Hypertension Guidelines: Is It Time to Reappraise Blood Pressure Thresholds and Targets?

Position Statement of the Latin American Society of Hypertension

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Since 1966, a large number of trials of blood pressure (BP) lowering drugs compared with placebo (or no treatment) in hypertensive patients, complemented by trials of more versus less intense BP lowering, have shown that antihypertensive treatment can significantly reduce the incidence of fatal and nonfatal events associated with hypertension.[1] A meta-analysis of all BP-lowering trials from 1966 to end of 2013 (68 trials in 245 885 individuals) has calculated that a 10/5 mm Hg systolic BP/diastolic BP (SBP/DBP) reduction significantly decreases stroke by 36%, heart failure by 38%, coronary events by 20%, cardiovascular mortality by 16%, and all-cause mortality by 10%.[2] In addition, head-to-head comparisons between treatments based on different antihypertensive drugs (meta-analyses of 50 trials with 58 two-drug comparisons in 247 006 individuals) have shown that what really matters for preventing cardiovascular events is lowering of BP, and how BP is lowered (ie, the types of drugs used) is of minor importance.[3]

Despite the very large number of trials of antihypertensive treatment, it must be recognized that, except for the benefits of reducing high BP and for the equivalence of the various classes of antihypertensive agents, the majority of questions of practical importance that doctors ask themselves every day when treating hypertension have not been approached by randomized controlled trials or have remained unanswered.[1–4] Examples of these unanswered questions are those to be discussed below such as initiation of drug treatment of hypertension, the BP targets to be aimed at, and the role of overall cardiovascular risk in treatment decisions.

Although the safest decisions are those that can be found according to results of randomized trials, their concordance, and/or meta-analyses, other decisions should necessarily be taken on the basis of other criteria such as post hoc analysis of trials, observational studies, pathophysiological and pharmacological knowledge, and experts' opinion.[4] Limiting guidelines recommendations only to those questions for which there is sufficient evidence provided by trials may lead to the risk of only making 1 or 2 firm recommendations, as has recently happened to the evidence-based guideline of experts appointed to the Joint National Committee (JNC-8) in the United States.[5] Management of hypertension and its guidelines must be necessarily based, now and in the near future, both on evidence and wisdom. What is important is that wisdom is not taken as evidence: taking wisdom for evidence has been a powerful deterrent to clarify unsolved questions of hypertension management by randomized clinical trials.[4] An important task of guidelines is to accompany their recommendations by indications of the strength of the recommendation and the level of evidence on which they are based, as was done in 2013 by the European Society of Hypertension and the European Society of Cardiology.[1]

Since then, several trials and meta-analyses designed to respond important unanswered issues, such as BP thresholds to initiate drug treatment of hypertension, BP targets to be aimed at, and the role of overall cardiovascular risk in treatment decisions, have been published.[6–9] The results of these studies justify a reappraisal of the current evidence supporting guidelines recommendations.

Initiation of Antihypertensive Treatment

Grade 2 and 3 Hypertension

The body of evidence in favor of antihypertensive treatment provided by randomized controlled trials was obtained in hypertensive patients whose baseline SBP was ≥160 mm Hg, who could presently be classified as grade 2 or 3 hypertensives. Some recent trials included patients with lower SBP values at randomization, but these patients already were under background antihypertensive treatment at the time of randomization and could likely be classified at least as grade 2 hypertensives. Therefore, the large reduction of fatal and nonfatal cardiovascular events induced by BP lowering in these trials and their meta-analyses[1,2] provides the strong recommendation that all individuals with BP in grade 2 or 3 hypertension range be treated with antihypertensive drugs. In all patients, drug treatment should be accompanied by lifestyle measures, and in grade 2 hypertensives, lifestyle measures can be used alone for a few weeks to test their effectiveness and the need for addition of drugs.

