**Effect of Two Different Therapeutic Approaches on
Total and Cardiovascular Mortality in a
Cardiovascular Study in the Elderly (CASTEL)**

Edoardo CASIGLIA, M.D., Paolo SPOLAORE, M.D.,*
Alberto MAZZA, M.D., Giuliana GINOCCHIO, M.D.,
Giovanna COLANGELI, M.D., Caterina ONESTO, M.D.,
Giuseppe DI MENZA, M.D., Lorenza PEGORARO, M.D.,
and Giovanni B. AMBROSIO, M.D.**

SUMMARY

Although limited numbers of elderly subjects have occasionally been included in population-based studies, only a few studies have been conducted specifically on elderly hypertensives, and practically none at a population level.

We studied 655 hypertensive subjects from a cohort of 2,254 elderly subjects. The intervention consisted of the creation of a Hypertension Outpatients' Clinic under our auspices but with complete co-operation from general practitioners, randomizing the identified hypertensive patients into pre-established therapeutic drug regimens, and early follow-up recording of mortality for 7 years. The drugs used were clonidine ($n = 61$), nifedipine ($n = 146$) and the fixed combination of atenolol+chlorthalidone ($n = 144$); 304 subjects underwent "free therapy" by their personal physicians without any special intervention. There were 1,404 normotensive subjects.

Overall 7-year follow-up mortality was 34.9% in the hypertensive subjects receiving "free therapy", 22.5% in those receiving "special care", and 24.2% in the normotensives. Cardiovascular mortality was respectively 23.7%, 12.2%, and 12.0%. Overall and cardiovascular annual cumulative mortality were significantly lower in the «special therapy» than in the «free therapy» group. The fixed combination of atenolol and chlorthalidone reduced mortality below that of the normotensives, independent of other cardiovascular risk factors. (Jpn Heart J 35: 589–600, 1994)

Key words: Epidemiology Elderly Mortality Hypertension
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From Institute of Clinical Medicine of the University of Padova, Italy, *Hypertension Outpatients' Clinic of the Castelfranco Veneto General Hospital, Italy, and **Department of Internal Medicine, Venice General Hospital, Italy.

Address for correspondence: Edoardo Casiglia, M.D., Institute of Clinical Medicine, Via Giustiniani, 2, 35128 Padova, Italy.

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ALTHOUGH many epidemiological studies have been performed in the last few years examining the effects of different antihypertensive drugs,^{1,2)} some questions remain unanswered, for example whether or not antihypertensive treatment reduces mortality in elderly hypertensive patients.

A limited number of elderly subjects have been included as a part of the dataset in population-based studies, for instance the Australian National Blood Pressure (ANBP) study³⁻⁵⁾ (a single-blind placebo-controlled study of active therapy vs placebo), the Hypertension Detection and Follow-up Program (HDFP)^{6,7)} (a comparison between normal therapy and special care), and the Medical Research Council (MRC) trial.⁸⁾ Only a few studies — the Hypertension in the Elderly in Primary Care (HEP),⁹⁾ the European Working Party on Hypertension in the Elderly (EWPHE),¹⁰⁻¹²⁾ the Systolic Hypertension in Elderly Program (SHEP),¹³⁻¹⁶⁾ the Swedish Trial in Old Patients with Hypertension (STOP),¹⁷⁻¹⁹⁾ the Japanese Double-Blind Trial of Mild Hypertension in the Aged,²⁰⁾ the General Practice study of Sprackling et al.²¹⁾ and the MRC Trial in Older Adults²²⁾ have been conducted specifically in elderly hypertensives. None of them was performed at a population level, thereby obtaining «hypertensives» and not «subjects» from a general population survey.

The CArdiovascular STudy in the ELderly (CASTEL), a population-based prospective intervention study performed in northern Italy,²³⁾ has been conducted in order to evaluate the prevalence of hypertension in a large population of subjects 65 years of age or more, the cardiovascular risk of elderly subjects from a general population, and the feasibility and effectiveness of a systematic, continuous, community-based hypertension control program in the elderly. The aim of this analysis was to define whether or not antihypertensive treatment was able to reduce mortality in elderly hypertensive patients, and if the effect on mortality was greater when a «special therapy» approach was used.

