Netherlands Heart Journal (2007) 15:25–27
DOI 10.1007/BF03086036

SATELLITE SYMPOSIA

Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial

Vienna, 4 September 2007

M. V. Huisman

Patients with type 2 diabetes are at increased risk of both macrovascular disease, including coronary heart disease and stroke, and microvascular disease, which includes retinopathy and nephropathy. Blood pressure and glucose levels are important determinants of the risk of developing vascular disease in patients with diabetes. For both these risk factors, the associations with macrovascular and microvascular disease appear continuous, with no evidence of a lower level of blood pressure or haemoglobin A1c below which the risks do not continue to decline.

Randomised trials have shown that lowering the blood pressure of hypertensive patients with diabetes leads to substantial reductions in major vascular events, with greater benefits for more intensive blood pressure lowering. In patients with diabetes and hypertension, all the mRole classes of antihypertensive drugs seem to reduce the risks of stroke and coronary heart disease. However, the role of routine blood pressure lowering in patients with diabetes, regardless of the initial blood pressure levels, and agRolest a background of standard care that may include an ACE inhibitor, remRoles unclear.

The ADVANCE study was a large-scale randomised controlled trial with a factorial design. The study separately determined whether there were worthwhile benefits of routine blood pressure lowering by a fixed combination of an angiotensin-converting enzyme (ACE) inhibitor (perindopril) and a diuretic (indapamide) in these patients, regardless of the level of blood pressure or the use of other blood pressure lowering drugs, and whether targeting low levels of haemoglobin A1c reduces the risk of major macrovascular disease and confers greater protection agRolest microvascular disease. The glucose lowering arm of the study will be reported later on.

Patients were eligible for inclusion if they were aged ≥55 years at entry, were at a substantially elevated risk of vascular disease, and in whom a diagnosis of type 2 diabetes mellitus was first made at ≥30 years of age. High risk for vascular disease was defined by a diagnosis of type 2 diabetes made ≥10 years earlier; or age ≥65 years at entry; or a history of any of the following: major macrovascular disease (including myocardial infarction, stroke, hospitalisation for transient ischaemic attack (TIA) or unstable angina, or re-vascularisation procedure), major microvascular disease (including macroalbuminuria, proliferative retinopathy or retinal photocoagulation, or macular oedema), or another major risk factor for vascular disease (current cigarette smoking, total cholesterol >6.0 mmol/l, HDL cholesterol <1.0 mmol/l or microalbuminuria). Importantly, hypertensive and nonhypertensive individuals were eligible for inclusion, and eligibility was not dependent upon the need for, or use of, ACE inhibitor therapy. Participants for whom therapy with an ACE inhibitor was indicated could be included, unless there was a specific indication for an ACE inhibitor other than perindopril 4 mg daily or less. Potentially eligible individuals commenced a run-in period on open fixed low-dose perindopril–indapamide. After six weeks, patients who proved to be eligible and who were tolerant of the run-in treatment were randomly assigned to two treatment comparisons: a double-blind comparison of the perindopril–indapamide combination (initially 2.0 mg/0.625 mg increasing to 4.0 mg/1.25 mg daily after three months) vs. matching placebo. Thiazide or thiazide-like diuretics could not be prescribed and if an ACE inhibitor was considered indicated, only perindopril (2 or 4 mg daily) could be used and was provided. Investigators were encouraged to continue usual practice for participants randomised to standard guideline-based therapy. The scheduled average duration of treatment and follow-up was 4.5 years.

There were two co-primary outcomes: the composite of nonfatal stroke, nonfatal myocardial infarction or cardiovascular death; and the composite of new or

worsening nephropathy or microvascular eye disease. Secondary outcomes included specific cerebrovascular and coronary outcomes, heart failure, peripheral vascular disease, microalbuminuria, visual deterioration, neuropathy, dementia and all-cause mortality.

A total of 12,877 potentially eligible participants were registered, 1737 (13.5%) were subsequently withdrawn during the six-week active run-in period, and 11,140 (86.5%) were randomised. Around a third of the patients had a history of major macrovascular disease and about 10% had a history of major microvascular disease at baseline. The mean entry blood pressure of randomised patients was 145/81 mmHg and 41% had a blood pressure less than 140 mmHg systolic and 90 mmHg diastolic. At randomisation, 47% of patients were receiving treatment with open-label perindopril (2 to 4 mg daily). Additionally, 47% of patients were receiving antiplatelet therapy, 35% were receiving cholesterol lowering drugs, and 91% were receiving oral hypoglycaemic agents at baseline. The mean duration of follow-up was 4.3 years and the range was from less than 1 month to 5.6 years. During follow-up, randomised treatment was continued for 20,001 patient-years (83%) in the active treatment group and 20,849 patient-years (87%) in the placebo group. At the end of follow-up, 4081 (73%) patients in the active treatment group and 4143 (74%) patients in the placebo group were adherent to the randomised therapy. The mRole reasons for permanent discontinuation were participant decision or inability to attend clinic visits (active 521 [9.4%], placebo 635 [11.4%]), cough (active 184 [3.3%], placebo 72 [1.3%]) and hypotension or dizziness (active 69 [1.2%], placebo 22 [0.4%]), and serious adverse events (active 67 [1.2%], placebo 66 [1.2%]). Serious suspected adverse drug reactions were reported in 47 (0.8%) patients randomised to active treatment and 31 (0.6%) patients allocated placebo, including five cases of angio-oedema (three active, two placebo), none of which were fatal.

