Viewpoints

How Low Should We Go With Blood Pressure?
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Traditional blood pressure (BP) measurement has made its time. We should familiarize ourselves with automated unattended BP measurements. This method will virtually eliminate the BP rise associated with the presence of doctors or even nurses. Using such a protocol in patients who meet the SPRINT (Systolic Blood Pressure Intervention Trial) inclusion/exclusion criteria, a blood pressure target of $\leq 120$ mmHg will lead to an important reduction in the risk of stroke and heart attack.

The SPRINT (Systolic Blood Pressure Intervention Trial), ClinicalTrials.gov number, NCT01206062, funded by the National Institutes of Health, is a landmark trial that, for the reasons outlined below, is expected to change our clinical approach to the management of hypertensive patient. The authors of this article believe that SPRINT significantly contributed to the progress of cardiovascular medicine although some implications of the study need to be assessed judiciously. To substantiate our opinion that BP goals should be reassessed lower after SPRINT, we will try to briefly summarize what SPRINT shows, what it confirms, and what it adds to existing knowledge.

What Does SPRINT Show?
The SPRINT trial randomized 9361 treated or untreated hypertensive patients with systolic BP of 130 to 180 mmHg at entry and high cardiovascular risk to a systolic BP goal of $<140$ mmHg (standard treatment group) or $<120$ mmHg (intensive treatment group). High cardiovascular risk was defined by either a previous evidence of overt cardiovascular disease except stroke, a Framingham score suggesting a 10-year risk of cardiovascular disease $>15\%$, subclinical cardiovascular disease defined by left ventricular hypertrophy or abnormal ankle brachial index or coronary artery calcium score, glomerular filtration rate 20 to 59 mL/min per 1.73 m$^2$, or age $\geq 75$ years.

The main exclusion criteria were diabetes mellitus, previous stroke, 1-minute standing systolic BP of $<110$ mmHg, heart failure (HF), polycystic kidney disease, age $<50$ years. Doctors involved in SPRINT were not blinded to randomization group, but all events were finally adjudicated by a committee who was unaware of the assigned BP target. SPRINT was stopped early (on September 11, 2016), by the Director of National Institutes of Health, because of an excess of benefit in the intensive treatment group. Such benefit consisted in a 25% reduction in the primary outcome ($P<0.001$), a 27% reduction in all-cause death ($P=0.003$), a 57% reduction in cardiovascular death ($P=0.005$), and a 33% reduction in HF ($P=0.002$). Although the intensive intervention was generally

A totally novel feature of SPRINT was related to the technique of BP measurement. BP was measured using the Omron HEM-907XL device. The machine was programmed to wait for 5 minutes after activation and then automatically take 3 measurements at 1-minute intervals, with calculation of the mean. Remarkably, such BP measurements were all unattended because the patient was let alone during the 5 minutes before measurements and during the subsequent 3 minutes while BP was measured. Such procedure inevitably removed, at least in part, the alerting reaction associated with the traditional attended BP measurement. Orthodox authorities in hypertension noted that the above procedure differs from that used in previous megatrials, thereby making SPRINT results not well comparable with those of previous studies. However, we must acknowledge that procedures for BP measurements in previous megatrials were not identical across the studies, and often not so much detailed and reproducible as in SPRINT. Having been involved in some of previous megatrials, we found different protocols for BP measurement, with doctors or nurses variably involved in the attended BP measurement and variable waiting periods before and during measurements. There is evidence that the presence of doctors and even nurses in the measurement office can variably increase BP. SPRINT has the great merit of precisely standardizing the BP measurement setting, thus removing part of expected BP variability because of anxiety of patients and other factors.

In SPRINT, antihypertensive treatment was left at choice of field investigators. It included drugs that provided the strongest evidence for reduction of cardiovascular disease. The use of long-acting drugs such as chlorthalidone and amlopidine was strongly encouraged. Several previous megatrials used hydrochlorothiazide, which is less potent and has a shorter duration of action than chlorthalidone and might be less effective than chlorthalidone to reduce cardiovascular risk.

The primary end point in SPRINT was a composite of nonfatal myocardial infarction (MI), other acute coronary syndromes, nonfatal stroke, cardiovascular death, hospitalization for HF. Doctors and nurses involved in SPRINT were not blinded to randomization group, but all events were finally adjudicated by a committee who was unaware of the assigned BP target.

Throughout 3.3 years of follow-up, the mean systolic BP was 134.6 mmHg in the standard treatment group and 121.5 mmHg in the intensive treatment group, a 13.1 mmHg systolic BP difference. Therefore, $>50\%$ of patients did not achieve the BP target in the intensive treatment group.