SUBJECTS AND METHODS

General protocol of the study: The community of the CASTEL (recruited in Castelfranco Veneto, in northern Italy) was composed of all 3,088 subjects aged 65 years or over living in that town, identified through the Register Office; a cohort of 2254 of them (73%) accepted the study design and were enrolled between 1983 and 1985.

The design of the CASTEL²³⁾ consisted of three main stages: 1) initial survey of the total resident population, 2) creation of a Hypertension Outpatients' Clinic under our auspices but with complete co-operation from general practitioners, and 3) a yearly follow-up recording of mortality for 7 years. At the 7th year, a complete final screening of the 1,676 survivor subjects was performed, with the

participation of 1,206 subjects (72%); only 7-year blood pressure (BP) values have been taken into consideration in this paper.

Sitting BP was measured by trained doctors using a Riva-Rocci sphygmomanometer. The systolic BP was defined as the reading at the first Korotkow sound and diastolic as the reading of the last one (phase 5). In order to reduce the impact of the «alert reaction», the BP was taken 3 times at 10-min intervals and the average value of the last 2 measurements was used. Hypertension was defined as a combination of elevated BP values (systolic BP > 160 and/or diastolic BP > 95 mmHg) and/or a history of hypertension for those who were currently under antihypertensive drugs.

Mortality was determined yearly and at the 7th year through the files of the Register Office. Causes of death were confirmed by analysis of hospital files for patients who died in a hospital. Cardiovascular mortality was defined as death due to heart disease (myocardial infarction, unstable angina, arrhythmias, or sudden death), cerebrovascular disease, or pulmonary embolism.

Intervention program: The normotensives numbered 1,404; the hypertensives 850. Six-hundred fifty five hypertensive subjects (whose basic pre-treatment characteristics are summarized in Table I) were composed of 231 males aged 68 to 88 years (average $\pm$ SD: 73.2 ± 4.9 years), and 424 females aged 65 to 89 years (74.0 ± 5.3 years), without age differences between sexes. They were treated as follows.

Three hundred fifty-one underwent a “special therapy” including 1) assignment to treatment with 0.15 mg/day clonidine ($n = 61$), 20 mg/day nifedipine ($n = 146$) or a fixed combination of 100 mg/day atenolol and 25 mg/day chlorthalidone ($n = 144$); 2) periodic visits carried out in the Hypertension Outpatients’ Clinic; and 3) strict co-operation of the general practitioners, which also avoided any drop-out.

Three hundred four underwent “free therapy”, i.e. conventional therapy freely established by various physicians, without any intervention or interference from our Hypertension Outpatients’ Clinic; they were simply observed (with periodic visits, where possible), and their mortality was determined yearly through the Register Office.

One hundred ninety-five hypertensives were not treated, due to their refusal, or to opposition by their physician, or to our decision to delay intervention. They were not included in this paper.

Data analysis: A comparison between the mean values of different classes was performed by analysis of variance (ANOVA), using Tukey’s correction as a post-hoc test. Correlations were evaluated by Pearson’s correlation coefficient with Bonferroni’s conservative correction. The difference of frequencies was evaluated with the χ^2 test.²⁴⁾ In all these analyses, p values < 0.05 were considered statisti-

Table I. Clinical and Laboratory Background of Subjects before Randomization.

