Isolated systolic hypertension: data from the European Working Party on High Blood Pressure in the Elderly

Kevin O'Malley, Patricia McCormack and Eoin T. O'Brien

The European Working Party on High Blood Pressure in the Elderly study (EWPHE) was a placebo-controlled, double-blind, inter-patient assessment of diuretic treatment in hypertensive patients aged 60 years or more.

Of the 840 patients included in the study 247 had isolated systolic hypertension (systolic blood pressure $\geq 160$ and diastolic blood pressure $\leq 95$ mmHg). In those ($n = 120$) randomized to active treatment (diazide-hydrochlorothiazide with triamterene $\pm$ methyldopa) blood pressure after 3 years was, on average, $19/8$ mmHg lower than in the placebo group ($n = 119$) and after 5 years the difference was $9/7$ mmHg.

Data on mortality and morbidity were insufficient for firm conclusions to be drawn. The data are presented here only to communicate the trends observed and to provide information that may be useful in the design of future trials. The trends observed for cardiac mortality, terminating non-fatal events (including severe heart failure) and combined fatal and non-fatal cardiovascular events follow a similar pattern to that observed in the trial overall, in that active treatment appeared to confer benefit. However, in the case of isolated systolic hypertension none of these differences between active and placebo treatment achieved statistical significance.

We conclude that, given the epidemiological data incriminating systolic hypertension as a risk factor and the data presented here, a rigorous assessment of the value of treating isolated systolic hypertension is justified.

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Introduction

Hypertension is a major risk factor for cardiovascular disease in the elderly [1]. Specifically, the Framingham study has shown that raised blood pressure is associated with cerebrovascular complications [1,2], ischaemic heart disease [3] and heart failure [4], and this is more marked in the elderly [5,6]. Furthermore, systolic blood pressure is a better predictor of complications than diastolic or mean arterial pressure [3,7]. Unlike diastolic blood pressure, which tends to plateau in the fifth and sixth decades of life in population studies, systolic blood pressure tends to increase into the ninth decade. In the elderly, therefore, disproportionate systolic hypertension is a dominant clinical finding, and thus there is an age-related increase in the prevalence of isolated systolic hypertension. Isolated systolic hypertension is defined here as a systolic pressure of $\geq 160$ mmHg and diastolic blood pressure of $\leq 95$ mmHg.

It is clear that we should consider systolic as well as diastolic blood pressure in assessing patients with hypertension. However, it has not been established whether isolated systolic hypertension is responsive to drug treatment or, more importantly, whether treating isolated systolic hypertension confers benefit in terms of mortality and morbidity. It is against this background that we decided to examine the outcome in patients with isolated systolic hypertension in the EWPHE study. Specifically, we describe the magnitude of blood pressure reduction and the effect of drug treatment on mortality and morbidity in isolated systolic hypertension.

We wish to emphasize that the subgroup of patients with isolated systolic hypertension was too small to be able to detect beneficial effects, and perhaps more
importantly, to arrive at negative conclusions concerning the value of active treatment. This paper describes trends in the data that may be of interest and documents the blood pressure lowering effect on the regimen used.

Some preliminary data in relation to drug efficacy in isolated systolic hypertension have previously been presented [8]. Two papers from the EWPH study, one on overall mortality and morbidity [9] and the second on the efficacy of antihypertensive drug treatment according to age, sex, blood pressure and previous cardiovascular complications [10], have been published.

Methods
The protocol used in the EWPH study has been described in detail elsewhere [11]. This was a placebo-controlled, double-blind, inter-patient assessment of treatment in hypertensive patients aged 30 years or more. During a run-in period with placebo, blood pressure was 160–230/90–119 mmHg. Patients (n = 840) were randomly assigned either to active treatment (hydrocholorothiazide + triamterene) or to matching placebo. If blood pressure remained raised, then methyldopa was added to the active regimen and matching placebo to the placebo regimen.

