Diuretics — a risk in the long-term treatment of hypertensive patients?

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The trial of the European Working Party on High blood pressure in the Elderly (EWPHE) revealed an overall decrease in cardiovascular mortality and morbidity in the actively treated patients. They received as first-line drugs a combination of hydrochlorothiazide and triamterene; methyldopa was added as necessary.

The present *post hoc* analysis examined the effect of the diuretic treatment on cardiovascular events, both when given alone and in conjunction with methyldopa, by calculating the relative hazard rates (RHR) for cardiovascular mortality and morbidity.

Using the Cox proportional hazard model, compared with placebo, a 34% reduction in cardiovascular mortality in the intention-to-treat analysis was demonstrated in the diuretic (hydrochlorothiazide and triamterene) group with an RHR of 0.66 and a 95% confidence interval (CI) of 0.44–0.97; the 16% decrease in the group treated with diuretics and methyldopa was not significant (RHR, 0.84; 95% CI, 0.56–1.25).

The effect of treatment in the latter combined group became significant (RHR, 0.62; 95% CI, 0.40–0.95) when all cardiovascular study terminating events were considered; they were reduced by 38%. No effect of treatment on mortality from all causes was detected.

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An obvious difference from other studies, where an apparent adverse effect of diuretics has been suspected, was that a potassium sparing agent was used in the trial.

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Introduction

Diuretics are used as first-line treatment in hypertension although they may produce metabolic disturbances such as glucose intolerance, decrease in serum and whole body potassium, decrease in serum magnesium, an increase in serum uric acid and, at least during short-term treatment, an increase in serum cholesterol and triglycerides.

On the other hand, several intervention trials [1–8] in which diuretics were used as first-line drugs have shown a decrease in cardiovascular morbidity and/or mortality. It is, however, possible that part of the beneficial effect seen in these trials was the result of other drugs used concurrently, such as reserpine or methylodopa.

The EWPHE trial [9,10] also reported a decrease in cardiovascular morbidity and mortality; diuretics were used as the first-line drug with the addition of methyldopa in those patients in whom blood pressure remained elevated.

The purpose of the present analysis was to determine whether the reduction in cardiac and cardiovascular morbidity and mortality in the EWPHE trial was observed in patients treated with diuretics alone, as well as in patients receiving diuretic and methyldopa treatment.

Methods

Study protocol

The protocol of the EWPHE trial has been published in detail [11]. Briefly, the entry criteria included:

(1) minimum age 60 years;
(2) sitting blood pressure on placebo during a run-in period of 160–239/90–119 mmHg.

The patients (n = 840) were randomized either to active treatment, with one or two capsules, of 25 mg hydrochlorothiazide + 50 mg triamterene (Dyazide®), or t matching placebo. If the blood pressure remained el vated, methyldopa (Aldromet®) was added to the activ regimen and matching methyldopa placebo to the placeb regimen. Table 1 gives some characteristics of patients a randomization.

Statistical methods

Most methods have been described previously [9–11]. Th Cox proportional hazard model was employed to estimat the effect on survival of an active diuretic when prescribe alone or in combination with methyldopa in compariso with placebo. Coding and interpretation of terms entere into the model are given below. Table 2 gives the codin of treatment groups in the model.

Table 2. Coding of terms entered into the Cox proportional hazard model.

Variables	Coefficients	Active diuretic only	Active diuretic + methyldopa	Placebo only
Diuretic (D)	β_D	1	0	0
Methyldopa (M)	β_M	0	1	0

The hazard rate (λ) represents the rate (death or event fo each patient group, given as follows:

Patients on active diuretic only: $\lambda = \lambda_{O\ exp}\ (\beta_D)$.

Patients on active diuretic + methyldopa: $\lambda = \lambda_{O\ exp}\ (\beta_M)$.

Patients on placebo: $\lambda = \lambda_O$

Table 1. Some characteristics of the patients at randomization

	Active treatment group		Placebo group		*P* between
	Only diuretic treatment	Methyldopa added	Only diuretic treatment	Methyldopa added	diuretic only groups
n	239	177	138	286	
Males/females	82/157	47/130	45/93	80/206	>0.1
Age (years)	72.3 ±7.7	70.7 ±8.3	74.0 ±8.5	70.9 ±7.7	= 0.037
Sitting blood pressure					
Systolic (mmHg)	181 ±16	186 ±19	179 ±16	184 ±16	>0.1
Diastolic (mmHg)	99 ±7	102 ±7	98 ±6	102 ±7	= 0.015
Cardiovascular complications (%)	36	36	33	37	>0.1

Values given are means ±s.d.

where λ_0 is the rate in the placebo group.

