

ORIGINAL ARTICLES

INFLUENCE OF ANTI-HYPERTENSIVE THERAPY ON SERUM CHOLESTEROL IN ELDERLY HYPERTENSIVE PATIENTS

Results of Trial by the European Working Party on High blood pressure
in the Elderly (EWPIIE)

Received for publication, March 9, 1981.

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**Influence of anti-hypertensive therapy on serum cholesterol in elderly
hypertensive patients** — *In the European Working Party trial on High
blood pressure in the Elderly, patients over 60 are randomly allocated either
to receive diuretic capsules containing 25 mg hydrochlorothiazide and*

50 mg triamterene or matching placebos. If the blood pressure remains high those receiving active diuretic treatment also receive methyldopa. Those receiving a placebo diuretic are given placebo methyldopa tablets. The study is double blind, started in 1974 and is still in progress.

Three hundred and thirty-one patients have now been followed for 1 year and of these 190 have been followed for 2 and 90 for 3 years. After 1 year the serum cholesterol in the placebo group fell by an average of 10.4 mg/100 ml; over 2 years the fall was 16.0 mg/100 ml and over 3 years 20.8 mg/100 ml (6.7%). The corresponding results for the actively treated group were falls of 3.1 mg/100 ml; 20.3 mg/100 ml and 17.3 mg/100 ml (6.6%). Over a period of up to 3 years the average fall in cholesterol was 5.9 mg/100 ml/year in the placebo group and 5.0 mg/100 ml/year in the actively treated group. Thus the changes in serum cholesterol were similar whether the patients received active or placebo medication. In particular there was no evidence for an increase in cholesterol nor for a smaller decrease during diuretic therapy.

In the actively treated group the fall in blood pressure in the more hypertensive patients was accompanied by a fall both in haematocrit and serum cholesterol. In patients with less severe hypertension, active treatment was not accompanied by a fall in either haematocrit or cholesterol. These different responses of serum cholesterol in the more and less severe hypertensives in the present study could explain some of the previous conflicting reports on the influence of diuretic treatment on serum cholesterol.

KEY WORDS

Serum cholesterol

Hypertension

Diuretics

Methyldopa

Introduction

There has been considerable controversy whether or not thiazide diuretic therapy increases the total serum concentration of cholesterol. Ames and Hill (1976) have reported an average increase of 22 mg/100 ml with hydrochlorothiazide or the functionally related drug chlorthalidone. The MRC Mild Hypertension Trial (1977) has shown that the group treated with 10 mg bendrofluazide had a rise of 8 mg/100 ml in men and 7 mg/100 ml in women after one year. Between 1 and 2 years in the trial there were further increases of 3 mg/100 ml and 5 mg/100 ml respectively. There were no significant changes in the placebo group. On the other hand

Kannel and colleagues (1977), using the Framingham data, failed to show an increase in serum cholesterol with diuretic treatment. The Oslo trial (Helgeland et al., 1978) has also shown that 50 mg hydrochlorothiazide was not associated with an increase in total cholesterol.

We thought that a similar analysis would be worthwhile in the European Working Party on High blood pressure in the Elderly (EWPHE) trial (Amery et al., 1973, 1977, 1978) as this trial compares a combination of hydrochlorothiazide and triamterene as first-line treatment with matching placebo capsules.

Patients and methods

The EWPHE is conducting a double-blind, randomised trial of the effect of treating hypertension in persons aged over 60. Patients randomised to active treatment receive a capsule containing 25 mg hydrochlorothiazide and 50 mg triamterene: if control of blood pressure is unsatisfactory, these patients are given 2 capsules daily, and, if necessary, methyl-dopa up to 4 tablets of 500 mg daily is added to the regimen. The control group receives matching placebo capsules and tablets.

By January 1980, 650 patients have entered the multi-centre trial and 335 have follow-up measurements of total cholesterol at 1, 2 or 3 years. The average age of these 335 was 71.2 ± 0.5 years; 69% were women. Two patients received clofibrate, 3 had a history of gall bladder disease and these 5 patients were excluded from the present analysis. 315 patients had a repeat measurement of serum cholesterol after one year. 190 patients after 2 years and 90 patients after 3 years.

