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Treatment of Isolated Systolic Hypertension: The SHELL Study Results

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Objective: Our aim was to compare the effect of lacidipine and chlorthalidone on cardiovascular outcome as a primary parameter and blood pressure as a secondary in elderly patients with isolated systolic hypertension in a prospective study with an open design. *Methods:* 1882 males and females outpatients ≥60 years were randomly assigned to the administration of chlorthalidone 12.5 mg o.d. or lacidipine 4 mg o.d. Patients were recruited if sitting systolic blood pressure was ≥160 mmHg with a diastolic blood pressure equal or lower than 95 mmHg. Primary endpoint was a composite of cardiovascular and cerebrovascular events. *Results:* At randomization mean systolic blood pressure was 178.1 mmHg in the lacidipine and 178.2 mmHg in the chlorthalidone group, the corresponding mean diastolic values being 86.9 and 86.8 mmHg. In both lacidipine and chlorthalidone groups treatment caused a significant ($p < 0.001$) and marked systolic blood pressure reduction which was maintained throughout the treatment period with a significant ($p < 0.001$) and steady although less marked reduction in diastolic blood pressure as well. At the end of treatment period (median 32 months), the reduction was 36.8/8.1 mmHg (systolic/diastolic) in the chlorthalidone and 38.4/7.9 mmHg in the lacidipine group, the final on treatment blood pressures being 142.0/79.2 and 143.2/79.5 mmHg, respectively. Treatments were similarly effective in males and females and in age groups between 60 and 69 years ($n = 763$), 70 and 79 years ($n = 744$) and ≥80 years ($n = 375$). Similar reductions were obtained in a subgroup of patients ($n = 209$) followed in double-blind fashion for 1 year. The overall incidence of the primary endpoints was 9.3% with no significant between-group difference. Total mortality was also similar between groups. *Conclusions:* In elderly patients with isolated systolic hypertension, administration of lacidipine or chlorthalidone markedly reduced systolic blood pressure with no difference in the incidence of cardiovascular events and total mortality. *Key words: calcium channel blocker, dihydropyridine, diuretic, hydrochlorothiazide, isolated systolic hypertension, mortality.*

INTRODUCTION

Isolated systolic hypertension is a major cardiovascular risk factor for the elderly because in subjects above 60 years of age an elevation in systolic blood pressure with a normal or low diastolic blood pressure is accompanied by a marked increase in cardio- and cerebrovascular morbidity and mortality [1–3]. It is, however, a reversible risk factor, because several trials have shown the increased cardiovascular morbidity and mortality to be reduced if blood pressure is reduced by drug treatment. In the SHEP trial [4], reduction in blood pressure by administration of a thiazide diuretic resulted in a significant and marked reduction in cardiovascular morbidity and mortality, respectively, compared to placebo. Similar results were obtained in the SYSTEUR and SYSTCHINA trials in which elderly patients with isolated systolic hypertension were randomized to a dihydropyridine calcium antagonist-based treatment or to placebo [5, 6].

Up-to-date data on the different protective effect of different antihypertensive drugs in isolated systolic hypertension are limited to subanalysis of trials involving patients with a systolic and/or a diastolic blood pressure elevation [7]. In particular, no study has ever been performed to compare the treatments shown to be protective against the complications of isolated systolic hypertension in placebo-controlled trials. This was the aim of the Systolic Hypertension in the Elderly: Lacidipine Long-Term study (SHELL) [8], in which elderly patients with isolated systolic hypertension were randomized to administration of chlorthalidone (the drug employed in the SHEP trial) or lacidipine, i.e. a dihydropyridine calcium antagonist belonging to the same class employed in the SYSTEUR and in the SYSTCHINA

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trials, and endowed with a gradual onset of activity, protracted duration of action, pronounced vascular selectivity and good tolerability. The trial had a multicenter structure and the centers were selected mainly among geriatric and internal medicine centers in charge of elderly outpatients in connections with family doctors to make it as representative as possible of the clinical practice.

