristics are shown in Table 1a. The majority of patients were white (97.8%), the mean duration of hypertension was 63.2 ± 71.1 months, and most patients (60.6%) had received previous antihypertensive medication. The four treatment groups were well matched at baseline, for clinical, biological characteristics, as well as for cardiovascular risk factors. The disposition of patients is shown in Fig. 1. Patients with ISH (n = 388) were on average older (63.9 ± 9.6 years) and had a higher proportion of women (57.7%) than the main study population. Within this group, the treatment groups were also well matched (Table 1a).

The mean duration of randomized treatment was 84.0 days, with only minor variation between treatment groups (ranging from 81.9 days with placebo to 85.4 days with indapamide SR). Overall compliance with treatment was 97.5%, with negligible variation between groups (ranging from 97.4% with indapamide SR to 97.6% with placebo).

The three active treatments reduced clinic systolic BP, diastolic BP, and PP significantly relative to placebo ($P <$ .0001; Table 2). There were no significant differences between the active treatment groups, although indapamide SR tended to produce a slightly larger decrease in systolic BP, and a slightly smaller decrease in diastolic BP than candesartan or amlodipine. Consequently, indapamide SR tended to reduce PP to a greater extent than the other treatments, a difference that was close to significant compared with amlodipine (P = .073). The proportion of responders was significantly higher with all active treat-

Table 1b. Demographics of the Intention-to-Treat Population in the X-CELLENT Ambulatory Blood Pressure Monitoring Ancillary Study (N = 576).*

	Indapamide SR	Candesartan	Amlodipine	Placebo
Main study population (*N* = 576)				
	***n* = 145**	***n* = 142**	***n* = 150**	***n* = 139**
Age, years	58.5 ± 10.1	59.0 ± 10.1	59.3 ± 10.1	58.8 ± 10.1
Male, *n* (%)	75 (51.7)	57 (40.1)	84 (56.0)	68 (48.9)
Caucasian, *n* (%)	140 (96.6)	139 (97.9)	144 (96.0)	138 (99.3)
Patients with isolated systolic hypertension (*N* = 106)				
	***n* = 31**	***n* = 20**	***n* = 33**	***n* = 22**
Age, years	65.5 ± 7.7	65.9 ± 8.3	66.2 ± 8.0	63.4 ± 10.2
Male, *n* (%)	15 (48.4)	6 (30.0)	20 (60.6)	5 (22.7)
Caucasian, *n* (%)	31 (100)	20 (100)	33 (100)	22 (100)

* Values are mean ± SD, unless otherwise indicated.

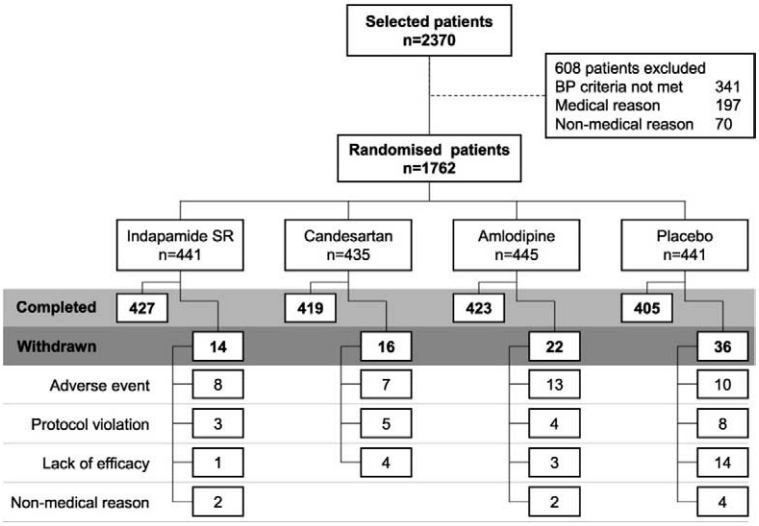

FIG. 1 Disposition of patients in the X-CELLENT trial.

ments (60.7%, 59.1%, and 61.0% for indapamide SR, candesartan, and amlodipine, respectively) compared with placebo (34.9%; $P < .0001$).

