EDITORIAL

EDWARD J. FILIPPONE, MD, FACP*
Clinical Associate Professor of Medicine,
Sydney Kimmel Medical College
at Thomas Jefferson University,
Philadelphia, PA

ANDREW J. FOY, MD
Assistant Professor of Medicine
and Public Health Sciences, Penn State
Milton S. Hershey Medical Center,
Hershey, PA

Blood pressure management in the wake of SPRINT

HIGH BLOOD PRESSURE is a major cause of morbidity and death worldwide.[1] Observational data from the general population show a log-linear relationship between both systolic and diastolic blood pressure and the rate of cardiovascular death.[2] Placebo-controlled trials have shown a clear-cut benefit in treating moderate to severe hypertension based on diastolic pressure in initial trials, and systolic pressure subsequently.[3] What remains uncertain is the optimal target for a particular patient, and whether other factors such as number of medications, starting blood pressure, and other comorbidities should influence this target.

See related article, page 187

We are unable to reconcile the difference in outcome between ACCORD and SPRINT

Publication of the Systolic Blood Pressure Intervention Trial (SPRINT) furthered the debate regarding the optimal blood pressure target in hypertension treatment.[4] SPRINT randomized 9,361 nondiabetic persons with systolic pressure higher than 130 mm Hg and increased cardiovascular risk but without prior stroke to intensive therapy (goal systolic pressure < 120 mm Hg) or standard therapy as control (goal systolic pressure < 140 mm Hg) and showed a significant reduction in the composite end point and all-cause mortality—at the expense of an increase in serious adverse events.

EARLIER TRIALS WERE GENERALLY NEGATIVE

Before SPRINT, approximately 20 randomized controlled trials attempted to define whether a more intensive target was better than standard control. These included the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial restricted to patients with diabetes[5] and the Secondary Prevention of Small Subcortical Strokes (SPS3) trial restricted to patients with lacunar infarcts.[6] These two groups of patients were specifically excluded from SPRINT.[6] Many of the other trials had primary renal end points, although several had primary cardiovascular end points.

As we reviewed previously in this *Journal*, individually these trials were generally inconclusive.[7] When analyzed by meta-analysis, a significant benefit was found for cardiovascular events, stroke, and end-stage renal disease, with a marginal benefit for myocardial infarction.[8] The validity of such analysis may be questioned due to heterogeneous populations, lack of individual patient data, different blood pressure targets and medication regimens, and different primary end points.

Together, ACCORD in patients with diabetes, SPS3 in patients with stroke, and SPRINT in patients at increased cardiovascular risk but without diabetes or stroke cover most hypertensive patients with more than low cardiovascular risk. All three trials were government-funded, and ACCORD and SPRINT used the same blood pressure targets and treatment algorithm. It remains speculative why ACCORD was essentially negative and SPRINT was positive.

CAUTION IN GENERALIZING THE RESULTS

In this issue of the *Journal*, Thomas and colleagues[9] review the SPRINT results in detail and attempt to reconcile the disparity with ACCORD.

Dr. Filippone has disclosed teaching and speaking for Mallinckrodt Pharmaceuticals.

doi:10.3949/ccjm.83a.16015

We agree with their interpretation that risks and benefits of a more intensive blood pressure target (ie, < 120 mm Hg systolic) need to be addressed in the individual patient and do not apply across the board to all hypertensive patients. This more intensive target would be appropriate for patients fulfilling criteria for entry into SPRINT, ie, no diabetes or prior stroke. They must be able to tolerate more intensive therapy and should not be frail or at risk for falls. Furthermore, the increased hypertension medication burden required for stricter control will increase side effects and complexity of overall medication regimens, and will possibly foster noncompliance.

In our opinion, one must be careful in generalizing the results of SPRINT to more than the type of patient enrolled. At best, one can say that a lower target is acceptable in a patient over age 50 at increased cardiovascular risk but without diabetes or stroke.

