STOP-Hypertension-2 and best practice for the future

Lennart Hannson

High blood pressure is a well recognised major risk factor for cardiovascular disease, which is a primary cause of morbidity and mortality in patients aged 70 years or more. A number of studies including STOP-Hypertension-1, SHEP, and MRC II have shown that by lowering blood pressure in the elderly, cardiovascular morbidity and mortality can be significantly reduced. In fact, treatment of the elderly hypertensive patient is probably more successful than treatment of the young or middle aged patient.

STOP-Hypertension-1 was a double blind trial of 1627 patients aged 70–84 years, which compared placebo with active treatment (one of three β blockers or a fixed ratio combination of hydrochlorothiazide and amiloride). Active treatment for 26 months lowered blood pressure 20/8 mm Hg more than placebo. This resulted in a significant reduction in major cardiovascular events (all strokes, all myocardial infarctions, and other cardiovascular mortality) by 40%, fatal and non-fatal strokes by 47%, and total mortality by 43%.

The STOP-Hypertension-2 study was designed to investigate how newer antihypertensive treatments (angiotensin converting enzyme (ACE) inhibitors and calcium antagonists) compare with the conventional treatments (β blockers and diuretics) shown to be effective in STOP-Hypertension-1. The study examined cardiovascular morbidity and mortality prevention. The primary aim was to assess the effect of the different treatments on mortality. A placebo group was not included for ethical reasons.

Study design

The STOP-Hypertension-2 study followed a PROBE design (prospective, randomised, open and blinded end point evaluation) and employed the same entry criteria as STOP-Hypertension-1: men and women aged 70–84 years with hypertension (≥ 180 mm Hg systolic, ≥ 105 mm Hg diastolic, or both). A total of 6628 patients were recruited with 6614 randomised to treatment; the study period extended just over five years.

Patients were randomly assigned to treatment with one of three classes of drugs: (1) β blockers, diuretics or both (atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or fixed ratio hydrochlorothiazide 25 mg plus amiloride 2.5 mg daily); (2) ACE inhibitors (enalapril 10–20 mg or lisinopril 10–20 mg daily); or (3) calcium antagonists (felodipine 2.5–5 mg or isradipine 2.5–5 mg daily). Approximately 2200 patients were assigned to each of the three treatment groups. No patients were lost to follow up in any of the groups.

The following comparisons were planned: β blockers/diuretics versus ACE inhibitors; β blockers/diuretics versus calcium antagonists; and ACE inhibitors versus calcium antagonists.

The study had a statistical power of 94% to detect a 25% difference in cardiovascular mortality between older and newer treatments.

Results

The baseline characteristics of the three groups were virtually identical as would be expected in a study with proper randomisation and sufficiently large numbers. Notably, the number of patients with diabetes at baseline was virtually identical for all three groups.

A comparison of STOP-Hypertension-1 and STOP-Hypertension-2 shows that baseline patient characteristics in each study were almost identical because the same entry criteria were used. The close similarity of the two studies allows comparisons to be made between the results from STOP-Hypertension-2 and the placebo group in STOP-Hypertension-1.

BLOOD PRESSURE LOWERING

The blood pressure lowering effects were similar in the three treatment groups. At baseline all three groups had exactly the same blood pressure of 194/98 mm Hg. By the end of the study this had been reduced to 158–159/80–81 mm Hg. It is important to note that in a substantial number of patients combined treatment was used.

ADVERSE EVENTS

Adverse events were recorded as the proportion of patients in each treatment group who, at any time during the trial, reported an event. A more thorough analysis of adverse events during STOP-Hypertension-2 will form the basis of a separate publication. The pattern of events was as expected: more shortness of breath, cold hands and feet in the β blocker/diuretic treatment group; more coughing in the ACE inhibitor group; and more swollen legs in the calcium antagonist group.

CARDIOVASCULAR EVENTS

A comparison between the results of STOP-Hypertension-1 and STOP-Hypertension-2 looking at major cardiovascular events—strokes, myocardial infarction plus other cardiovascular mortality—reveals an incidence of 55 per 1000 patient years in the placebo group; 34 in the actively treated group in STOP-Hypertension-1; and 41 in STOP-Hypertension-2.

