NEJM GROUP

TOPIC COLLECTION: TREATING HYPERTENSION — LOWER IS BETTER, IRRESPECTIVE OF RISK STATUS

Letter from the NEJM Group Guest Editor

The questions of whom to treat for hypertension and how aggressively to treat have received considerable recent attention, with at least some partial answers. A recent analysis of the final results of the landmark SPRINT study published in the *New England Journal of Medicine* confirmed that treatment of patients at high risk for cardiovascular (CV) disease (but without prevalent diabetes or stroke) to a systolic blood pressure (BP) goal of 120 mm Hg leads to substantial benefits compared with treating to 140 mm Hg. After more than 3 years of follow-up, intensive treatment resulted in a 27% reduction in a composite measure of CV events and a 25% reduction in all-cause mortality. There was a slightly increased risk in the intensive-treatment group for some adverse events, including hypotension, syncope, electrolyte abnormalities, and renal damage, but no difference in overall adverse events.

These results were reinforced in a meta-analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration that combined the results of 48 randomized clinical trials totaling 344,000 patients. The studies included patients with and without CV disease and a substantial number with a baseline systolic BP <130 mm Hg. A 5 mm Hg reduction in systolic BP, irrespective of the baseline BP or underlying CV disease, led to a 10% relative risk reduction for composite CV events.

A different approach to answering this question, while not a treatment study, was taken by Malik and colleagues who used a genetic databank to assess a large population of patients for whom genetic variants led to a range of diastolic and systolic BPs. About 256,000 patients without CV disease or taking antihypertensive medications were followed for up to 12 years. A 10 mm Hg higher systolic BP was associated with a 49% increased risk for CV events, without any threshold below which there was no effect.

Much of the question about how to treat hypertension centers on the trade-off of the benefits of aggressive lowering with the risk of serious adverse events. One answer to this question is to promote nonpharmacologic approaches to treatment, such as reduced sodium intake, which would generally avoid most adverse events. To explore the potential benefit of reduced sodium intake, Filippini and colleagues conducted a meta-analysis of 85 studies of the correlation between sodium intake and blood pressure. Sodium intake ranged up to 7.6 g/day. A reduction of a little over 2 g/day in sodium intake was associated with mean reductions in systolic and diastolic BP of about 6 mm Hg and 2 mm Hg, respectively. The benefit of lower levels of sodium intake were greater for higher baseline levels of intake, but there was no floor beyond which there was no benefit.

Taken together, recent evidence suggests that blood pressure reduction, however achieved, has significant benefit in reducing CV events and mortality, irrespective of the baseline blood pressure or the risk status of the patient. This conclusion puts even greater emphasis on the importance of aggressively screening for hypertension, so as to capture the largest possible population-based benefits of diagnosis and treatment. The US Preventive Services Task Force recently reaffirmed

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its 2015 recommendation strongly endorsing the benefit of screening for hypertension using out-of-office determinations (either ambulatory or home blood pressure measurements) for diagnostic confirmation.

The high prevalence of undiagnosed and/or undertreated hypertension is a major public health problem that deserves much more attention.

Thomas L. Schwenk, MD

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ORIGINAL ARTICLE

Final Report of a Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

ABSTRACT

BACKGROUND

In a previously reported randomized trial of standard and intensive systolic blood-pressure control, data on some outcome events had yet to be adjudicated and post-trial follow-up data had not yet been collected.

METHODS

We randomly assigned 9361 participants who were at increased risk for cardiovascular disease but did not have diabetes or previous stroke to adhere to an intensive treatment target (systolic blood pressure, <120 mm Hg) or a standard treatment target (systolic blood pressure, <140 mm Hg). The primary outcome was a composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes. Additional primary outcome events occurring through the end of the intervention period (August 20, 2015) were adjudicated after data lock for the primary analysis. We also analyzed post-trial observational follow-up data through July 29, 2016.

RESULTS

At a median of 3.33 years of follow-up, the rate of the primary outcome and all-cause mortality during the trial were significantly lower in the intensive-treatment group than in the standard-treatment group (rate of the primary outcome, 1.77% per year vs. 2.40% per year; hazard ratio, 0.73; 95% confidence interval [CI], 0.63 to 0.86; all-cause mortality, 1.06% per year vs. 1.41% per year; hazard ratio, 0.75; 95% CI, 0.61 to 0.92). Serious adverse events of hypotension, electrolyte abnormalities, acute kidney injury or failure, and syncope were significantly more frequent in the intensive-treatment group. When trial and post-trial follow-up data were combined (3.88 years in total), similar patterns were found for treatment benefit and adverse events; however, rates of heart failure no longer differed between the groups.

