Update on the ADVANCE study: implications for clinical practice
Actualización sobre el estudio ADVANCE: implicaciones para la práctica clínica

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Introduction
Almost 10 years ago, the presentation of the main results of the UKPDS study (United Kingdom Prospective Diabetes Study)\(^1\) opened the way towards an era of therapeutic optimism, that ended on February 7\(^{\text{th}}\) 2008 with the publication of the excellent results of the multifactorial intervention trial Steno-2\(^2\).\(^2\) Only two days later, this optimism was shattered with the news of the early interruption of the intensive glycemic control group in the ACCORD study (Action to Control CardiOvascular Risk in Diabet-es),\(^3\) as a relevant excess of total and cardiovascular mortality has been detected. Short after, the data of the VADT study (Veterans Administration Diabetes Trial)\(^4\) have been presented in which an excess of mortality has also been observed, though it was not relevant, associated to the intensive hypoglycemic treatment.

The ADVANCE study (Action in Diabetes and Vascular disease: preterAx and diamicroN modified release Controlled Evaluation)\(^5\) contrasts with the ACCORD and VADT studies, as it shows that an intensive hypoglycemic treatment strategy based on the administration of maximum doses of modified release gliclazide might reduce the incidence of the main complications of the T2D, without increasing the mortality risk. Moreover, it has proved that the optimization of the blood pressure control has an additive effect to the intensive hypoglycemic treatment on the reduction of the complications and mortality.

Design and methodology of the ADVANCE study
The ADVANCE study is the largest intervention study in T2D available at present as regards to the number of patients. In order to perform it, 11,140 patients have been recruited in 215 sites of 20 countries (43% were women), aged 66 years a T2D of 8 years of evolution and a glycosylated hemoglobin (HbA\(_{1c}\)) of 7.5% as average. Its target was double: on one hand, to determine the effects of an anti-hypertensive treatment (fixed combination of perindopril plus indapamide) additional to the usual treatment versus placebo; on the other hand, by means of a crossed factorial design 2 X 2, the intention was to study the effect of an intensive hypoglycemic treatment based on maximum doses of modified release gliclazide, with the addition of other drugs (included insulin) staggered according to the need for keeping a HbA\(_{1c}\) at <6.5%. A main objective has been assessed targeted to micro vascular and macro vascular events (progression of the nephropathy and retinopathy, acute myocardial infarction, cerebrovascular accident and cardiovascular death), with a foreseen follow-up of 5 years.

Summary of the main results of the ADVANCE study
The blood pressure control group of ADVANCE\(^6\) study was interrupted early, as a relevant reduction of total mortality (14%) and cardiovascular mortality (18%) was detected in the active treatment group, besides renal and coronary events (21 and 14%, respectively), associated to a modest reduction but relevant of the blood pressure (5.6 and 2.2 mmHg for the systolic and diastolic, respectively).

In the glycemic control group\(^5\), a target HbA\(_{1c}\) of 6.5% has been achieved in the group that received intensive treatment, versus 7.3% in the group treated conventionally. This reduction was obtained progressively during the first 36 months. The serious hypoglycemia index was extraordinarily low (0.7 and 0.4 events per 100 patients/year in the intensive and conventional groups, respectively). This index is equivalent to half of what has been observed in the UKPDS study\(^1\) for the intensive treatment with glibenclamide and a sixth part observed in the intensive group of the ACCORD study.\(^5\) No increase in body weight has taken place during the follow-up in the intensive treatment group in the ADVANCE study,\(^5\) which contrasts with relevant increases in the ACCORD\(^1\) and VADT\(^4\) studies.

The intensive treatment group showed a relevant reduction (p=0.013) of the relative risk of 10% for the primary combined tar-
get of micro vascular and macro vascular events. In fact, this result was due principally to the reduction of renal events (21% global, with 30% of reduction in the presentation of macroalbuminuria and 36% in the progression to terminal renal failure), with a scarce reduction in the retinopathy progression (5% [not relevant]). A tendency towards the reduction of cardiovascular events (9%) and cardiovascular disease (12%) could be observed, which did not result relevant. These tendencies did not appear until the last year of follow-up, giving place to the possibility of a relevant difference during a more extended follow-up; similar to what has been observed in the UKPDS and Steno-2 study extensions.

In spite of the bad results of the ACCORD and VADT studies, a recent meta-analysis of the large studies of intensive glycemic control in the T2D (Included the ADVANCE study) show that the intensive strategies reduce significantly the risk of cardiovascular events (9%), especially the acute myocardial infarction (15%), though they do not reduce the mortality.

