6th Risk, Diagnosis and Treatment of Cardiovascular Disease in Women

Hypertension Treatment ACCORDing to SPRINT

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Hypertension (HTN) is recognized worldwide as the leading risk factor for death and disability in adults. It kills more people globally than does tobacco use (9 vs 6 million).[1] Approximately 1 billion adults worldwide have high blood pressure (BP), and this number is expected to increase to 1.56 billion by 2025.[2] The World Health Organization has reported a global HTN prevalence of 40%, which is compounded by genetic factors, lifestyle choices, salt-rich diets, and physical inactivity.[3] According to the National Health and Nutrition Examination Survey, one third of adults >20 years old in the United States have HTN.[4] Self-reported rates of HTN are similar (Fig. 1). In the U.S. population, 64.9% of adults older than age 60 years develop HTN, and only half have well-controlled BP.[5] By age 50 years, isolated systolic HTN is the prevalent form of HTN,[6] and systolic BP (SBP) is the main risk predictor for stroke, adverse coronary events, heart failure, and end-stage renal disease (ESRD).[7] The control and treatment of HTN is associated with a reduced risk of cardiovascular (CV) disease, including stroke (by 35%–40%), myocardial infarction (MI) (by 15%–25%), and heart failure (by up to 50%).[8,9]

Although results of observational studies have suggested an increasing CV risk associated with SBP >110 mmHg,[10] the guidelines for the treatment of HTN provided in The Seventh Report of the Joint National Committee in 2008 and The Eighth Report of the Joint National Committee in 2014 were based on randomized trials in which specific drug regimens (thiazide-based diuretics, calcium channel blockers, and β-receptor blockers) and not specific BP-treatment targets were evaluated.[11] The guidelines were formulated on the basis of strong clinical trial evidence to support the treatment of HTN in patients older than 60 years to a BP goal <150/90 mmHg; and in those of age 30 to 59 years, to a diastolic goal of <90 mmHg. Evidence was insufficient to make stricter or broader treatment recommendations.

The ACCORD BP Experience

Diabetic patients have the greatest risk of CV death, and the results of previous large HTN trials (Hypertension Optimal Treatment [HOT], and the UK Prospective Diabetes Study) suggested that more intensive control of SBP decreased the occurrence of cardiac events in diabetic patients.[12,13] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial (ACCORD BP) investigated the benefit of maintaining tighter control of SBP on CV events with specific SBP targets in 4,733 higher-CV-risk type II diabetic patients who had mild-to-moderate HTN (SBP, 130–180 mmHg, and were taking ≤3 medications).[14] To enrich the risk pool, diabetic patients who had a hemoglobin A_1C level >7.5% were included. Patients were included if they were 40 to 55 years of age and had clinical evidence of CV disease, or if they were >55 years of age and had subclinical evidence of substantial atherosclerosis (for example, left ventricular hypertrophy, albuminuria, or >2 risk factors for CV disease). Patients who had significant renal insufficiency (serum creatinine, >1.5 mg/dL) and those >80 years of age were excluded.

Patients were randomized but not blinded to one of 2 treatment strategies: intensive therapy with an SBP target of <120 mmHg, or standard therapy with an SBP target of <140 mmHg. The primary composite outcome was nonfatal MI, nonfatal stroke, and death from CV causes. The protocol enabled the use of various drugs and drug combinations to achieve the desired BP goal in accordance with randomized assignment. A 2-drug therapy was initiated for the intensive-therapy group: a thiazide-type

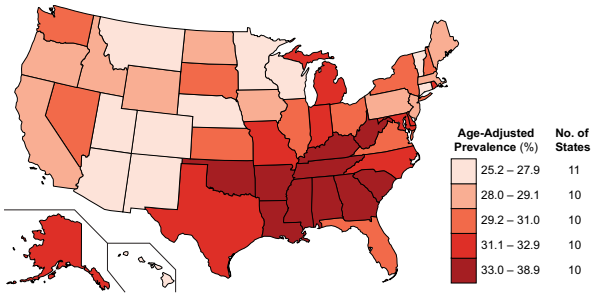

Fig. 1 *Centers for Disease Control and Prevention (CDC). Prevalence of Hypertension, 2011: U.S. adults ages 20 and older (percentage).*

From: Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System

diuretic plus an angiotensin-converting enzyme inhibitor, an angiotensin II receptor blocker, or a β-blocker. Other drugs could be added or titrated at each visit to achieve the specific BP goal.

Despite marked early and sustained differences in the mean SBP between the intensive- and standard-therapy groups, after a mean follow-up period of 4.7 years, intensive therapy to an SBP <120 mmHg versus standard therapy to <140 mmHg did not reduce the rate of fatal or nonfatal major CV events in diabetic patients. The secondary outcome of nonfatal and fatal stroke was lower in the intensive-therapy group than in the standard-therapy group. However, adverse events, including syncope, hypotension, and hypokalemia, occurred more often in the intensive-therapy group. The same number of participants in both groups developed ESRD; however, the intensive-therapy group had a lower mean glomerular filtration rate at the end of the study.

