Clinical Perspective

The HOPE study: Comparison with other trials of secondary prevention

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Introduction

The HOPE study results[1], have started a debate on extending the current indications for angiotensin converting enzyme inhibitor treatment to the area of cardiovascular prophylaxis. The recently published recommendations of the second joint task forces of European and other societies on coronary prevention[2], include ACE inhibitor treatment as one of the five first line drug classes for hypertension. Such treatment is particularly indicated in patients with persistent left ventricular dysfunction. The treatment goal is to obtain a blood pressure below 140/90 mmHg. ACE inhibitor treatment is also recommended in patients with symptoms and signs of heart failure at the time of myocardial infarction, and in asymptomatic left ventricular dysfunction following a myocardial infarction. It is also increasingly used in diabetics with hypertension and microalbuminuria[3–5].

In the European guidelines on the prevention of coronary heart disease, a treatment goal is also to reduce blood lipids to a total cholesterol <5.0 mmol . l⁻¹ and LDL cholesterol to <3.0 mmol . l⁻¹. Preference should be given to the HMG CoA reductase inhibitors (statins), as this class of lipid lowering drug has the strongest evidence in coronary heart disease patients for reducing coronary morbidity, mortality and prolonging survival[2].

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These recommendations are based on prior evidence from large clinical trials with ACE inhibitors and statins. It now seems appropriate to discuss the HOPE results in comparison with those from the earlier ACE inhibitor and statin trials. Since the treatment effects in HOPE are as powerful and cost effective as those prior trials, it may be appropriate to incorporate these into future guidelines.

In this paper we compare the magnitude and statistical robustness of the HOPE results with previous trials that have importantly affected clinical practice.

Assessment of treatment results

The Danish College of General Practitioners[6] have suggested a simplified approach to evaluate clinical trial results using an example from the 4S trial[7]:

During this trial, with a mean follow-up of 5·4 years, the placebo mortality was 256/2223 (11·5%) and treatment mortality 182/2221 (8·2%).

The relative risk in the treatment group was: 8·2%/11·5%=0·71.

The relative risk reduction was accordingly: 1−0·71=0·29 or 29%.

The absolute risk reduction (ARR) was: 11·5%−8·2%=3·3% over a 5·4 year period.

These figures enable us to calculate the number needed to treat (NNT) to postpone one death over a 5·4 year period:

Treatment difference: 256 – 182 = 74 deaths. There were 2221 patients randomized to simvastatin. NNT is then derived from: 2221/74=30 or 1/ARR: 1/0·033=30

As an attempt to adjust for the study duration, the treatment difference has been extrapolated to one year of treatment according to: 74/64 × 12 = 14, when using 64 months as the mean study duration of 4S. This means that on average, 14 deaths were postponed per year during the study period.

NNT to postpone one event per year (NNT-1y) is then: NNT-1y=2221/14=159.

Key Words: Prevention, HOPE study, treatment effect, ACE inhibition in heart failure, statin trials.

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constant throughout a trial, this method is an acceptable and quick method of adjustment for the study duration when evaluating the treatment effect as reflected from NNT.

We have calculated NNT and NNT-1y using the risk reduction in the three ACE inhibitor trials SOLVD treatment[8], SAVE[9] and AIRE[10] as well as in the three major secondary prophylaxis statin trials, 4S[7], CARE[11] and LIPID[12]. These results have then been compared with similar calculations from the HOPE study[1].

Table 1 Mean: age, study duration and treatment effect on the primary end-point in the three ACE inhibitor trials SOLVD treatment (tr.) SAVE and AIRE; the three statin trials 4S, CARE and LIPID, and HOPE