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Grade 1 Hypertension

Evidence of the benefits of antihypertensive treatment in grade 1 hypertension is weak because (1) the greater majority of BP-lowering trials—as mentioned above—was in patients with baseline SBP ≥160 mm Hg; (2) those patients whose randomization SBP was between 140 and 160 mm Hg were already under background antihypertensive drugs and could not be classified in grade 1 hypertension; and (3) the few trials performed, mostly in 1970 to 1980s, in so called mild hypertension classified hypertension on the basis of DBP only, so that the term mild hypertension has a rather loose relation with what we now call grade 1 hypertension.[10] An attempt to meta-analyze data from individual patients with grade 1 characteristics within the mild hypertension trials had too low statistical power to attain statistical significance.[11] As a consequence, recommendations in various recent guidelines are cautious and only based on experts' opinion. The 2011 UK NICE (The National Institute for Health and Care Excellence) guideline[12] recommends confirming hypertension by ambulatory BP monitoring and restricting treatment to grade 1 hypertensives with signs of organ damage or at high total cardiovascular risk. The 2013 ESH-ESC (European Society of Hypertension–European Society of Cardiology) hypertension guidelines,[1] the JNC-8 guideline,[5] and the American Society of Hypertension–International Society of Hypertension clinical practice guidelines,[13] all recommend drug treatment after several months of unsuccessful lifestyle measures on the basis of indirect evidence (class IIa, Level B in 1) or expert opinion (grade E in 5). The arguments favoring drug treatment of grade 1 hypertensives even at low-to-moderate cardiovascular risk according to ESH/ESC guidelines are that: (1) waiting increases total cardiovascular risk, and high risk is not always entirely reversible; (2) safe antihypertensive drugs are available now and treatment can be personalized in such a way as to enhance its efficacy and tolerability; and (3) many antihypertensive agents are out of patent and cheap, with a good cost–benefit ratio.[1]

Some further arguments strengthening the recommendation of initiating drug treatment in grade 1 hypertensive patients, even when at low-to-moderate cardiovascular risk, result from a recent meta-analysis of BP-lowering trials, including all those in which patients were randomized in absence of treatment, so that 32 trials including 104 359 patients could be classified as investigating grade 1, 2, or 3 hypertension on the basis of the average baseline BP values.[6] Significant reductions of all major cardiovascular outcomes (except all-cause death in grade 3) were found by BP lowering at all grades of hypertension with no trend toward different relative risk reductions at different hypertension grades. An additional analyses including trials of grade 1 hypertension at low-to-moderate cardiovascular risk (cardiovascular death <5% in 10 years) also showed BP lowering produced relative and absolute reductions in stroke, coronary events, and all-cause mortality in these individuals with moderate BP elevation and moderate overall risk. Admittedly, stratification of trials in grades according to the mean values of SBP and DBP at randomization is an approximation, as part (although a minority) of the patients may have been out of the BP ranges defining the grades. However, the constancy of the relative risk reduction throughout the hypertension grades shown by this meta-analysis[6] favors the conclusion that all grades of hypertension benefit from BP lowering[14] and provides a stronger support to the recommendation to initiate drug treatment in grade 1 low-to-moderate risk hypertensives than the arguments that could be used in the 2013 ESH/ESC guidelines.[1] It is thought that this recommendation could be given now a higher level, such as Class I, Level A or B.

Grade 1 Hypertension in the Elderly

The number of randomized placebo-controlled trials showing the benefits of BP lowering in the elderly (variably defined as >60, 65, or 70 years) is large and the conclusions undisputable. However, all these trials have enrolled patients with baseline SBP ≥160 mm Hg,[11] and therefore, evidence-based recommendations are that it is imperative to provide antihypertensive drug treatment to elderly with SBP ≥160 mm Hg. As previously mentioned, lack of evidence is not equal to evidence against, and consideration can be given to treat elderly patients with SBP in the grade 1 range (140–159 mm Hg) provided they are fit and antihypertensive treatment is well tolerated.[1] This is an opinion-based suggestion, and the doctor's decision can be more flexible and personalized. The JNC-8 recommendation of treating the elderly when SBP is ≥150 mm Hg[5] seems an unjustified compromise between the evidence supporting a threshold of 160 mm Hg and prudence suggesting a more liberal threshold of 140 mm Hg as in younger patients.[15]

In the very old (≥80 years of age), evidence of benefits is available only from one trial enrolling subjects with SBP ≥160 mm Hg and in relatively good health,[16] and therefore HYVET (Hypertension in the Very Elderly Trial) evidence can only be translated into a cautious recommendation favoring drug antihypertensive treatment of the very elderly. A recent subanalysis of the HYVET, showing that in this trial the group that benefited most from treatment was that of octogenarians who were already on antihypertensive treatment (analysis of this group showed significantly less fatal and nonfatal events in those individuals who continued antihypertensive treatment as compared with those who interrupted it being randomized to placebo),[17] suggests that the strongest recommendations resulting from HYVET is in favor of continuing well-tolerated antihypertensive treatment when a hypertensive individual becomes octogenarian.

