

RAPID APPRAISAL

Name of Trial: 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.

Reference: ADVANCE Collaborative Group. Lancet 2007;370:829-40

Question: Does a fixed daily combination dose of perindopril 4 mg plus indapamide 1.25 mg affect macro- and microvascular complications in patients with type 2 diabetes?

Summary: The combined endpoint of major macro- and microvascular events was reduced in absolute terms by 1.3% (95% CI 0% to 2.7%, $p = 0.041$) after a mean of 4.3 years of treatment compared to placebo. The effect on major macro- and microvascular events individually was not statistically significant. Benefits of combination treatment compared to placebo were also seen for other outcomes such as coronary death and microalbuminuria. The trial reinforces the importance of lowering blood pressure in diabetic patients and demonstrates that this can be effectively achieved with an ACE inhibitor and a thiazide diuretic. The trial does not prove that these effects are specific to the combination studied (perindopril and indapamide).

Did the study ask a clearly focussed question?

Yes. The study investigated the effects of routine administration of an ACE inhibitor plus thiazide diuretic combination on serious vascular events in patients with diabetes, irrespective of initial blood pressure or the use of other blood pressure lowering drugs. The study population were subject to two separate interventions forming two distinct trials: one relates to the study reported here and the other to an investigation of the effect of modified-release gliclazide on the same outcomes (not yet reported).

Was the study design appropriate?

Yes. The study was a large ($n = 11,140$), relatively long-term (mean follow up = 4.3 years; range = <1 month to 5.6 years), randomised, controlled trial performed in over 200 centres worldwide. Patients had a history of type 2 diabetes, were aged at least 55 years (mean = 66 years), with a history of major cardiovascular disease or at least one risk factor for cardiovascular disease. Major cardiovascular disease was defined as stroke, myocardial infarction, transient ischaemic attack, unstable angina, revascularisation, or amputation due to vascular disease. Risk factors for cardiovascular disease were defined as major microvascular disease (e.g. microalbuminuria or diabetic retinopathy), smoking, total cholesterol > 6 mmol/L, HDL cholesterol < 1 mmol/L, diabetes for ≥ 10 years, or age ≥ 65 years. Patients were recruited irrespective of their blood pressure reading and maintained on their existing drug therapy, except those already taking an ACE inhibitor. During a six week run-in phase patients were treated with a combination of perindopril 2 mg and indapamide 625 micrograms once daily, after which patients were randomly assigned to continued treatment with the combination or placebo. After three months the dose was increased to perindopril 4 mg and indapamide 1.25 mg once daily or matching placebo.

Were participants appropriately allocated to intervention and control groups?

Yes. Allocation to treatment group was random although groups were prospectively balanced with respect to treatment centre, history of macro- and microvascular disease, and perindopril use at baseline. The two groups (active $n = 5,569$ and placebo $n = 5,571$) were balanced with respect to several demographic and clinical parameters.

Were participants, staff and study personnel 'blind' to participants study group?

Yes. During the run-in period patients taking an ACE inhibitor other than perindopril had this medication stopped and replaced with open-label perindopril 2 or 4 mg daily. Patients who tolerated the run-in medication were subsequently randomised to treatment in a double-blind fashion.

Were all of the participants who entered into the trial accounted for at its conclusion?

Yes. Only 15 patients (0.001%) were lost to follow-up and nearly 90% progressed to assessment at final visit with about 74% still adhering to treatment. However 13.5% of registered patients withdrew during the run-in phase.

Were the participants in all groups followed up and data collected in the same way?

Yes. Patients were assessed three, four, and six months after randomisation and six-monthly thereafter. If patients were on perindopril at randomisation (as were 47% in each group), they were continued on this treatment at a maximum daily dose of 4 mg. Therefore, if they were allocated to active treatment, the maximum dose of perindopril would correspond to 8 mg daily. At study end 45% of patients in the active treatment group were on additional perindopril.

Patients were permitted to be commenced on any additional drug treatment, including antihypertensives (although not thiazide diuretics or other ACE inhibitors unless study medication was withdrawn), deemed necessary during the study. At study end, 55% of patients in the placebo group were on perindopril and 5% in each group were on another ACE inhibitor.

Was the study large enough?