In patients with ISH, active treatments showed significant and similar efficacy in reducing systolic BP (Table 3), and the systolic BP reductions were similar to those observed in the

Table 2. Changes in Office Blood Pressures Measured Using the Omron 705CP Device, by Treatment Group ($N = 1758$).

	Indapamide SR *n* = 440	**Candesartan *n* = 435**	**Amlodipine *n* = 444**	**Placebo *n* = 439**
SBP (mmHg)				
Baseline	164.4 ± 8.4	164.2 ± 8.4	164.6 ± 8.4	164.6 ± 8.5
Change from baseline	−16.7 ± 16.1	−15.9 ± 16.7	−16.2 ± 16.0	−7.3 ± 16.8
Difference *vs* placebo				
[95% CI]	−9.5 [−12.0; −6.9]	−8.7 [−11.3; −6.2]	−8.9 [−11.4; −6.4]	
P-value	<0.0001	<0.0001	<0.0001	
Difference *vs* indapamide SR				
[95% CI]		−0.73 [−3.1; 1.7]	−0.56 [−2.9; 1.8]	
P-value		0.721	0.821	
DBP (mmHg)				
Baseline	96.5 ± 8.4	96.7 ± 7.9	97.1 ± 8.5	96.3 ± 8.7
Change from baseline	−7.4 ± 10.4	−8.3 ± 9.5	−8.9 ± 10.3	−3.5 ± 10.6
Difference *vs* placebo				
[95% CI]	−3.8 [−5.3; −2.4]	−4.6 [−6.0; −3.1]	−5.0 [−6.4; −3.5]	
P-value	<0.0001	<0.0001	<0.0001	
Difference *vs* indapamide SR				
[95% CI]		0.72 [−0.7; 2.1]	1.11 [−0.3; 2.5]	
P-value		0.397	0.127	
PP (mmHg)				
Baseline	67.9 ± 12.1	67.5 ± 11.7	67.5 ± 12.3	68.3 ± 12.1
Change from baseline	−9.3 ± 13.9	−7.6 ± 13.5	−7.3 ± 13.4	−3.8 ± 14.0
Difference *vs* placebo				
[95% CI]	−5.6 [−7.6; −3.7]	−4.2 [−6.1; −2.2]	−3.9 [−5.9; −1.9]	
P-value	<0.0001	<0.0001	<0.0001	
Difference *vs* indapamide SR				
[95% CI]		−1.47 [−3.3; 0.4]	−1.73 [−3.6; 0.1]	
P-value		0.146	0.073	

Table 3. Changes in Office Blood Pressures Using the Omron 705CP Device, in Patients With Isolated Systolic Hypertension at Baseline (N = 388), by Treatment Group.

	Indapamide SR n = 96	Candesartan n = 94	Amlodipine n = 100	Placebo n = 98
SBP (mmHg)				
Baseline	166.0 ± 6.4	165.9 ± 6.2	166.9 ± 6.8	165.3 ± 6.6
Change from baseline	−16.9 ± 16.7	−16.3 ± 18.4	−16.2 ± 18.5	−9.1 ± 15.7
Difference *vs* placebo [95% CI]	−7.4 [−13.2; −1.6]	−6.9 [−12.7; −1.1]	−6.24 [−12.0; −0.5]	
P-value	0.007	0.015	0.028	
Difference *vs* indapamide SR [95% CI]		−0.51 [−6.0; 5.0]	−1.15 [−6.6; 4.2]	
P-value		0.969	0.850	
DBP (mmHg)				
Baseline	83.5 ± 4.9	84.5 ± 4.3	84.3 ± 5.1	82.7 ± 5.0
Change from baseline	0.5 ± 7.6	−2.6 ± 9.1	−3.0 ± 9.2	1.7 ± 8.3
Difference *vs* placebo [95% CI]	−0.7 [−3.5; 2.0]	−3.2 [−6.0; −0.4]	−3.7 [−6.4; −1.0]	
P-value	0.859	0.018	0.004	
Difference *vs* indapamide SR [95% CI]		2.45 [−0.1; 5.0]	2.96 [0.4; 5.5]	
P-value		0.067	0.020	
PP (mmHg)				
Baseline	82.5 ± 8.4	81.4 ± 7.4	82.6 ± 8.2	82.6 ± 8.2
Change from baseline	−17.4 ± 15.2	−13.7 ± 14.9	−13.3 ± 15.0	−10.9 ± 15.0
Difference *vs* placebo [95% CI]	−6.6 [−11.5; −1.7]	−3.5 [−8.4; 1.5]	−2.4 [−7.3; 2.4]	
P-value	0.005	0.232	0.505	
Difference *vs* indapamide SR [95% CI]		−3.11 [−7.8; 1.6]	−4.17 [−8.8; 0.4]	
P-value		0.241	0.081	