PATIENTS AND METHODS

Outpatients of both genders were recruited from 134 units located in northern, central and southern Italy. Their age was $\geq$60 years and their sitting office blood pressure was $\geq$160 mmHg, systolic, and $\leq$95 mmHg, diastolic. Blood pressure values were based on the average of three sphygmomanometric measurements obtained after 5 min of rest, through the use of the first and the fifth Korotkoff sounds to identify systolic and diastolic values, respectively. Exclusion criteria were: (i) hypertension of secondary nature; (ii) malignant hypertension; (iii) myocardial infarction, myocardial revascularization or stroke within the previous 6 months; (iv) advanced renal damage (serum creatinine $>$2 mg/dl); (v) altered hepatic function (ALT and AST twice the upper normality values; (vi) contraindications or hypersensitivity to the drugs employed in the study or to angiotensin-converting enzyme (ACE) inhibitors (see below); and (vii) severe concomitant diseases.

Patients were seen at a screening visit, at which a complete medical history, physical examination and standard laboratory examinations were obtained. If they were under antihypertensive treatment, they were seen after a 15-day washout period. They were then randomly assigned to the administration of chlorthalidone, 12.5 mg once daily (o.d.), or lacidipine, 4 mg o.d. Randomization was made by BETA Trial Center, Genoa (Italy), using a sequentially based criterion. If the systolic blood pressure response was not satisfactory (reduction $\leq$20 mmHg and absolute value $>$160 mmHg) at the end of the first 4 weeks, treatment was titrated upward first by increasing the dose of the initial monotherapy (chlorthalidone 25 mg and lacidipine 6 mg) and by bringing back the monotherapy dose to the initial step and adding fosinopril 10 mg o.d. or any other ACE inhibitor at an equivalent dose after another 4 weeks of treatment. This approach was adopted to minimize, in elderly individuals, the risk of an excessive blood pressure fall.

Follow-up visits were made at monthly intervals during the first 3 months after randomization and thereafter after 6 months and every year for a maximum of 5 years. At each visit, blood pressure was measured as for the baseline visits. Heart rate was measured by the palpatory method throughout. The primary endpoints were a composite of fatal and non-fatal stroke, sudden death, fatal and non-fatal myocardial infarction, fatal and non-fatal congestive heart failure, myocardial revascularization and carotid endarterectomy. Secondary endpoints were all-cause mortality, transient ischemic attacks (TIA) and non-Q myocardial infarction. The study was conducted in an open fashion. However, in 12 additional centers, patients were followed in double-blind fashion for the first year of treatment to evaluate objectively the efficacy and tolerability of the drugs employed.

Events were assessed according to predefined criteria by an independent committee unaware of the treatment group to which patients belonged. Data were analyzed on an intention-to-treat basis by BETA Trial Center.

The study design and procedures were approved by the ethical committees of the outpatient centers involved. An informed consent was obtained from all patients.

The study began on June 1993 and ended on August 2000.

Statistical analysis

The comparison between the two treatment groups of change from baseline measure in blood pressure values at planned visits was made by means of Student's *t*-test for unpaired data. For primary and secondary endpoints, time to event has been calculated for all patients from the day of randomization until the date of fatal or non-fatal cardiovascular event, whichever occurred first. Overall survival has been calculated for all patients from the day of randomization until the date death is reported. Patients in which either fatal or non-fatal cardiovascular events were not observed, or who have not died, have been censored at the last date they are known to be alive. Event-free survival and overall survival curves in both arms have been estimated using Kaplan–Meier technique and compared by means of log-rank test. The estimated treatment effect has been expressed as a hazard ratio (chlorthalidone vs lacidipine) with two-sided 95% confidence interval. All analyses were performed with the SAS System v. 8.0 statistical package.

RESULTS

Our original assumption was that in the lacidipine group, the incidence of major cardiovascular events would be 25% less than in the chlorthalidone group, in which the incidence was estimated as being 3% per year. This led to a sample-size calculation of 4800 patients to be followed for 5 years to achieve a power of 80% at a p level of 5%. However, recruitment was more difficult than was expected due to problems posed by the often difficult interaction between practitioners and recruiting centers, including lack of practitioners' perception of the benefit of treating elderly patients with systolic hypertension.

Table I. *Baseline characteristics of randomized patients*

	Chlorthalidone ($n = 940$)	Lacidipine ($n = 942$)
Age (years)	72.4 ± 7.6	72.3 ± 7.5
Gender (M/F%)	37.8/62.2	39.6/60.4
SBP (mmHg)	178.2 ± 10,3	178.1 ± 10,2
DBP (mmHg)	86.8 ± 5.8	86.9 ± 5.7
HR (beats/min)	76.3 ± 9.5	76.0 ± 9.4
History of CVD (%)	29.2	32.1
Smokers (%)	9.8	11.2
Ex-smokers (%)	16.3	14.5
Diabetes mellitus (%)	12.7	13.8
Previous antihypertensive treatment (%)	51.4	52.1
Abnormal ECG (%)*	42.2	40.4

Data are mean ± SD * High QRS voltage, ST depressions.

