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Blood pressure targets for hypertension: What's the evidence?

Recent trials have confirmed that lowering blood pressure significantly reduces the risk of cardiovascular risk, but the evidence about the degree of BP lowering below 140/90 mm Hg needs to consider patients' associated conditions.

ABSTRACT: Epidemiological studies have demonstrated that lower blood pressure is associated with lower cardiovascular risk. Today family physicians can use a number of strategies to lower blood pressure to levels that have been shown in clinical trials to produce benefit. Blood pressure targets are the levels set as goals for the recommended antihypertensive therapy, which can involve pharmacological and nonpharmacological treatment. In general, the BP target is less than 140/90 mm Hg for all patients and 130/80 mm Hg or less for patients with certain conditions. Patients who have previously had a stroke benefit from lower targets. Patients with diabetes mellitus are also likely to benefit from lower targets. Despite current controversies, benefits are known to result from family physicians setting blood pressure targets for individual patients using a protocol-based approach and their clinical judgment.

There is a direct and continuous relationship between blood pressure (BP) and the development of cardiovascular disease. A meta-analysis of 1 million adults with no previous vascular disease from 61 prospective observational studies found that for persons in middle and old age, blood pressure is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg.[1] Nevertheless, there is concern that lowering blood pressure to excessively low levels can also lead to increased morbidity or mortality. Thus, clinicians must use the available evidence for clear and demonstrated morbidity and mortality benefit in lowering BP to a certain level. These BP levels are considered BP targets.

BP targets can differ from BP thresholds, which are the BP criteria used to decide when to initiate antihypertensive (pharmacological, nonpharmacological, or both) interventions. BP targets are the BP levels set as goals for recommended antihypertensive therapy. This includes the pharmacological and nonpharmacological approaches chosen, the number of antihypertensive drugs required, and any other strategies recommended to lower blood pressure.

Clinical practice guidelines such as the Canadian Hypertension Education Program (CHEP) recommendations have concluded that for adults with hypertension without specific conditions or indications for specific agents, the systolic blood pressure (SBP) treatment goal is a pressure level of less than 140 mm Hg. The diastolic blood pressure (DBP) treatment goal is a pressure level of less than 90 mm Hg.[2] Data from the Hypertension Optimal Treatment (HOT) trial, which involved randomly assigning 18 790 people to a DBP of 90 mm Hg or less, 85 mm Hg or less, and 80 mm Hg or less, indicate that the lowest incidence of major cardiovascular events occurred at a mean achieved DBP of 82.6 mm Hg and the lowest risk of cardiovascular mortality occurred at 86.5 mm Hg.[3] Data and guidance regarding how much lower than 140/90 mm Hg BP would need to be to provide a net patient benefit are not available, but implicit in the recommendation for a BP of less than 140/90 mm Hg is that once this is attained, there is no com-

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pelling need to reduce blood pressure much further.[4] The effectiveness of antihypertensive drugs is not dependent on starting blood pressure level, suggesting that high-risk individuals with mild blood pressure elevation benefit significantly from antihypertensive drug therapy[5]

"Excessive" blood pressure lowering

The possibility of a J-shaped relationship between BP achieved by treatment and cardiovascular events has been debated for decades. The relationship proposed is one where lowering BP reduces cardiovascular events until a certain low BP level is achieved, after which there is an increase in cardiovascular mortality. The popularity of this idea is based on at least two factors: first is the commonsense notion that a threshold BP must exist below which survival is impaired, and second is the physiological data showing that excessively low blood pressure can compromise organ blood flow.[6] Identifying the potentially harmful BP level and determining whether it can be attained with antihypertensive drugs or effectively combated by organ autoregulatory mechanisms has been difficult. Most antihypertensive drug trials have not been designed to test the benefits or harms of achieving prespecified target BP levels or have not been successful in doing so. Three major antihypertensive drug trials (HOT, PROGRESS, and UKPDS) concluded that a J-curve does not exist, while other trials (INDANA meta-analysis, IDNT, INVEST, and ONTARGET) suggest that it may exist.[6] It is generally recognized that the argument in favor of a J-shaped relationship comes from retrospective data analysis (in which the strength of randomization is lost) of trials where the numbers of subjects and events in the lowest SBP/DBP group were very small and subjects in the lowest BP groups differed markedly from those with higher BP and were often at increased baseline cardiovascular risk.[6] A powerful argument against a J-shaped relationship being produced by antihypertensive drugs is the finding that a J-shaped relationship was found for DBP in placebo-treated patients.[7] Furthermore, in a trial of lipid-lowering therapy in which blood pressure was unchanged, a J-shaped relationship was found between BP and cardiovascular events.[8] These data suggest that one can not assume a J-shaped relationship between antihypertensive drugs and cardiovascular risk. Further support is found in the Syst-Eur trial of patients mainly *without* cardiovascular disease, where lowering of DBP with active antihypertensive treatment to about 55 mm Hg did not increase cardiovascular mortality.[7]