High Normal Blood Pressure

Although cardiovascular risk is continuously related to SBP and DBP values from at least 115/75 mm Hg upwards,[18] this relation is logarithmic, which means that at the lowest BP values the absolute increment of risk per mm Hg increase and the possible risk reduction per mm Hg decrease are small.[4] Even when the total cardiovascular risk is high because of the presence of other risk factors or diseases, it is unlikely that reducing the small risk component because of the small BP elevation can substantially modify the overall risk. Trial evidence on this issue is scanty and poor. Two large trials of patients with prediabetes (metabolic syndrome) and BP values mostly in the high BP range (partly because of concomitant antihypertensive treatment) had no reductions in cardiovascular mortality or morbidity when randomized to addition of

ramipril or valsartan in comparison with placebo.[19,20] In diabetes mellitus, only a very small low-powered trial was conducted in high normal blood pressure patients, with uncertain results,[21] and in other high risk patients (previous stroke, previous coronary disease), trial results have been controversial and inconclusive.[10]

The very recent results of the Heart Outcomes Prevention Evaluation (HOPE)-3 trial[9] also support that antihypertensive treatment in patients at intermediate risk without previous cardiovascular events and high normal blood pressure is not associated with a reduction of major cardiovascular events compared with placebo. Only in patients with a basal SBP higher than 143.5 mm Hg (mean 154 mm Hg) a benefit in reducing the primary outcomes was observed.

Therefore, at present, no evidence is available suggesting initiation of antihypertensive drug treatment in high normal blood pressure individuals. When other risk factors are present in these subjects, as often occurs, lifestyle measures or pharmacological treatment of these risk factors (such as cholesterol or blood glucose–lowering drugs) are likely to be more definitely beneficial.

Blood Pressure Treatment Targets

The Lower the Better Versus the J-Shaped Curve Hypothesis

Although the target values to which BP should be brought by drugs to optimize treatment benefits is a prominent interest of the patient and the treating physician, it is surprising that, among the large number of antihypertensive treatment trials, so few (only 14) have compared the effects of more versus less intense BP lowering, and even less have investigated precise SBP or DBP targets. As a consequence of these limitations, the evidence about BP targets is scanty and controversial. The very fact that there is still a wide debate between supporters of the lower the better concept and of the J-curve hypothesis is a good demonstration that evidence on the issue is lacking, thus leaving space to an endless debate. Indeed, both concepts are so far unsupported by trial evidence, and mostly based on observational, nonrandomized studies. The lower the better concept rests on the above-mentioned large meta-analysis of observational studies showing a continuing direct relationship between BP and outcomes down to 115 mm Hg SBP and 75 mm Hg DBP[18] and makes the unproven assumption that the same relationship holds true when blood pressure is decreased by treatment. The J-curve hypothesis was born and is kept alive by periodic post hoc analyses of trial results in which incident event rates are related to the SBP or DBP values achieved in various groups of patients independently of randomization. Some of these post hoc analyses show that outcome incidence may rise at the lowest achieved BP values, whereas other analyses do not show this rise. The limitations of these analyses have been discussed in detail in a recent review,[22] which concludes that, although a J-curve must definitely exist for BP (at 0 mm Hg BP all will be dead), whether the point of curve inflection is within the range of BP values achieved by treatment or not is presently unknown, and the dilemma of the lower the better versus the J-curve can only be solved by suitable randomized trials.

SBP Targets

Because only very few trials, mostly in small groups of patients and with small number of incident outcomes and hence with low statistical power, have specifically investigated the possible benefits of lowering SBP below given cutoffs, indirect evidence on optimal SBP goals of treatment has been sought for by analyzing the results of trials in which SBP in the actively or more actively treated group, and SBP in the placebo or less actively treated group were respectively below and above given cutoff values. In a recent meta-analysis of 32 BP-lowering trials (including 128 232 individuals), relative and absolute outcome reductions were significant for SBP differences (treated versus control) across 150 and 140 mm Hg cutoffs. When SBP values below were compared with SBP above the cutoff of 130 mm Hg, only stroke and all-cause death were significantly reduced.[6]