Biochemical methods

Serum cholesterol estimations were done in the laboratories of the collaborating centres using both enzymatic and non-enzymatic methods of estimation.

The precision and accuracy with which these analyses were performed were determined with control serum, which was analyzed in each laboratory three times, at weekly intervals, each analysis being performed in quadruplicate. Intralaboratory precision showed a coefficient of variation (i.e. S.D. $100/\bar{x}$) ranging from 1 to 9.3. As to accuracy, the means of the measured values were also found to be within acceptable limits (Cooper, 1976), taking into account the various methods of estimation. The percentage deviation from expected values ranged from -7% to +7%, with two exceptions of -12% and +9% respectively.

Statistical methods

The average results for selected groups were compared using unpaired t-tests. The change in cholesterol after 1 year was computed as the serum cholesterol at 1 year minus the serum cholesterol at entry to the trial. The changes after 2 years and 3 years were computed in the same manner to express the change over the total period of 2 and 3 years. The percentage change was computed for each person and each time interval with initial cholesterol equal to 100%. Also calculated was the change in cholesterol per year per person, those being followed for 3 years having the three year change in cholesterol divided by three and those being followed for two years, by two. The changes in blood pressure and haematocrit did not alter at a constant rate per year of follow-up and are therefore presented as the change after 1, 2 or 3 years, the longest interval being selected.

Results

Table I reports certain characteristics of the patients followed for 1, 2 and 3 years. There were no significant differences between the placebo and active groups at entry to the trial nor between these groups in changes in cholesterol or body weight with time.

In 157 patients given placebo the serum cholesterol fell by an average of 10.4 mg/100 ml in the first year (-2.5%); in 91 patients followed for two years the average fall was 16.0 mg/100 ml/2 years (-5.0%) and in 42 patients followed for 3 years, 20.8 mg% (-6.7%). The decreases in cholesterol were significantly different from zero at 1, 2 and 3 years.

The decreases in serum cholesterol in the actively treated group were similar, an average fall in cholesterol of 3.1 mg/100 ml after one year (+0.3%), 20.3 mg/100 ml after 2 years (-6.8%) and 17.3 mg/100 ml after 3 years (-6.6%). The average change in the actively treated group was significantly different from zero at 2 and 3 years. The annual change in cholesterol averaged a fall of 5.9 mg/100 ml/year in the placebo treated group and 5.0 mg/100 ml/year in the actively treated group. 95% confidence limits encompassed falls of 1.8 to 10.0 mg/100 ml/year in the placebo group and the limits were a gain of 0.3 and a fall of 10.3 mg/100 ml/year in the actively treated group.

The yearly change in serum cholesterol for all individual patients had a standard deviation of 30.7 mg/100 ml/year. Because of this extensive variation we were interested in the factors related to it.

A correlation matrix for the relationship between change in cholesterol/year and other measurements showed that there were no significant

Table 1. — Average results and S.E.M. for serum cholesterol and weight for patients followed for 1, 2 and 3 years.

The changes in these variables are also given. There were no significant differences between the placebo and actively treated groups

	Placebo group	Actively treated group
<i>Results after 1 year</i>		
Number followed	157	158
Initial serum cholesterol	253.5±4.1	250.8±4.3
Change in cholesterol over 1 year (mg/100 ml/yr)	-10.4 **±3.3	-3.1±3.7
% change in 1 yr/patient	-2.5%	+0.3%
Initial weight (kg)	67.9±1.0	66.8±0.9
Change in weight over 1 yr (kg/yr)	-0.9±0.4	-1.0 ***±0.3
<i>Results after 2 years</i>		
Number followed	91	99
Initial serum cholesterol	262.7±5.6	261.4±5.4
Change in cholesterol over 2 years (mg/100 ml)	-16.0 ***±4.6	-20.3 ***±4.7
% change in 2 yrs/patient	-5.0%	-6.8%
Initial weight (kg)	67.5±1.3	67.2±1.2
Change in weight over 2 years (kg/yr)	-1.3 *±0.6	-1.2±0.7
<i>Results after 3 years</i>		
Number followed	42	48
Initial serum cholesterol	259.4±7.5	255.6±7.2
Change in cholesterol over 3 years (mg/100 ml)	-20.8 ***±5.4	-17.3 **±5.7
% change in 3 yrs/patient	-6.7%	-6.6%
Initial weight (kg)	68.7±1.9	68.5±1.9
Change in weight over 3 years (kg/yr)	-1.6±1.0	-0.8±0.9
Average change in cholesterol (mg/100 ml/yr)	-5.9 **±2.1	-5.0±2.7
95% confidence limits of the mean (mg/100 ml/yr)	-1.8, -10.0	+0.3, -10.3

