EDITORIAL

Should we use intensive hypoglycemic treatment in patients with advanced type 2 diabetes?

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The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial[1] sought to assess the effect of intensive glycemic control and the use of antihypertensive medications in patients over 55 years of age with type 2 diabetes and a history of major macrovascular or microvascular disease, or at least 1 other risk factor for vascular disease. Participants in the intensive glycemic control group followed a treatment strategy that used gliclazide and other glucose lowering medications—including insulin—targeting a glycated hemoglobin (HbA_{1c}) level of 6.5% or lower. After a median follow-up of 5 years, the mean HbA_{1c} values were 6.5% in the intensive glycemic control group and 7.3% in the standard control group. ADVANCE showed a reduction in the development of albuminuria, but no changes in the incidence of severe nephropathy, retinopathy, or macrovascular events. The 5-year posttrial follow-up of the ADVANCE study, called ADVANCE-ON,[2] has recently been published. After a posttrial follow-up of almost 6 years, ADVANCE-ON failed to find favorable results in the risk of major macrovascular events or death from any cause with intensive glycemic control. The need for renal replacement therapy was reduced, but relatively few events were recorded raising concerns for imprecision.

The results of ADVANCE and ADVANCE-ON are, in several aspects, consistent with the findings from the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACCORD) and Veterans Affairs Diabetes Trial (VADT) trials.[3-5] These two studies also evaluated the effects of intensive glucose control in patients with long-standing type 2 diabetes and at high risk for cardiovascular disease. Compared with standard therapy (HbA_{1c} levels of 7.5% in the ACCORD study, and 8.4% in the VADT study), the use of intensive therapy (HbA_{1c} levels of 6.4% in the ACCORD study, and 6.9% in the VADT study) delayed the progression of albuminuria, but had no significant effect on the rates of other microvascular complications or cardiovascular mortality. In fact, the ACCORD study was terminated early after 3.7 years because of increased cardiovascular and all-cause mortality in the intensive glycemic therapy group. Nevertheless, these last findings must be interpreted with caution as overestimation of harm by chance in truncated trials can lead to misleading conclusions.[6]

Should we aim for an intensive glycemic control (ie, HbA_{1c} ≤6.5%) in patients with long-standing type 2 diabetes and at risk for cardiovascular disease? The results from the ADVANCE, ACCORD, and VADT trials suggest that this strategy is not justified, as the renal benefit appears to be small, and no other significant improvements in patient-important outcomes were evident. Intensive glycemic control can lead to higher risk of hypoglycemia, and potentially also to escalation of costs and burden of treatment, as more medications will be required to achieve these tight glycemic targets. It should be noted, however, that in none of these studies the control arms had very poorly controlled diabetes (eg, mean HbA_{1c} levels >9%), and therefore the effect of standard glycemic management versus clearly poor control on long-term complications cannot be inferred from them. Also, because of the heterogeneity of interventions used to achieve intensive glycemic control, the ADVANCE, ACCORD, and VADT trials are not useful to dissect the individual benefits and harms of the different glucose-lowering medications that were used. Furthermore, heterogeneity of cointerventions may also have affected the results of some outcomes (eg, different antihypertensive treatments could have different effects on the progression of diabetic nephropathy).

Should we aim for a tighter glycemic control in younger patients (eg, age <55 years) with

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Received: November 12, 2014.
Revision accepted: November 13, 2014.
Published online: November 14, 2014.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2014; 124 (12): 657-658

newly diagnosed type 2 diabetes and no major cardiovascular risks? In contrast with the results from the ADVANCE, ACCORD, and VADT trials, the United Kingdom Prospective Diabetes Study (UKPDS)[7] involved lower-risk patients who were about a decade younger and had newly diagnosed type 2 diabetes. Among patients whose body weight was over 120% of their ideal weight, and who received metformin as the primary intervention, there was a reduction in all-cause mortality by 36%.[8] The median HbA_{1c} during the 10 years of follow-up was 7.4% in the metformin group and 8.0% in the group treated with diet. On the other hand, patients treated with sulfonylureas or insulin had a nonsignificant reduction in the risk of myocardial infarction and a reduction by 25% in a composite outcome of microvascular events, which was mainly driven by fewer cases of retinal photocoagulation,[8] despite achieving similar reductions in HbA_{1c} levels compared with the control arm as the trial arm based on metformin. These results published in 1998 had a major influence on subsequent diabetes treatment guidelines, and raised the question of whether the treatment with metformin had a pleiotropic effect beyond its hypoglycemic action, particularly at the cardiovascular level.[9] The 10-year posttrial follow-up of the UKPDS trial showed persistent and significant risk reductions for all cause mortality (27%) and myocardial infarction (33%) in the metformin group.[10] Interestingly, significant risk reductions for myocardial infarction (15%) and death from any cause (13%) emerged in the sulfonylurea–insulin group. These benefits were observed in UKPDS participants despite the fact that the between-group differences in HbA_{1c} levels were lost the first year after the trial stopped. Although there is no other trial evidence confirming these findings, UKPDS results support the current practice of targeting HbA_{1c} levels close to 7% in the majority of patients with newly diagnosed type 2 diabetes, and to use metformin as the first-line therapy after diet and lifestyle modification.

The inconsistency in results, imprecision in the estimates of the effect on patient-important outcomes, and considerations of harm due to hypoglycemia and burden related to self-management, access and use of healthcare, and complex and expensive medication regimens strongly suggest the elimination of dogmatic approaches to achieve a universal glucose target for all patients. Instead, this evidence supports a patient-centered approach that takes into account the context and informed preferences of the patient living with type 2 diabetes. In fact, the recent American Diabetes Association guidelines recommend engaging patients in shared decision making.[11] Tools, such as the Diabetes Medication Choice cards,[12] are available and can be effective in enabling patient-centered conversations that result in diabetes treatment regimens consistent with the values and preferences of an informed patient.

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