main study population. However, there were significant differences between the treatments in their effects on diastolic BP in ISH patients. No significant changes in diastolic BP were noted with indapamide SR, whereas candesartan and amlodipine reduced diastolic BP significantly relative to placebo (P = .018 and P = .004, respectively). The difference between indapamide SR and the other agents with respect to the change in diastolic BP was significant for amlodipine (P = .020) and close to significant for candesartan (P = .067). Moreover, indapamide SR produced a significant reduction in PP, relative to placebo (P = .005), whereas neither candesartan nor amlodipine reduced PP (P = .232 and P = .505, respectively). Again, the difference in reduction in PP between indapamide SR and amlodipine showed a clear trend (P = .081).

Ambulatory BP Monitoring Ancillary Study

The ABPM ancillary study was performed in 576 patients whose demographic and clinical characteristics were similar to the main study population. The treatment groups were again well matched at baseline (Table 1b).

All three active treatments produced highly significant reductions in 24-h systolic BP, diastolic BP, and PP relative to placebo (all $P < .0001$; Table 4). Changes in systolic BP and PP were similar with the three treatments, but indapamide SR produced a significantly smaller decrease in diastolic BP than candesartan (P = .039; Table 4).

In those patients with ISH (Table 5), indapamide SR produced a significantly larger decrease in 24-h systolic BP than amlodipine (P = .037). None of the treatments decreased 24-h diastolic BP significantly. Indapamide SR was the only treatment to produce a significant reduction in 24-h PP relative to placebo (P = .030). The change in 24-h PP with indapamide SR was significantly larger than with amlodipine (P = .017).

Safety

All three drugs were well tolerated. The main emergent clinical adverse events with obviously different frequencies among treatment groups were headache (more frequent in the placebo group than in the other groups), and peripheral edema and hot flushes (more frequent in the amlodipine group) (Table 6). No serious adverse events were related to treatment. Two deaths occurred, one from myocardial infarction in the indapamide SR group, and

Table 4. Average Blood Pressures in the Ambulatory Blood Pressure Monitoring Ancillary Study, by Treatment Group ($N = 576$).