* $p < 0.05$;

** $p < 0.01$ and

*** $p < 0.001$ for comparison of average result with zero change.

correlations in the group treated with a placebo but in the actively treated group, the change in cholesterol was positively related to the change in haematocrit ($r = +0.32$, $p < 0.001$) and the change in systolic pressure on treatment ($r = +0.23$, $p < 0.001$) and negatively related to the initial untreated systolic pressure ($r = -0.18$, $p < 0.05$).

In order to illustrate these relationship the patients in the placebo and actively treated groups were divided into "quartiles" according to their initial systolic blood pressure. Figure 1 shows that the "quartile" in the actively treated group with the highest initial systolic blood pressure was

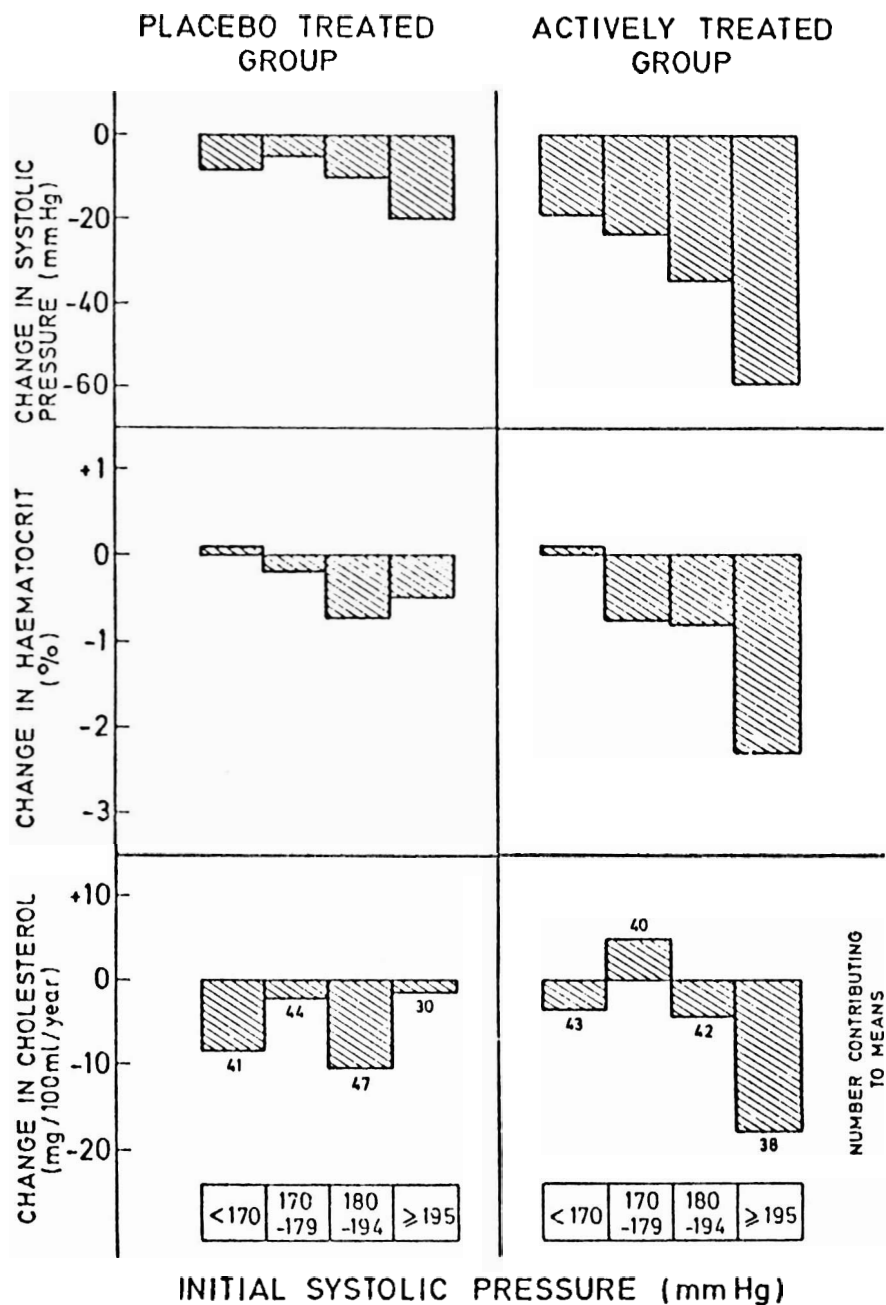


Fig. 1. — Change in serum cholesterol (mg/100 ml/year), change in haematocrit (%) and change in systolic blood pressure (mmHg) observed in four "quartiles" of the two treatment groups. The quartiles were selected on the basis of the level of initial systolic blood pressure.

characterised by a large fall in blood pressure on treatment, and significant falls in both haematocrit and cholesterol.

The quartile of the actively treated group with lowest initial systolic blood pressure did not show a significant change in haematocrit or serum cholesterol. In the placebo treated group the change in cholesterol was not related to the initial systolic blood pressure and in neither group were changes in cholesterol related to changes in weight.

Discussion

1. *Influence of antihypertensive therapy on serum cholesterol*

The results demonstrate that the daily diuretic combination of up to 50 mg hydrochlorothiazide and 100 mg triamterene did not increase serum cholesterol in elderly hypertensive patients. In fact there was a similar decrease in cholesterol with time in the active and placebo groups but the range between individuals was large.

Therefore factors which could be related to the change in cholesterol were examined. A strong positive association was observed between change in cholesterol and change in haematocrit. This was to be expected from Böttiger and Carlson's work (1972) suggesting that a fall in haematocrit may be expected to be associated with a decrease in cholesterol concentration. In the present study this association did not appear to be due to haemoconcentration resulting