Item	Free therapy group (n = 304)	Special care group (n = 351)	Bartlett t test statistics		All (n = 655)
			T	p-value	
Age (years)	74.1 ± 5.3	73.4 ± 5.1	1.747	0.081	73.7 ± 5.2
Weight (kg)	70.9 ± 13.6	69.7 ± 12.1	1.205	0.229	70.2 ± 12.8
Height (cm)	160.5 ± 8.8	160.2 ± 8.5	0.533	0.595	160.3 ± 8.7
BMI	27.5 ± 4.3	27.1 ± 4.1	0.986	0.325	27.3 ± 4.2
SBP (mmHg)	176.8 ± 26.2	177.6 ± 21.5	6.061	0.116	177.0 ± 24.8
DBP (mmHg)	96.2 ± 13.5	96.6 ± 11.3	4.706	0.231	96.4 ± 12.3
Cigarettes/day	7.4 ± 4.7	8.5 ± 5.4	0.894	0.375	8.0 ± 5.1
Wine (l/day)	1.4 ± 0.8	1.5 ± 0.8	1.324	0.186	1.5 ± 0.8
Glucose (mg/dl)	112.9 ± 34.5	112.0 ± 28.5	0.522	0.602	112.2 ± 31.9
Uric acid (mg/dl)	5.9 ± 1.7	5.6 ± 1.5	2.594	0.010	5.8 ± 1.6
Cholesterol (mg/dl)	222.4 ± 40.9	229.3 ± 44.6	2.035	0.142	226.1 ± 43
HDL (mg/dl)	62.2 ± 19.0	65.0 ± 17.3	1.914	0.056	63.6 ± 18
Creatinine (mg/dl)	0.99 ± 0.38	0.94 ± 0.24	2.070	0.039	0.967 ± 0.31
	Free therapy group (n = 304)	Special care group (n = 351)	χ ² statistics		All (n = 655)
			χ ²	p-value	
M/F ratio	0.58	0.51	0.616	0.432	0.55
Prevalence of ISH	34.5%	39.3%	1.593	0.287	37.1%
History of angina	3.6%	2.9%	1.116	0.972	3.2%
History of MI	5.3%	2.9%	2.745	0.098	3.8%
Prevalence of diabetes	9.9%	9.7%	0.028	0.375	8.0 ± 5.1

M = males; F = females; BMI = body mass index; SBP and DBP = systolic and diastolic blood pressure; HDL = HDL-cholesterol; ISH = isolated systolic hypertension; MI = myocardial infarction.

cally significant.

Correction of the rate of mortality by age, sex, body mass index (BMI) calculated as the ratio between body weight (in kg) and square of body height (in m), total (TC) and HDL serum cholesterol, blood uric acid, cigarette smoking, diabetes, and proteinuria, was made including these parameters as independent variables in a multivariate backward stepwise logistics regression, overall and then cardiovascular mortality being the dependent variables.^{25,26)} A level < 0.02 was considered significant.

Cox's survival analysis was performed in order to define the relative weight of each parameter on mortality.

RESULTS

BP values: BP at survey (mean ± SD) was 161.9 ± 26.2/90.3 ± 12.2 mmHg, i.e. 152.6 ± 21.3/86.5 ± 10.6 mmHg in the normotensives, 176.8 ± 26.2/96.2 ± 13.2 mmHg in the 304 hypertensives treated by their physicians («free therapy» group), and 177.6 ± 21.5/96.6 ± 11.3 mmHg in the 351 treated with «special therapy» by the Hypertension Outpatients' Clinic, with no difference

between classes.

Among the 351 subjects in the «special therapy» group, the 61 on clonidine had a BP of $181.6 \pm 22.1/97.1 \pm 9.4$ mmHg, the 146 in the nifedipine group $180.8 \pm 23.7/97.4 \pm 12.1$ mmHg, and the 144 in the fixed combination group $175.4 \pm 20.1/95.8 \pm 10.9$ mmHg, with no difference between groups.

Systolic/diastolic BP at the 7th year was decreased by 9.1/11.6% in the 198 hypertensive survivors who received free therapy, and by 10.2/11.0% in the 272 surviving patients who received «special therapy». Taking into consideration only the survivors on «special care», BP decreased by 12.0/11.8% in those treated with clonidine, by 9.5/11.0% in those treated with nifedipine, and by 10.2/10.6% in those treated with the fixed combination of atenolol+chlorthalidone. All differences vs initial survey were significant ($p = 0.0001$), while there was no difference between «free therapy» and «special therapy».

Mortality: Overall 7-year crude mortality was 34.9% in the hypertensive patients treated with «free therapy» (106/304), 22.5% in those on «special therapy» (79/351), and 24.2% in the normotensives (340/1404). Overall mortality was significantly different in the two treatment groups ($\chi = 12.282$, $p = 0.0001$).