	Indapamide SR $n = 145$	Candesartan $n = 142$	Amlodipine $n = 150$	Placebo $n = 139$
24-h SBP (mmHg)				
Baseline	140.0 ± 12.0	140.3 ± 13.4	141.1 ± 13.2	140.6 ± 12.7
Change from baseline	−8.0 ± 9.7	−8.9 ± 10.1	−8.0 ± 9.2	0.2 ± 9.1
Difference *vs* placebo				
[95% CI]	−8.3 [−10.8; −5.9]	−9.2 [−11.7; −6.7]	−8.0 [−10.4; −5.6]	
P-value	<0.0001	<0.0001	<0.0001	
Difference *vs* indapamide SR				
[95% CI]		0.85 [−1.4; 3.2]	−0.34 [−2.6; 1.9]	
P-value		0.619	0.923	
24-h DBP (mmHg)				
Baseline	84.7 ± 8.7	84.5 ± 9.7	85.4 ± 9.3	84.7 ± 9.0
Change from baseline	−4.1 ± 5.6	−5.5 ± 6.1	−4.7 ± 5.8	−0.1 ± 5.7
Difference *vs* placebo				
[95% CI]	−4.0 [−5.5; −2.5]	−5.5 [−7.0; −4.0]	−4.5 [−6.0; 3.0]	
P-value	<0.0001	<0.0001	<0.0001	
Difference *vs* indapamide SR				
[95% CI]		1.48 [0.1; 2.9]	0.49 [−0.9; 1.9]	
P-value		0.039	0.655	
24-h PP (mmHg)				
Baseline	55.3 ± 9.9	55.8 ± 9.5	55.7 ± 10.7	55.9 ± 10.4
Change from baseline	−3.9 ± 6.5	−3.4 ± 5.2	−3.3 ± 4.9	0.2 ± 4.7
Difference *vs* placebo				
[95% CI]	−4.3 [−5.7; −2.9]	−3.7 [−5.1; −2.3]	−3.6 [−4.9; −2.2]	
P-value	<0.0001	<0.0001	<0.0001	
Difference *vs* indapamide SR				
[95% CI]		−0.60 [−1.9; 0.7]	−0.74 [−2.0; 0.6]	
P-value		0.492	0.343	

one from cerebral hemorrhage in the amlodipine group, not related to the study drugs according to the investigator's opinion.

There were no clinically relevant differences between groups with respect to the frequency of orthostatic hypotension, body weight changes, or heart rate. No unexpected biochemical or hematologic changes were observed in any of the groups. In the indapamide SR treatment group, the mean plasma potassium concentration decreased from 4.29 ± 0.37 mmol/L to 4.08 ± 0.43 mmol/L; only 16 patients presented kalemia <3.4 mmol/L, and no severe hypokalemia (<3.0 mmol/L) was noted. There were no significant differences between groups in plasma glucose levels, or in total cholesterol, triglycerides, HDL or LDL levels. Hepatic and renal function were not affected by any of the treatments.

Discussion

In the present study, in which most patients had combined systolic–diastolic hypertension, indapamide SR produced reductions in systolic and diastolic BP similar to those of candesartan and amlodipine. Indapamide SR showed a tendency to reduce PP more than the other treatments, but this only approached significance compared with amlodipine. Such specific effects have already been shown with thiazide diuretics, which reduced more systolic BP and PP than other antihypertensive agents.[17,20] However, in the subset of patients with ISH, indapamide SR produced clearly different results from the other treatments. In ISH patients, all three treatments produced similar reductions in systolic BP. Candesartan and amlodipine both produced significant decreases in diastolic BP, but indapamide SR left diastolic BP values (which were in any case already normal) unchanged in these patients. Indapamide SR was also the only treatment that produced a significant reduction in PP in ISH patients.

The BP-lowering profile of indapamide SR revealed in the present study is of particular interest in the light of recent results concerning the relative importance of the different components of BP in predicting cardiovascular risk. In patients with combined systolic–diastolic hypertension, the predominant form in younger individuals,[13] reduction in either or both components reduces cardiovascular risk. In patients with ISH (the predominant form in older subjects), reducing systolic BP has been shown to be

Table 5. Changes in 24-h Mean Blood Pressures in Patients with Isolated Systolic Hypertension, by Treatment Group ($N = 106$).

