SPRINT Blood Pressure
Sprinting Back to Smirk's Basal Blood Pressure?

Gianfranco Parati, Juan Eugenio Ochoa, Grzegorz Bilo, Alberto Zanchetti

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Epidemiological data indicating that the linear relationship between blood pressure (BP) and cardiovascular outcomes continues even below the traditional thresholds defining hypertension have led to the hypothesis that in high-risk patients, in whom small relative risk reductions translate into large absolute benefits, achieving BP values below lower thresholds might be clinically useful. The results of the few intervention studies specifically designed to provide an answer to the long debated question on how low BP should be attained in patients at high cardiovascular risk were not sufficiently consistent to support any solid recommendation in this regard, however.2–6

With the recent publication of the SPRINT (Systolic Blood Pressure Intervention Trial), it seemed that strong evidence in favor of lowering systolic BP <120 mm Hg in selected high-risk patients was finally provided.7 Briefly, 9361 high-risk participants without diabetes mellitus or stroke history and with a clinic systolic BP (SBP) of ≥130 mm Hg were randomly allocated to a standard treatment group with a SBP target <140 mm Hg or to an intense treatment group with a SBP target <120 mm Hg. Significantly lower rates of cardiovascular events (by 25%) and all-cause mortality (by 27%) were observed in the intense treatment group than in the standard treatment one.7

However, SPRINT results have raised several controversies on the applicability of its findings to hypertensive patients seen in a daily practice clinic,8 also because of many debated methodological aspects. In particular, a serious methodological issue is related to how BP was measured, because in SPRINT clinic BP was measured 3 times automatically with a validated oscillometric device after the patient had been left alone for 5 minutes in the examination room.9–11 This approach, called by Kjeldsen et al11 unobserved automated BP, is substantially identical to the automated office BP (AOBP) measurement proposed by Canadian researchers12 and widely implemented in Canada, with the principal aim of minimizing the alarm (white coat) reaction induced by the presence of medical staff during clinic measurements.13 Compared with previous studies on AOBP, where measurements were almost invariably performed with the BpTRU device (BpTRU Medical Devices, Ltd, Coquitlam, British Columbia, Canada), in SPRINT, a different device was used (HEM-907 XL; Omron Healthcare), and the number of measurements was lower (three versus five). However, good agreement between these 2 devices had been shown,14 and, therefore, clinic BP in SPRINT can be reasonably labeled as AOBP. An important feature of AOBP in this setting is that it provides significantly lower BP values compared with the conventional observed clinic BP taken by a physician. Therefore, if clinic BP were measured conventionally, mean SBP achieved in the intense and in the standard BP-lowering arm of SPRINT (121.5 and, respectively, 134.6 mm Hg) would likely have been higher. In other words, the intense BP lowering might have not been so intense as it appears at first glance. Thus, paradoxically, the effort of SPRINT researchers to obtain high-quality clinic BP measurements in the end made their results more vulnerable to criticism.11

In this context, the results of the SPRINT ambulatory blood pressure ancillary study, reported by Drawz et al,15 seem to be of particular interest, considering the well-documented diagnostic and prognostic value of ambulatory blood pressure (ABP).16 ABP monitoring was conducted in 897 SPRINT participants with clinical characteristics similar to those in the core trial. The primary outcome variable was nighttime SBP, considered the single ABP variable most closely related with outcomes.16 Other ABP-derived variables (daytime SBP, 24-hour SBP, night–day SBP ratio, and 24-hour BP variability) and clinic BP (AOBP) were also assessed. These variables were compared between the 2 study arms after 27 months of study, a comparison that unfortunately was not done at baseline. Overall, in the intense treatment group, automated clinic, nighttime, daytime, and 24-hour SBP values were all significantly lower than those in the standard treatment group, and a parallel reduction in BP variability was observed, with no differences in the night–day BP ratio. Additionally, only a limited agreement between ABP and automated clinic BP was observed.15

These results were largely expected, as it is well known that the reduction in clinic BP by treatment is accompanied by a parallel although smaller reduction in ABP.17,18 What is of crucial importance among the data shown by Drawz et al,15 in spite of some limitations, is the report of absolute systolic and
diastolic ABP values achieved during treatment in the 2 arms of the SPRINT. Indeed, ABP is the only BP measurement in SPRINT that was also obtained with comparable methodology in other intervention trials and observational studies that measured both ABP and conventional clinic BP at least in a subset of participants. A critical comparison of the ABP values achieved by treatment in SPRINT with the ABP and clinic BP values achieved in these other trials may thus allow an estimation of the clinic BP values that should have been measured in SPRINT if this trial had used the conventional clinic BP measurements of the other trials. This comparison may help understanding whether the target BP values recommended by SPRINT investigators on the basis of their trial can be extrapolated to medical practices that, worldwide, use conventional BP measurements in most cases.