Cardiovascular mortality was 23.7% in the «free therapy» group (72/304, i.e. 23 deaths due to left ventricular failure, 15 to stroke, 12 to myocardial infarction or unstable angina, 15 to arrhythmias or cardiac arrest, and 7 to pulmonary embolism), 12.2% in the «special care» group (43/351, i.e. 11 deaths due to left ventricular failure, 6 to stroke, 11 to myocardial infarction or angina,

Figure 1. Cumulative annual overall mortality during the 7 years of follow-up. Left panel: 304 hypertensives treated with «free therapy» (FT: $\triangle$ — $\triangle$) and 351 with «special care» (SC: $\blacksquare$ — $\blacksquare$). Right panel: the 351 subjects on special care are considered separately for nifedipine (N: $\blacksquare$ — $\blacksquare$; $n = 146$), clonidine (C: $\circ$ — $\circ$; $n = 61$), or the association atenolol+chlorthalidone ($\bullet$ — $\bullet$; $n = 144$). By comparison, mortality of normotensive subjects ($N=1,404$) is also shown (.....).

Table II. Logistic Regression with Overall and Cardiovascular Mortality as Dependent Variables

Independent variables	At entry			At stay		
	β coeff	Wald	Sig	β coeff	Wald	Sig
Overall mortality						
Age	0.1133	34.4233	0.0000	0.1162	38.2810	0.0000
Sex	-0.7550	12.7648	0.0004	-0.7384	12.6497	0.0004
TC	-0.0005	0.0438	0.8342		removed	
HDL	0.0050	0.5481	0.4591		removed	
Uric acid	0.1026	2.5662	0.1092	0.1049	2.8898	0.891
Proteinuria	0.2934	2.3265	0.1272		removed	
Diabetes	0.5145	13.0959	0.0003	0.5322	14.3313	0.0002
Smoking	0.6101	3.6831	0.0550	0.6360	4.1368	0.0420
BMI	-0.0387	2.2622	0.1326	-0.0435	2.9687	0.0849
SBP	0.0028	0.3829	0.5361		removed	
DBP	0.0124	1.7780	0.1824		removed	
Therapy*	-0.5608	8.6414	0.0033	-0.5638	8.9124	0.0028
Cardiovascular mortality						
Age	0.1080	25.3584	0.0000	0.1089	28.7951	0.0000
Sex	-0.2213	0.8043	0.3698		removed	
TC	0.0015	0.3315	0.5648		removed	
HDL	0.0035	0.2071	0.6490		removed	
Uric acid	0.1178	2.6589	0.1030	0.1222	3.4192	0.0644
Proteinuria	0.2166	0.9498	0.3298		removed	
Diabetes	-0.0096	0.8198	0.3652		removed	
Smoking	0.2555	0.4359	0.5091		removed	
BMI	-0.346	1.3211	0.2504		removed	
SBP	0.0016	0.0912	0.7627		removed	
DBP	-0.0096	0.8198	0.3652		removed	
Therapy*	-0.7542	11.3919	0.0007	-0.7449	11.4446	0.0007

Wald = Wald coefficients; Sig = statistical significance; Therapy* = treatment regimen (free therapy or special therapy).

9 to arrhythmias or cardiac arrest, and 6 to pulmonary embolism), and 11.9% (167/1404) in the normotensives (respectively 60, 33, 21, 39, and 14 cases). Cardiovascular mortality was significantly different in the two treatment groups ($\chi^2 = 14.713$, $p = 0.0001$).

Overall cumulative annual mortality after dividing subjects into drug regimens («free therapy» and «special therapy») is taken into account in the left panel of Figure 1, while in the right panel of the same figure the «special therapy» group is evaluated after separating patients by treatment, i.e. nifedipine, clonidine and the fixed combination of atenolol+chlorthalidone (global $\chi^2 = 38.9$, $p = 0.01$; «special therapy» vs «free therapy»: $\chi^2 = 13.8$, $p = 0.05$). Figure 2 shows in the same way the cardiovascular cumulative mortality (global $\chi^2 = 23.2$, $p = 0.01$; «special therapy» vs «free therapy»: $\chi^2 = 13.8$, $p = 0.05$).

The type of pharmacological approach («free therapy» or «special therapy») was a predictor of both overall and cardiovascular mortality according to the results of the logistic regression (Table II).

Table III. Cox Analysis for Overall and Cardiovascular 7-year Mortality.