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CVD, cardiovascular disease; ECG, electrocardiogram.

Only 1882 patients were thus randomized from patients screened. As shown in Table I, patients were often above 70 and not infrequently above 80 years of age. They were predominantly females. Their systolic blood pressure was on average quite high, i.e. close to 180 mmHg. Patients under previous antihypertensive treatment were only slightly above 50%. All patient characteristics were well matched between the two groups (Table I).

Figure 1 shows that in the whole group of patients systolic blood pressure fell markedly during treatment with a smaller reduction in diastolic blood pressure. The reductions were similar in the two treatment groups and the changes were maintained throughout the follow-up period (median 32 months; 95% CI 30–33 months). Similar reductions were obtained: (i) in patients aged 60–69, 70–79 and ≥80 years (Fig. 2) and (ii) in males and females (Fig. 3). The reductions were also similar when the smaller number of patients followed for 1 year in a double-blind fashion was considered (Fig. 4). Heart rate never showed any significant change. Patients kept in lower-dose monotherapy were 72% in the lacidipine group and 47% in the chlorthalidone group, while those in higher-dose monotherapy were 12.8% and 25%, respectively. The corresponding figures for the group followed in a double-blind fashion were 71.1%, 66.7, 12.4% and 15.2%, respectively.

During follow-up, patients who remained on randomized treatment were 79.5% in the lacidipine group and 75.5% in the chlorthalidone group.

Table II reports the events observed in the two groups. The overall incidence of the primary endpoint was 9.3% (about 3% per year) with no significant between-group difference. The overall mortality rate (obtained by death certificates) was higher (14.2%) due to a high incidence of deaths diagnosed as of non-cardiovascular or unknown origin. There was again no between-group difference in all-cause mortality. The event-free curves were superimposable in the two groups throughout, both for primary endpoints and for the primary and secondary endpoints combined (Fig. 5). Patients lost to follow-up were 12.3% in the lacidipine and 11% in the chlorthalidone group, respectively.

As shown in Table III, patients under lacidipine treatment showed a greater incidence of pretibial edema, whereas patients under chlorthalidone treatment showed a greater incidence of fatigue. Other side-effects were similar between the two groups. Similar data were obtained in the patients of the double-blind protocol and in patients aged ≥80 years (data not shown).

DISCUSSION

In our elderly patients with isolated systolic hypertension, administration of chlorthalidone or lacidipine alone or in combination with an ACE inhibitor markedly reduced the

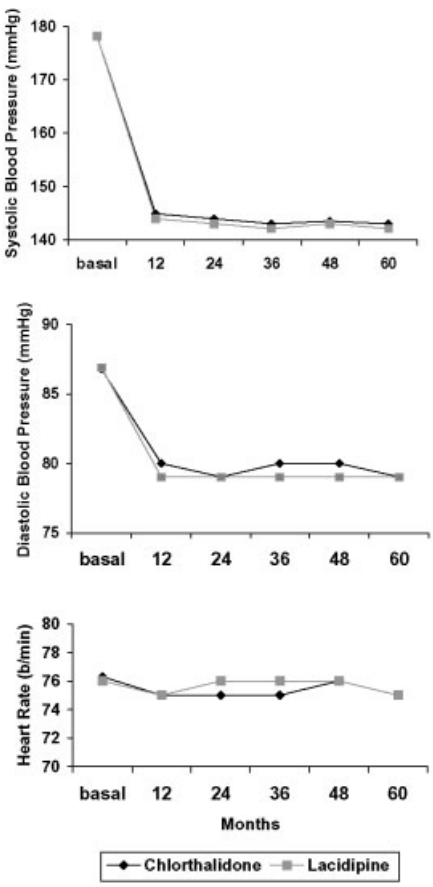

Fig. 1. Systolic and diastolic blood pressure and heart rate at randomization and during treatment in all patients. Data are shown as means.