CONCLUSIONS

Among patients who were at increased cardiovascular risk, targeting a systolic blood pressure of less than 120 mm Hg resulted in lower rates of major adverse cardiovascular events and lower all-cause mortality than targeting a systolic blood pressure of less than 140 mm Hg, both during receipt of the randomly assigned therapy and after the trial. Rates of some adverse events were higher in the intensive-treatment group. (Funded by the National Institutes of Health; SPRINT ClinicalTrials.gov number, NCT01206062.)

The members of the writing committee (Cora E. Lewis, M.D., M.S.P.H., Lawrence J. Fine, M.D., Dr.P.H., Srinivasan Beddhu, M.D., Alfred K. Cheung, M.D., William C. Cushman, M.D., Jeffrey A. Cutler, M.D., M.P.H., Gregory W. Evans, M.A., Karen C. Johnson, M.D., M.P.H., Dalane W. Kitzman, M.D., Suzanne Oparil, M.D., Mahboob Rahman, M.D., David M. Reboussin, Ph.D., Michael V. Rocco, M.D., M.S.C.E., Kaycee M. Sink, M.D., M.A.S., Joni K. Snyder, B.S.N., M.A., Paul K. Whelton, M.B., M.D., Jeff D. Williamson, M.D., M.H.S., Jackson T. Wright, Jr., M.D., Ph.D., and Walter T. Ambrosius, Ph.D.) assume responsibility for the overall content and integrity of this article.

The affiliations of the members of the writing committee are listed in the Appendix. Address reprint requests to Dr. Lewis at the Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, RPHB 210C, 1720 2nd Ave. S., Birmingham, AL 35294-0022, or at celewis@ubmc.edu.

*A complete list of the members of the SPRINT Research Group is provided in the Supplementary Appendix, available at NEJM.org.

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Should Blood Pressure Be Lowered in All Patients at High Risk for Adverse Cardiac Events?

A meta-analysis shows that a fixed decrease in BP provided the same relative risk reduction, regardless of baseline BP.

Patient selection and treatment targets for blood pressure (BP) reduction remain controversial, particularly among patients with high-normal BP and without previous cardiovascular (CV) disease. Researchers combined patient-level data from 48 large randomized, controlled trials (344,000 total patients) in which BP-lowering medications were compared with placebo or with one another, or in which more-intensive versus less-intensive treatment regimens were evaluated. Trials that were done exclusively in patients with heart failure were excluded. Twenty percent of patients with previous CV disease and 8% of patients without previous CV disease had baseline systolic BP <130 mm Hg.

After a median 4 years of follow-up, reduction of systolic BP by 5 mm Hg was associated with a 10% relative reduction in risk for major adverse CV events (i.e., fatal or nonfatal stroke, fatal or nonfatal ischemic heart disease, or hospitalization or death due to heart failure), regardless of baseline BP or previous diagnosis of CV disease.

COMMENT

This huge patient-level meta-analysis suggests that a fixed BP reduction is equally effective for primary and secondary prevention of CV disease, even at baseline BP levels currently considered to be too low to merit treatment. The authors call for revision of clinical guidelines to eliminate arbitrary BP levels and history of CV disease as criteria for treatment and, instead, to view BP reduction as a tool for risk reduction in all patients with high absolute risk for CV disease. ***— Bruce Soloway, MD***

Dr. Soloway is Associate Professor of Family Medicine and Attending Family Physician, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx.

Blood Pressure Lowering Treatment Trialists' Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: An individual participant-level data meta-analysis. **Lancet** *2021 May 1; 397:1625. (https://doi.org/10.1016/S0140-6736(21)00590-0)*

Blood Pressure and Cardiovascular Risk: Another Way to Assess the Connection

Lower blood pressure is indeed better, according to an analysis of the effects of genetic variants.

Blood pressure (BP) targets continue to generate lots of discussion and even confusion. For further insights, investigators made use of UK Biobank data to conduct mendelian randomization analyses examining whether BP has a nonlinear effect on cardiovascular risk. These types of studies leverage randomly allocated genetic variants, in this case variants associated with BP levels, to determine differences in risk.

The 255,714 participants did not have baseline cardiovascular disease (CVD) and were not taking antihypertensive medications. Over a maximum of 12 years, they experienced 10,606 incident CVD events (8430 coronary artery disease events and 2176 stroke events). The genetically proxied systolic and diastolic BPs were strongly associated with CVD events. For an increase of 10 mm Hg in systolic BP, the hazard ratio was 1.49. For an increase of 5 mm Hg in diastolic BP, the HR was 1.35. There was no evidence of nonlinearity in the relationship, including a J-shaped relationship between BP level and risk. Subgroup analyses by sex yielded findings consistent with the main results.

