The MICRO-HOPE Study: Evidence for an important role for ACE inhibitors

The MICRO-HOPE (Microalbuminuria, Cardiovascular and Renal Outcomes–Heart Outcomes Prevention Evaluation) trial was a sub-study of the HOPE trial. 3577 individuals with diabetes (the majority with type 2), aged 55 years and older, were randomised to receive ramipril or placebo for 5 years. This intervention led to 25% relative risk reduction for the primary outcome (cardiovascular death, non-fatal stroke, non-fatal myocardial infarction) and total mortality relative risk reduction of 24% in the ramipril group. The rate of increase in urine albumin/creatinine ratio was significantly lower in the ramipril group. This trial, along with others, helped to establish the use of ACE inhibitors as an important intervention in people living with diabetes, especially if microalbuminuria is present.

Take-home messages

- Ramipril, an angiotensin-converting-enzyme inhibitor, significantly reduces the rates of death, myocardial infarction and stroke in those at high risk for cardiovascular events.
- The addition of ramipril to other proven prevention strategies should further lower the risk of cardiovascular and microvascular events, including nephropathy in people with diabetes.
- Ramipril can prevent the progression of microalbuminuria to proteinuria.
- Supplemental vitamin E does not reduce vascular complications or nephropathy in people living with diabetes.

The HOPE (Heart Outcomes Prevention Evaluation) Study was a randomised clinical trial started 20 years ago, with a 2×2 factorial design that evaluated the effects of vitamin E and the angiotensin-converting-enzyme (ACE) inhibitor ramipril in patients at high risk for cardiovascular (CV) events. At the time of recruitment for this trial, ACE inhibitors had already been established as a treatment for hypertension, but investigators wanted to evaluate if they had a specific vasculo-protective effect beyond that anticipated from the modest blood pressure reduction demonstrated by these agents. The HOPE Study was designed to find out if the addition of the ACE inhibitor ramipril to the medical regimen of individuals at high risk of having further cardiovascular events reduced the risk of such events. Those eligible for this trial were 55 years or older and had CV disease or diabetes with at least one additional coronary risk factor (HOPE Study Investigators, 2000a).

The MICRO-HOPE (Microalbuminuria, Cardiovascular and Renal Outcomes–Heart Outcomes Prevention Evaluation) trial was a sub-study of the HOPE Study that consisted of 3577 subjects aged 55 years and older, living with mainly type 2 diabetes (81 with type 1 diabetes). They were randomised to receive ramipril or placebo for 5 years (Lonn et al, 2002).

Study design

The HOPE trial itself had 9297 subjects with known CV disease or diabetes, plus at least one other CV risk factor. The primary outcome was a composite of myocardial infarction (MI), stroke, or death from CV causes. This is broadly similar to the primary outcome of 3P-MACE (composite of CV death, non-fatal MI and non-fatal stroke) that has been mandated by the FDA for contemporary cardiovascular outcome trials (CVOTs). There were pre-planned analyses to determine whether ramipril delayed or prevented microalbuminuria or overt nephropathy in participants with diabetes. The monitoring board eventually recommended termination of the study because of the clear evidence of a beneficial effect of ramipril.

The HOPE protocol included a run-in period for tolerance. During this period, all 10 576 initially eligible participants received a

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2.5-mg dose of ramipril for 7–10 days; thereafter, they received a matching placebo for 10–14 days. This approach was taken to identify those prone to early side effects, and/or those who experienced an exclusionary change in serum electrolytes or creatinine. Approximately 10% of the population, or 1035 participants, were excluded for these reasons. The remaining 9541 subjects were randomised to ramipril or placebo, beginning with a titration phase of 2.5 mg/day for 1 week, followed by 5 mg/day for 3 weeks. Thereafter, participants received 10 mg/day until study completion and this was designed to be the therapeutic dose in the trial.

Study outcomes

The HOPE study demonstrated that the ramipril sub-group had a 0.78 relative risk (RR) of the primary outcome and 0.84 RR of death from any cause. Of the total HOPE cohort, 1956 had microalbuminuria, making up approximately 21% of each treatment group. The effect of ramipril to decrease CV endpoints was demonstrated whether subjects did or did not have microalbuminuria. Ramipril treatment prevented a new diagnosis of diabetes in participants without diabetes by 34% (HOPE Study Investigators, 2000b). It is important to understand that the HOPE study was not a hypertension study as such, and no attempt was made to treat blood pressure to any predetermined target.

When the vitamin E treatment arm was assessed, it was concluded that the daily administration of 400 IU vitamin E for an average of 4.5 years to middle-aged and elderly people with diabetes and CV disease and/or additional coronary risk factor(s) has no effect on CV outcomes or nephropathy (Lonn et al, 2002).

The results in the 3577 subjects with diabetes in the MICRO-HOPE study were even more striking than the findings of the main study. There were highly significant 25% RR reductions for the combined primary outcome, 22% for MI, 33% for stroke and 37% for CV death. Whilst these trials are not directly comparable, it is worth noting that both empagliflozin, in EMPA-REG, and liraglutide, in LEADER, significantly reduced CV death, by 38% and 22%, respectively. In addition, overt nephropathy was reduced by 24%. As was observed in the main study, the benefits observed were consistent across all subgroups and occurred independently of age and gender, and regardless of whether participants were taking beta blockers, aspirin, or lipid-lowering agents. ■

Clinical perspective – the HOPE and MICRO-HOPE studies

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The use of ACE inhibitors is now imbedded in our management of type 2 diabetes, especially in those with hypertension, microalbuminuria or both. This intervention has also been further reinforced by its inclusion in the Quality and Outcomes Framework.

Whilst we take this for granted, it is important to remember that the MICRO-HOPE study, with its substantial benefits in mortality and morbidity with the use of ramipril in a large group of subjects at high risk of future cardiovascular event, was the catalyst for this. The implications for individuals with diabetes are particularly striking. ACE inhibitor therapy had previously been proven to be of benefit to those with left ventricular dysfunction, hypertension and diabetes with proteinuria. It was the MICRO-HOPE study that encouraged us to use an ACE inhibitor at an earlier stage when microalbuminuria appears.

Those of us using ACE inhibitors will know they can be frustrating to prescribe because of side effects, particularly coughing, but also electrolyte disturbances. The HOPE study clearly demonstrates this problem with approximately 10% of the intention-to-treat population being excluded with side effects in the 17–24-day run-in period with low dose ramipril, and this aligns with our findings in practice.

It was the MICRO-HOPE study that underlined the need to robustly address cardiovascular risk in people living with diabetes, and to use ACE inhibitors to protect against the progression of microalbuminuria and the risk cardiovascular disease. In so doing, some of the benefits obtained can be similar to the contemporary CVOTs.

References

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