	Indapamide SR *n* = 31	Candesartan *n* = 20	Amlodipine *n* = 33	Placebo *n* = 22
24-h SBP (mmHg)				
Baseline	138.7 ± 10.3	138.9 ± 11.7	141.4 ± 13.8	139.5 ± 13.6
Change from baseline	−9.8 ± 9.2	−9.4 ± 13.3	−5.3 ± 8.2	−4.2 ± 11.5
Difference *vs* placebo				
[95% CI]	−5.9 [−12.0; 0.2]	−5.4 [−12.2; 1.4]	−0.40 [−6.4; 5.6]	
P-value	0.061	0.145	0.997	
Difference *vs* indapamide SR				
[95% CI]		−0.49 [−6.4; 5.5]	−5.50 [−10.7; −0.3]	
P-value		0.975	0.037	
24-h DBP (mmHg)				
Baseline	79.1 ± 8.5	77.2 ± 9.4	79.2 ± 7.1	77.4 ± 7.9
Change from baseline	−4.3 ± 4.6	−4.9 ± 8.0	−2.9 ± 4.3	−2.1 ± 6.8
Difference *vs* placebo				
[95% CI]	−1.59 [−4.9; 1.7]	−2.9 [−6.6; 0.8]	−0.2 [−3.5; 3.1]	
P-value	0.518	0.160	0.998	
Difference *vs* indapamide SR				
[95% CI]		1.27 [−2.0; 4.5]	−1.41 [−4.2; 1.4]	
P-value		0.590	0.433	
24-h PP (mmHg)				
Baseline	59.6 ± 8.5	61.7 ± 9.0	62.2 ± 11.5	62.1 ± 12.3
Change from baseline	−5.5 ± 6.7	−4.5 ± 5.7	−2.4 ± 4.8	−2.2 ± 5.9
Difference *vs* placebo				
[95% CI]	−3.9 [−7.5; −0.3]	−2.5 [−6.4; 1.5]	−0.3 [−3.8; 3.3]	
P-value	0.030	0.316	0.996	
Difference *vs* indapamide SR				
[95% CI]		−1.44 [−4.9; 2.1]	−3.63 [−6.7; −0.6]	
P-value		0.560	0.017	

of major benefit,[14] but lowering diatolic BP is probably of no benefit, and may even be harmful.[14,15]

The results of the ABPM ancillary study were broadly consistent with those of the main study. In patients with ISH, indapamide SR was the only treatment to produce a significant reduction in 24-h PP. In these patients, amlodipine reduced 24-h diastolic BP to only a small extent, but this was matched by small decreases in 24-h systolic BP and 24-h PP. The ABPM study also showed that all three treatments produced consistent reductions in BP throughout the 24-h dosing interval. Indapamide SR is a sustained-release formulation with a low dose of 1.5 mg. After a single administration, this formulation shows a much longer time to maximum plasma concentration (t_{max}), and a much lower peak plasma concentration (C_{max}) than the former formulation, immediate-release indapamide 2.5 mg. After repeated administration, the 24-h peak-to-trough fluctuation was fourfold lower with indapamide SR than with

Table 6. Emergent Clinical Adverse Events Occurring in >4% of Patients, or at Obviously Different Frequencies, During the Study Period ($N = 1760$).*

	Indapamide SR *n* = 440	Candesartan *n* = 436	Amlodipine *n* = 444	Placebo *n* = 440
Headache	7 (1.6)	7 (1.6)	8 (1.8)	20 (4.5)
Peripheral edema	0 (0)	1 (0.2)	19 (4.3)	2 (0.5)
Back pain	6 (1.4)	9 (2.1)	6 (1.4)	7 (1.6)
Nausea	3 (0.7)	3 (0.7)	8 (1.8)	1 (0.2)
Diarrhea	1 (0.2)	2 (0.5)	8 (1.8)	0 (0)
Hot flushes	0 (0)	0 (0)	6 (1.4)	0 (0)

* Values are *n* (%).

the conventional, immediate-release formulation.[21] It is likely that the sustained-release formulation contributed to the consistent 24-h efficacy seen with ABPM for indapamide SR in the present study. A smooth 24-h reduction in BP has been shown to be beneficial in preventing target organ damage.[22]

The main office BP measurements in the present study were obtained using an automatic device, the Omron 705CP. This device has been validated[18] and is recommended by the European Society of Hypertension.[23] Similarly, for the 24-h ABPM study, only devices recommended by the European or national hypertension society were allowed.