SPRINT may not even be representative of all such patients, however. Patients requiring more than four medications were excluded from the trial, as were patients with systolic pressure higher than 180 mm Hg, or with pressure higher than 170 mm Hg requiring two medications, or with pressure higher than 160 mm Hg requiring three medications, or with pressure higher than 150 mm Hg requiring four medications. Hence, SPRINT has not determined the appropriate approach to the patient with a systolic pressure between 150 and 180 mm Hg already on multiple medications above these cutoffs. It is not hard to envision the potential for adverse events and drug interactions using four or more antihypertensive medications to achieve a lower target, in addition to other classes of medications that many patients need.

The average systolic pressure on entry into SPRINT was 139 mm Hg, and patients were taking an average of 1.8 medications. In fact, one-third of patients had systolic pressures between 130 and 132 mm Hg, a range where most physicians would probably not want to intensify therapy. By protocol, such patients in the standard treatment group in SPRINT would actually have had their baseline antihypertensive therapy reduced if the systolic pressure fell below 130 mm Hg on one occasion or below 135 mm Hg on two consecutive visits. Reduction of therapy would seem to bias the trial against the standard treatment. An identical algorithm was used in ACCORD.

We are unable to reconcile the differences in outcome between ACCORD and SPRINT, although they were congruent in one important aspect: significantly higher rates of serious adverse events with more intensive therapy. ACCORD had fewer patients, but they were at higher risk since all had diabetes, and more had previous cardiovascular events (34% vs 17% in SPRINT). This is reflected in higher event rates:

- Myocardial infarction occurred in 1.13% per year in the intensive therapy group, and 1.28% per year with standard therapy in ACCORD, compared with 0.65% and 0.78% per year, respectively, in SPRINT.
- Cardiovascular death occurred in 0.52% per year with intensive therapy and 0.49% per year with standard therapy in ACCORD, compared with 0.25% and 0.43% per year, respectively, in SPRINT. Event rates for stroke were similar.

Overall, 445 primary end points occurred in ACCORD compared with 562 with SPRINT. After subtracting heart failure from the SPRINT data (not included in the primary end point of ACCORD), 400 events occurred, actually less than in ACCORD. The early termination of SPRINT may be partly to blame. In our opinion ACCORD and SPRINT were equally powered. While cardiovascular event risk reductions in ACCORD trended in the same direction as those in SPRINT, the total mortality rate trended in the opposite direction. Perhaps the play of chance is the best explanation.

SPRINT should be interpreted in the context of prior trials and its inclusion and exclusion criteria

ONE TARGET DOES NOT FIT ALL

SPRINT clearly added much needed data, but results should be interpreted in the context of previous trials as well as of the specific inclusion and exclusion criteria. One target does not fit all, and systolic pressure of less than 120 mm Hg should not automatically be the target for all hypertensive patients.

Should patients with diabetes be targeted to systolic pressure of less than 140 mm Hg based on the ACCORD results, and patients with stroke to systolic pressure of less than 130 mm Hg based on the SPS3 results? We are un-

sure. More data are clearly required, especially in patients already on multiple antihypertensive medications with unacceptable blood pressure.

As pointed out by Thomas and colleagues, lower systolic pressure may be better in select patients, but only as long as adverse events can be avoided or managed.

REFERENCES

1. **Lim SS, Vos T, Flaxman AD, et al**. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380:2224–2260.
2. **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; 360:1903–1913.
3. **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.
4. **SPRINT Research Group; 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.
5. **ACCORD Study Group; 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.
6. **SPS3 Study Group; Benavente OR, Coffey CS, Conwit R, et al**. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. Lancet 2013; 382:507–515.
7. **Filippone EJ, Foy A, Newman E**. Goal-directed antihypertensive therapy: lower may not always be better. Cleve Clin J Med 2011; 78:123–133.
8. **Lv J, Neal B, Ehteshami P, et al**. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: a systematic review and meta-analysis. PLoS Med 2012; 9:e1001293.
9. **Thomas G, Nally JV, Pohl MA**. Interpreting SPRINT: how low should you go? Cleve Clin J Med 2016; 83:187–195.

***ADDRESS**: Andrew J. Foy, MD, Penn State Hershey Heart and Vascular Institute, 500 University Drive, Hershey, PA 17033; e-mail: afoy@hmc.psu.edu*