During follow-up, blood pressure was reduced by an average of 5.6 (SE 0.2) mmHg systolic and 2.2 (SE 0.1) mmHg diastolic in patients assigned active treatment compared with those assigned placebo.

The co-primary endpoints major macrovascular or major microvascular events occurred in 1799 study patients during follow-up: 861 (15.5%) in the active treatment group and 938 (16.8%) in the placebo group (relative risk reduction 9% [95% CI 0 to 17%; $p = 0.041$]). This translates into to a number needed to treat of 66 (95% CI 34 to 1068) to avoid at least one major macrovascular or microvascular event over five years. The proportional effects of active treatment on major macrovascular outcomes (relative risk reduction 8% [95% CI –4 to 19%; $p = 0.16$]) and major microvascular outcomes (9% [–4 to 20%; $p = 0.16$]) were similar, though not separately significant.

During the study 879 participants died, of whom 408 (7.3%) in the active treatment group and 471 (8·5%) in the placebo group (relative risk reduction 14% [95% CI 2 to 25], $p = 0.025$). Over five years, one death in every 79 (95% CI 43 to 483) patients assigned active treatment was estimated to have been averted. This reduction in total mortality was mRolely due to a reduction in cardiovascular deaths (3.8 vs. 4.6%; relative risk reduction 18% [95% CI 2 to 32%], $p = 0.027$) in participants assigned active treatment, with no significant difference between randomised groups in noncardiovascular deaths (3.5 vs. 3.8%; 8% [–12 to 24%], $p = 0.41$).

Significantly fewer total coronary events occurred in participants randomly assigned to active treatment compared with those assigned placebo (8.4 vs. 9.6%; 14% [2 to 24%], $p = 0.020$). Over five years, one patient in every 75 assigned active treatment would have avoided at least one coronary event. There was no significant difference between randomised groups in either total cerebrovascular events (relative risk reduction 6% [95% CI –10 to 20%], $p = 0.42$) or heart failure (2% [–20 to 19%], $p = 0.86$).

Active treatment was associated with a significant 21% reduction in all renal events (95% CI 15 to 27%, $p < 0.0001$), with a significant reduction in the development of microalbuminuria (19.6 vs. 23.6%; 21% [14 to 27%]; $p < 0.0001$). Over five years, one patient in every 20 (95% CI 15 to 30) assigned active treatment would have avoided one renal event (mostly the onset of new microalbuminuria). There was no significant difference between randomised groups in the rate of new or worsening retinopathy (relative risk reduction –1% [–18 to 15%], $p = 0.94$), including the need for retinal photocoagulation (–14% [–41 to 8%], $p = 0.23$).

Comments

This study has demonstrated that routine administration of a fixed combination of an ACE inhibitor perindopril and a diuretic indapamide to patients with type 2 diabetes reduced the risk of macrovascular and microvascular events. Importantly, the typical person who benefited in this trial was a 55 year old who had had diabetes for several years or had a risk factor, including a prior major macrovascular or microvascular event or smoking. While a significant 9% difference in the primary endpoint between the intervention and control group was observed, the absolute difference in the primary outcome between the groups was relatively small. In addition, the separate reductions in the co-primary endpoints

macrovascular and microvascular events were similar but were not independently significant. The major contributor to the 9% overall reduction in the risk of major macrovascular or microvascular events was a significant 18% reduction in the risk of death from cardiovascular disease, which largely accounted for the significant 14% reduction in total mortality. Although effects of blood pressure lowering agents on total mortality have rarely been seen in individual trials in patients with hypertension or diabetes, meta-analyses have previously confirmed that drugs for lowering blood pressure can improve survival. From the results of ADVANCE, it can be computed that over five years, one death would be averted in every 79 patients commencing treatment with the study drugs; the confidence limits of this estimation are wide, however, and ranged from 34 to 1068 over five years. Study treatment produced a one-fifth reduction in the development of microalbuminuria, which is consistent with other data indicating that ACE inhibitors, compared with placebo or calcium antagonists, are effective in preventing the development of microalbuminuria. Such effects of treatment are important in view of the high risk of progression to endstage renal failure and premature death in patients who develop diabetic nephropathy, as well as the emerging evidence of substantial cardiovascular risks associated with progression of renal impairment. The consistency of the relative effects of active treatment across subgroups indicates that the absolute benefits conferred by treatment will be established mRolely by each patient's future risk of vascular complications, rather than their initial level of blood pressure alone. These results support an important shift in paradigm: treating not on the basis of arbitrary cut-offs for blood pressure, but rather on assessment of vascular risk, which is raised in patients with type 2 diabetes mellitus, even in the absence of hypertension. This study has important implications for the target level of blood pressure in patients with type 2 diabetes mellitus. Although guidelines recommend that blood pressure be lowered to 130/80 mmHg in this population, until now there was no good support to target this level of blood pressure.

The results of this study reinforce the concept that diabetic patients should be treated aggressively to get their blood pressure down. Finally, the fixed combination perindopril-indapamide could be superior to any combination of other blood pressure lowering agents agRolest hypertension-related consequences for patients with type 2 diabetes, even if the latter would lower blood pressure as much without giving side effects. This trial was not designed, however, to compare different combinations of blood pressure lowering agents. It should be remembered that lowering the blood pressure is considered by many experts to be more important than the way in which it is lowered.