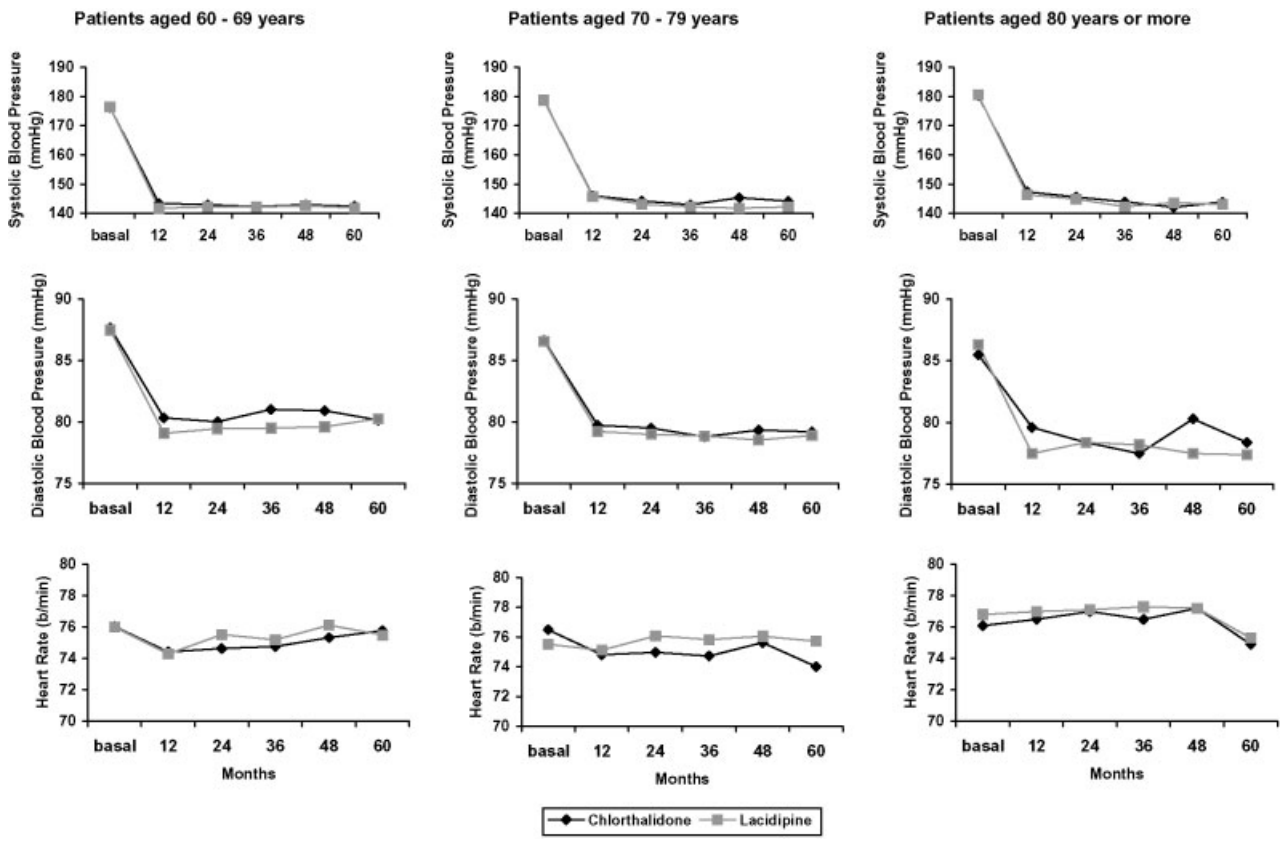

Fig. 2. Systolic and diastolic blood pressure and heart rate at randomization and during treatment in patients aged 60–69, 70–79 and ≥80 years. Data are shown as means.

elevated systolic blood pressure. This was accompanied by an incidence of the cardiovascular events pre-specified as the primary endpoint of the study similar in the two groups. The incidence of secondary endpoints also showed a between-group similarity with a superimposition of the curves indicating free-event survival throughout the study. Given the demonstration provided by previous trials, that the two treatments employed reduced the incidence of cardiovascular morbidity and mortality when compared to placebo [4–6], this allows us to suggest that the benefit is likely to be similar for the two types of treatment.