The SPRINT Experience

The Systolic Blood Pressure Intervention Trial (SPRINT) was a randomized trial designed to compare intensive versus standard BP therapy in 9,361 nondiabetic patients who had HTN (SBP, 130–180 mmHg) and who were at risk of developing heart or kidney disease. The treatment-regimen algorithms used in SPRINT were similar to those in the ACCORD BP trial. In SPRINT, nondiabetic patients who were >50 years of age and at elevated cardiac risk were randomly assigned to receive either intensive therapy (SBP target, <120 mmHg) or standard therapy (SBP target, <140 mmHg). The participants' mean BP at baseline was 139.7/78.2 mmHg, with 90% of the patients receiving baseline HTN therapy. Patients who had ESRD or a history of stroke were excluded. The composite primary endpoint included heart failure, acute coronary syndromes without MI, CV-related death, nonfatal stroke, and nonfatal MI. The 2 treatment strategies resulted in a rapid and persistent reduction in SBP, which met the specific goals of each strategy (Fig. 2).[15] The SBP was reduced by 18 mmHg in the intensive-therapy group and by 5 mmHg in the standard-therapy group. Intensive therapy required, on average, 3 antihypertensive medications, compared with 2 in the standard-therapy group. After a median follow-up period of 3.26 years, the relative risk of a major CV event was 25% lower for the participants in the intensive-therapy group. In addition, intensive therapy reduced the occurrence of other important outcomes, including heart failure (a 38% lower relative risk), death from CV causes (a 43% lower relative risk), and all-cause death (a 27% lower relative risk). In the intensive-therapy group, the number needed to treat to prevent a major event or death was 61; in the standard-therapy group, it was 90. Reduction in heart failure necessitating hospitalization was the primary driver of the composite endpoint (P=0.002). There was no significant effect on rates for MI (P=0.19), non-MI acute coronary syndrome (P=0.99), or stroke (P=0.5).[16]

The overall occurrence of severe adverse events was not significantly different between groups. However, severe adverse events associated with hypotension, syncope, and electrolyte abnormalities, and acute kidney injury or renal failure, were more prevalent in the intensive-therapy group.

The CV and survival benefits of lowering SBP to a goal of 120 mmHg observed in SPRINT illustrates the importance of treating nondiabetic and even elderly at-risk patients who have mild and moderate HTN.

Making Sense of ACCORD after SPRINT

Although SPRINT had an older population than did the ACCORD trial (median age, 68 vs 63 yr), it excluded patients who had diabetes mellitus and a history of stroke.

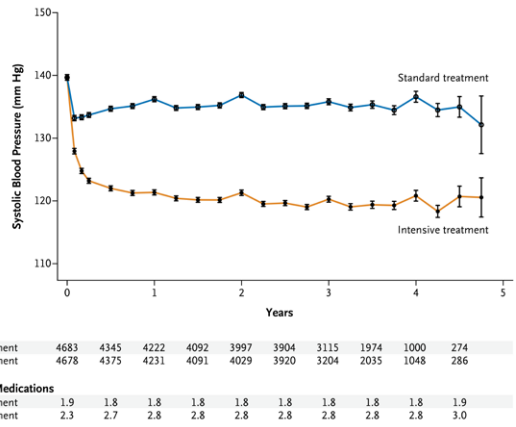

Fig. 2 *Graph shows comparison of systolic blood pressure measurements between the SPRINT treatment groups.*

From: Sprint Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373(22):2103-16.[15] Copyright © 2015 Massachusetts Medical Society. Reprinted with permission.

The 2 trials had similar HTN-treatment algorithms and treatment goals. In both studies, patients with difficult-to-control or severe HTN were excluded (Fig. 3).[17]

As shown in the editorial that accompanied the SPRINT results,[18] the effects on individual outcomes in the SPRINT and ACCORD trials were generally consistent. Two important differences between the trials might contribute to the apparent disparity in the results. The primary composite event in SPRINT included heart failure, which significantly affected the composite outcome in this elderly cohort (28% of SPRINT participants were >79 yr of age) that had more patients at risk of heart failure (for example, those who had chronic renal insufficiency). The statistical power of the ACCORD trial was lower than that of SPRINT. The sample size for the ACCORD trial was roughly half of that for SPRINT (4,733 vs 9,361). The projected placebo event rate in the ACCORD trial was double the actual event rate (4% vs 2.09%), which reduced the power to detect a treatment effect <27%. The ACCORD trial had a complicated factorial trial design with treatment comparisons of standard and intensive glycemia and lipid targets, which might also have diluted the risk pool. In SPRINT, which had a larger sample size than the ACCORD trial and, thus, greater power to discern a treatment effect, the combined endpoint was reduced by 25%; and deaths, by 27%. In the ACCORD trial, a similar composite CV outcome was lowered nonsignificantly by 12%, with a wide 95% confidence interval.

