CLINICAL GUIDELINES

Blood pressure goals in T2DM: a Latin American perspective

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Consensus documents are typically generated by a panel of experts that reviews data and integrates data interpretation focused on the treatment and management of patients. A novel consensus report on blood pressure targets in diabetes mellitus does this and much more by focusing on the diversity of different populations in Latin America and by tailoring approaches to blood pressure and diabetes management beyond the demographics in each subgroup.

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Over the past 30 years, the notion of what a guideline should comprise has continuously evolved and has culminated in an approach on how best to judge goal blood pressures to reduce cardiovascular risk. **[Au: OK?]** This evolution is especially true for diseases such as chronic kidney disease (CKD), which is characterized by an estimated glomerular filtration rate <60 ml/min/1.73 m^2 and type 2 diabetes mellitus (T2DM). Both disorders are associated with a very high risk of adverse cardiovascular events—a risk that is independent of blood pressure level.[1]

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The first prospective trial to determine cardiovascular outcomes of patients with T2DM who were randomly allocated to different blood pressure targets was the UKPDS 38, which was conducted by the United Kingdom Prospective Diabetes Study Group.[2] In this trial, the patient group randomly allocated to tighter blood pressure control had a mean systolic blood pressure of 144 mmHg and had significant reductions in the rates of diabetes-related deaths and complications compared with the control group, whose mean systolic blood pressure was 154 mmHg. Since then, researchers of the Action to Control Cardiovascular Risk in Diabetes–Blood Pressure (ACCORD-BP) trial randomly allocated 4,733 high-risk patients with T2DM to two separate target systolic blood pressures, <120 mmHg or <140 mmHg.[3] After 4.7 years, no difference between the two groups was observed for the primary outcomes of nonfatal stroke and nonfatal myocardial infarction or cardiovascular-event-related and all-cause mortality. The lower blood pressure goal of <120 mmHg was associated with fewer strokes but with more serious adverse events than the target of <140 mmHg.

Using evidence from the aforementioned trials to develop guidelines for blood pressure goals would be considered very good, as this so-called ‘class 1’ evidence is based on good-quality data derived from randomized placebo-controlled studies. Statements derived from such studies have more creditability than those using data from retrospective or observational studies, which would be labelled ‘class 2’.[1,4–6] Class 2 data are weaker and do not have the imprimatur of class 1 data, regardless of their quality.

Examples of class 2 evidence with respect to blood pressure goals in T2DM include post-hoc analyses from two large prospective trials of patients with diabetes mellitus. The first is a subgroup analysis of 6,400 patients with T2DM, hypertension or coronary artery disease from the International Verapamil SR–Trandolapril Study (INVEST).[7] Although this analysis is in line with data derived from prospective trials such as ACCORD, in that it shows no additional benefit of having a target systolic blood pressure of <130 mmHg compared with one of 130–139 mmHg, its findings would be considered class 2 evidence.

The second class 2 study is the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial,[8] in which 11,140 patients with T2DM were randomly allocated to receive a fixed combination therapy of perindopril and indapamide or to receive a placebo. The investigators did not prospectively randomize blood pressure goals. After 4.3 years, the mean systolic/diastolic blood pressures were 135/74 mmHg for the combination therapy group and 140/76 mmHg for the placebo group. A post-hoc analysis demonstrated fewer cardiovascular outcomes among patients with low blood pressure that extended below 130 mmHg. The results of ADVANCE support a systolic/diastolic blood pressure target below 130/80 mmHg, but they should be interpreted with caution. Not only are they class 2 grade in terms of quality but also the comparison involved a drug intervention rather than randomized blood pressure groups.