This is in line with the evidence provided by the meta-analysis of previous trials [9] comparing different antihypertensive drugs in a total of about 75000 patients with systo-diastolic hypertension, i.e. that cardiovascular morbidity, cardiovascular mortality and total mortality are similar in groups treated with dihydropyridines or diuretics. This has recently been found also in ALLHAT study [10] in nearly 25000 patients. Our study has a number of limitations: (i) the study had an open design; (ii) there were fewer patients recruited than were originally planned, which means that the number of events collected was smaller with a reduction in the statistical power needed to support the conclusion; (iii) there was in the study a relatively large number of deaths of unknown origin, which makes quantification of the primary endpoint possibly somewhat inaccurate because it is likely that a proportion of these deaths had a cardiovascular nature. These limitations were largely due to the fact that the study was performed in a geriatric population in which the responsibility to treat the elevated blood pressure fell not only on specialized centers but also on practicing physicians. In other words, the purpose of the study was held in a context closer to clinical practice than that of most previous studies, thereby minimizing the criticism that trials are performed in somewhat artificial conditions and that their data cannot have an easy application by practicing physicians. It should be emphasized, however, that the above limitation is unlikely to affect the conclusion of the similarity of the two treatments employed, because the incidence of all-cause deaths was also similar in the two groups.

Several other results of our study are worthy of a mention: (i) in our study, isolated systolic hypertension was defined by a systolic value ≥160 mmHg and a

diastolic one ≤95 mmHg, whereas in other studies, a diastolic cut off of <95 or 90 mmHg has been selected. However, the number of patients with a diastolic blood pressure of 95 mmHg was a small fraction (6.1%) of the total and the average diastolic blood pressure before randomization was 86.8 and 86.9 mmHg in the chlorthalidone and lacidipine groups, lower than those reported for the Systeur trial (87.4 and 87.3 mmHg in the placebo and active treatment group, respectively), in which recruitment was based on a diastolic blood pressure of <95 mmHg. (ii) In our patients, treatment was accompanied by a marked reduction in systolic blood pressure throughout the treatment period, with an achieved average value only slightly above the value now recommended as the goal of treatment in the elderly by international guidelines [11]. This was obtained in more than two-thirds of the patients by just one drug, indicating that control of systolic hypertension by treatment may not be as difficult to obtain as it has sometimes been maintained [12]. Interestingly, treatment was equally effective with chlorthalidone and lacidipine, a finding that was observed also in the subgroup of patients followed on a double-blind fashion. (iii) As in previous studies, administration of antihypertensive drugs not only lowered systolic but also diastolic blood pressure. Whether this adds to the benefit is uncertain. It does not seem to represent an inconvenience, however, because in the SHEP study [4], cardiovascular morbidity and mortality were reduced despite a reduction in diastolic BP to slightly below 70 mmHg, suggesting no impairment of vital organ perfusion at least down to these values. In our study, diastolic BP decreased to values around 80 mmHg, i.e. greater than those reported for the SHEP study [4]. Interestingly, the reduction was similar in both genders and across all age groups, including patients above 80 years of age, with no reflection on the rate of adverse events. (iv) There was in our patients no increase in heart rate with lacidipine treatment, confirming that when a slow and long-acting calcium antagonist of the dihydropiridine class is employed, reflex sympathetic activation does not occur. (v) Despite the marked systolic blood pressure fall and the diastolic blood pressure reduction, treatment was by and large well tolerated, with a relatively small incidence of reported orthostatic hypotension and dizziness, i.e. symptoms which might indirectly signal an undue fall in blood pressure when the standing position is assessed.

Our study provides additional data of some interest.