No evidence is available that hypertensive patients at high cardiovascular risk because of diabetes mellitus or previous cardiovascular events should have SBP brought to lower targets than patients at lower overall risk,[10] and indeed, the only trial that has directly explored the matter in diabetic patients, the Action to Control Cardiovascular Risk in Diabetes (ACCORD),[23] was unable to show a reduction of cardiovascular events in diabetic patients whose SBP was reduced to 119 mm Hg as compared with 133 mm Hg. In elderly hypertensive patients, evidence from trials is that incident cardiovascular events are significantly reduced when SBP is brought down to a range between 150 and 140 mm Hg,[10] but no evidence is available that values below 140 mm Hg are harmful. The Latin America consensus on hypertension in patients with type 2 diabetes mellitus and metabolic syndrome recommended a SBP target of less than 140 mm Hg as in nondiabetic hypertensive individuals.[24]

Concerning SBP values to be achieved in patients after stroke, a systematic review of the relationship between BP reduction and secondary stroke prevention and other vascular events[25] analyzed 7 randomized, controlled trials: the Dutch Transient Ischemic Attack (TIA) trial,[26] the Post-Stroke Antihypertensive Treatment Study (PATS),[27] the HOPE trial,[28] the Perindopril Protection against Recurrent Stroke Study (PROGRESS),[29] and 3 other smaller trials,[30–32] with a combined sample size of 15 527 participants. Treatment with antihypertensive drugs was associated with significant reductions in all recurrent strokes even in patients with normal BP (though often normalized by treatment). In a combined analysis of the Prevention Regimen for Effectively Avoiding Secondary Stroke (PROFESS)[33] and Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects with Cardiovascular Disease (TRANSCEND)[34] trials in patients with cardiovascular disease or diabetes mellitus with end-organ damage, the incidence of the composite of stroke, myocardial infarction, or vascular death was 12.8% for telmisartan versus 13.8% for placebo (hazard ratio, 0.91; 95% confidence interval, 0.85–0.98; P=0.013).[35] The overall reductions in stroke and all vascular events were related to the degree of BP lowering achieved in the range between 140 and 130 mm Hg, but in no one of these studies was the average achieved BP <130 mm Hg.

The Secondary Prevention of Small Subcortical Strokes (SPS3)[36] included 3020 patients with lacunar (small-vessel disease) strokes who were randomized in an open-label study to 2 different target levels of SBP control: <150 mm Hg versus <130 mm Hg. At 12 months, achieved average SBP was 138 mm Hg in the higher-target group versus 127 mm Hg in the lower-target group. The primary outcome of recurrent stroke tended to be lower in the lower-target group, but differences were not significant (hazard ratio, 0.81; 95% confidence interval, 0.64–1.03). In a very recent post hoc observational analysis of the SPS3 trial data[37] evaluating the association of mean achieved BP, 6 months after randomization, and recurrent stroke, the lowest risk occurred at a nadir between 120 and 128 mm Hg SBP and between 65 and 70 mm Hg DBP values.

In fact, the only trial specifically designed to explore this issue is the European Society of Hypertension—Chinese Hypertension League Stroke in Hypertension Optimal Treatment trial (SHOT),[38] a prospective, multinational, randomized trial with a 3×2 factorial design comparing 3 different SBP targets (<145–135 versus <135–125 versus <125 mm Hg), and 2 different low-density lipoprotein cholesterol targets (2.8–1.8 versus <1.8 mmol/L). The trial is ongoing and will be conducted on 7500 patients aged at least 65 years with hypertension and a stroke or transient ischemic attack 1 to 6 months before randomization. The primary outcome is time to stroke (fatal and nonfatal).

