"Go Low" or "Say No" to Aggressive Systolic BP Goals?

The SPRINT trial demonstrated the benefits—and risks—of reaching a systolic target < 120 mm Hg in nondiabetic patients at high risk for cardiovascular events. Here's who might benefit.

Margaret Day, MD, MSPH, James J. Stevermer, MD, MSPH

PRACTICE CHANGER

Consider treating nondiabetic patients ages 50 and older to a systolic blood pressure (SBP) target < 120 mm Hg (as compared to < 140 mm Hg) when the benefits—lower rates of fatal and nonfatal cardiovascular (CV) events and death from any cause—are likely to outweigh the risks from possible additional medication.[1]

STRENGTH OF RECOMMENDATION

B: Based on a single, good-quality randomized controlled trial (RCT).[1]

A 55-year-old man with hypertension and stage 3 chronic kidney disease (CKD) presents for routine care. His blood pressure is 135/85 mm Hg, and he is currently taking lisinopril 40 mg/d. Should you increase his antihypertensive regimen?

Hypertension is common and leads to significant morbidity and mortality, but pharmacologic treatment reduces incidence of stroke by 35% to 40%, myocardial infarction (MI) by 15% to 25%, and heart failure by up to 64%.[2-4] Specific blood pressure targets for defined populations continue to be studied.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial found that more intensive BP targets did not reduce the rate of major CV events in patients with diabetes, but the study may have been underpowered.[5] The members of the Eighth Joint National Committee (JNC 8) recommended treating patients older than 60 to BP goals < 150/90 mm Hg.[6] This was based on evidence from six RCTs, but there remains debate—even among the JNC 8 committee members—as to appropriate BP goals in patients of any age without CV disease who have BP measurements of 140-159/90-99 mm Hg.[7-13]

STUDY SUMMARY

Treating to SBP < 120 mm Hg lowers mortality

The Systolic Blood Pressure Intervention Trial (SPRINT) was a multicenter RCT designed to determine if treating to lower SBP targets in nondiabetic patients at high risk for CV events improves outcomes, compared with standard care. Patients were at least 50, had an SBP of 130 to 180 mm Hg, and were at increased CV risk; the last was defined as clinical or subclinical CV disease other than stroke; CKD with a glomerular filtration rate (GFR) of 20 to 60 mL/min/1.73 m^2; 10-year risk for CV disease > 15% on Framingham risk score; or age 75 or older. Patients with diabetes, prior stroke, polycystic kidney disease, significant proteinuria or symptomatic heart failure within the past six months, or left ventricular ejection fraction < 35% were excluded.[1]

Patients (N = 9,361) were randomly assigned to an SBP target < 120 mm Hg in the intensive group or < 140 mm Hg in the standard treatment group, in an open-label design. Allocation was concealed. The study protocol encouraged, but did not require, the use of thiazide-type diuretics, loop diuretics (for those with advanced renal disease), ACE inhibitors or angiotensin receptor blockers, calcium channel blockers, and ß-blockers. Clinicians could add other agents as needed. All major classes of antihypertensives were used.

Medication dosing adjustments were based on the average of three BP measurements taken with an automated measurement system with the patient seated after 5 minutes of quiet rest. Target SBP in the standard therapy group was 135 to 139 mm Hg. Medication dosages were lowered if SBP

continued on page 50 >>

Margaret Day and **James J. Stevermer** are in the Department of Family and Community Medicine at the University of Missouri-Columbia.

>> *continued from page 31*

was < 130 mm Hg at a single visit or < 135 mm Hg at two consecutive visits.[1]

The primary composite outcome included the first occurrence of MI, acute coronary syndrome, stroke, heart failure, or death from CV causes. Secondary outcomes were the individual components of the primary composite outcome; death from any cause; and the composite of the primary outcome or death from any cause.[1]

Study halted early. The study was stopped early due to significantly lower rates of the primary outcome in the intensive therapy group versus the standard therapy group (1.65% vs 2.19% per year, respectively; hazard ratio [HR], 0.75 with intensive treatment). The resulting median follow-up time was 3.26 years.[1] This corresponds to a 25% lower relative risk for the primary outcome, with a decrease in event rates from 6.8% to 5.2% over the trial period. All-cause mortality was also lower in the intensive therapy group: 3.4% vs 4.5% (HR, 0.73).