Results
Of the 840 patients who entered the EWPH study, 247 fulfilled the above criteria for isolated systolic hypertension and their characteristics at randomization are set out in Table 1; the average blood pressure was 178/93 mmHg in both the placebo and the active groups. Values for the two groups over the 5 study years are shown in Fig. 1. After 3 years the difference was 19/8 mmHg.

Table 1. Characteristics at randomization of the isolated systolic hypertension subgroup. Patients were selected with diastolic blood pressure (DBP) ≤ 95 and systolic blood pressure (SBP) ≥ 160 mmHg.

<table>
<thead>
<tr>
<th></th>
<th>Placebo group</th>
<th>Active group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>119</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>73.8 ± 8.1</td>
<td>72.8 ± 8.1</td>
<td>0.339</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28</td>
<td>37</td>
<td>0.415</td>
</tr>
<tr>
<td>Female</td>
<td>91</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.4 ± 11.9</td>
<td>66.1 ± 11.0</td>
<td>0.648</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158 ± 9</td>
<td>159 ± 9</td>
<td>0.280</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>178 ± 15</td>
<td>178 ± 16</td>
<td>0.831</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>93 ± 2</td>
<td>93 ± 2</td>
<td>0.680</td>
</tr>
<tr>
<td>Heart rate</td>
<td>78 ± 10</td>
<td>80 ± 12</td>
<td>0.232</td>
</tr>
</tbody>
</table>

Data are means ± s.d. for each value. P is the probability of a difference between the two groups. Blood pressures are sitting values.

Fatal events during the study are set out in Table 2 and suggest that all-cause mortality was reduced by 25%. There was a 27% reduction in all cardiovascular deaths, with a 61% decrease in fatal cardiac events, but data for cerebrovascular complications were too few even to draw a tentative conclusion.

Fig. 1. Mean sitting blood pressure (BP) in the placebo (■) and actively treated (□) groups at randomization (R) and subsequently throughout 5 years. N is the total number of patients in the study for the respective blood pressure values.

Discussion
There are some differences between the findings reported here and those for the entire group of 840 patients [9,10] as regards blood pressure reduction with the active regimen. The efficacy data are probably valid, though the number (62) of patients for whom 5-year data are available is relatively small. In the overall study the blood pressure reduction after 5 years was 21/10 mmHg, whereas in the isolated systolic hypertension subgroup it was 9/6 mmHg. In contrast, the corresponding values after 3 years were roughly similar (23/9 versus 19/8 mmHg). There appears to be a tendency for blood pressure to fall with time in the placebo group, but as data for different patients make up each mean this may be more apparent than real. However, the placebo versus treatment blood pressure differences are less marked after 5 than after 3 years. If the benefit of treatment is directly related to the magnitude of blood pressure reduction, then the active regimen may have less impact on mortality and morbidity in isolated systolic hypertension. Possibly, alternative regimens should be examined in this clinical setting.

The morbidity and mortality data must be interpreted with great caution. Small numbers of patients and events preclude definitive conclusions. Notwithstanding, the results may suggest trends in the effects of treating patients with isolated systolic hypertension. The most striking finding is a reduction in cardiac mortality of 61%. However, the overall effect on cardiovascular mortality is attenuated by an unchanged cerebrovascular death rate.
As the number of patients and events is greater in the cardiac mortality category, one may be more confident than in the case of cerebrovascular deaths where the numbers are very small indeed. The effect of treatment on terminating non-fatal events and on the combination of fatal and non-fatal cardiovascular events were both reduced, and to an extent similar to that observed in the EWPHE study overall [9,10].

In the overall study, systolic but not diastolic blood pressure [10] was an important independent determinant of cardiovascular mortality and of the cardiovascular terminating events studied. The percentage benefit observed was independent of the systolic blood pressure level. However, as those with high systolic blood pressure have the greatest absolute risk, the benefit associated with antihypertensive treatment is greater in those with highest systolic blood pressure. Therefore, there appears to be a good a priori basis for treating isolated systolic hypertension in elderly patients. However, the hypothesis needs testing, and to this end the SHEP study [12] in the USA is presently underway. A European study of the effect of treatment in isolated systolic hypertension in the elderly (Systeur) is at the planning stage.

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### References

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