The SPRINT results indicate that treating even mildly elevated SBP in nondiabetic patients, including the elderly, reduces the risk of heart failure, CV-related death, and all-cause death. The conferred benefit was clearly shown for an SBP-treatment goal of <120 mmHg and was unrelated to the HTN-treatment regimen. In diabetic patients, the SBP treatment goal remains <140 mmHg, although stroke risk was diminished when SBP was lowered to 120 mmHg.

Clearly, there is a need for standardization of SBP measurements in the clinic before beginning treatment, in order to avoid overtreatment. SPRINT raises our awareness of the need for accurate SBP measurements during the patient's office visit. The in-office "snapshot" SBP measurement should be obtained after 5 minutes of rest, with 3 measurements made at least one minute apart.[19] Although out-of-office BP readings are prognostically superior to in-office readings,[16] carefully performed in-office BP readings still dictate treatment. Careful monitoring of SBP in and out of the office should ensure that most patients attain the current minimum treatment goal.

Total costs for HTN treatment in the U.S. were estimated to be $73.4 billion in 2009. Despite these costs, only 50% of patients undergoing pharmaceutical treatment for HTN attained BP control. The chief reasons for inadequate BP control are lack of adherence to the therapy because of its complexity (for example, missing doses of an antihypertensive medication), the cost of

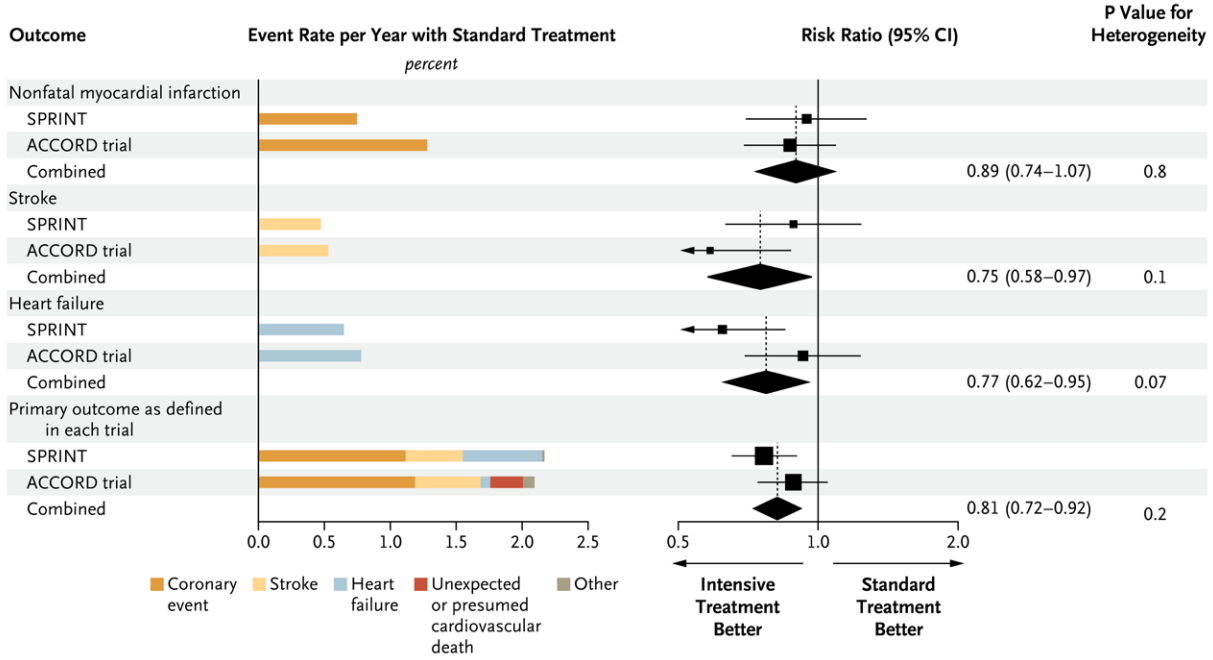

Fig. 3 *Graph shows individual and combined outcomes of the SPRINT and ACCORD trials.*

From: Perkovic V, Rodgers A. Redefining blood-pressure targets--Sprint starts the marathon. N Engl J Med 2015;373(22):2175-8.[17]

treatment regimens, and lack of persistence (unilateral discontinuation of an antihypertensive medication). One third of hypertensive patients need a single medication for BP control, one third need 2 medications, and the remaining third need 3 or more medications.[20] Multiple medications increase costs; however, for every 10% increase in the number of people whose SBP is controlled, 14,000 deaths in the U.S. might be prevented.[1,21]

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