Hypertension and diabetes mellitus

The combination of diabetes mellitus and hypertension places a patient at a significantly increased risk for the development of cardiovascular disease. The case for a lower blood pressure target for patients with this combination of conditions rests on data from the HOT study. In 1501 patients with diabetes mellitus, those randomly assigned to antihypertensive treatment with a diastolic blood pressure goal of less than 80 mm Hg had a 51% reduction in major cardiovascular events compared with those assigned to a diastolic blood pressure target of less than 90 mm Hg.[3] Primarily based on this trial, the BP target recommended by numerous bodies is to achieve a DBP less than 80 mm Hg and, based on weaker observational evidence, to attain a target SBP of less than 130 mm Hg. Recently, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial sought to clarify the optimal BP target by randomly assigning 4733 patients with type 2 diabetes to either an intensive BP-lowering group with a target SBP of less than 120 mm Hg, or a standard treatment group with a target SBP of less than 140 mm Hg.[9] This 2×2 factorial design trial also simultaneously examined the effect of intensive versus standard glucose control. Achieved SBPs were 119 mm Hg in the intensive treatment group and 133 mm Hg in the standard treatment group. After a mean follow-up of 4.7 years, the use of intensive BP lowering was not found to significantly reduce the annual rates of the primary outcome, nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes (1.87% vs 2.09%; HR 0.88; 95% CI 0.73–1.06).[9] Intensive treatment did, however, reduce stroke, a prespecified secondary endpoint (0.32% vs 0.53%; HR 0.59; 95% CI 0.39–0.89).[9] Intensive therapy also increased the risk of major adverse events, including symptomatic hypotension, bradycardia, arrhythmia, and hypokalemia.[9]

After considering the ACCORD trial results, the CHEP recommendations task force had several reservations that precluded changing the current recommendation.[2] First, there was concern that ACCORD may have been underpowered, as event rates were nearly 50% lower than expected. Second, their standard treatment subjects had systolic BPs close to 130 mm Hg, and ACCORD did not explicitly examine the currently accepted BP threshold of 130 mm Hg, meaning the trial data cannot directly contribute to determining whether current thresholds are most appropriate. Third, there was evidence of possible statistical interaction between the BP-lowering and glucose-lowering parts of the study. The presence of such interaction requires that the study be interpreted within the factorial subgroups,[10]

which was not done. A recent meta-analysis that included ACCORD data reported a significant reduction (31%) in stroke risk in subjects treated to lower BP levels, but no significant reduction in MI risk.[11]

Based on current evidence available, CHEP recommends that persons with diabetes mellitus be treated to attain systolic blood pressures of less than 130 mm Hg and diastolic blood pressures of less than 80 mm Hg. These BP targets are the same as the threshold BP to initiate treatment. Caution should be exercised, however, in patients more likely to have difficulty tolerating a substantial fall in blood pressure (e.g., elderly patients and patients with autonomic neuropathy).

Persons with diabetes mellitus should be treated to attain systolic blood pressures of less than 130 mm Hg and diastolic blood pressures of less than 80 mm Hg ... while ... blood pressure should be decreased to less than 140/90 mm Hg in persons with nondiabetic chronic kidney disease.

Nondiabetic chronic kidney disease

CHEP recommend that for patients with nondiabetic CKD, the target BP is less than 140/90 mm Hg rather than the previous more stringent target of less than 130/80 mm Hg.[2] The strength of the evidence in this patient group is not as strong as in other patient groups because it comes from smaller studies without the same number of subjects with hard endpoints. In addition, chronic kidney disease is heterogeneous and patients with different types of disease may respond differently to blood pressure reduction targets. In the Modification of Diet in Renal Disease (MDRD) study, 840 patients, who had a glomerular filtration rate (GFR) of 32 mL/min/1.73 m^2 were randomized to a lower (< 125/75 mm Hg for persons age 60 or younger) or higher BP target. There was no benefit found with intensive BP lowering overall. In a subgroup analysis of patients with proteinuria, intensive BP lowering was associated with slowing the progression of renal dysfunction.[12] However this was a *posthoc* analysis, which limits the strength of its conclusion. In the ESCAPE trial, intensified blood pressure control, with target 24-hour blood pressure levels in the low range of normal, was found to confer a substantial benefit on renal function among children with chronic kidney disease.[13] In adults with non-proteinuric renal disease, a BP target of less than 140/90 mm Hg but not less than 130/80 mm Hg is supported by other studies. In a meta-analysis of blood pressure targets in adults with CKD, three trials with a total of 2272 participants—African American Study of Kidney Disease (AASK),[14] MDRD, and Ramipril Efficacy in Nephropathy-2 (REIN-2)—showed that a BP target of less than 130/80 mm Hg is not more beneficial than a target of less than 140/90 mm Hg.[14,15] Thus, the data for benefit for less intensive BP lowering is strongest in patients with nondiabetic chronic kidney disease without proteinuria. A case can be made for considering lower blood pressures in patients with CKD and proteinuria.