The number needed to treat (NNT) over 3.26 years to prevent a primary outcome event, death from any cause, and death from CV causes was 61, 90, and 172, respectively. Serious adverse events occurred more frequently in the intensive therapy group than in the standard therapy group (38.3% vs 37.1%; HR, 1.04), with a number needed to harm (NNH) of 46 over the study period.[1]

Rates of serious adverse events that were identified as likely associated with the intervention were 4.7% vs 2.5%, respectively. Hypotension, syncope, electrolyte abnormalities, and acute kidney injury/acute renal failure reached statistical significance. The incidence of bradycardia and injurious falls, although higher in the intensive treatment group, did not reach statistical significance. In the subgroup of patients 75 or older, 48% in each study group experienced a serious adverse event.[1]

Throughout the study, mean SBP was 121.5 mm Hg in the intensive therapy group and 134.6 mm Hg in the standard treatment group. Patients in the intensive therapy group required, on average, one additional BP medication, compared to those in the standard treatment group (2.8 vs 1.8, respectively).[1]

WHAT'S NEW

Lower SBP produces mortality benefits in those younger, and older, than 75

This trial builds on a body of evidence that shows the advantages of lowering SBP to < 150 mm Hg[7,11,12] by demonstrating benefits, including reduced all-cause mortality, for lower SBP targets in nondiabetic patients at high risk for CV disease. The SPRINT trial also showed that the benefits of intensive therapy remained true in a subgroup of patients 75 or older.

The incidence of the primary outcome in the cohort 75 or older receiving intensive therapy was 7.7%, compared with 10.9% for those receiving standard therapy (HR, 0.67; NNT, 31). All-cause mortality was also lower in the intensive therapy group than in the standard therapy group among patients 75 or older: 5.5% vs 8.04% (HR, 0.68; NNT, 38).[1]

CAVEATS

Many do not benefit from—or are harmed by—increased medication

The absolute risk reduction for the primary outcome is 1.6%, meaning 98.4% of patients receiving more intensive treatment will not benefit. In a group of 1,000 patients, an estimated 16 patients will benefit, 22 patients will be seriously harmed, and 962 patients will experience neither benefit nor harm.[14] The difference between how BP was measured in this trial (an average of three readings after the patient had rested for 5 minutes) and what occurs typically in clinical practice could potentially lead to overtreatment in a "real world" setting.

Also, reducing antihypertensive therapies when the SBP was about 130 to 135 mm Hg in the standard therapy group likely exaggerated the difference in outcomes between the intensive and standard therapy groups; this is neither routine nor recommended in clinical practice.[6] Finally, the trial specifically studied nondiabetic patients at high risk for CV disease who were 50 or older, limiting generalizability to other populations.

CHALLENGES TO IMPLEMENTATION

Who will benefit/who can achieve intensive SBP goals?

Identifying patients most likely to benefit from more intensive BP targets remains challenging. The SPRINT trial showed a mortality benefit, but at a cost of increased morbidity.[1,14] Caution should be exercised particularly in the subgroup of patients 75 or older. Despite a lower NNT than the rest of the study population, this group experienced serious adverse events more frequently. Also, this particular cohort of volunteers may not be representative of those 75 or older in the general population.

Additionally, achieving inten-

sive SBP goals can be challenging. In the SPRINT trial, only half of the intensive target group achieved an SBP < 120 mm Hg.[1] And in a 2011-2012 National Health and Nutrition Examination Survey, only 52% of patients in the general population achieved a BP target < 140/90 mm Hg.[15] Lower morbidity and mortality should remain the ultimate goals in the management of hypertension, requiring clinicians to carefully assess an individual patient's likelihood of benefit versus harm. **CR**

REFERENCES

1. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med.* 2015;373:2103-2116.
2. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA.* 2003;289:2560-2572.
3. Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet.* 2000;356:1955-1964.
4. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta-analysis. *JAMA.* 1997;277:739-745.
5. Margolis KL, O'Connor PJ, Morgan TM, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. *Diabetes Care.* 2014;37:1721-1728.
6. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA.* 2014;311:507-520.
7. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med.* 2008;358:1887-1898.
8. Verdecchia P, Staessen JA, Angeli F, et al. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. *Lancet.* 2009;374:525-533.
9. JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertens Res.* 2008;31:2115-2127.
10. Ogihara T, Saruta T, Rakugi H, et al. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. *Hypertension.* 2010;56:196-202.
11. Staessen JA, Fagard R, Thijs L, et al; the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet.* 1997;350:757-764.
12. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA.* 1991;265:3255-3264.
13. Cundiff DK, Gueyffier F, Wright JM. Guidelines for managing high blood pressure. *JAMA.* 2014;312:294.
14. Ortiz E, James PA. Let's not SPRINT to judgment about new blood pressure goals. *Ann Intern Med.* 2016 Feb 23. [Epub ahead of print]
15. Nwankwo T, Yoon SS, Burt V, et al. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011-2012. *NCHS Data Brief.* 2013;1-8.

ACKNOWLEDGEMENT

The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center For Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.