Covariates	Coefficient	S.E.	Coeff./S.E.	Exp (Coeff.)
Overall mortality				
Uric acid	0.1071	0.0478	2.2403	1.1130
TC	-0.0024	0.0018	-1.3284	0.9976
Proteinuria	-0.0420	0.1040	-0.4044	0.9588
Diabetes	0.3927	0.1060	3.7052	1.4810
Hypertension	0.9933	1.0062	0.9873	2.7003
Smoking	0.2893	0.1986	1.4567	1.3355
Therapy (1)	0.0034	0.0762	0.0443	1.0034
Therapy (2)	0.0098	0.0078	1.2624	1.0099
Cardiovascular mortality				
Uric acid	0.0741	0.0670	1.1069	1.0769
TC	0.0021	0.0025	0.8572	1.0021
Proteinuria	-0.1717	0.1478	-1.1618	0.8423
Diabetes	0.4165	0.1396	2.9838	1.5166
Hypertension	0.2235	1.0135	0.2206	1.2505
Smoking	-0.2348	0.3365	-0.6980	0.7907
Therapy (1)	0.0735	0.1007	0.7301	1.0763
Therapy (2)	0.0235	0.0105	2.2365	1.0238

The coefficients of Cox's analysis are shown in Table III, where S.E. is the asymptotic standard error; Coeff/S.E. is the coefficient/standard error ratio (equivalent to *t* statistic), Exp (Coeff.) is the conversion factor relating the effect of each covariate on the hazard function, Therapy (1) is the randomized choice between «free therapy» and «special care», and Therapy (2) is the randomized choice between clonidine, nifedipine or the fixed combination of atenolol+chlorthalidone in the 351 patients receiving special therapy.

DISCUSSION

Does antihypertensive treatment reduce mortality? Although high BP is considered to be a major cardiovascular risk factor, in many studies reducing BP did not convey any benefit in reduction of mortality.^{1,22,27-34)} This was attributed to the choice of antihypertensive drugs, and particularly to β -blockers and thiazide diuretics whose harmful metabolic effects on serum cholesterol, uric acid and glucose tolerance might have counteracted the beneficial effects of blood pressure reduction.³¹⁻³⁴⁾ Furthermore the relatively small study groups and short observation period made it unreasonable to expect a significant effect on mortality; in fact, when a large number of subjects were recruited^{35,36)} and followed for a considerable number of years, a significant reduction of mortality was observed in the group of patients treated more vigorously with «special therapy» in a Hypertension Unit than in those treated with «free therapy» by their personal physicians.^{6,35,36)}

Doubts are even greater with respect to the benefits of treating elderly hypertensives in that not only has the effectiveness of drug therapy in reducing mortality in patients over 65 years not been clearly demonstrated, but even the opportunity of reducing BP in elderly hypertensive patients is under debate. Ekbom et al, who studied 961 elderly patients born between 1890 and 1914, considered BP a very weak predictor of mortality in the elderly.³⁷⁾ On the contrary, Mattila et al found a higher mortality in very old subjects having the lowest BP values,³⁸⁾ and Langer et al a lower mortality in those having the highest BP values.³⁹⁾ The ANBP showed that, although the incidence of cerebrovascular events was reduced in the stepped-care-treated elderly patients vs the referred-care coeval controls, the mortality rate was not different in the actively treated and in the placebo-treated elderly subjects, while a 53% reduction of mortality was observed in the younger subjects of the same cohort.⁵⁾ Finally, Morgan et al⁴⁰⁾ even demonstrated a higher mortality in elderly subjects treated with a thiazide diuretic than in either the normotensives or the non-treated hypertensives.

Only a few studies have been performed specifically in the elderly. Although a recent meta-analysis of these studies by Thijs et al⁴¹⁾ suggested a trend towards reduction of mortality (especially cardiovascular mortality) in the treated or in the more actively treated subjects, the analysis of individual studies is contradictory. In the HEP⁹⁾ (a non-population-based open study of 1,724 elderly hypertensives) subjects actively treated with atenolol and when necessary bendrofluazide followed by α -methyldopa, had a reduction of both fatal and non-fatal stroke in comparison to the non-treated ones, but total and cardiovascular mortality were not reduced. In the SHEP¹³⁻¹⁶⁾ (including 4,737 subjects aged 60 years or more with isolated systolic hypertension treated with chlorthalidone and, when necessary, atenolol versus placebo for 5 years) mortality was not lower in the active-treatment than in the placebo group, although the incidence of stroke, cardiovascular events, fatal- and non-fatal coronary events was lower (from -25 to -31%).¹⁵⁾ Both the Japanese Study by Kuramoto et al²⁰⁾ and the Open Randomised study by Sprackling et al²¹⁾ failed to show any reduction in mortality rate. Finally, in the MRC Trial in Older Adults a reduction of events was shown, but only an insignificant reduction of cardiovascular mortality and no reduction of all-cause mortality.²²⁾

