doi:10.1093/eurheartj/ehab400

Weekly Journal Scan

A SPRINT towards tighter control of blood pressure in hypertension

Massimo Volpe [1]* and Carlo Patrono[2]

[1]Cardiology Department, Sapienza University of Rome, Sant'Andrea Hospital, Via di Grottarossa 1035-1039, 00189 Rome, Italy; and [2]Department of Pharmacology, Catholic University School of Medicine, Via di Grottarossa 1035-1039, 00189, Rome, Italy

Comment on 'Final Report of a Trial of Intensive versus Standard Blood-Pressure Control' which was published in the *New England Journal of Medicine*, doi: 10.1056/NEJMoa1901281.

Key Points

- In the final report of the Systolic Blood Pressure Intervention Trial (SPRINT),[1] the authors analysed additional primary outcome events occurring through the end of the intervention period after data lock for the primary analysis (20 August 2015) and post-trial observational follow-up data through July 29, 2016.
- The study enrolled 9361 adults aged ≥50 years with a systolic blood pressure (SBP) between 130 and 180 mmHg at increased risk for cardiovascular disease (CVD) but without a history of diabetes or stroke, who were randomly assigned to an intensive (SBP <120 mmHg) or a standard treatment target (SBP <140 mmHg). The primary outcome was a composite of myocardial infarction (MI), acute coronary syndrome not resulting in MI, stroke, acute decompensated heart failure (HF), or CV death.
- At a median 3.3-year follow-up, the rate of the primary outcome was significantly lower in the intensive-treatment than in the standard-treatment group [1.77% vs. 2.40% per year; hazard ratio (HR), 0.73; 95% confidence interval (CI), 0.63–0.86; $P < 0.001$], with consistent results after the exclusion of non-fatal HF (HR, 0.75; 95% CI, 0.63–0.89; $P = 0.001$). All-cause mortality was 25% lower in the intensive-treatment group (HR, 0.75; 95% CI, 0.61–0.92; $P = 0.006$). When intervention and post-intervention results were combined, the primary outcome and death rates remained significantly lower in the intensive treatment than in the standard treatment group (HR 0.76; 95% CI, 0.65–0.88; $P < 0.001$ and 0.79; 95% CI, 0.66–0.94; $P = 0.009$, respectively). However, rates of HF no longer differed between the groups and showed a higher incidence in the intensive-treatment group during the post-intervention period (HR, 1.63; 95% CI, 1.02–2.57; $P = 0.001$ for interaction).
- In the intervention and post-intervention periods, overall rates of serious adverse events did not differ significantly between the groups, though hypotension, electrolyte abnormalities, and acute kidney injury or renal failure occurred more often in the intensive-treatment group. In fact, a ≥30% reduction in estimated glomerular filtration ratio occurred in a higher percentage of intensively treated patients without chronic kidney disease (CKD), though the incidence of albuminuria was significantly reduced in this group compared to those receiving standard treatment.

Comment

The SPRINT trial[2] was promoted and supported by the US National Institutes of Health to answer the question whether a tighter BP control would be beneficial for hypertensive patients at high CV risk. Its positive results have represented a supporting pillar of the 'the lower the better' concept in the contemporary treatment of hypertension, together with other studies and meta-analyses.[3–5] Accordingly, the most recent European[6] and US[7] Guidelines have recommended a tighter BP control, aiming at BP targets of <130/80 and <120/80 mmHg, respectively, in most hypertensive patients aged ≤65 years.

