Blood pressure targets in various clinical situations in diabetic patients

Objetivos de presión arterial en diversas situaciones clínicas en pacientes con diabetes

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Abstract
The objective of this paper is to review the evidence that supports the recommendations of the Clinical Practice Guidelines on arterial hypertension and diabetes mellitus with regard to blood pressure control targets. Nearly all the Guidelines currently state, with certain nuances, that the targets are to achieve and maintain a systolic blood pressure of <130 mmHg and a diastolic blood pressure of <80 mmHg. Apart from certain exceptions—diabetic nephropathy with proteinuria greater than 1 g/24 hours is the only one—those targets do not vary according to the presence of other pathologies associated with diabetes. The review of the clinical trials makes it possible to conclude that blood pressure lowering is, without a doubt, beneficial. Nevertheless, even in the conditions of the clinical trials, which are very far removed from the practical reality of Primary Health Care, a substantial percentage of patients do not achieve the control targets recommended in the guidelines; this is especially true in the case of systolic blood pressure, despite the use of combinations of two or more antihypertensive drugs.

Keywords: diabetes mellitus, hypertension, control.

Resumen
El objetivo de este trabajo es revisar las evidencias que avalan las recomendaciones de las guías de práctica clínica sobre la hipertensión arterial y la diabetes mellitus en relación con los objetivos de control de la presión arterial (PA). En la actualidad, la práctica totalidad de las guías coinciden, con algunos matices, en que los objetivos son alcanzar y mantener unas cifras de presión arterial sistólica (PAS) <130 mmHg y de presión arterial diastólica <80 mmHg. Con alguna excepción (la nefropatía diabética con proteinuria superior a 1 g/24 h es la única), estos objetivos no varían en función de la presencia de otras patologías asociadas a la diabetes. La revisión de los ensayos clínicos permite concluir que la reducción de las cifras de PA es, sin duda, beneficiosa. Sin embargo, incluso en las condiciones de los ensayos clínicos, muy apartadas de la realidad práctica de la atención primaria, un porcentaje considerable de pacientes no alcanzan los objetivos de control propuestos en las guías, especialmente de PAS, a pesar de la utilización de combinaciones de dos o más fármacos antihipertensivos.

Palabras clave: diabetes mellitus, hipertensión, control.

Introduction
From the vascular point of view, the diabetic patient with blood hypertension (BHT) ages earlier. The co-existence of BHT and T2D speeds up the progression of the atherosclerosis and at the same time the onset of macrovascular complications (heart disease, brain vascular disease and peripheral arteriopathy) but also the microangiopathies (nephropathy, retinopathy and neuropathy). Therefore, the clinical practice guidelines (CPG) about the BHT consider the hypertensive and diabetic patient as a person at high cardiovascular risk (CVR).

On the other hand, the blood pressure (BP), both in a population context and regarding to the CVR, is a con-
tinuous variable, so the limits in order to determine the BHT diagnosis are arbitrary. The epidemiologic studies prove that values of BP >115/75 mmHg are associated to an increase in the incidence of cardiovascular events (CV) and mortality in diabetic subjects. In this sense, the CPG of the European Societies of BHT and Cardiology of 2007, and the American Diabetes Association (ADA) in its document of 2009 consider lower levels of BP (≥130/80 mmHg, compared to the recommendations of ≥140/90 mmHg, in general) to determine the diagnosis of BHT and recommend the starting of an hypertensive treatment.

Therefore, the treatment of the diabetic patient as regards to the BP has certain characteristics that differentiate it from other clinical situations. As previously mentioned, the CPG recommend to start the antihypertensive treatment earlier and from the lowest possible levels of BP. Moreover, and according to what has been mentioned, the tensional control objectives recommended in the CPG are stricter in diabetic patients than in other hypertensive patients without diabetes. The most agreed proposal is to achieve and maintain values of BP <130/80 mmHg, compared with the general target of BP <140/90 mmHg.

Benefits of the hypertensive treatment in diabetes

There are several clinical studies performed in diabetic patients that have proved important benefits of the antihypertensive treatment, in terms of CV complications reduction. Most of the specified studies have included hypertensive patients, though in the ABCD (Appropriate Blood Pressure Control in Diabetes) and the ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicron-MR Controlled Evaluation) a considerable percentage of the patients show normal blood pressure.

Several studies have evaluated specifically, the benefits of the different strategies with antihypertensive drugs on the progression of the diabetic nephropathy, as it is the case of the RENAAL (Reduction of Endpoints in NIDDM with the AI Antagonist Losartan), BENEDICT (BErgamo NEphrologic Diabetes Complications Trial), IRMA-2 (Irbesartan in patients with type 2 diabetes and MicroAlbuminuria) and IDNT (Irbesartan Diabetic Nephropathy Trial). The control objectives in several of these studies were values of BP <135/85 mmHg, even lower in the case of the BENEDICT study (<120/80 mmHg), in spite of the fact that the mean values were of 139/80 mmHg during this study.

As regards to the heart disease, the sub-study in diabetic patients of the INVEST (INternational VErapamil SR-trandolapril study), performed in subjects with ischemic cardiopathy history, used an algorithm based on reaching BP levels of <130/85 mmHg, that have been achieved in more than 40% of the patients. However, a tendency to a higher number of events could be observed with BP values of <110/60 mmHg.

In all these trials, as in most of the trials, about the BHT, the benefits of the treatment are due mostly to the reduction per se of the BP, which has been achieved in most of the cases with the use of the combination of two or more antihypertensive drugs. In the case of the diabetes, up to the third part of the patients shall need three or more antihypertensive drugs. Therefore, the combination therapy is the rule and the use of fixed combinations is recommendable in order to facilitate the therapeutic compliance.