The substantial failure of the treatment of hypertension in the elderly in these studies could be explained by too great a delay in beginning of therapy, by lack of a population based approach, and/or to adverse metabolic effects of drugs on serum lipids and glucose tolerance which could have counteracted the effects of the blood pressure drop, making the treatment «sub optimal».^{31,33)}

On the other hand, in both the EWPHE¹⁰⁻¹²⁾ and the STOP,¹⁹⁾ mortality was lower in the active treatment groups (including β -blockers) than in the pla-

Figure 2. The CArdiovascular Study in the ELderly (CASTEL): cumulative annual cardiovascular mortality during the 7 years of follow-up. Legend and symbols as in Figure 1.

cebo groups.

In our population-based study, «special therapy» reduced mortality below that of the normotensives constantly and significantly over the 7 years of follow-up. On the contrary, although «free therapy» was initially able to reduce mortality, this effect was lost after the 2nd year. As one can see in the left panel of Figure 2, this trend was particularly evident for cardiovascular mortality, which took into account the reduction of overall mortality. In fact, non-cardiovascular mortality was similar in the two treatment groups.

Apart from the type of therapeutic approach and choice of drugs, the «special care» and the «free therapy» groups were different in that the former received more strict and assiduous attention to their hypertension than the latter. Although in the CASTEL no structured non-pharmacological approach was planned, we cannot exclude the possibility that an improvement in the general habits of the patients (such as reducing smoking, alcohol consumption or calorie intake) may have contributed to reducing the overall mortality in the «special care» group. The results of logistic regression do not clash directly with this hypothesis.

The solid line indicated by ■—■ in the left panels of the two figures simply represents the average of three different «special care» treatments (i.e. clonidine, nifedipine or the fixed combination of atenolol + chlorthalidone). After separating this line into those of the three special regimens, it appears that only the fixed combination reduced mortality to below that of the normotensives, while clonidine and nifedipine had an inconstant and short-lived effect. The effect on

mortality of the «special care» and particularly of the fixed combination of atenolol+chlorthalidone cannot be attributed simply to the blood pressure reduction, which was practically the same (about 10%) in subjects receiving «free therapy» or «special therapy», and in those taking clonidine, nifedipine or the combination. One can speculate that an intrinsic effect of β -blocker was involved. In fact other studies which employed β -blockers^{12,19} also obtained this significant reduction of mortality.

The trend of mortality in the clonidine and the nifedipine groups was more complex. In a first period, lasting 4 years for clonidine and 5 for nifedipine, overall mortality was slightly lower in the treated hypertensive subjects than in the normotensives, while after this period neither clonidine nor nifedipine contribute to mortality reduction as the fixed combination did. Considering cardiovascular mortality, that of both the clonidine and nifedipine groups was constantly higher than that of the normotensives, while that of the atenolol + chlorthalidone group was lower.

Another interesting finding is that the effect on cardiovascular mortality of both the therapeutic approach («free therapy» or «special therapy») and the drug regimen employed (clonidine, nifedipine or the association) were independent of the effect of other well-known risk factors. In fact, serum cholesterol and HDL, cigarette smoking, BMI, and proteinuria had no influence on mortality as demonstrated by logistic regression and by Cox's analysis. Only serum uric acid (whose importance as a risk factor in the elderly we recently emphasized)⁴² and diabetes were predictors of mortality.

Conclusion: The «special therapy» type of therapeutic approach drastically modified cardiovascular mortality in hypertensive subjects from a general-population-generated cohort of elderly hypertensives, reducing mortality below that of the normotensives. Particularly, «special care» consisting of a combination of a β -blocker and a diuretic was highly effective, independent of any other cardiovascular risk factor. The «free therapy» approach was less effective.

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