Yes. Based on an assumed annual rate of 3% for each of macrovascular and microvascular events separately, the study was designed to provide 90% power to detect at least a 16% relative risk reduction between groups. However half way through follow-up the overall event rates were lower than expected (combined annual incidence of only 4%). The primary outcome was therefore changed from focussing only on macrovascular events to the combined outcome reported. Treatment and follow-up were also extended by 12 months. The power to detect the differences was thus maintained, with a combined observed relative risk reduction of 17%.

How are the results presented and what is the main result?

The primary outcome measure was a composite of major macro- and microvascular events. Patients assigned to treatment with perindopril and indapamide demonstrated an event rate of 15.5% compared to 16.8% in the placebo group, an absolute difference of 1.3% (95% confidence interval [CI] 0.0 to 2.7%, $p = 0.041$). Individually the differences were not significant with a macrovascular event rate of 8.6 vs. 9.3% and a microvascular event rate of 7.9 vs. 8.6% respectively ($p = 0.16$ for each comparison). Patients in the active treatment group also demonstrated a significantly reduced mortality rate of 7.3 vs. 8.5% ($p = 0.025$) with most of this effect attributed to a reduced incidence of cardiovascular death (3.8 vs. 4.6%, $p = 0.027$). The incidence of renal events (nephropathy or microalbuminuria) was also significantly reduced (22.3 vs. 26.9%, $p < 0.0001$) with almost all of this effect attributed to the incidence of microalbuminuria; an observation that would be expected with increased ACE inhibitor use. Overall, the intervention group had lower blood pressure than the placebo group with average reductions in diastolic pressure of 5.6 mm Hg and systolic pressure of 2.2 mm Hg.

How safe were the regimens?

During the six-week run-in phase prior to randomisation, patients were withdrawn if treatment was not tolerated. During this period 3.6% of patients withdrew due to side effects and at study end the difference in the number of patients still receiving treatment was only 1%

between the two groups (73% in the active group and 74% with placebo). The principal reasons for treatment discontinuation in each treatment group were (active vs. placebo respectively): patient choice (9.4 vs. 11.4%), hypotension or dizziness (1.2 vs. 0.4%), serious adverse event (1.2 vs. 1.2%). The incidence of discontinuation due to cough was low (3.3% in the active treatment group vs. 1.3% placebo group). However it should be noted that 43% of patients were already taking an ACE inhibitor at registration and 1.8% of patients dropped out during the run-in phase due to cough. Safety and tolerability were poorly reported in the published study.

How precise are the results?

The results are precise with quite small confidence intervals due to the large number of patients included in the study. However, the 95% CI for the primary end-point result includes the level of no effect. The primary outcome measure is a composite of twelve individual endpoints which obscures the actual effect of treatment on the individual measures.

Can the results be applied to the local population?

Yes. The trial recruited a large number of patients with type 2 diabetes from a diverse background. Perhaps the most important observation in terms of relevance to a UK-derived population is a relatively low level of statin use despite all patients having a history of, or risk factor(s) for, cardiovascular disease. At randomisation only 29% of patients in each group were prescribed a statin which had increased to about 45% by the end of the study.

Does a fixed daily combination dose of perindopril 4 mg and indapamide 1.25 mg affect macro- and microvascular complications in patients with type 2 diabetes?

Yes. However there is no evidence to prove that the observed benefit is specific to the combination of perindopril and indapamide used in the study, or use of a fixed-dose combination. It is likely that the same benefit can be achieved with any ACE inhibitor and thiazide diuretic combination that produces a similar reduction in blood pressure. However, due to the specific renal protective effects of ACE inhibitors a similar reduction in blood pressure using other drugs, such as beta-blockers or calcium channel blockers, may not produce the same effect due to the inclusion of renal outcomes in the composite endpoint. The ADVANCE study reinforces the importance of tight blood pressure control in patients with diabetes² and underlines the known advantages of using ACE inhibitors in this patient group.

REFERENCES

1. ADVANCE collaborative group. 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. *Lancet* 2007;370:829-40 (RCT)

2. The Royal College of General Practitioners Effective Clinical Practice Unit. Clinical guidelines for type 2 diabetes – Blood pressure management. National Institute for Health and Clinical Excellence 2002. (G)

KEY: RCT - randomised controlled trial; G - guideline

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