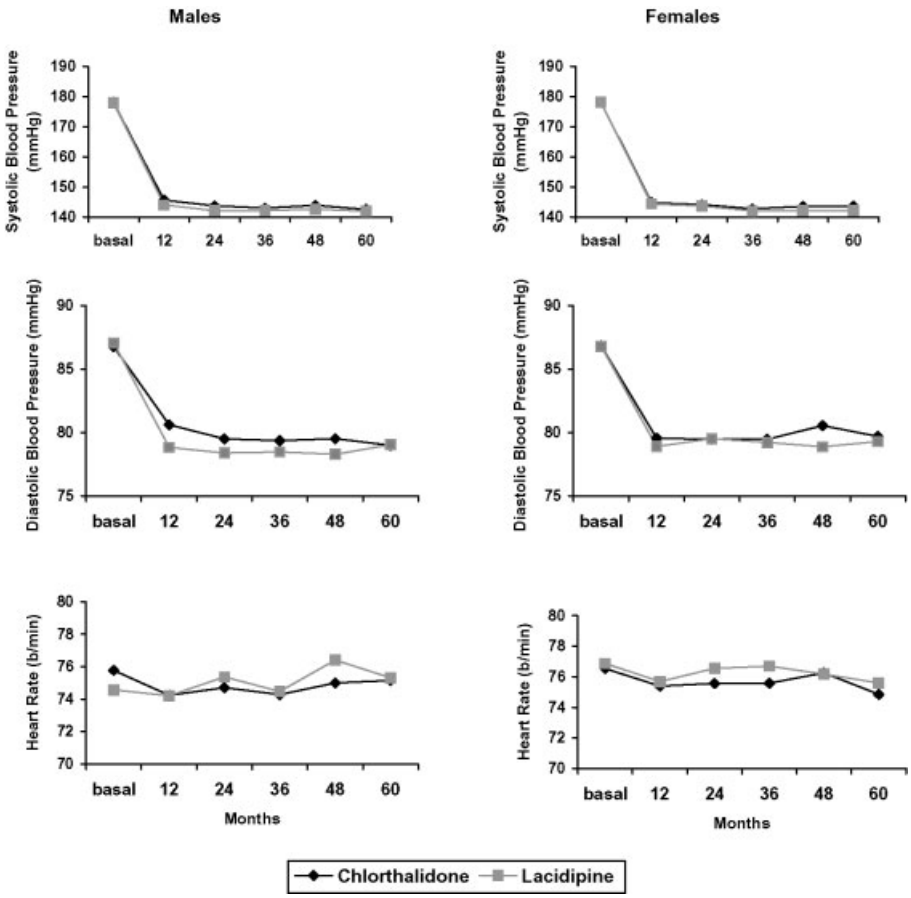

Fig. 3. Systolic and diastolic blood pressure and heart rate at randomization and during treatment in males and females. Data are shown as means.

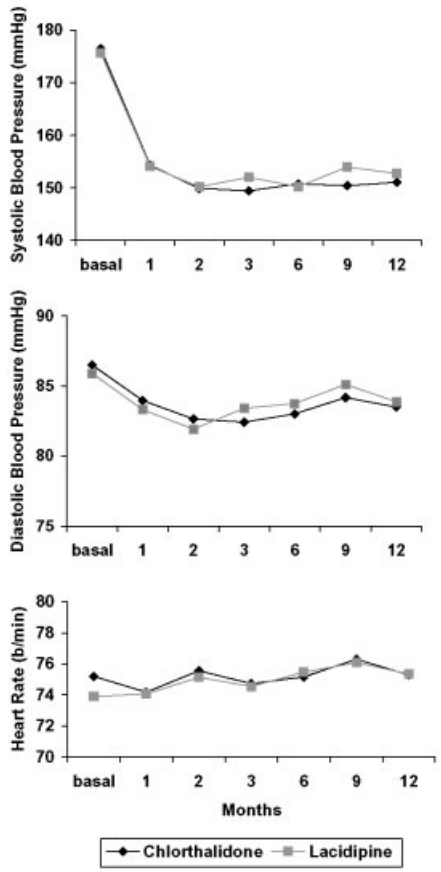

Fig. 4. Systolic and diastolic blood pressure and heart rate at randomization and during treatment in the double-blind group. Data are shown as means.

More than 50% of the patients recruited had never been under antihypertensive treatment. This emphasizes how low the Italian physician's perception was that isolated systolic hypertension is a risky condition in the mid-1990s. As mentioned previously, together with the erroneous thinking that blood pressure reduction may be harmful, this was probably one of the reasons for the limitations of the recruitment in the study. Finally, given the large involvement of geriatric units, our study was able to include 375 patients aged $\geq$80 years. In this group, the results in terms of efficacy and tolerability were similar to those of younger patients, confirming that treatment of isolated systolic hypertension is relatively safe in very old patients as well. Whether in these patients a blood pressure reduction leads to a reduction of cardiovascular morbidity and mortality is under evaluation [13], although *post hoc* analysis of currently available data support that this may be so [14].

