Treatment of Hypertension and Prevention of Cardiovascular Morbidity and Mortality

G. Mancia

Introduction

Large-scale epidemiological studies have shown that hypertension is associated with an increased rate of coronary artery disease, cerebrovascular disease, congestive heart failure, renal insufficiency, and peripheral artery disease, and that, therefore, cardiovascular morbidity, cardiovascular mortality, and overall mortality are greater in subjects with elevated blood pressure than in those in whom blood pressure is normal [1]. This has led researchers to conduct intervention trials that have proved the benefit of antihypertensive treatment, i.e., the fact that lowering elevated blood pressure leads to a reduction of the risk inherent in the hypertensive condition [2].

This paper will briefly recall the favorable effects on cardiovascular morbidity and mortality that result from treating hypertension which have emerged from the most important trials that have addressed this issue. It will then focus on a number of less successful data which came out of these trials, in order to outline the areas where progress is needed, and new therapeutic approaches are expected to offer an advantage.

Reduction in Cardiovascular Morbidity and Mortality in Intervention Trials on Hypertension

In the early 1960s Freis et al. [3] randomized several hundred male subjects with overall severe hypertension to antihypertensive drug treatment or placebo, and followed them for about 5 years in a double-blind fashion. Cardiovascular morbidity was 55% in the placebo group and 18% in the patients who received antihypertensive treatment. Cardiovascular mortality was also much less pronounced in the latter than in the former group, and in both instances the difference was statistically significant. Thus, this trial proved the benefit of antihypertensive treatment. It also showed that, in severe hypertension, the benefit can be so large as to prevent about three-fourths of the fatal and nonfatal cardiovascular complications that would otherwise occur.

It was more difficult to perform intervention trials in subjects with less severe hypertension because
a) these conditions are associated with a smaller increase in risk, and
b) many more subjects are needed to collect the number of fatal and/or nonfatal cardiovascular events required to prove a difference between treated and untreated patients.

This problem was addressed, however, in three trials exclusively or mainly focused on subjects with a mild or moderate increase in diastolic blood pressure and with no cardiovascular complications [4–6]. As shown in Table 1, in two trials (i.e., the ANBPS and MRC trials) cardiovascular morbidity and mortality were significantly less in the treated than in the placebo group. Furthermore, in the third trial (i.e., the HDFP trial) cardiovascular mortality was significantly less in a more actively treated group than in a less actively treated one. Thus, the benefit of antihypertensive treatment extends to a modest blood pressure rise, which is still devoid of clinical consequences.

<table>
<thead>
<tr>
<th>Study</th>
<th>Control (%)</th>
<th>Treatment (%)</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANBPS (n = 2218)*</td>
<td>9.8</td>
<td>8.6</td>
<td>−13.9</td>
</tr>
<tr>
<td>HDFP (n = 7825)*</td>
<td>7.4</td>
<td>5.9</td>
<td>−20.3</td>
</tr>
<tr>
<td>MRC (n = 17354)*</td>
<td>8.2</td>
<td>6.7</td>
<td>−18.3</td>
</tr>
</tbody>
</table>

* Numbers refer to events which occurred during the entire study. In the ANBPS and MRC studies, the control group was on placebo, while in the HDFP study the control group was less treated than the treated group. (From [4], [5], and [6])

Subanalysis of the data of the above mentioned trials showed that antihypertensive treatment is also associated with less cardiovascular morbidity and mortality in hypertensive subjects above 60 or 65 years of age [3–6]. This has been conclusively confirmed in two trials specifically addressing elderly hypertensive patients [7, 8]. In one double-blind, randomized, placebo-controlled trial conducted over a period of 7 years, the reduction of cardiovascular morbidity and mortality induced by treatment was greater than 30% (Fig. 1) [7]. This leaves no doubt as to the advantage of lowering blood pressure in aged hypertensive individuals as well.

**Limitations and Uncertainties of Intervention Trials**

Most intervention trials on hypertension did not show a significant reduction in overall mortality, raising the question of the impact of antihypertensive treatment as a general health measure. These trials, however, were not designed to test the effect of treating hypertension on overall mortality. Furthermore, the subjects recruited were not sufficient to address with the required power an end point depending to a considerable degree on noncardiovascular diseases and, thus, unaffected by antihypertensive treatment. When the number of subjects was increased, by performing a metaanalysis of all major trials, the overall mortality was