Clinical practice guidelines and control objectives of the blood pressure in diabetic patients

Some of the mentioned studies, as the ABCD, or the HOT (Hypertension Optimal Treatment) and the UKPDS (United Kingdom Prospective Diabetes Study), have been designed with the objective to prove if a stricter control of the BP entailed major benefits and in fact this was proved indeed. Precisely, these trials are the best possible evidence to determine the current recommendations about the control of the pressure values in diabetic patients. However, in the UKPDS the mean final BP was of 144/82 mmHg in the “intensive control” group (target BP <150/85 mmHg) and 154/87 mmHg in the control group (target BP <180/105 mmHg).

In more recent trials, as ADVANCE and STENO-2, the reduction of the BP that has been achieved with the treatment was considerable and close to the target values of the CPG. In the ADVANCE trial, the initial values of BP were 145/81 mmHg and 137/75 mmHg at the end of the study in the group assigned to the active treatment. In the Steno-2 study, 51% of the patients assigned
to the intensive intervention group reached systolic arterial pressure (SAP) of <130 mmHg at the end of the trial, while 72% could maintain a diastolic arterial pressure (DAP) of <80 mmHg. However, after a follow-up of more than 13 years, the mean values of the BP were of 140/74 mmHg in the intensive treatment group. Therefore, even in the conditions of the clinical trials, the BP targets dated in the CGP, especially the systolic component, related to an increase in the arterial rigidity are not easy to achieve. An excellent review of Mancia and Grassi stated the difficulties to achieve pressure control objectives in general and in diabetic patients, especially in the SAP. The figure 1 depicts the BP values at the starting and end of a long series of clinical trials. If a considerable number of trials reach the DAP targets of <80-85 mmHg, the same does not happen with the SAP <130-135 mmHg.

Up to 2003, there have been considerable differences among the CPG on the BHT control targets in the diabetic patients. At present there is a generalized agreement in considering that the objectives are to achieve and maintain SAP and DAP values of <130 and <80 mmHg respectively, with certain nuances on the recommendation level. Table 1 sums up the control objectives, in different clinical situations, in some of the reviewed CPG. Thus, for the ADA and the Canadian Diabetes Association, the SAP target of <130 mmHg is level C recommendation and DAP <80 mmHg is level B, while the Canadian Guideline of BHT considers the control target of the DAP of <80 mmHg as level A and SAP <130 mmHg as level C. The CPG of the European Societies of BHT and Cardiology reflect these same targets. But, surprisingly, their authors consider that the criterion of SAP of <130 mmHg are not only wrongly documented but besides it is difficult to achieve. A recent work proved that trying to achieve the SAP objectives <130 mmHg, which in this study was reached in a third part of the patients, suggests that more than half of the patients reduces the values of DAP less than 70 mmHg; this situation might increase the CV risk in elder patients or patients with heart disease. Some CPG, as the National Institute for Clinical Excellence (NICE), with a more realistic approach, state some “audit” objectives in the region of 140/80

Figure 1. Effects of the antihypertensive treatment on the systolic arterial pressure (SAP) and diastolic arterial pressure (DAP), in hypertensive patients with diabetes in several trials. The discontinued lines correspond to the guidelines targets (BP <130/80 mmHg at present, the BP targets <135/85 mmHg) are also depicted. B: values of basal BP; T: values of BP during the treatment. Taken from Mancia and Grassi21
mmHg. The always expected and influencing American CPG of the Joint National Committee (JNC), has not been updated since 2003.24

The most differentiated clinical situation in the CPG as regards to the DM, is the diabetic nephropathy, which with levels of proteinuria >1 g/day sets out stricter control objectives (BP <125/75 mmHg). The evidences that support this recommendation are scarce and extrapolated of studies performed with different populations. The AASK25 (African American Study of Kidney Disease and Hypertension), conducted in Afro-American hypertensive patients with hypertensive nephropathy (nephroangiosclerosis) compared the effect of two control objectives of mean BP (“usual” of 102-107 mmHg and “stricter” ≤92 mmHg) on the reduction of the glomerular filtration, as main variable. No relevant differences were observed at the end of the study between both strategies.

Which is the reality as regards to the blood pressure control in diabetes?
In different studies performed in Spain in the primary care field, an improvement in the BHT control level is observed. The study Controlpres,26 of 2003, showed a percentage of 38%. And the PRESCAP,27 of 2006, exceeded the 40%. However, in this last study, the control rate in diabetic hypertensive patients, with the criterion of BP <130/80 mmHg was very low (approximately of 15%). In the study DISEHTAC II28 (Diagnosis and Monitoring of Hypertension in Catalonia) the level of the BHT control was of 32.4%, while in the diabetic patients with a BP target of <130/85 mmHg, the control values were in the region of 10.9%. Therefore, the recommendations of the CPG, at least in primary care, are difficult to comply. This important gap among the CPG recommendations and the real control level of the risk factors might be a consequence of the therapeutic inertia.29 The distrusts in the acceptance of the GPC objectives are recognized as one of the causes of certain conservative attitude when intensifying the BHT treatment. However, there is a wide improvement margin, seen positively.

Conclusions
There is wide evidence among the benefits of the BP reduction in diabetic patients. As regards to the BP control targets, the most agreed proposal is to achieve and main-
tain values of <130/80 mmHg, which are difficult to achieve in the clinical practice in spite of using combinations of three or more hypertensive drugs.

Declaration of potential conflicts of interests
M. de la Figuera states that there are no conflicts of interests as regards to the content of this article.

References