Our data pose again a question that is a matter of current discussion, i.e. whether protection against hypertension depends on the target blood pressure achieved by treatment, regardless of which drugs are employed, or for the same blood pressure reduction can differences between different treatments be seen. The former conclusion is supported by the meta-analysis of hypertension trials [9] as well as by the data from the recently published ALLHAT trial [10], which, however, do not deal specifically with patients with isolated systolic hypertension. The latter is supported by the results of the LIFE trial, in which a subgroup of patients with isolated systolic hypertension showed significantly less incidence of cardiovascular disease if treated with an angiotensin II antagonist than with a beta-blocker [7]

SHELL INVESTIGATORS

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Table II. *Clinical outcomes by treatment group*

	Chlorthalidone (no. of events)	Lacidipine (no. of events)	HR (95% CI)	*p*-value
Composite primary endpoint	88	90	1.01 (0.75–1.36)	0.94
Components of primary endpoint				
F/NF stroke	38	37	0.96 (0.61–1.51)	0.87
Sudden death	13	16	1.22 (0.58–2.53)	0.60
F/NF myocardial infarction	14	12	0.85 (0.39–1.83)	0.67
F/NF heart failure	19	23	1.20 (0.65–2.20)	0.56
Revascularization	4	2	0.50 (0.09–2.70)	0.41
Secondary endpoints				
TIA	13	15	1.14 (0.54–2.40)	0.72
All-cause mortality	122	145	1.23 (0.97–1.57)	0.09

F, fatal; NF, non-fatal; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack.

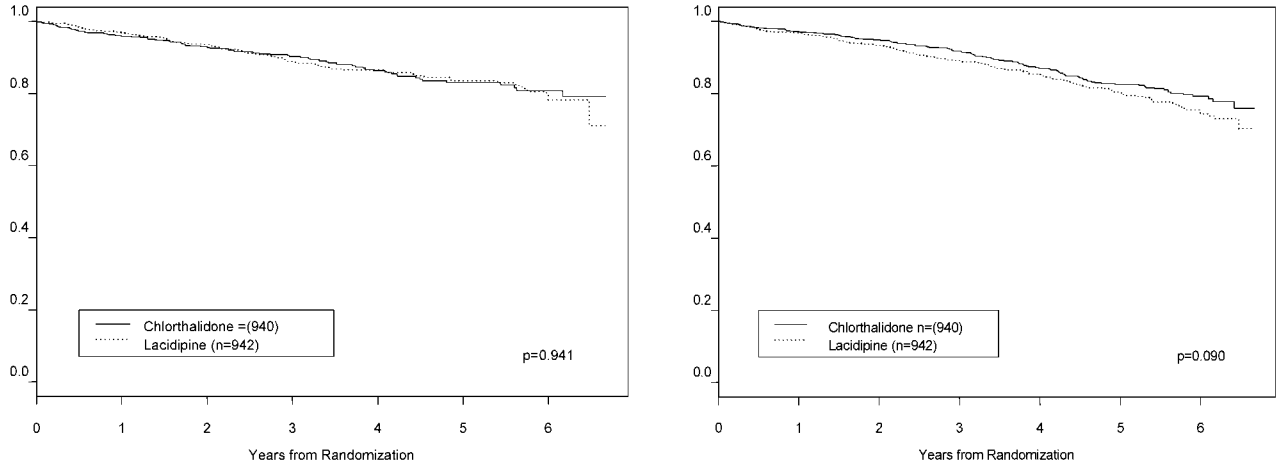

Fig. 5. Probability of event free survival for the primary endpoint (left graph) and cumulative endpoint (right graph).

