Should all patients with type 2 diabetes receive initial combination therapy: an assessment of the ADVANCE trial

Czy u wszystkich chorych na cukrzycę typu 2 należy od początku stosować skojarzone leczenie hipotensyjne? Analiza badania ADVANCE

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The Action in Diabetes and vascular disease: preterAx and diamicoN-MR Controlled Evaluation (ADVANCE) trial was designed to assess the effects of blood pressure lowering, irrespective of initial blood pressure levels or the use of other blood pressure lowering drugs, on vascular disease in patient with type 2 diabetes [1]. In this randomized trial, 11,140 patients with type 2 diabetes, older than 55 years with other cardiovascular risk factors were randomized to a fixed dose of the ACE inhibitor (perindopril) with a thiazide-like diuretic (indapamide) and compared to placebo. All other concurrent medications except for the randomized drugs classes were allowed to continue. The primary endpoint of this trial was the composite of major macro and microvascular events.

After a mean follow-up of 4.3 years, patients on the fixed dose combination of perindopril and indapamide had a mean reduction in blood pressure of 5.6/2.2 mmHg compared to placebo. The relative risk of major micro and macro vascular event was reduced by an additional 9% in this group. The separate reductions in microvascular and macrovascular events were not significant. The relative risk of death from any cardiovascular cause was reduced by 18% and all cause mortality by 14%. Thus, for every 79 patients treated one death could be avoided. Based on these data the authors conclude that a fixed dose combination of perindopril and indapamide should be recommended for all patients with type 2 diabetes, irrespective of their existing blood pressure.

The question is did ADVANCE advance our knowledge? The cardiovascular benefits of ACE inhibitors in patients with type 2 diabetes are well established by multiple clinical trials. The HOPE trial showed that ramipril reduced rates of death, cardiovascular events in patients with type 2 diabetes and supported the use of ramipril in every patient with diabetes regardless of blood pressure status [2]. Additionally, the PROGRESS trial that studied the same agents as in ADVANCE, demonstrated that when a diuretic was added to an ACE inhibitor stroke incidence was reduced, but this too was related to a lower blood pressure [3]. So, should all patients with type 2 diabetes take a fixed dose combination of perindopril+indapamide or should we simply aim at lowering blood pressure to recommended goals using the best tolerated most cost effective agents?

Other large clinical trials have shown that tight control of blood pressure in patients with diabetes resulted in better outcomes. Cardiovascular events were reduced by 51 % in the diabetic subgroup of the Hypertension Optimal Treatment (HOT) trial [4], a trial that randomized a dihydropyridine calcium antagonist compared to conventional treatment. In HOT the group with the lower events had a 4 mmHg lower diastolic blood pressure. In the United Kingdom Prospective Diabetes Study (UKPDS) patients who had tight control of blood pressure i.e. 10/5 mmHg lower than control, had a 24% risk reduction for any diabetes related endpoint. In UKPDS, however, no differences were observed between ACE inhibitor and β-blocker randomized patients [5]. The conclusion of these studies is that blood pressure lowering regardless of agent was similarly effective in reducing incidence of diabetic complications. To further bolster this argument in the ADVANCE trial, because of the study design, 55% of patients in placebo group were receiving perindopril at the end of the follow up however, none were allowed to receive a thazide diuretic. Thus, one could argue that like PROGRESS, where the addition of the diuretic resulted in further blood pressure lowering and a lower stroke risk, this is what we see in ADVANCE.

One may come to the conclusion that the beneficial effects of the perindopril+ indapamide combination are not exclusive to this combination. Moreover, it is clear that a diuretic is needed to further lower blood pressure when an ACE inhibitor is used in such patients. Furthermore, there was no significant difference in tolerability and adherence between groups in

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ADVANCE (73% of active group vs. 74% in placebo), further arguing for use of thiazide diuretics in concert with agents that block the renin angiotensin system

We conclude that ADVANCE confirms the importance of blood pressure lowering in patients with type 2 diabetes, irrespective of their baseline blood pressure. Since there were blood pressure differences and the placebo group did not receive any new diuretics, it is very difficult to argue that a fixed dose combination of a particular ACE inhibitor and diuretic be used when there was no active comparator group. Moreover, while diuretics other than indapamide were allowed t be continued in the placebo group, it is unclear what the doses of the diuretics were raising the issue of appropriate use of diuretics in this setting. Therefore, the message to clinicians is lower blood pressure to recommended guideline goals and use agents that are well tolerated, can be given once daily, in a single pill, if possible, and are cost effective.

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From the Editor

Synopsis: Patel A, MacMahon S, Chalmers J, ADVANCE Collaborative Group, et al. 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: 829-840.

In this randomised controlled trial of 11 000 patients with type 2 diabetes mellitus it has been shown that the administration of a fixed combination of perindopril (4 mg) and indapamide (1.25 mg) irrespective of initial blood pressure levels resulted, compared to placebo, in the risk reduction of death from any cause, cardiovascular death, coronary events, renal events (also microalbuminuria) and the risk reduction of a composite endpoint of macro- and microvascular events. There was no significant effect of the active treatment on macrovascular and microvascular events analysed separately, major coronary events and major cardiovascular events.

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