Editorial

The more individualised the blood pressure, the better

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Hypertension with high global prevalence is the main risk factor for cardiovascular diseases and death. It is known from observational studies in patients without other risk factors that there is a continuous and linear increase in cardiovascular risk associated with pressure elevations from 115 and 75 mmHg for systolic and diastolic blood pressures (BPs), respectively (1). However, the ideal target for pressure control remains undetermined. In addition, there is no evidence from large population studies about the real benefit of strict BP control (2-4). Thus, the therapeutic target for systolic and diastolic pressure in under 60-year-old individuals remains hypothetical. However, based on the opinion of experts, hypertension guidelines recommend target values of less than 140/90 mmHg (5-10). With respect to the elderly, most guidelines maintain the target of 140/90 mmHg, with the exception of the Egyptian and American guidelines that recommend 150/90 mmHg (11,12) and the Canadian high BP education program which advocates a systolic blood pressure (SBP) <150 mmHg for individuals >80 years (13).

Recently, two important randomized trials were designed to assess the BP target for subgroups at high cardiovascular risk: the ACCORD (Action to Control Cardiovascular Risk in Diabetes) BP study (14), which enrolled patients with diabetes mellitus and the SPRINT (Systolic Blood Pressure Intervention Trial) in patients without diabetes (15). These randomized controlled trials compared cardiovascular outcomes in groups with intensive BP control (SBP <120 mmHg) versus standard BP control (SBP <140 mmHg). The ACCORD BP study followed 10,251 adult patients (mean age of 62 years and 48% women) with type II diabetes over 4.7 years. About 30% of patients had cardiovascular disease. Participants were allocated to two groups, an intensive-therapy group (systolic pressure 119 mmHg) and a standard-therapy group (systolic pressure 134 mmHg). The mean annual rate of combined outcomes, which included nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (P=0.20). Rates of death from any cause were 1.28% per year in the intensive-therapy group and 1.19% in the standard-therapy group (P=0.55). Rates of death from cardiovascular causes were 0.52% per year in the intensive-therapy group and 0.49% in the standard-therapy group (P=0.74). However, the stroke rate (a prespecified secondary outcome) was slightly but significantly lower in the intensive-therapy group 0.32% and 0.53% in the standard-therapy group P=0.01) (14).

Meanwhile, the SPRINT included 9,361 hypertensive adults with a mean age of 68 years who had at least one of the following additional risk factors for cardiovascular disease: clinical or subclinical cardiovascular disease (except stroke), age equal to or greater than 75 years (minimum 50 years), chronic kidney disease defined as a estimated glomerular filtration rate from 20 to 60 mL/min/1.73 m^2 calculated using the Modification of Diet in Renal Disease (MDRD) equation, or Framingham risk score greater than or equal to 15%. After one year of follow-up, the mean

SBP in the intensive BP control group was 121.5 compared to 134.6 mmHg in the standard group. Regarding the outcomes, the SPRINT, initially designed for a follow-up of 5 years, was stopped early after an average follow-up of 3.26 years. This was necessary because of the significantly lower rate for the primary composite endpoint in the intensive treatment group compared to the standard group. Death from any cause was also significantly lower in the intensive BP control group. However, the serious adverse event rate, such as hypotension, syncope, electrolyte abnormalities and acute or terminal renal failure, was higher in the intensive BP control group.

Thus, the conclusion of the SPRINT was that intensive SBP control (around 120 mmHg) compared to the standard control (<140 mmHg) in patients with a high risk of cardiovascular events but without diabetes or previous stroke resulted in fewer fatal and nonfatal cardiovascular events and less mortality from any cause, although the rate of adverse events was higher.

It is also important to remember that generally more classes and higher doses of antihypertensive drugs are necessary for a more rigid SBP target; this implies more side effects and a greater probability of noncompliance with the combined therapy. The mean number of medications was naturally higher in the intensive BP control group than the standard control group in the SPRINT (2.8 *vs.* 1.8 tablets). Therefore, while the consistent results of the SPRINT support the concept that "lower BP is better", the benefits and risks of intensive control should be balanced in the clinical practice.

Hence, on evaluating these studies, it is important to recognize that the mechanistic reading of a study (scientific relevance) should require statistical power capable of detecting lower reductions of risk than the reading considering the pragmatic concept (clinical relevance of the effect). Minor reductions in outcome may suggest causality, and thus they do not imply a therapeutic indication because of their small clinical impact. Therefore, when interpreting a study from the mechanistic point of view, one must be very attentive to the statistical power, since it is usually calculated under the pragmatic concept.

Admittedly, meta-analyses of randomized controlled trials are at the top of the evidence hierarchy. Even so, this model has problems such as the limitation of evaluating only direct comparisons in pairs. In this setting, new analytical methods have been developed that provide estimates of the relative effect (efficacy or comparative safety) of various treatments through indirect comparisons, considering the complete network of available studies (16).

Network meta-analyses in the context of a systematic review are particularly appropriate for an approach in which three or more treatments are compared using either direct comparisons of the interventions of a randomized controlled trial or indirect comparisons between randomized controlled trials using a standard comparator. Moreover, based on valid statistical inference methods, it is possible to classify the investigated treatments to identify which are the best and which are the worst. These meta-analyses are commonly referred to in the literature as network meta-analyses, multiple-analyses, multiple treatments meta-analyses or mixed treatment comparison meta-analyses (17-20).

In the recent issue of *The American Journal of Medicine*, the meta-analysis by Bangalore *et al*. (21) entitled "*Optimal Systolic Blood Pressure Target after SPRINT: Insights from a Network Meta-Analysis of Randomized Trials*" tested the efficacy and clinical safety of different BP targets. The five target BPs (<160, <150, <140, 130, and <120 mmHg) were evaluated using a meta-analysis network that allows a comparison of different BP therapeutic targets individually and to determine the impact of these targets on individual results.

The study sample consisted of 17 studies involving 55,163 patients who were followed up for a mean period of 3.7 years, corresponding to 204,103 patient-years. The very encouraging results of this network meta-analysis point to a significant reduction in events such as stroke and myocardial infarction with SBP targets <120 and <130 mmHg compared to targets of <140 and <150 mmHg. However, in relation to death from any cause, cardiovascular death and heart failure, there was no significant difference when comparing any of the BP targets. Even so, the point estimate favored lower BP targets (<120 mmHg, <130 mmHg) when compared to higher BP targets (<140 or <150 mmHg).

However, there was a significant increase in serious adverse effects with the SBP target <120 mmHg compared to SBP targets <140 and <150 mmHg. Thus, SBP targets <120 mmHg are considered effective in protecting against cardiovascular events, and SBP targets <140 and <150 mmHg are safe to avoid serious adverse effects. While, a SBP target <130 mmHg has an excellent balance between efficacy and safety.

Results such as those presented by Bangalore *et al*. solidify the need to revise the BP targets recommended by guidelines. However, one important issue is how to replicate such favorable results reported in clinical trials in

our clinical practice applied to individual patients. In order to recommend lower BP targets, some key aspects should be taken into account, such as the age of the patients, the choice of antihypertensive drugs, careful titration and, in particular, cautious extrapolation for diabetic patients, individuals with previous cerebrovascular events, those with chronic renal impairment and, of course, the very elderly.

In conclusion, we can affirm that network meta-analyses with indirect and mixed comparisons are a valuable tool together with conventional techniques of meta-analyses, increasing the process of synthesis of the best available evidence to aid decision making.

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