By including both diuretic and methyldopa in the model, the coefficients β_D and β_M compare the rates (events or death) in two groups with the placebo group as shown.

$\exp(\beta_D)$ = diuretic only rate/placebo rate

$\exp(\beta_M)$ = diuretic + methyldopa rate/placebo rate

Other terms for age, sex, blood pressure and prior cardiovascular complications were entered stepwise into the model.

On the intention-to-treat basis, all actively treated patients were prescribed diuretic at some stage.

Results

Cardiovascular mortality in the intention-to-treat analysis

In the patients treated with an active diuretic, the RHR for cardiovascular mortality was 0.67 in the first step of the Cox model (Fig. 1) when treatment with only active diuretics was compared to the total placebo group employing variables D and M (see Statistical methods, Table 2). This suggests that in the patients receiving active diuretic treatment only (57% of the active treatment group), the cardiovascular mortality was reduced by 33%. Figure 1 shows that the RHR varies between 0.69 and 0.65 by stepwise and cumulative introduction of other variables. This suggests that the reduction in mortality with active diuretic treatment alone remains between 31 and 35%, independent of the other variables such as age, sex, systolic blood pressure and cardiovascular complications at randomization.

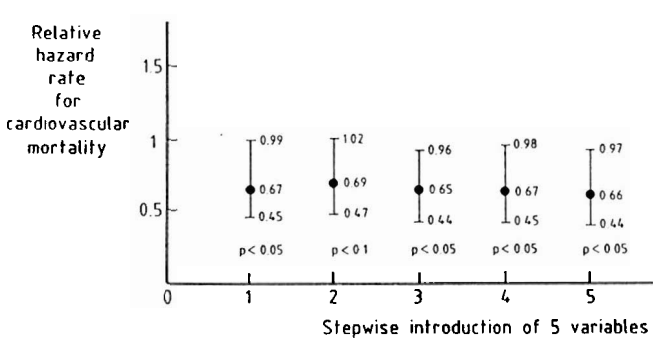

Fig. 1. Relative hazard rate for cardiovascular mortality in the intention-to-treat analysis after stepwise and cumulative introduction of five variables: (1) effect of active diuretic treatment alone compared to placebo; (2) allowing also for age in addition to (1); (3) allowing also for sex in addition to (2); (4) allowing also for entry systolic blood pressure in addition to (3); (5) allowing also for cardiovascular complications at randomization to (4). The figure illustrates, at each step, the relative hazard rate and the 95% confidence limits.

The full Cox proportional hazard model is given in Table 3 and also reports the effect of methyldopa given in combination with the diuretic. As no patient received methyldopa alone, the separate influence of methyldopa could not be analysed. Compared to the total placebo group the influence of combined treatment with active methyldopa and diuretics was not significant (P = 0.4), but the estimated hazard rate was 0.84 and the 95% CI (0.56–1.25) overlapped that for diuretics alone (0.44–0.97).

Table 3. Cardiovascular mortality (intention-to-treat).

Variable	Relative hazard rate	95% Confidence limits	2 P
Diuretic alone	0.66	0.44–0.97	<0.05
Methyldopa + diuretic	0.84	0.56–1.25	= 0.4
Age (years)	1.12	1.10–1.14	<0.001
Sex (male)	1.88	1.29–2.72	<0.001
Systolic BP (mmHg)	1.01	1.00–1.02	<0.05
Cardiovascular complications	1.50	1.09–2.04	<0.01

The cardiovascular mortality in the intention-to-treat analysis increased by 12% for each 1-year increase in age and by 1% for each 1-mmHg increase in entry systolic blood pressure. Mortality was 88% higher in the males and 50% higher in those with cardiovascular complications at randomization when these variables were simultaneously introduced in the model.

Cardiovascular mortality on randomized treatment

In the total Cox model (Table 4) the RHR associated with giving active diuretics only was 0.47, and for patients receiving diuretic and methyldopa, 0.78. This suggests that, independent of other factors introduced in the model, the contribution of diuretic treatment reduced cardiovascular mortality on randomized treatment by 53%.