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well tolerated, without any statistical excess in orthostatic hypotension with dizziness, injurious falls or bradycardia, the incidence of acute renal failure (4.1 versus 2.5%), electrolyte abnormalities (3.1% versus 2.3%), and hypotension (2.4% versus 1.4%) was higher in the intensive treatment group. On balance, the benefits of intensive BP reduction outweighed the harms. Unfortunately, 111 were lost to follow-up in the intensive treatment group and 134 in the standard treatment group.

What Does SPRINT Confirm?
Several investigators have found, in metaregression analyses, an association between the degree of systolic BP reduction and the risk of a composite pool of cardiovascular events, variably defined across the trials. The greater the BP reduction, the greater the benefit. SPRINT confirms that a persistently lower systolic BP by 13 mmHg is associated with a 25% less risk of primary cardiovascular outcome. In a metaregression analysis, we tried to improve precision of the estimate of total cardiovascular risk by considering only trials that clearly predefined and reported a triple (nonfatal MI, nonfatal stroke, cardiovascular death) or quadruple (nonfatal MI, nonfatal stroke, cardiovascular death, and HF) end point. SPRINT used a quadruple end point with further inclusion of non-MI coronary syndromes. In the context of such limitation, the observed relative risk in SPRINT (0.75; 95% confidence interval, 0.63–0.89) did not differ significantly from that predicted by our metaregression equation (0.70; 95% confidence interval, 0.62–0.77; P value for the difference=0.418). Thus, the observed risk reduction is well in line with the evidence accrued in many previous outcome trials, and SPRINT confirms a strict relationship between the magnitude of BP reduction and cardiovascular benefit.

What Does SPRINT Add?
SPRINT should be put in the context of available trials that compared different BP goals, not different antihypertensive drugs. We recently completed a trial sequential analysis of 18 of such trials, SPRINT included, that randomized a more intensive and a less intensive BP-lowering strategy on the risk of major cardiovascular events and death. Stroke, MI, HF, cardiovascular death, and all-cause death were the outcome measures. Seven of these studies targeted a systolic BP level of <130 mmHg and 7 a diastolic BP target of <80 mmHg, in the more intensive treatment arm. Achieved BP was 7.6/4.5 mmHg lower with the more intensive than with the less intensive BP-lowering strategy. In the analysis of stroke and myocardial infarction, the cumulative Z-curve (Figure) crossed the efficacy monitoring boundary after the SPRINT study. Thus, only after the addition of SPRINT, we obtained firm cumulative evidence that a more intensive BP-lowering strategy is superior to a less intensive strategy for reducing the risk of stroke and MI. For cardiovascular death and HF, the cumulative Z-curve crossed the conventional significance boundary, but not the sequential monitoring boundary, after SPRINT. Although neither MI nor stroke were significantly reduced in the intensive arm than in the standard arm of SPRINT, this study allowed to accrue supportive evidence to the conclusion that a more intensive BP-lowering strategy is superior to a less intensive strategy for prevention of stroke and MI. Cardiovascular death and HF are also likely to be reduced by a more intensive BP-lowering strategy, as shown in SPRINT, but cumulative trial evidence is not yet conclusive.

In conclusion, it is out of question that SPRINT will modify our approach to the management of hypertensive patients for several reasons. The well-standardized technique of BP measurement used in this study should become a standard in our clinical practice, with the aim of improving the reproducibility of office BP measurements, thereby limiting the white-coat effect as much as possible. Using this SPRINT-like technique of BP measurement, the patients with inclusion/exclusion criteria as in the SPRINT study should be treated more intensively than currently recommended, with the aim to lower their systolic BP to a target of ≤120 mmHg. This position has been recently endorsed by the Canadian Hypertension Education Program. Caution should be used in applying SPRINT results to traditional BP measurements, as well as

Figure. Cumulative trial sequential analysis of the effect of more intensive vs less intensive blood pressure reduction on the risk of stroke and myocardial infarction. Reproduced with permission from Verdecchia et al11 with permission of the publisher. Copyright ©2016, American Heart Association, Inc. CI indicates confidence interval; OR, odds ratio; and SPRINT, Systolic Blood Pressure Intervention Trial.
to patients with contraindications to a more aggressive BP-lowering strategy, most notably a standing systolic BP of <110 mm Hg, unwilling or inability of patients to adhere to multiple medications, and the inability to measure BP accurately. In particular, renal deterioration and orthostatic hypotension should be checked with great accuracy during treatment.

At the end of year 2016, the stage seems set for lower BP targets to further reduce the risk of stroke and heart attacks, but cum judicio.

Disclosures
None.

References

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