Should the results of the HOPE study affect nephrological practice?

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Which hypothesis was tested?

The renin–angiotensin system (RAS) is well known for its role in blood pressure and electrolyte and volume homeostasis. Experimental evidence from recent years linked the RAS with inflammatory processes; the stimulation of interstitial fibrosis and of mesangial sclerosis may be taken as examples in nephrology [1,2]. In a more general perspective, the RAS was shown experimentally to promote the initiation and progression of atherosclerosis by its pro-inflammatory and pro-coagulatory actions. In accordance with this notion, epidemiologic evidence associated activation of the RAS with a higher prevalence of atherosclerotic complications in hypertensive patients [3,4]. Obviously, ACE inhibitors interfere also with kinins. It is therefore entirely possible that stimulation of bradykinin contributes to the effects of ACE inhibitors [5].

The HOPE study tested the hypothesis that inhibition of the RAS and stimulation of bradykinin by the ACE inhibitor Ramipril would reduce cardiovascular events in patients at high cardiovascular risk—including predominately normotensive patients [6–9]. The ambition to go from experimental evidence to clinical investigation was prompted by the success of ACE inhibitor treatment in patients with reduced left ventricular function [10]. In the latter patients the ACE inhibitors, unexpectedly, appeared to reduce not only the frequency of cardiac failure but also the rate of myocardial infarction [10].

What was done?

More than 9000 patients at high cardiovascular risk, 55 years of age or more, with (i) evidence of vascular disease or with (ii) diabetes plus one other cardiovascular risk factor were followed for 4–6 years [6]. Heart failure and low ejection fraction were major exclusion criteria. In a double-blind, randomized, placebo-controlled 2×2 factorial design, Ramipril (up to 10 mg/day) and vitamin E (400 U/day) were tested. The primary end-point was a composite of myocardial infarction, cardiovascular death and stroke. Total mortality, revascularization procedures and diabetic complications were among the secondary end-points. The majority of patients (>60%) were included because of evidence of coronary heart disease, >25% because of diabetes plus one other risk factor and the rest (about 10%) because of peripheral vascular disease or stroke. The active treatment was added to any other drugs the patient needed. At the end of the trial, about 80% of the patients were on antiplatelet drugs and about 40–50% each on betablockers, on calcium antagonists and on lipid lowering drugs.

What was found?

Vitamin E was without any effect on outcomes. On Ramipril, a total of 653 (14.1%) patients reached a primary end-point and 824 (17.7%) on placebo (relative risk, RR, 0.78, \( P < 0.001 \)). Ramipril significantly (\( P < 0.01 \)) reduced myocardial infarction (9.9 vs 12.2%), cardiovascular death (6.1 vs 8.1%), stroke (3.4 vs 4.9%), revascularization procedures (16.0 vs 18.6%), and diabetic complications (6.2 vs 7.4%, \( P = 0.03 \)). Unexpectedly, diabetes mellitus was diagnosed de novo during the trial less frequently in patients on Ramipril (n = 105) than in patients on placebo (n = 154, relative risk 0.68, \( P = 0.002 \)). The major problem associated with Ramipril was a 5% rate of cough. It appeared that the relative benefit of Ramipril became greater with time and was evident in all pre-defined subgroups. Such groups included hypertensive (47% of the population), diabetic (38%), male and female patients (26%), those with microalbuminuria (21%) and those without known cardiovascular disease. Treating 1000 patients for 4 years would prevent about 150 major events in 70 people. The small but significant blood pressure lowering effects of Ramipril by about 3/2 mm Hg could not fully explain the beneficial effects of the drug in these patients most of whom were treated by other drugs.

How do the results affect patient management by the nephrologist?

The HOPE study was carried out on patients that nephrologists see daily. It was not a sample of the general population, but people with a dramatic burden of cardiovascular disease, including evidence of coron-
ary disease in 80%, of peripheral vascular disease in 43% and type 2 diabetes in almost 40%. Exactly those patients come to renal wards and clinics, first because of the coincidence of diabetic nephropathy with atherosclerosis, second because of ischaemic nephropathy in people with widespread atherosclerosis and third—much less well established and appreciated—because people with renal disease are at risk for atherosclerotic complications. Ramipril should be administered as a medication able to reduce the cardiovascular risk in such patients, independent of or in addition to the known ability of ACE inhibitors to reduce proteinuria and progression of renal disease [11,12].

Patients with proteinuria above the level of microalbuminuria were not included in the HOPE study. However, a subset of people with renal insufficiency, up to a serum creatinine level of 2.3 mg/dl (204 μmol/l), was included [6]. Unpublished data of the HOPE study indicate that the serum creatinine level was linearly correlated with the risk of future cardiovascular disease. In addition, mild renal failure as a strong predictor of cardiovascular events was independent from other factors such as age, microalbuminuria, hypertension and diabetes. The data identifying renal insufficiency as a cardiovascular risk factor are in accordance with data from the HDFP study [13]. In the latter study, patients with hypertension were followed and a small number with mild- to-moderate renal insufficiency were included. Again, renal insufficiency was found to be a strong risk factor for future cardiovascular disease. Thus we learn from the HOPE study that the high cardiovascular risk associated with even modest reduction of renal function is reduced by treatment with the ACE inhibitor Ramipril. The drug should therefore not be withheld from such patients.

References

6. The HOPE investigators. THE HOPE study: the design of a large, simple randomized trial of an ACE inhibitor (Ramipril) and vitamin E in patients at high risk of cardiovascular events. Can J Cardiol 1996; 12: 127–137