Consistent with the first publication,[2] the final report[1] confirms and reinforces the significant benefits of an intensive BP-lowering strategy. However, some important questions raised by the original SPRINT report[2] remain unanswered. First, due to specific methodological criticisms linked to the unattended BP measurement technique used by SPRINT participants, it is still unclear whether and how much BP goals achieved in the SPRINT trial[2] are comparable with those reported in other trials which were based on conventional office BP measurements.[8] Moreover, the characteristics of the enrolled patients are representative of approximately 20-30% of the total hypertensive population, making further studies desirable to confirm the SPRINT[2] results also in patients with diabetes, previous stroke or higher

*Corresponding author. Tel: +390633775979, Email: massimo.volpe@uniroma1.it

estimated CV risk.[8] Finally, the BP goals achieved in the intensive arm of SPRINT[2] (mean SBP 121.4 mmHg) are hard to reach and maintain in clinical practice. In fact, after participants and their physicians were left free to change or continue BP medications during the post-intervention period, at the close-out visit the mean SBP was 6.9 and 2.6 mmHg higher in the intensive and standard treatment groups, respectively, compared to the last intervention-period visit.[1]

Another intriguing issue is represented by the results obtained with respect to the outcome of acute decompensated HF. Although the incidence of this specific end-point was significantly lower in the intensive treatment than in the standard treatment group during the intervention period, the event rate of HF was indeed higher in the intensive treatment group during the post-intervention period. This is difficult to explain, although the authors suggest that the increase in SBP levels and the decreased use of low-dose thiazide-like diuretics, angiotensin converting enzyme inhibitors and hydralazine in the intensive-treatment group may have played a role.[1] However, in the current report, the benefits of intensive treatment remained highly significant combining data from the intervention and post-intervention periods, both when HF events were included or excluded from the analysis.[1]

The results obtained in the post-intervention period of the current study support a 'legacy effect', consisting in the long-term persistence of the benefits deriving from previous effective BP-lowering treatment after conclusion of the randomized trial.[9]

With regard to the safety profile of the intensive treatment strategy, most of the adverse events were mild and were followed by nearly complete resolution within 1 year. However, worsening renal function was reported in a high proportion of intensively treated patients without CKD.

Although further studies conducted with conventional BP measurements and in a more representative population would be important to define the beneficial role of intensive BP reductions, there is no question that the current SPRINT data further support 'the lower the better' concept in the pharmacological management of high blood pressure.

Conflict of interest: M.V. reports personal fees for speaker bureau and/or consulting in Advisory Board from Amgen, Astra Zeneca, Daiichi-Sankyo, Menarini Int, MSD, Novartis Pharma, and Novo Nordisk outside the submitted work. C.P. reports personal fees from Acticor Biotech, personal fees from Amgen, personal fees from Bayer, personal fees from GlaxoSmithKline, personal fees from Tremeau, personal fees from Zambon, grants from AIFA (Italian Drug Agency), grants from European Commission, and other from Scientific Advisory Board of the International Aspirin Foundation, outside the submitted work.

References

1. Lewis CE, Fine LJ, Beddhu S, Cheung AK, Cushman WC, Cutler JA, Evans GW, Johnson KC, Kitzman DW, Oparil S, Rahman M, Reboussin DM, Rocco MV, Sink KM, Snyder JK, Whelton PK, Williamson JD, Wright JT, Jr, Ambrosius WT; SPRINT Research Group. Final report of a trial of intensive versus standard blood-pressure control. *N Engl J Med* 2021;**384**:1921–1930.
2. Wright JT, Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC, Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–2116.
3. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;**387**:957–967.
4. 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;**397**:1625–1636.
5. Volpe M, Patrono C. The key role of blood pressure lowering in cardiovascular prevention irrespective of baseline blood pressure and risk profile. *Eur Heart J* 2021.
6. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**:3021–3104.
7. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr, Collins KD, Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Sr, Williamson JD, Wright JT. Jr, 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;**71**:e13–e115.
8. Ruiz-Hurtado G, Banegas JR, Sarafidis PA, Volpe M, Williams B, Ruilope LM. Has the SPRINT trial introduced a new blood-pressure goal in hypertension? *Nat Rev Cardiol* 2017;**14**:560–566.
9. Gallo G, Battistoni A, Coluccia R, Tocci G, Volpe M. Legacy effect in the treatment of hypertension: persistent cardiovascular protection after conclusion of randomized clinical trials in hypertension. *Curr Hypertens Rep* 2019;**21**:85.