Table 4. Cardiovascular mortality on randomized treatment

Variable	Relative hazard rate	95% Confidence limits	2 P
Diuretic alone	0.47	0.27–0.82	<0.01
Methyldopa + diuretic	0.78	0.49–1.26	= 0.38
Age (years)	1.11	1.09–1.14	<0.001
Sex (male)	2.41	1.51–3.85	<0.001
Systolic BP (mmHg)	1.02	1.01–1.03	<0.01
Cardiovascular complications	1.66	1.12–2.45	<0.05

BP, blood pressure.

Cardiovascular study terminating events

These events include cardiovascular mortality and non-fatal morbid cardiovascular events, such as severe congestive heart failure and the appearance of exudates or haemorrhages in the retina [11].

In the total Cox model (Table 5), the RHR associated with active diuretic treatment was 0.48, and for patients receiving both active diuretic and methyldopa, 0.62. This suggests again that, independent of other variables, cardiovascular study terminating events were decreased by 52% in the patients receiving diuretics (P <0.01), and by 38% in those receiving combined treatment (P <0.05).

Table 5. Cardiovascular study terminating events.

Variable	Relative hazard rate	95% Confidence limits	2 P
Diuretic alone	0.48	0.30–0.76	<0.01
Methyldopa + diuretic	0.62	0.40–0.95	<0.05
Age (years)	1.10	1.07–1.12	<0.001
Sex (male)	1.84	1.23–2.74	<0.01
Systolic BP (mmHg)	1.02	1.01–1.03	<0.01
Cardiovascular complications	1.77	1.27–2.49	<0.001

BP, blood pressure.

Table 7. Mortality from all causes (intention-to-treat)

Variable	Relative hazard rate	95% Confidence limits	2 P
Diuretic alone	0.97	0.73–1.27	>0.1
Methyldopa + diuretic	0.88	0.64–1.21	>0.1
Age (years)	1.12	1.20–1.14	<0.001
Sex (male)	1.90	1.44–2.15	<0.001
Systolic BP (mmHg)	1.01	1.00–1.01	<0.01
Cardiovascular complications	1.48	1.17–1.88	<0.05

BP, blood pressure.

Cardiac mortality

After stepwise introduction of other variables (Table 6), the RHR for cardiac mortality, associated with active diuretic treatment only, was 0.39. This suggests that, independent of the other variables, cardiac mortality was decreased by 61% in these patients.

Cardiac mortality during randomized treatment includes mortality from myocardial infarction (n = 7 out of 16 for active treatment and placebo group, respectively), congestive heart failure (n = 6 out of 8), and sudden death (n = 4 out of 5). The number of deaths in each subgroup

Table 6. Cardiac mortality on randomized treatment.

Variable	Relative hazard rate	95% Confidence limits	2 P
Diuretic alone	0.39	0.17–0.90	<0.05
Methyldopa + diuretic	0.77	0.37–1.61	>0.1
Age (years)	1.13	1.09–1.18	<0.001
Sex (male)	4.47	2.27–8.82	<0.001
Systolic BP (mmHg)	1.01	0.99–1.02	>0.1
Cardiovascular complications	1.71	0.95–3.06	<0.1

BP, blood pressure.

of cardiac deaths is, however, too low to allow any meaningful statistical analysis to be made in an attempt to establish whether diuretics alone have a different effect in one of the subgroups, than diuretics in combination with methyldopa.

Mortality from all causes (intention-to-treat)

The above tables have considered the statistical significant and biologically important results of the EWPHE trial. For completeness, Table 7 provides the same analysis for total mortality on an intention-to-treat basis. The data indicate that treatment, either by diuretics alone or combined treatment, did not significantly influence mortality from all causes. The latter was related to age, sex, systolic blood pressure and the presence of cardiovascular complications at randomization.

Discussion

Hypertension is an important risk indicator for both myocardial infarction and stroke. Previous placebo-controlled trials of antihypertensive therapy have all demonstrated a highly significant reduction in stroke, averaging about 45%. The reduction in myocardial infarction events in these trials was much smaller (7%) and was not statistically significant [12]. There has been speculation that this smaller-than-expected reduction in the incidence of myocardial infarction was due to an adverse effect of thiazide diuretics which formed the foundation of almost all the treatment regimes.