<table>
<thead>
<tr>
<th></th>
<th>SOLVD tr.</th>
<th>SAVE</th>
<th>AIRE</th>
<th>4S</th>
<th>CARE</th>
<th>LIPID</th>
<th>HOPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>2569</td>
<td>2231</td>
<td>2006</td>
<td>4444</td>
<td>4195</td>
<td>9014</td>
<td>9279</td>
</tr>
<tr>
<td>Age, years (±1 SD*)</td>
<td>59*</td>
<td>59*</td>
<td>65 (± 71)</td>
<td>58 (± 7)</td>
<td>59 (± 9)</td>
<td>62 (median)</td>
<td>66 (± 7)</td>
</tr>
<tr>
<td>Study duration, months (range*)</td>
<td>41 (22–25)</td>
<td>42 (24–60)</td>
<td>15 (min 6)</td>
<td>64 (59–76)</td>
<td>60 (48–74)</td>
<td>74*</td>
<td>50*</td>
</tr>
<tr>
<td>Primary end-point</td>
<td>TM</td>
<td>TM</td>
<td>TM</td>
<td>TM</td>
<td>CD+NFMI</td>
<td>CD</td>
<td>CVD+NFMI+S</td>
</tr>
<tr>
<td>Placebo: Incidence</td>
<td>510/1284</td>
<td>275/1116</td>
<td>222/982</td>
<td>256/2233</td>
<td>274/2078</td>
<td>373/4502</td>
<td>826/4652</td>
</tr>
<tr>
<td>Treatment: Incidence</td>
<td>452/1285</td>
<td>228/1115</td>
<td>170/1004</td>
<td>182/2221</td>
<td>212/2081</td>
<td>287/4512</td>
<td>651/4645</td>
</tr>
<tr>
<td>Treatment difference, n</td>
<td>58</td>
<td>47</td>
<td>52</td>
<td>74</td>
<td>62</td>
<td>86</td>
<td>175</td>
</tr>
<tr>
<td>NNT to postpone one primary end-point</td>
<td>22</td>
<td>24</td>
<td>19</td>
<td>34</td>
<td>34</td>
<td>52</td>
<td>26</td>
</tr>
</tbody>
</table>

tr.=treatment; TM=total mortality; CD=coronary death; CVD=cardiovascular death; NFMI=non-fatal myocardial infarction; S=stroke; NNT=number needed to treat.

*not presented in the study publication.

ACE inhibitor trials

In these three trials, total mortality was the primary end-point. We calculated follow-up time, treatment difference and NNT for a primary end-point (summarized in Table 1).

Patients in the SOLVD treatment trial had chronic heart failure and were in NYHA classes 2 and 3 with a left ventricular ejection fraction (LVEF) ≤35%[8]. They were randomized to enalapril or placebo. In SAVE, patients with asymptomatic left ventricular dysfunction (LVEF <40%) were included 3–16 days after a myocardial infarction[9]. The AIRE trial included patients 3–10 days following an acute myocardial infarction with clinical or radiological signs of heart failure[10]. As can be seen in Table 1, the study duration was similar in SOLVD and SAVE, but much shorter in AIRE. The lowest NNT to postpone one death was 19 in AIRE, followed by 22 in SOLVD and 24 in SAVE.

Statin trials

Similar data from the three statin trials are also included in Table 1. Note that these trials had different primary end-points: total mortality in 4S; coronary death and non-fatal myocardial infarction in CARE; and coronary death in LIPID. A prior myocardial infarction was present in 80% of the patients in 4S, 100% of CARE and 64% of the LIPID population. In 4S they were randomized to simvastatin or placebo, in CARE and LIPID to pravastatin or placebo. The time from their myocardial infarction to randomization was at least 3 months in CARE and LIPID, 6 months in 4S. The mean study duration was between 5·0 and 6·1 years, and thus somewhat longer than in the ACE inhibitor trials. NNT to postpone a primary end-point was 30 in 4S, followed by 34 in CARE and 52 in LIPID.

The HOPE study

Table 1 provides similar data from HOPE as from the ACE inhibitor and statin trials. HOPE was, with the exception of LIPID, substantially larger than the other studies. The primary end-point was a composite of myocardial infarction, stroke, or death from cardiovascular causes. NNT to prevent a primary end-point was 26, similar to the other ACE inhibitor and statin studies.

Comparisons between HOPE and the other studies

Compared with patients in the ACE inhibitor studies, those in HOPE were older, but none had heart failure or a measured LVEF <40%. There were fewer smokers, more diabetics and hypertensives, and more patients on lipid lowering drugs, aspirin and beta-blockers in HOPE. The number with prior myocardial infarction was 53% in HOPE vs 65% in SOLVD treatment.