The higher figures for the STOP-Hypertension-2 patients compared with the...
STOP-Hypertension-2 study

Patients at risk

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>ACE inhibitors</th>
<th>Calcium antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium antagonists</td>
<td>2196</td>
<td>2094</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>2205</td>
<td>2104</td>
</tr>
<tr>
<td>Conventional drugs</td>
<td>2213</td>
<td>2057</td>
</tr>
</tbody>
</table>

**Table 1**  Number of events per treatment group (incidence per 1000 patient years)

<table>
<thead>
<tr>
<th>Event</th>
<th>Conventional</th>
<th>ACE inhibitors</th>
<th>Calcium antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>33.1 (369)</td>
<td>34.4 (380)</td>
<td>32.8 (362)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>19.8 (221)</td>
<td>20.5 (226)</td>
<td>19.2 (212)</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>4.9 (55)</td>
<td>4.3 (48)</td>
<td>5.3 (59)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>4.6 (51)</td>
<td>4.5 (50)</td>
<td>4.2 (46)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>4.8 (53)</td>
<td>5.3 (59)</td>
<td>4.7 (52)</td>
</tr>
<tr>
<td>Other cardiovascular mortality</td>
<td>5.6 (62)</td>
<td>6.2 (69)</td>
<td>5.0 (55)</td>
</tr>
<tr>
<td>All myocardial infarction</td>
<td>14.1 (154)</td>
<td>12.8 (139)</td>
<td>16.7 (179)</td>
</tr>
<tr>
<td>All stroke</td>
<td>22.2 (237)</td>
<td>20.2 (215)</td>
<td>19.5 (207)</td>
</tr>
<tr>
<td>All major cardiovascular events</td>
<td>44.1 (460)</td>
<td>41.9 (437)</td>
<td>43.6 (450)</td>
</tr>
<tr>
<td>Incidence of diabetes mellitus</td>
<td>10.0 (97)</td>
<td>9.6 (93)</td>
<td>9.9 (95)</td>
</tr>
<tr>
<td>Incidence of atrial fibrillation</td>
<td>16.4 (177)</td>
<td>13.9 (149)</td>
<td>17.5 (186)</td>
</tr>
<tr>
<td>Incidence of congestive heart failure</td>
<td>16.4 (177)</td>
<td>13.9 (149)</td>
<td>17.5 (186)</td>
</tr>
</tbody>
</table>

STOP-Hypertension-1 patients can be attributed to the longer duration of the study (five years compared with two years), which meant that patients had the chance of becoming three years older. As patients were already 76 years old on entry, the extra three years is very important in terms of cardiovascular mortality and morbidity. In addition, there was a higher prevalence of previous myocardial infarction, stroke, and diabetes mellitus in the STOP-Hypertension-2 study patients at baseline.

**Comparison of results**

In STOP-Hypertension-2 there were 19.8 fatal cardiovascular events per 1000 patient years in the β blocker/diuretic group; 20.5 in the ACE inhibitor group; and 19.2 in the calcium antagonist group. These are very small differences that are not significant (fig 1).

There were no significant differences in cardiovascular mortality, all myocardial infarction, all stroke, all major cardiovascular events, total mortality, incidence of diabetes mellitus, incidence of atrial fibrillation or incidence of congestive heart failure, between the newer drugs (ACE inhibitors or calcium antagonists) and the older drugs (β blocker/diuretic). Old and new drugs did equally well in this comparison (table 1).

**ACE inhibitors versus conventional drugs**

Looking at the same variables, there were no significant benefits or disadvantages of either treatment when ACE inhibitors and conventional drugs were compared. They were equally effective in preventing events.

**Calcium antagonists versus conventional treatment**

There were also no significant benefits or disadvantages of choosing calcium antagonists or conventional drugs.

**ACE inhibitors versus calcium antagonists**

Interestingly, in the comparison of ACE inhibitors and calcium antagonists, the frequency of myocardial infarction and congestive heart failure was significantly lower in patients treated with ACE inhibitors (fig 2). These results should, however, be interpreted with caution as 48 statistical comparisons were performed on the data from this study. With a 5% significance level, it is expected that one in 20 events will be significant by chance alone. In addition, myocardial infarction and congestive heart failure are not independent factors but are closely linked to each other. A patient who suffers a myocardial infarction has a greater risk of developing congestive heart failure.

**Conclusion**

All three classes of treatment were equally effective in lowering blood pressure. In addition, all three were equally effective in preventing cardiovascular morbidity and mortality, and were significantly better than the placebo arm in STOP-Hypertension-1.

Notably, ACE inhibitors were better than calcium antagonists in preventing myocardial infarction and congestive heart failure, but...
this should be interpreted with caution owing to the number of statistical comparisons performed.

The reduction of blood pressure is important in elderly hypertensive patients. If blood pressure is reduced effectively there will be a significant impact on major cardiovascular end points. The findings of this study are clearly in agreement with those of the HOT study and support the recently published guidelines of the World Health Organization–International Society of Hypertension.1

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