**ADVANCE 2 × 2: glycemic control plus blood pressure control**

Very recently, the intensive combined results of blood pressure and glycemic control have been published in the ADVANCE study though in the essential the results have been known at the end of 2008. The effects of both treatments were completely additive, without relevant interaction in any case, for all the pre-specified targets (figure 1). Compared to the conventional treatments, the hypoglycemic intensive treatment combined with the hypertensive reduced in 33% the nephropathy progression risk (26% for the presentation of microalbuminuria and 54% for the microalbuminuria progression), in 24% the cardiovascular mortality and 18% the total mortality. All these reductions were statistically relevant. However, the retinopathy progression was not hardly reduced (4% [not relevant]), though the treatment reduced the risk of some lesions (hard exudates, microaneurysms, macular edema) in a relevant marginally way. No reduction was either observed in the risk of cerebrovascular events. The reduction of risk for the combined primary target was of 15% (p=0.02).

These results proved those previously published of the Steno-2 trial and the recommendations of the main therapeutic guidelines for the treatment of the T2D, standing out the benefits of the intensive multifactorial treatment. Moreover, they show that this strategy is adequate for almost all the patients with T2D, and not only for those with hypertension and/or microalbuminuria.

**The ADVANCE in the XX Congress of the International Diabetes Federation**

In the recent congress of the International Diabetes Federation (IDF) (Montreal, October 18th-22nd 2009), new analysis was presented corresponding to the results of the ADVANCE study. The results of the glycemic control were significantly similar in the different groups, defined by the following aspects:

- Previous treatment (without previous treatment, addition to metformin or change of another sulphonylurea).
- Patients’ age (<65, 65-75 and >75 years).
- Duration of the diabetes (<5, 5-15 or >15 years).
- Body mass index (<25, 25-30 or >30).

The HbA1c obtained reduction was directly proportional to the initial level, achieving reductions over 4% in patients with initial values >10% (figure 2). In all the cases, the HbA1c reduction was kept during the five years follow-up. The datum of ADVANCE about morbidity and cardiovascular mortality have allowed developing a formula for the estimation of risk based on the age, the duration of the T2D, the levels of HbA1c, the blood pressure and lipids, etc. This formula replaces the derivatives of the Fram-
ingham and UKPDS studies, already obsolete due to the recent therapeutic changes.

Moreover, the availability of the ADVANCE genetics sub-study has been announced, that will allow going into depth in the knowledge of the genetics markers regarding to the meta-diabetic complications, facilitating its prevention by means of the pre-clinical diagnosis. But the most important announcement corresponded to the starting of the ADVANCE-ON study, with an additional follow-up of 5 years for most of the original cohort, with the total mortality and the cardiovascular events as main assessment objectives. This study extension might allow elucidating the pending matter about the effect at long terms of the intensive hypoglycemic treatment based on modified release gliclazide.

**Lessons of ADVANCE for the clinical practice**

We can summarize the main ADVANCE lessons in a Decalogue, along with the rest of the recent intensive glycemic control trials:

- The systematic anti-hypertensive treatment with a fixed combination of perindopril and indapamide at low doses is safe and beneficial for most of the patients with T2D.
- The effects of the hypoglycemic and intensive anti-hypertensive treatments are additive. The treatment of the T2D should be multi-factorial.
- For the hypoglycemic treatment of the T2D, the chosen therapeutic strategy is at least as important as the HbA1c objective.
- The hypoglycemic treatment based on long release gliclazide and intensified staggered allows achieving demanding objectives of HbA1c to most of the patients with a minimum risk of hypoglycemia and without gaining weight.
- In contrast to the most aggressive strategies used in the ACCORD and VADT studies, the strategy used in the ADVANCE study does not increase the mortality risk nor the cardiovascular events.
- A relevant reduction of the meta-diabetic complications risk can be obtained with this strategy, at the expense basically of renal complications.
- The modified release gliclazide might be safer and effective than the conventional sulphonylureas.
- It is important to individualize the hypoglycemic treatment: the aggressive treatments might be especially dangerous in patients with a long T2D evolution, with a previous deficient glycemic control and with a history of cardiovascular events.
- To keep an adequate glycemic control as from the beginning is the most effective way of preventing the possible meta-diabetic complications.
- Finally, it has to be pointed out that trials at very long term should be performed in order to prove the benefits of the intensive hypoglycemic treatment.

**Declaration of potential conflict of interests**

The author received fees for presentations and/or documents by Abbott, Bayer, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, GSK, Infocinia, Lilly, Menarini, MSD, Novartis, Novo Nordisk, Pﬁzer, sanofi-aventis, Servier, Solvay, Takeda and Wolters-Kluwers Health.

**References**