Compared with the statin trials, HOPE patients were older. The percentage of diabetics was 39% in HOPE vs 5% in 4S, 15% in CARE and 9% in LIPID. Patients with heart failure were not allowed into HOPE or the statin trials, but patients with LVEF ≥25% were included in the CARE study.
The placebo mortality in HOPE and the other studies is shown in Table 2, with adjustment for the time of follow-up. The highest mortality was found in heart failure patients with reduced LVEF\(^8,9\) and in the AIRE population\(^10\). The total placebo mortality in HOPE was slightly higher than among patients included in the statin trials\(^7,9,10\).

The relative risk reduction for total mortality and for the primary end-point in these studies is presented in Table 3. The treatment effect in HOPE was well within the range of the other studies, and especially so for the relative risk reduction for a primary end-point. The relative risk reduction for a myocardial infarction was 29 (95% CI: 11–34)% in SOLVD and 25 (5–40)% in SAVE.

The respective NNTs to postpone one death and one primary end-point in HOPE vs the other studies are shown in Table 4, including adjustment for the study duration by calculating NNT-1y (see above). The studies with total mortality as the primary end-point have been performed in high-risk patients and, accordingly the NNTs are lower. NNT to postpone one primary end-point in HOPE is definitely within the range of the other studies. The NNT-1y for a primary end-point in HOPE is somewhat higher than in the ACE inhibitor trials, but definitely lower than in the statin trials.

**Discussion**

When comparing the HOPE data with those from the older ACE inhibitor studies, it is clear that patients with heart failure and left ventricular dysfunction are at higher risk. But the relative risk reduction obtained in HOPE was similar to the older studies. There was a higher NNT for total mortality, but not for the composite primary end-point in HOPE. HOPE was not designed for total mortality in view of the anticipated lower risk (compared to patients with congestive heart failure or LV dysfunction).

The placebo mortality in HOPE was comparable to that in the statin trials. The relative risk reduction for total mortality and the primary end-point with ramipril in HOPE was similar to that in the statin trials. Using NNT-1y as a measure of the treatment effect, the HOPE results are even stronger than in the ACE inhibitor trials, but definitely lower than in the statin trials.

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inhibitor trials in heart failure, and in the statin trials. It would therefore be logical to extend the indications for ACE inhibitor treatment, as secondary prevention for coronary heart disease, to patients aged >55 years with established cardiovascular disease: coronary heart disease with or without prior myocardial infarction; prior stroke or transient ischaemic attacks; peripheral atherosclerotic disease; also to older patients with diabetes mellitus with at least one of the following risk factors: hypertension, hypercholesterolaemia, smoking, microalbuminuria.

Are the HOPE results applicable to ramipril or is this a ‘class effect’ for all ACE inhibitors? In keeping with the arguments put forward by Furberg et al., we suggest that until further studies prove otherwise, ramipril 10 mg o.d. should be the recommended initial treatment. However the HOPE study was designed as a result of the unexpected reduction in myocardial infarction that was seen in the earlier heart failure trials with a variety of different ACE inhibitors.

There have been suggestions that higher risk patients might have greater relative benefit, as seen in those with the highest baseline blood pressure in HOPE, or in diabetics in other studies. However, this was not seen in meta-analyses of trials of patients with isolated systolic hypertension or in the large diabetic population in HOPE.

Although the HOPE population was heterogenous, the relative risk reduction of ACE inhibitor in different subgroups e.g. hypertensive or not, or patients with established cardiovascular disease was remarkably similar. It is a matter of clinical judgement whether the absolute risk reduction is worthwhile in lower risk patients.

Conclusions

The HOPE study has provided us with unusually secure new indications for ACE inhibitor treatment in the prevention of serious cardiovascular complications in a relatively high risk population without LV dysfunction or uncontrolled hypertension. The benefits of ramipril were additive to (and of similar magnitude to) those from other proven prophylactic treatments, such as aspirin, statins, beta-blockers, or other antihypertensive agents.

Preliminary analyses suggest that this strategy is highly cost effective.

For high risk populations without contraindications, ACE inhibitor with ramipril should be expanded beyond the current indications of hypertension, left ventricular dysfunction, or diabetes with microalbuminuria.

References