

## Look before you SPRINT: look at the data and look at the consequences

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### Introduction

The recently proposed revision of the Eighth Joint National Committee (JNC-8) guideline on hypertension supported by the American Heart Association (AHA), and the American College of Cardiology (ACC) [1], recommends a target systolic blood pressure (SBP) of 130 mm Hg or lower for all hypertensive individuals. This requires a disruptive practice change, by lowering the threshold SBP for initiation of antihypertensive therapy by 10 to 20 mm Hg. The recommendations of the guideline were heavily influenced by the results of the SPRINT trial [2], which compared a standard treatment group with a target SBP <140 mm Hg with an intensive treatment group with a target SBP of <120 mm Hg, in patients at high cardiovascular risk. An SBP target of <120 mm Hg resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, but in significantly higher rates of some adverse, when compared with an SBP target of <140 mm Hg.

There are, however, several characteristics of the SPRINT trial that limit its external and internal validity. First, in SPRINT blood pressure measurements were performed using automated office equipment and made three times unobserved. This is critically important because SBP when measured this way may be 5 to 10 mm Hg lower than when measured with a manual instrument, or when patients are being observed or talking, or in a room that is not quiet [3]. Second, the strict inclusion and exclusion criteria mean that older persons with common diseases such as stroke and diabetes, and geriatric syndromes such as dementia and malnutrition were not included. Third, the trial was stopped prematurely because of clear evidence of benefit, and there is empirical evidence that trials stopped early for benefit tend to overestimate the magnitude of the treatment effect [4].

In line with this, the American Association of Family Physicians (AAFP) has recently declined to endorse the revised guideline [5]. Even though the American College of Physicians (ACP) / AAFP blood pressure guideline has itself been criticised for lacking author expertise [6], this

cannot be taken too seriously, as primary care physicians are probably best equipped and positioned as generalists to make an overall clinical judgment on the management of hypertension in older adults and to practice the “first, do no harm” principle.

So far, the debate has almost exclusively focused on limitations in external validity of the SPRINT trial, whereas its internal validity has not been criticised [7, 8]. Here, we question SPRINT’s internal validity at three relevant points.

### Protocol violation of baseline systolic blood pressure criterion in about a third of subjects included in the SPRINT trial

About a third of the subjects in SPRINT did not have a SBP  $\geq 130$  mm Hg at time of randomisation, but had a lower SBP at baseline (<125 mmHg), although this was an exclusion criterion. The lowest tertile of the 9361 randomised patients had a baseline SBP  $\leq 132$  mmHg [2]. This means that a third of the patients in a trial looking at treatment of older subjects with SBP between 130 and 180 mm Hg had a SBP distributed within a 3 mm Hg range: between 130 and 132 mm Hg. This directly proves serious selection bias towards the lower limit of the SBP inclusion criterion (i.e., 130 mm Hg). This should have been recorded as a protocol violation, as the protocol clearly states that at randomisation all inclusion and exclusion criteria should be fulfilled. Probably, the SBP below the cut-off of 130 mm Hg in the intensive and standard treatment groups was caused by the first part of regression to the mean, from screening to the baseline blood pressure measurement at randomisation. The very purpose of the randomisation visit after screening was to confirm the absence of a regression to the mean in the blood pressure. In reality, such regression was present, and thus we do not have evidence for valid SBP criteria that defined start of treatment.

### Can stopping antihypertensive drugs in hypertensive patients inform a guideline to initiate antihypertensive drug treatment?