The three active treatments were all well tolerated. Apart from those related to the expected effects of diuretics on plasma electrolyte levels,[24] indapamide SR showed a similar adverse event profile to candesartan and placebo, and avoided the peripheral edema associated with amlodipine. In particular, there were no differences between treatment groups with respect to plasma glucose and blood lipid levels, as already shown earlier.[25] It may be that the low-dose sustained release formulation, by limiting peak drug levels, contributed to the absence of metabolic changes and the low impact on biological parameters observed with indapamide SR.[26]

A strength of this study was the inclusion of a placebo group. This allowed the absolute sizes of the BP reductions to be interpreted reliably, and directly demonstrated the assay sensitivity of the study. A disadvantage of this design is that ethical concerns over the use of a placebo group when treatments of proven benefit are available meant that patients with severe hypertension or additional risk factors could not be included. As a consequence, the study population was relatively young (mean age 58.9 years) and only a minority of patients (22%) had ISH. Some significant differences between treatment groups were obtained for the ISH subset. It is possible that further significant differences could have been found if more patients with ISH had been included.

The recent large-scale Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) study has confirmed diuretics as first-choice antihypertensive agents.[27] This position is reflected in recent US guidelines, which described diuretics as virtually unsurpassed in clinical trials in preventing cardiovascular complications of hypertension, and recommend them as first-line therapy.[4] This viewpoint has been intensively debated and is not generally accepted according to the European guidelines.[23] However, it is now widely accepted in both the US and Europe that many hypertensive patients will require two to four antihypertensive drugs to control hypertension, and that one of these drugs should always be a diuretic. The distinctive profile of indapamide SR in affecting different BP components may be particularly relevant in preventing the increases in PP and in the prevalence of ISH with aging, which are currently not effectively prevented by conventional antihypertensive therapy.[28]

Perspectives

Recent guidelines emphasize the importance of controlling systolic BP, and in patients with ISH, reducing diastolic BP may not be beneficial. In this study, indapamide SR reduced systolic BP in all patients to the same extent as two antihypertensive agents currently in wide use, candesartan and amlodipine. In patients with ISH, indapamide SR, unlike the other agents, maintained diastolic BP in those patients with normal diastolic BP. This distinctive BP-lowering profile of indapamide SR seems highly desirable in the light of emerging concepts of the prognostic value of systolic BP, diastolic BP, and PP and their evolution over time.

Acknowledgments

We thank all the investigators and the patients who participated in this study. We are grateful to the monitors and the staff of Institut de Recherches Internationales Servier, France (Dr. Luc Feldmann, Dr. Martine de Champvallins, Dr. Benoît Tallot, Corentin Le Camus, Elsa Merkling).

List of Participating Investigators

France Abenhaim N, Becq JP, Beignot Devalmont P. Blanchard P, Boucher L, Boutboul S, Boye A, Brule JP, Campagne A, Chagnoux B, Churet JB, Copéré C, De La Chevasnerie A, De Sainte Lorette E, Dubourg D, El Sawy A, Etchegaray G, Faugas G, Grandmottet G, Lafont C, Lafont P, Latté T, Lejay D, Liotard F, Magnani C, Marty J, Mongin G, Musso S, Paulet C, Pineau-Valenciennes D, Rebot J, Sarfati RP, Sicard J, Spilthooren F, Taminau D.

Germany Adler J, Brommer P, Glanz R, Kapelle A, Kaspari S, Keck M, Kombacher D, Lossow J, Mikolaiczik M, Muller O, Scherenberg R, Schmidt J, Schreckenberg A, Schumacher M, Taj A, Von Manteuffel G, Ziegenhorn H.

Spain Bueno J, Cabrera Sole R, De Alvaro F, Garcia Puig J, Gil Extremera B, Honorato Perez J, Martin Hidalgo A, Martos R, Nieto J, Olivan J, Oliveras A, Romero R, Ruilope LM.