Chronic coronary artery disease or previous stroke

Target blood pressures for patients with coronary artery disease (CAD) or previous stroke likely reflect current concepts of differences in the impact of autoregulation of coronary and cerebral blood flow. Studies such as Syt-Eu that did not find a J-shaped relationship in persons without cardiac disease were concerned about one for DBP less than 60 mm Hg in persons with CAD. The positions of CHEP and the American Heart Association are similar in that their guidelines say blood pressure should be less than 140/90 mm Hg.[16] CHEP has not suggested BP targets lower than 130/80 mm Hg. American guidelines, however, suggest a BP target below 130/80 mm Hg, while stating that "lowering to these levels must be done slowly, and caution is advised in inducing falls of DBP below 60 mm Hg." Diastolic blood pressure values below 60 mm Hg "should alert the clinician to assess carefully any untoward signs or symptoms, especially those due to myocardial ischemia."[6]

In contrast, for patients who have had a stroke, the data show more consistently that low blood pressures are better. Clinical results demonstrate improved survival with antihypertensive therapy and no evidence for in-

creased morbidity or mortality at lower blood pressures for patients who have had a stroke. For example, the PROGRESS trial of 6105 individuals randomly assigned to active treatment (n = 3051) or placebo (n = 3054) found combination drug therapy, which lowered BP the most, produced the greatest reduction in stroke risk.[17] Guidelines for BP targets in acute stroke, however, are still evolving.

Summary

An intensive management approach to achieving blood pressure control in hypertensive patients is effective and significantly reduces cardiovascular risk. While patients who have had a stroke benefit from BP levels lower than 130/80 mm Hg, the evidence is less conclusive for lower BP levels in patients with diabetes mellitus. Despite these uncertainties, family physicians can help patients by setting individual blood pressure targets using a protocol-based approach and their clinical judgment once BP is reduced to less than 140/90 mm HG.[18]

Competing interests

None declared.

References

1. Lewington S, Clarke R, Qizilbash N, et al.; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360(9349):1903-1913. Erratum in: Lancet 2003;361(9362):1060.
2. Daskalopoulou SS, Khan NA, Quinn RR, et al. The 2012 Canadian Hypertension Education Program recommendations for the management of hypertension: Blood pressure measurement, diagnosis, assessment of risk, and therapy. Can J Cardiol 2012;28:270-287.
3. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998;351(9118):1755-1762.
4. Arguedas JA, Perez MI, Wright JM. Treatment blood pressure targets for hypertension. Cochrane Database Syst Rev 2009;(3): CD004349.
5. Czernichow S, Zanchetti A, Turnbull F, et al.; Blood Pressure Lowering Treatment Trialists' Collaboration. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: Meta-analysis of randomized trials. J Hypertens 2011; 29:4-16.
6. Zanchetti A. Blood pressure targets of antihypertensive treatment: Up and down the J-shaped curve. Eur Heart J 2010;31:2837-2840.
7. Fagard RH, Staessen JA, Thijs L, et al. On-treatment diastolic blood pressure and prognosis in systolic hypertension. Arch Intern Med 2007;167:1884-1891.
8. Bangalore S, Messerli FH, Wun CC, et al. J-curve revisited: An analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. Eur Heart J 2010;31:2897-2908.
9. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575-1585.
10. McAlister FA, Straus SE, Sackett DL, et al. Analysis and reporting of factorial trials: A systematic review. JAMA 2003; 289:2545-2553.
11. Reboldi G, Gentile G, Angeli F, et al. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: A meta-analysis in 73,913 patients. J Hypertens 2011;29: 1253-1269.
12. Sarnak MJ, Greene T, Wang X, et al. The effect of a lower target blood pressure on the progression of kidney disease: Long-term follow-up of the modification of diet in renal disease study. Ann Intern Med 2005;142:342-351.
13. ESCAPE Trial Group, Wuhl E, Trivelli A, Picca S, et al. 2009. Strict blood-pressure control and progression of renal failure in children. N Engl J Med 2009;361:1639-1650.
14. Appel LJ, Wright JT Jr, Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med 2010;363:918-929.
15. Upadhyay A, Earley A, Haynes SM, et al. Systematic review: Blood pressure target in chronic kidney disease and proteinuria as an effect modifier. Ann Intern Med 2011;154:541-548.
16. Rosendorff C, Black HR, Cannon CP, et al. American Heart Association Council for High Blood Pressure Research; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Epidemiology and Prevention. Treatment of hypertension in the prevention and management of ischemic heart disease: A scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation 2007;115:2761-2788. Erratum in: Circulation 2007;116:e121.
17. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001; 358(9287):1033-1041. Errata in: Lancet 2001;358(9292):1556 and Lancet 2002; 359(9323):2120.
18. Godwin M, Birtwhistle R, Seguin R, et al. Effectiveness of a protocol-based strategy for achieving better blood pressure control in general practice. Fam Pract 2010;27:55-61. BCMJ