The so called standard treatment group in SPRINT did not reflect standard clinical practice in a large group of par-

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ticipants. More than a third of participants in this group had a baseline SBP of <132 mm Hg. Therefore, in order to achieve “a target goal of less than 140 mm Hg”, antihypertensive drugs had to be stopped or reduced. This intervention is completely different from initiating antihypertensive drugs in treatment-naïve hypertensive individuals. It comes as no surprise that the lowest SBP tertile in the standard treatment group experienced an increase in SBP to reach a target blood pressure <140 mm Hg. This increase was caused by a per protocol step-down procedure, consisting of a dose reduction or reduction in number of antihypertensive drugs. This step-down procedure was started directly at the randomisation visit in many of these patients on standard treatment. As was recently shown in a systematic review, withdrawal of hypertensive agents frequently leads to adverse effects such as changes in biochemistry, heart rate, pulse rate and kidney function and rebound hypertension in a larger proportion of patients [9]. Moreover, in patients with elevated cardiovascular risk, as in SPRINT, this might also lead to a serious increase in primary outcomes through a rebound effect in the standard treatment group. This increase in risks by reduction of antihypertensive therapy and lessening of beneficial lifestyle adherence may have distorted the beneficial effect, which in SPRINT is completely attributed to the beneficial effect of intensive blood pressure control.

Interestingly, hazard ratios (HRs) for the comparison of intensive with standard treatment for SPRINT’s primary outcome (a composite outcome of myocardial infarction, other coronary syndromes, stroke, heart failure or death from cardiovascular causes) were lower in the lowest tertile of baseline SBP (HR 0.7; 95% confidence interval [CI] 0.51–0.95) than in the middle (HR 0.77; 95% CI 0.57–1.03) and the highest tertile (HR 0.83; 95% CI 0.63–1.09) of baseline blood pressure. This is in contradiction to the fact that lowering blood pressure provided highest relative protection at the higher baseline SBP levels in a recent meta-analysis including 74 trials with more than 300,000 individuals [10]. Assuming balanced baseline cardiovascular risk in all tertiles of baseline SBP, larger differences in risk reduction between intensive and standard treatment groups in individuals with lower baseline SBP may reflect an increase in adverse effects due to a surge in SBP in the standard treatment rather than a beneficial effect of more aggressive treatment in the intensive treatment group.

### Was the observed effectiveness in SPRINT caused by intensified antihypertensive drugs alone or by a more complex multifactorial antihypertensive treatment?

Last but not least, the SPRINT trial was an open-label study in older subjects in whom SBP reduction is usually hard to achieve when they have age-related high blood pressure, mediated by atherosclerosis and increased peripheral vascular resistance. The lifestyle changes in SPRINT were coordinated by a Lifestyle and Background Therapy Working Group, which actively spread materials supporting medical nutrition therapy, weight management, physical activity, smoking cessation and antithrombotic therapy. However, SPRINT publications so far have not reported the within- or the between-group changes in ad-

herence to a more healthy lifestyle, though they were part of SPRINT in both arms. A SBP <120 mm Hg within 3 months after start, as was realized on average in the lowest tertile, probably an important boost to continue a healthier lifestyle. In the standard treatment the message of “your SBP is too low” or “your SBP is falling quickly”, leading per protocol to a step-down of drug treatment, is also likely to affect the lifestyle behaviour of the subjects in the standard treatment group, but now in the opposite direction of liberalisation (e.g. increased salt intake). Though the net trial effects are the combination of a very complex combined open-label intervention of antihypertensive drugs and lifestyle, they are now completely attributed to the drugs. This does not comply with the trial design and analysis required for complex interventions [11].

### Conclusion

The SPRINT trial’s serious problems in internal and external validity require great caution in implementing the new US blood pressure guideline. Therefore, we propose to at least temporarily make a step backwards to the safer, more evidence-based, and more attainable general JNC-8 treatment goals, which advise initiation of treatment when the blood pressure is 150/90 mm Hg or higher in adults 60 years or older, or 140/90 mm Hg or higher in adults younger than 60 years. The new European Society of Cardiology / European Society of Hypertension blood pressure guideline is expected to be published in June 2018. Hopefully, it will be more thoughtful and patient-oriented than the ACC/AHA guideline.

### Disclosure statement

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