References

1. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R: Prospective studies collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903–1913.
2. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH: Blood pressure, stroke, and coronary heart disease. Part 2. Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990;335:827–838.
3. PROGRESS Collaborative Group: Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001; 358:1033–1041.

4. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P, on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring: European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens 2003;21:821–848.
5. Black HR: The paradigm has shifted, to systolic blood pressure. Hypertension 1999;34:386–387.
6. Izzo JL, Levy D, Black HR: Importance of systolic blood pressure in older Americans. Hypertension 2000;35:1021–1024.
7. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D: Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. Circulation 1999;100:354–360.
8. Blacher J, Staessen JA, Girerd X, Gasowski J, Thijs L, Liu L, Wang JG, Fagard RH, Safar ME: Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. Arch Intern Med 2000;160:1085–1089.
9. Benetos A, Rudnichi A, Safar M, Guize L: Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. Hypertension 1998;32:560–564.
10. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D: Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension 1995; 25:305–313.
11. Franklin SS, Gustin W, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D: Hemodynamic patterns of age-related changes in blood pressure. Circulation 1997;96:308–315.
12. Franklin SS, Jacobs MJ, Wong ND, L'Italien GJ, Lapuerta P: Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. Hypertension 2001;37:869–874.
13. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, Levy D: Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation 2001;103:1245–1249.
14. Staessen JA, Gasowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, Coope J, Ekbom T, Gueyffier F, Liu L, Kerlikowske K, Pocock S, Fagard RH: Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. Lancet 2000;355:865–872.
15. Somes GW, Pahor M, Shorr RI, Cushman WC, Applegate WB: The role of diastolic blood pressure when treating isolated systolic hypertension. Arch Intern Med 1999;159:2004–2009.
16. Lloyd-Jones DM, Evans JC, Larson MG, O'Donnell CJ, Roccella EJ, Levy D: Differential control of systolic and diastolic blood pressure: factors associated with lack of blood pressure control in the community. Hypertension 2000;36:594–599.
17. Morgan T, Lauri J, Bertram D, Anderson A: Effect of different antihypertensive drug classes on central aortic pressure: Am J Hypertens 2004;17:118–123.
18. O'Brien E, Mee F, Atkins N, Thomas M: Evaluation of three devices for self-measurement of blood pressure according to the revised British Hypertension Society Protocol: the Omron-705CP, Philips HP5332, and Nissei DS-175. Blood Press Monit 1996;1:55–61.
19. O'Brien E, Waeber B, Parati G, Staessen J, Myers MG: Blood pressure measuring devices: recommendations of the European Society of Hypertension. BMJ 2001;322:531–536.
20. Morgan TO, Anderson AI, MacInnis RJ: ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. Am J Hypertens 2001;14:241–247.
21. Schiavi P, Jochemsen R, Guez D: Pharmacokinetics of sustained and immediate release formulations of indapamide after single and repeated oral administration in healthy volunteers. Fund Clin Pharmacol 2000;14:139–146.
22. Frattola A, Parati G, Cuspidi C, Albini F, Mancia G: Prognostic value of 24-hour blood pressure variability. J Hypertens 1993;11: 1133–1137.
23. European Society of Hypertension–European Society of Cardiology Guidelines Committee: 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003;21:1011–1053.
24. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ, and the National High Blood Pressure Education Program Coordinating Committee: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–1252.
25. Weidmann P: Metabolic profile of indapamide sustained release in patients with hypertension. Drug Saf 2001;24:1155–1165.
26. Donnelly R: Clinical implications of indapamide sustained release 1.5 mg in hypertension. Clin Pharmacokinet 1999;37(Suppl 1):21–32.
27. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288: 2981–2997.
28. Mourad J-J, Blacher J, Blin P, Warzocha U, PHASTE study: Conventional antihypertensive drug therapy does not prevent the increase of pulse pressure with age. Hypertension 2001;38:958–962.