Additionally, information regarding overall cardiovascular risk has emerged from meta-analyses over the past year for patients with T2DM and CKD. Three separate meta-analyses, each involving over 1 million patients, presented a unifying message about the presence of diabetes mellitus and CKD.[1,5,6] Presence of CKD was associated with a higher risk of all-cause mortality and/or cardiovascular-related mortality compared with the presence of a

prior myocardial infarction or diabetes mellitus,[1,5,6] thus making CKD an independent risk factor for cardiovascular-related death. Moreover, the cardiovascular risk status of CKD was independent of high blood pressure.[1]

The latest clinical practice guidelines from the American Diabetes Association (ADA) and the Kidney Disease Improving Global Outcomes (KDIGO) group note that the strongest evidence base for a blood pressure goal is a value <140/80 mmHg or <140/90 mmHg, respectively.[9] These data are derived from primary analyses of prospective trials, including ACCORD and UKPDS 38,[2,3] as well as secondary analyses of these trials, using rules of evidence analysis outlined and agreed upon by a panel of experts on evidence assessment. **[Au: OK?]** The previous goals of <130/80 mmHg have a weaker, class 2 evidence base and are largely derived from observational studies, as described above.

In the current issue of the *Journal of Hypertension*, López-Jaramillo and colleagues present a consensus report on hypertension in patients with diabetes mellitus and the metabolic syndrome.[10] This report, although not applying the criteria of an evidence review, such as the guidelines by the ADA and KDIGO,[9] does a good job of summarizing the epidemiology of T2DM, hypertension and metabolic syndrome in Latin America. Moreover, it focuses uniquely on issues relevant to Latin America and makes proposals for an approach to help understand and manage issues more comprehensively.

The report by López-Jaramillo *et al.* uses definitions of hypertension consistent with those used previously by the ADA and European and Joint National Committee (JNC). Moreover, the recommended goal blood pressure agrees with the <140/90 mmHg goal of the latest ADA and KDIGO guidelines. The consensus report does a comprehensive job of summarizing the pertinent data and provides a good rationale for why the experts reached their decision on blood pressure goal.

The consensus document further focuses on epigenetics, the science that explains the variation of gene expression in response to changes in environmental conditions. The report notes that high-risk groups such the elderly, Afro-Latin Americans and those that live in the Andes have different control rates for blood pressure, and other risk factors differ depending on region and demographic. Moreover, the authors make the point that malnutrition, especially in pregnant women and in children early in their development, might increase cardiovascular risk later in life. **[Au: OK?]**

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The report is not only a complete review of the literature regarding blood pressure and risk-factor management but an appeal to the Pan American Health Organization to provide funding support to help understand the diversity of environment and resultant variations seen in cardiovascular risk factors. For example, the predominant diastolic hypertension prevalent in people living in the Andes is not seen in those living at lower altitudes.

In conclusion, the unified approach in the consensus report is timely and unique to the area of the world where the data were gathered. Whereas the approach to blood pressure management in patients with T2DM is now unified between the Americas and Europe regarding general blood pressure goals, many specific questions remain unanswered in Latin America, which can only be approached by more research in areas in which specific gaps in data exist. The authors plea for more research to provide data derived from understudied groups, such as those who live at different altitudes. Thus, a more diverse focus on specific groups within the general population of Latin America must be initiated with regards to both research and funding. **[Au: OK?]**

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Competing interests
The author declares no competing interests.

1. Mahmoodi, B. K. *et al.* Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. *Lancet* **380**, 1649–1661 (2012).
2. [No authors listed] Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* **317**, 703–713 (1998).
3. Cushman, W. C. *et al.* Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N. Engl. J. Med.* **362**, 1575–1585 (2010).
4. Bonow, R. O. *et al.* ACCF/AHA methodology for the development of quality measures for cardiovascular technology: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures. *J. Am. Coll. Cardiol*. **58**, 1517–1538 (2011).
5. Fox, C. S. *et al.* Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* **380**, 1662–1673 (2012).
6. Tonelli, M. *et al.* Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet* **380**, 807–814 (2012).
7. Cooper-DeHoff, R. M. *et al.* Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA* **304**, 61–68 (2010).
8. Chalmers, J. & Arima, H. Importance of blood pressure lowering in type 2 diabetes: focus on ADVANCE. *J. Cardiovasc. Pharmacol.* **55**, 340–347 (2010).
9. [No authors listed] Summary of revisions for the 2013 clinical practice recommendations. *Diabetes Care* **36** (Suppl. 1), S3 (2013).
10. López-Jaramillo, P. *et al.* Latin American consensus on hypertension in patients with diabetes type 2 and metabolic syndrome. *J. Hypertens.* **31**, 223–238 (2013).