from taking blood with the venous return occluded, as a significant relationship was not observed in the placebo group. It is possible that the marked fall in cholesterol observed in the more severely hypertensive and actively treated patients was due to the effect of treatment, the large reduction in systolic blood pressure being associated with both a fall in haematocrit and a fall in serum cholesterol.

The actively treated group as a whole revealed a significant ($p < 0.01$) fall in haematocrit of 0.9% whereas the placebo group experienced only a 0.3% fall, which was not significant. However, patients with mild hypertension experienced small falls in blood pressure with treatment and no significant change in haematocrit or cholesterol. Patients with more severe hypertension experienced large falls in systolic pressure and significant falls in both haematocrit and cholesterol.

The Medical Research Council trial has reported an increase in cholesterol when a relatively large dose of diuretic (bendrofluazide 10 mg) was given to mildly hypertensive patients (MRC Working Party, 1977). On the other hand in the Oslo trial (Helgeland et al., 1978) 50 mg hydrochloro-

and elderly hypertensive patients (Bulpitt et al., 1979) and elderly females in general (Forette et al., 1979). Thus it is possible that a high serum cholesterol will not be accompanied by a higher mortality in our population and an exhaustion of susceptibles is therefore less likely to occur.

ACKNOWLEDGEMENTS

This study is supported by the Belgian Hypertension Committee, the Belgian Research Fund (FGWO) and the World Health Organization (Z. Pisa and T. Strasser). Tablets of alpha-methyl-dopa and placebo are kindly supplied by Merck, Sharp and Dohme and capsules of hydrochlorothiazide and triamterene and placebo by Smith, Kline and French; their support is gratefully acknowledged. We also thank A. De Maesschalck and G. Van Herpe for their help and advice in processing the drugs and J. Vanhollenbeke, Boehringer Pharma for his help in the design and evaluation of the quality control of biochemical estimations. E. Freis, F. Gross, and S. Hoobler gave most valuable criticism and advice. Last but not least we are particularly indebted to Mrs. M. Cober-Stinissen, and Mrs. K. Van Horenbeeck-Bijttebier for their competent and most appreciated collaboration.

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