COMMENT

This study adds important weight to the idea that lower BP is better — and that people with variants linked to lower BP benefit from the life-long advantages of low BP provided by the variants. The benefit of drug therapy that lowers levels beyond those shown as helpful in treatment trials is not yet known. However, sensible nonpharmacological interventions would seem to merit use for primary prevention. ***— Harlan M. Krumholz, MD, SM***

Dr. Krumholz is the Harold H. Hines, Jr., Professor of Medicine in the Section of Cardiovascular Medicine at the Yale University School of Medicine, New Haven, Connecticut.

Malik R et al. Relationship between blood pressure and incident cardiovascular disease: Linear and nonlinear mendelian randomization analyses. **Hypertension** *2021 Apr 5; [e-pub]. (https://doi.org/10.1161/HYPERTENSIONAHA.120.16534)*

Dose–Response Relationship of Salt and Blood Pressure in Experimental Studies

A linear relationship was identified between sodium intake and systolic and diastolic BPs in both hypertensive and normotensive populations.

Many studies have established that dietary sodium intake affects blood pressure (BP). To examine a remaining question about their dose–response relationship, investigators conducted a meta-analysis of 85 trials that assessed dietary sodium intake and BP; most studies enrolled people with hypertension.

Sodium intake ranged from 0.4 to 7.6 g/day, and follow-up lasted from 4 weeks to 36 months. Overall, a linear relationship was identified between sodium intake and systolic and diastolic BPs. For every 100 mmol/day reduction in urinary sodium excretion (87 mmol/day corresponds to 2 g/day), mean systolic BP decreased by 5.56 mm Hg and mean diastolic BP decreased by 2.33 mm Hg. The curve did not flatten at the bottom or top of the range. The presence of hypertension did not affect the results. The effects on BP from high sodium intake were stronger among participants who had a higher baseline level of sodium intake. The gradient was steeper in shorter-term studies, especially for systolic BP.

COMMENT

This study is a robust compilation and analysis of experimental studies examining the effect of sodium intake on BP, and the study's principal contribution is its illumination of the largely linear relationship. The implications for patients are that lower is better for BP control and that those with high levels of consumption can gain a lot from dietary interventions.

— Harlan M. Krumholz, MD, SM

Dr. Krumholz is the Harold H. Hines, Jr., Professor of Medicine in the Section of Cardiovascular Medicine at the Yale University School of Medicine, New Haven, Connecticut.

Filippini T et al. Blood pressure effects of sodium reduction: Dose–response meta-analysis of experimental studies. **Circulation** *2021 Apr 20; 143:1542. (https://doi.org/10.1161/CIRCULATIONAHA.120.050371)*

Hypertension Screening in Adults Yields Substantial Net Benefit

The U.S. Preventive Services Task Force reaffirms its 2015 recommendation, including blood pressure monitoring outside of the clinical setting.

Sponsoring Organization: U.S. Preventive Services Task Force (USPSTF)

Background

The USPSTF has updated its 2015 recommendation for screening for hypertension in adults (*NEJM JW Gen Med* Nov 15 2015 and *Ann Intern Med* 2015; 163:778).

Key Points

- The USPSTF concluded, with a high level of certainty, that screening for hypertension in adults without known hypertension has substantial net benefit. However, diagnostic confirmation requires blood pressure (BP) determinations outside the clinical setting (A Recommendation).
- The USPSTF did not find clear evidence to support specific screening intervals but suggests every 3 to 5 years for young adults (age, 18–39) with normal BP and without additional risk factors, and annually for older adults (age, ≥40). The Task Force identified no major harms from screening.

COMMENT

The two approaches for out-of-office BP determinations, ambulatory BP monitoring and home BP measurements, have different barriers to their use: Access to and patient acceptance of ambulatory monitoring, and training and insurance reimbursement issues for home monitoring. Some clinicians (and the USPSTF) consider ambulatory monitoring to be the gold standard, but home monitoring is equally accurate, so either approach is acceptable.

Out-of-office BP measurements cover the problem of "white-coat" hypertension. "Masked" hypertension (hypertension detected by out-of-office determinations when screening measurements are normal) is not addressed by these screening protocols, but the clinical effect of diagnosing or treating masked hypertension is unclear. Finally, the benefits of detecting hypertension by any method, in any setting, only accrue with appropriate treatment and follow-up. ***— Thomas L. Schwenk, MD***

Dr. Schwenk is Dean and Professor of Family and Community Medicine, University of Nevada, Reno School of Medicine; and Vice President of Health Sciences, University of Nevada, Reno.

US Preventive Services Task Force. Screening for hypertension in adults: US Preventive Services Task Force reaffirmation recommendation statement. **JAMA** *2021 Apr 27; 325:1650. (https://doi.org/10.1001/jama.2021.4987)*

Guirguis-Blake JM et al. Screening for hypertension in adults: Updated evidence report and systematic review for the US Preventive Services Task Force. **JAMA** *2021 Apr 27; 325:1657. (https://doi.org/10.1001/jama.2020.21669)*