Recently, the Systolic Blood Pressure Intervention Trial (SPRINT) enrolled 9361 participants aged ≥50 years in ≈100 medical centers throughout the United States.[8] SPRINT excluded patients with diabetes mellitus mellitus and stroke survivors since previous clinical trials, such as ACCORD[23] and SPS3,[36] included those populations. Patients were randomly allocated into a standard treatment group to achieve a SBP target <140 mm Hg and into an intensive treatment group to achieve a SBP target <120 mm Hg. The study was stopped early because of a positive effect. The target SBP <120 mm Hg group had reduced rates of the composite primary outcome that included myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes by 25% and the risk of death from all causes by 27%, when compared with the target SBP of <140 mm Hg. The SPRINT results have raised obvious interest, but also a series of concerns. For example, it has been found surprising that, among cardiovascular outcomes, stroke and myocardial infarction were not significantly reduced by more intense BP lowering (in all trials stroke is the outcome most sensitive to the benefits of BP reduction), whereas the most important benefit observed in SPRINT was reduced heart failure risk, which may have resulted from a larger use of diuretics and renin-angiotensin system blockers in the group with lower BP.[39] Concern has also been raised by the fact that, in the more intensely treated group of SPRINT, the increased number of episodes of hypotension, syncope, and acute renal failure far exceeded the number of cardiovascular events prevented.[39] The point has been recently raised that the method of BP measurement in SPRINT was quite different from that used in all other trials: BP was apparently measured by an automatic device in absence of a doctor or nurse with the purpose of avoiding the alert or white-coat effect; accordingly, it has been argued that, if measured by the usual office technique, the SPRINT BP values would likely be higher than those reported,[40] although it is difficult to say how large the difference would be.

In any case, the results of SPRINT[8] and another recent trial[7] have been included in an updated meta-analysis of all 35 trials of BP lowering (138 452 individuals) that could be stratified according to the usual cutoffs of achieved SBP. Lowering SBP below 130 mm Hg was found to reduce relative risk of major cardiovascular outcomes, but the absolute cardiovascular risk reduction was definitely smaller,[41] and the risk of permanent treatment discontinuations for adverse events significantly greater[42] than in the trials in which SBP was lowered across the cutoff of 140 mm Hg.

DBP Target

Data on DBP target can also be derived by meta-analysis of trials in which achieved DBP were below and above the cutoff of 90 mm Hg (in actively treated versus placebo-treated patients) or below and above the cutoff of 80 mm Hg. Significant reductions of all major outcomes were found both below 90 mm Hg and below 80 mm Hg.[6,41] This supports the conclusion of the Latin American consensus on hypertension in patients with type 2 diabetes mellitus and metabolic syndrome,[24] which recommends a DBP target between 80 and 85 mm Hg on the basis of the results of the Hypertension Optimal Treatment (HOT)[43] and United Kingdom Prospective Diabetes Study (UKPDS)[44] trials.

In conclusion, the general evidence-based recommendation can be given to aim at SBP values below 140 mm Hg (between 140 and 130 mm Hg) and DBP values below 90 mm Hg in all hypertensive patients independently of their level of cardiovascular risk. Also, SBP values below 130 appear safe, but the benefits of a more intense reduction are smaller and must be balanced with the risk of excessive side effects. In our opinion, this recommendation can now be classified as Class I, Level A. Evidence for SBP targets in elderly hypertensives provided by trials is limited to benefits of BP lowering to a target somewhere between 150 and 140. Only Wei et al.[7] and SPRINT[8] show beneficial effects for values below 140 mm Hg, although BP values in SPRINT are not comparable to the previous trials because of technique of BP measurement used.

Total Cardiovascular Risk and Decision to Treat

A recent meta-analysis of 68 BP-lowering trials has stratified these trials according to increasing levels of total cardiovascular risk, measured as incidence of cardiovascular death in the control groups.[45] Relative reduction of all outcomes did not differ at the various levels of risk, but absolute reductions significantly increased with increasing cardiovascular risk. However, also residual risk significantly increased with increasing cardiovascular risk. This means that, while reserving antihypertensive treatment to high risk hypertensives maximizes the cost–benefit ratio, only treatment of low-to-moderate risk hypertensives may prevent the increasing number of treatment failures when treatment is initiated at higher risk. The very recent results of the HOPE-3 study[9] reinforces the fact

that treating subjects at low-to-intermediate risk in the high-to-normal BP range with antihypertensive drugs has no benefit in reducing morbidity and mortality. However, reducing not only BP but also cholesterol levels in subjects with grade 1 hypertension and low-to-intermediate risk have beneficial effects in reducing fatal and nonfatal cardiovascular events.[46]

Conclusions

The forthcoming new edition of the Latin American guidelines for the management of hypertension, now in advanced preparation, will be based on the evidence discussed in this article and will provide the recommendations on BP thresholds and targets for treatment given in this article.

Disclosures

None.

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