Cabasino Francesco, Cagliari; Caione Fernando, L'aquila; Califano Mariano, S. Felice A Cancello (Ce); Caruso Domenico, Napoli; Caso Angelo Antonio, Piedimonte Matese (Ce); Cassani Pietro, Domodossola (Vb); Castiglioni Giuseppe, Cassano D'adda (Mi); Catamo Antonio, Parma; Cesareo Errico, Pagani (Sa); Chiarappa Raffaele, Bari; Chiavinato Claudio, Camposampiero (Pd); Ciaburri Michele, Cerreto Sannita (Bn); Cicerone Fernando, Bentivoglio (Bo), Cicognani Roberto, Forli'; Cilla Donatina, Forli'; Coglitore Antonino, Messina; Colombo Fabrizio, Merate (Lc); Compagnone Domenico, Catania; Corigliano Pietro, Abbiategrasso (Mi); Corradini Paolo, Grosseto; Cozzio Susanna, Tione (Tn); Cristofari Mario, Desio (Mi); Dal Monte Edoardo, Faenza (Ra); De Matteis Carmine, S. Felice A Cancello (Ce); Decembrino Michele, Melzo (Mi); Di Biasi Domenico, Eboli (Sa); Di Fresco Pietro, Palermo; Dolce Ernesta, Bari; Donadon Valter, Pordenone; Farina Giovanni, Terracina (Lt); Fogari Roberto, Pavia; Forestiero Giuseppe, Penne (Pe); Franzone Giuseppina, Citta' S. Angelo (Pe); Fusari Gian Pietro, Verona; Galetti Giuseppe, Monza (Mi); Garognoli Oriana, Citta' Di Castello (Pg); Gaudio Giuseppe, Cosenza; Giannella Raffaele, Torino; Giorda Carlo, Chieri (To); Giustiniani Stefano, Sondrio; Glorioso Nicola, Sassari; Granata Paolo, Vizzolo Predabissi (Mi) Grezzana Luigi, Verona; Guala Adriano, Biella; Guizzardi Giuseppe, Pescara; Ierardi Biagio, Potenza; Indelicato Vincenzo, Sciacca (Ag); Infriccioli Pietro, S. Benedetto Del Tronto (A.P.); Ingignoli Biagio, Torino; Landmann Ermanno, Napoli; Laurini Giorgio, Dolo (Ve); Lecciso Giovanni, Lecce; Lo Pinto Giuliano, Genova; Lombardo Antonio, Catania; Lopez Vincenzo, Ravenna; Lunati Fabio, Novara; Lutri Valter, Siracusa; Manca Cosimo, Putignano (Bari); Mancarella Sandro, Cinisello Balsamo (Mi); Mancini Marcello, Parma; Maniscalchi Tiziana, Palermo; Manopulo Roberto, Bologna; Mantini Giovanni, S. Giovanni V. (Fi); Marc Albert, Bolzano; Marchi Paola, Ferrara; Marrocco Fausto, Cassino (Fr); Martorano Michele, Bari; Marullo Luciano, Mondragone (Ce); Marzara Giovanni, Imola (Bo); Mastropasqua Arturo, Garbagnate M. (Mi); Mazzeo Vincenzo; Polla (Sa); Meroni Maria Rachele, Milano; Montanari Loris, Ravenna; Moscato Paolo, Magenta (Mi); Mossuti Ernesto, Avola (Sr); Nardelli Carolina, Latina; Novati Paola, Saronno (Va); Noviello Diego, Teano (Ce); Orso Angelo, La Spezia; Pagliarani Gabriele, Forli'; Palese Eugenio, Casarano (Le); Palleschi Massimo, Roma; Palumbo Gaetana, Milano; Parenti Mario, Rimini; Pessano Bruno, Cantu' (Co); Piazza Simona, Milano; Porcellati Carlo, Perugia; Prete Salvatore, Copertino (Le); Pugliese Silvio, Bologna; Raffaele Narciso, Montebelluna (Tv); Righi Alberto, Sezze (Lt); Romano Felice, Catania; Romis Leone, Lacco Ameno (Na); Rossini Arturo, Formia; Rovero Enrica, Orbassano (To); Russo Vittorio, Napoli; Salazzari Carlo, Negrar (Vr); Sani Carlo, Reggio Emilia; Santilli Davide, Nemi (Roma); Scala Aldo, Pozzuoli

Table III. *Side-effects*

Side-effect	Chlorthalidone (% of patients)	Lacidipine (% of patients)
Dizziness	12.4	12.7
Fatigue	20.5	13.7
Headache	6.4	9.6
Edema	4.9	14.3
Skin rush	1.6	4.0
Itching	3.8	3.7
Skeletal muscle disorders	7.9	6.6
Paresthesia	4.6	3.4
Constipation	5.7	4.5
Orthostatic hypotension	2.5	1.9
Cough	4.0	3.5

(Na); Scandiani Lucia, Milano; Schipani Giuseppe, Battipaglia (Sa); Semeraro Sergio, Bologna; Severin Elzo, Crocetta Montello (Tv); Stagni Barbara, Bologna; Stimolo Antonino, Udine; Taurino Fernando, Galatina (Le); Tommasi Marcella, Brescia; Tozzi Nicola, Benevento; Trimarchi Michele, Enna; Triolo Lelio, Trieste; Uguccioni Massimo, Roma; Vancheri Federico, Caltanissetta; Vietri Giancarlo, Avellino; Villa Giuseppe, Pavia; Viscanti Giovanni, Lanciano (Ch); Vitale Francesco, Piedimonte Matese (Ce); Viti Vito, Pisa; Vitolo Carlo, Sarno (Sa); Viviani Giorgio, Genova; Zanasi Massimo David, Foggia; Zottarel Gabriella, Conegliano (Tv).

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Statistical Committee: L. Boni, P. Bruzzi, L. Belluomini.

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