New challenges in the clinical practice

Can be still admitted a target of HbA$_{1c}$ of $<7\%$? Considerations about ACCORD, ADVANCE and the new consensus from ADA-EASD

¿Puede admitirse todavía un objetivo de hemoglobina glucosilada inferior al 7%?
Reflexiones sobre el ACCORD, el ADVANCE y el nuevo consenso ADA-EASD

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The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have recently published (December 2008) a “new” consensus$^1$ for the pharmacological treatment of T2D. A group of experts of both societies proposed a new algorithm that roused certain controversy and that positions itself clearly stating debatable priorities among the available drugs. The most outstanding contributions of this new document, which its intention is to integrate the new data provided by the studies ACCORD, ADVANCE, VADT and UKPDS-PTM, in follow-up phase open 10 years after the study was communicated, might be summarized in two points:$^1$

- A glycemic control objective is kept under 7% of HbA$_{1c}$.
- As regards to the new proposed algorithm, it is insisted in starting the treatment with quality life changes and metformin, and to change early to new therapeutic regimes in the patients who can not achieve the mentioned objectives, especially guidelines with sulphonylureas and insulin. Moreover, it states clearly the exclusion of the rosiglitazone and, however, it places the use of pioglitazone in a second therapeutic level (“less well validated therapies”); an extremely careful posture is adopted as regards to the DPP-4 inhibitors (vildagliptin, sitagliptin), seeking protection in the cardiovascular safety lack of knowledge at long term, but the use of exenatide (GLP-1 analogue) is surprisingly prioritized.

The first point, which constitutes the main objective of this consideration, is not excessively controversial, as it is kept within the previous recommendations,$^2$ based on the well-established benefits of reducing the micro and macro-vascular complications (which reduce the quality of life in patients considerably), without trying to go beyond the HbA$_{1c}$ target $<7\%$ as other guidelines defend.$^3,4$ The data of DCCT$^5$ (in T1D) and of UKPDS$^6$ (in T2D) are clear and unquestionable. The new data of ADVANCE also ratify a reduction of renal damage with a reduction of the HbA$_{1c}$ over than $7\%$ though without great achievements in macrovascular events. As the 2008 was a prolific year as regards to the spreading of great studies results (ACCORD,$^7$ ADVANCE,$^8$ VADT$^9$) that have tried to explain if the intensive control (HbA$_{1c}$ of 6.5% versus standard control of $>7\%$) might reduce the macrovascular complications. The results in this sense, well known at that time, do not reduce the HbA$_{1c}$ excessively as general rule beyond $7\%$, but admit certain nuances. More than reduction levels of HbA$_{1c}$, the studies compare different therapeutic strategies among ones and other studies, though the set out HbA$_{1c}$ objective is achieved. Moreover, the general patients evaluated had a very advanced disease.$^{10}$

There is a clear suggestion of benefit in diabetic patients of relative short evolution, of lower risk and/or without
determined cardiovascular disease. On the contrary, it has been noted to the serious hypoglycemia as possible and valid neutralizing cause of the benefit, especially in patients with determined cardiovascular disease. The follow-up data in open phase of the UKPDS study suggest that the macrovascular benefit, the clinic events and the cardiovascular mortality seem to require more time of glycemic control in order to show its beneficial effects. Possibly, the most preventive role of the strict glycemic control is achieved before the clinical cardiovascular disease is developed.

In view of the above, once more, and as it happens in other fields of the cardiovascular therapeutics, it is a need to individualize the patients, treatment, having to consider the existence of hypoglycemia history and/or risk of showing them as fundamental factors, as well as the years of the evolution of the diabetes and the presence of determined vascular disease. Many patients with a more benign or early profile of the disease might take benefit of a more intensive control, especially the younger patients, without a determined disease and with low risk of hypoglycemia. On the contrary, it is valid that in older patients with determined disease (often advanced atherosclerosis) and who show a greater tendency to serious hypoglycemias with higher lesion risk, the intensive control (HbA1C of 6.5% or less) implies more risks than benefits. In any case, the current controversy should not be extrapolated to the patients with an inadequate glycemic control (>8%), which is the real setting in the usual clinical practice in our environment, and even in sites of excellence, as it might be perverse to lead to a greater therapeutic nihilism/inertia and to give up the achievement of glycemic objectives within an integrator approach of the disease.

As regards to the second point object of this comment—the new proposal of algorithm—admits a higher level of controversy and especially it has to be object of a reasoned criticism. First, it is more arguable to provide a new concrete algorithm (displacing the one spread during the last year, with several options in a second step after the metformin), when there are scarce evidences in results “body to body” among different drugs and even among different therapeutic strategies, at least as regards to the “hard” targets of clinical events or cardiovascular mortality. Secondly, the proposed strategy after metformin in the first step does not seem to take into account the capital importance of minimizing hypoglycemias, the higher value of the DPP4 inhibitors and the worse adverse effect of the sulphonylureas, not even the convenience of avoiding the weight increase, the constant adverse effect of the glitazones, the sulphonylureas and insulin, when all of them are elements that have to be present when determining a therapeutic strategy. In this sense, it cannot be clearly stated why the pioglitazone can be in a second therapeutic step (“Less well validated therapies”) if it has known adverse effects (bone fractures), or because it can be especially prioritized as regards to other therapeutic groups. Likewise, neither the frequent digestive effects nor the necessary parenteral administration of the GLP-1, introduced in the United States in 2005 and recently in our environment, seem to be object of unfavorable consideration in spite of the doubtful tolerability and difficulty of acceptance of this treatment modality in our environment.

Therefore, the criteria that have led to this new therapeutic algorithm proposed for the treatment of the patient with T2D by a group of experts deserve an open discussion. As the authors state, the therapeutic individualization has always to prevail. The proposal presents, probably, a certain load of subjectivity and a focused view in the economic considerations and in the clinical experience obtained with some hypoglycemiants drugs on the other side of the Atlantic Ocean.

Declaration of potential conflict of interests

P. Conthe stated that there are no conflicts of interest as regards to the content of this article.

References


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