Some support for the latter hypothesis came from the MRFIT study [13], where subgroup analysis suggested that deaths from coronary disease were increased in the special intervention group who had resting ECG abnormalities at entry. Also, Morgan *et al.* [14] reported, in patients with mild hypertension receiving diuretics, an increased mortality due to an excess number of deaths from myocardial infarction and sudden death. In the Oslo study, Helgeland [15] found no difference between the hydrochlorothiazide and placebo groups in total mortality and mortality from cardiovascular events, but the differences in coronary heart disease, including incidences of sudden death, tended to be higher in the treated group. There was also some evidence in the MRC trial [8] to suggest that sudden cardiac deaths were more frequent in the diuretic group than in the porpranolol-treated group, although neither differed significantly from the placebo group.

The EWPHE reported a 27% reduction in cardiovascular mortality ($P = 0.037$) with a 38% reduction in cardiac mortality ($P = 0.036$), compared with placebo. The proportional reduction in events was similar in patients with and without cardiovascular complications at entry, although the absolute reduction was greater in those with complications.

The EWPHE treatment regimen involved two steps. All patients began treatment with a combination of hydrochlorothiazide and triamterene (Dyazide®); methyldopa (Aldomet®) was added if control was inadequate on the diuretic alone. Methyldopa was used in 177 of the 416 actively treated patients. As methyldopa reduces efferent sympathetic activity, the favourable effect upon cardiac mortality might have been due to the action of this drug.

The Cox proportional hazard analysis represented in the tables suggests that the beneficial effects observed in the EWPHE trial, including the reduction in cardiac mortality, cannot be explained by the addition of methyldopa.

In younger patients there are some important differences between the EWPHE findings in the elderly and

the results of other placebo-controlled hypertension trials. Congestive heart failure, unresponsive to digitalis alone, was an important contribution to non-fatal, study terminating events in the EWPHE placebo group. A favourable effect of a diuretic would be expected in patients who are at risk of developing heart failure. There is epidemiological evidence that hypertension is a powerful predictor of the development of heart failure as age advances [16]. Clinical trials in younger patients with mild to moderate hypertension have shown an extremely low incidence of heart failure in the placebo groups.

Additional reasons for the favourable effect on cardiovascular mortality observed in the EWPHE trial may have been the relatively low dose of the thiazide, larger reduction in blood pressure than has been achieved in most other trials, and the use of a fixed ratio regimen which combined a potassium losing with a potassium sparing diuretic. Therefore, the average serum potassium levels during the trial [17] remained within normal limits in the active treatment group (4.05 mmol), as well as the placebo group (4.25 mmol/l), while the serum potassium levels in the MRC trial [18] after 3 years treatment averaged 3.72 mmol/l in men and 3.62 mmol/l in women.

Several controlled studies have investigated whether a β-blocker- or a diuretic-based treatment is better as a first-line regimen in preventing cardiovascular complications of hypertension.

Comparing the diuretic and the β-blocker group in the MRC trial [18], no significance differences were found, but there is some evidence that the incidence of sudden cardiac death was increased in the diuretic group compared with the propranolol group, while the incidence of strokes tended to be lower in the diuretic group. The IPPPSH trial [19] compared an oxprenolol-based regimen with a treatment regimen without a β-blocker, where thiazides were mainly used as the first-line drug. No difference in the occurrence of major events was observed between the two groups. The HAPPHY trial [20] was restricted to men and compared a diuretic group with a β-blocker group; atenolol was used in some centres and metoprolol in the others. Again, no significant differences were observed in the occurrence of major events. More recently, Wikstrand *et al.* [21] reported a primary prevention trial comparing metoprolol and thiazide treatment in men aged 40–64 years. Total mortality was lower ($P = 0.028$) in the β-blocker than in the diuretic group. This was due to a reduction in cardiovascular mortality and a similar trend in non-cardiovascular mortality. The latter trial was, in fact, a subgroup analysis of the previous HAPPHY trial based on the centres where the trial was continued for a longer time, namely those centres using metoprolol. Although the results of the MAPHY trial seem to be divergent from those of the three other trials, the 95% confidence limits show that the differences are not significant from those of the other trials when these limits are calculated at the end of the trial, and compared to the confidence limits of the male subgroup of the other trials [22].

By using the Cox model we have endeavoured to compare diuretics alone, and diuretics plus methyldopa, with placebo. However, it must be recognized that the decision to add methyldopa to the diuretic was taken because the blood pressure was difficult to control with a diuretic alone. Thus, the group given combined treatment may well have differed from the monotherapy group in other ways which were not adjusted for in the Cox model. It is important therefore to be cautious about the interpretation of the data. We conclude only that the reduction of cardiovascular events in the EWPHE trial cannot be explained solely by the addition of methyldopa.

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