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Intensive or standard blood glucose level control in type 2 diabetics. Part I: The ADVANCE Study.

The worldwide increase in the prevalence of type 2 diabetes mellitus, with serious consequences for the cardiovascular system (mainly, increases in both micro- and macroangiopathy),¹ raises many questions. One of the most practically important is the question of the prospective influence of close control of blood glucose levels, and, thus, of glycosylated hemoglobin levels, upon the incidence of major cardiovascular events in type 2 diabetics.

The Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) study is a randomized, multicenter trial performed in 215 collaborating centers in the world,² including 11 140 patients with type 2 diabetes mellitus of longer duration, with a history of one or more signs of macro- or microvascular involvement, or at least one more (besides diabetes mellitus) risk factor for cardiovascular disease, who were, at the time of entering the trial, at least 55 years old. During the 6-week run in period, all participants obtained a fixed combination of perindopril plus indapamide. Those who were compliant and eligible were randomly assigned to either standard or intensive blood glucose control, the latter being achieved by administration of gliclazide (modified-release) in place of all sulfonylurea group oral antidiabetics, and by stepwise adding, or increasing doses of metformin, thiazolidinediones, acarbose, or insulin to achieve the target value of glycosylated hemoglobin of 6.5%. During the study, patients in the standard blood glucose control group were not administered gliclazide. Those initially on that drug were discontinued, and, if necessary, treated with another sulfonylurea.

As reported previously,³ treatment with 2 mg of the angiotensin-converting enzyme inhibitor (ACEI) perindopril plus 0.625 mg of a diuretic indapamide for 4.3 years on average resulted, when compared with placebo, in a decrease of systolic blood pressure of 5.6 mm Hg, and of diastolic blood pressure of 2.2 mm Hg. The ACEI plus diuretic treatment was associated with a significant decrease in the incidence of acute coronary events and, mainly, in a highly significant ($P < 0.0001$) decrease in the incidence of all renal events and a borderline decrease of further impairment of existing nephropathy ($P = 0.055$). The intensive

blood glucose level control, analyzed after 5 years of observation in average, decreased incidence of combined major microvascular and macrovascular events ($P = 0.01$), mainly by a significant decrease in the incidence of nephropathy ($P = 0.006$). The incidence of retinopathy was not influenced, and neither were the incidence of major macrovascular events, death from cardiovascular reasons, or death from any cause. The interpretation of these results is necessarily complex. Part of the beneficial effect of the intensive medication on signs of nephropathy may be caused by the perindopril plus indapamide medication. One of the reasons for the missing influence of this medication on major cardiovascular events including death would certainly be the lower-than-anticipated incidence of these events, caused, most probably, by intensive therapy with statins, antiplatelet drugs, and by antihypertensives in general.

It has to be stated that the intensive blood glucose level control resulted in more frequent hypoglycemia (2.7%) compared with the standard control group (1.5%). However, these events were, in comparison with previous studies, very infrequent (eg, approximately 25% of those in the UKPDS Study),⁴ and did not negatively influence mortality.

In conclusion, it should be stated that intensive blood glucose level control in the ADVANCE Study has had a clear beneficial effect on renal microvascular changes of patients with type 2 diabetes mellitus. In contrast to the ACCORD trial, which is the subject of the next issue of *The European Cardiologist – Journal by Fax*, intensive blood glucose level control in the ADVANCE Study did not increase mortality of diabetic patients.

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