The Table summarizes clinic BP and ABP values attained in several BP-lowering trials in which a subset of participants had their on-treatment BP measured both conventionally and by ambulatory monitoring. In these previous studies, average clinic SBP and diastolic blood pressure measured by a physician (or nurse) was higher than average daytime ABP, the 2 sets of values tending to become progressively closer at lower clinic BP levels. Indeed, several authors, and particularly our group, have described the relationship between ABP and clinic BP across the range of clinic BP values recorded in different types of studies. A common finding in population studies in which BP was measured by ABP and by the conventional clinic technique (PAMELA [Pressioni Arteriose Monitorate E Loro Associazioni]28), in a cohort of children and adolescents with different BP levels, and in trials of antihypertensive

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Age</th>
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<th>Clinic DBP</th>
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<th>Clinic BP Measurement Method</th>
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<td>120</td>
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<td>84</td>
<td>5/1</td>
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All BP values in mm Hg. ABP indicates ambulatory blood pressure; AOBP, automated office blood pressure; A/P, amlodipine/perindopril; A/T, atenolol/thiazide; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; b, baseline; ELSA, European Lacidipine Study on Atherosclerosis; HOPE, Heart Outcomes Prevention Evaluation; HOT, Hypertension Optimal Treatment; HYVET, Hypertension in the Very Elderly Trial; IDACO, International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes; LIFE, Losartan Intervention for Endpoint Reduction; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; PAMELA, Pressioni Arteriose Monitorate E Loro Associazioni; SPRINT, Systolic Blood Pressure Intervention Trial; Sust HT, sustained hypertension; and t, on treatment.
therapies (such as ELSA [European Lacidipine Study on Atherosclerosis],26 the only trial in which ABP monitoring was obtained together with clinic BP measurement in all randomized patients both at baseline and repeatedly on treatment) was that clinic BP values are higher than ABP values in the higher range of clinic BP distribution, but the differences between clinic and ABP values become progressively smaller the lower is clinic BP, until the 2 sets of BP values become superimposable at SBP/diastolic blood pressure levels of ≈115 to 117/70 to 73 mm Hg, below which ABP values become progressively higher than conventional clinic BP.31 Figure (A) illustrates the relationships between clinic BP and 24-h ABP values in the population study PAMELA,28 and Figure (B) shows the same relationship in the treated patients of the ELSA trial.26

Surprisingly, in SPRINT patients, Drawz et al15 did not find similar relationships between clinic BP and 24-hour ABP. At variance from what found in previous studies, not only in the more intensely treated SPRINT patients (whose AOBP was 119.6 mm Hg, 24-hour ABP was 122.8 mm Hg, and daytime ABP was 126.7 mm Hg) but also in those treated less intensely (whose AOBP was 135.5 mm Hg, 24-hour ABP was 134.0 mm Hg, and daytime ABP was 138.8 mm Hg) ABP values were higher than, or at best equal to, AOBP. Moreover, it has to be noted that in the less intensely treated SPRINT group, ABP values were above the currently accepted normalcy limits (130 mm Hg for 24-hour SBP and 135 mm Hg for daytime SBP), that is, they were clearly uncontrolled by treatment.

In the Figure, we have also calculated which would have been the clinic SBP values in SPRINT, if measured with the conventional technique used in all other hypertension trials and in medical practice, based on the relationships described in the population study PAMELA25 or in the interventional hypertension trial ELSA.26 Both these exercises indicate that, in the less intensely treated group of SPRINT, achieved conventional clinic SBP would have been rather high (calculated clinic SBP=152 mm Hg according to the PAMELA relationship or ≈147 mm Hg according to the ELSA relationship). In the more intensely treated group of SPRINT, achieved clinic SBP would have been 132 mm Hg when estimated according to PAMELA,26 and 127 mm Hg when estimated according to ELSA.26 Similar values can be calculated from the ABP substudy of LIFE,24 in which ABP data were similar to those reported for SPRINT patients under standard treatment, and conventional clinic SBP was ≈150 mm Hg (Table). Likewise, in ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial)22 with combination treatment, achieved clinic SBP values were similar (≈136 mm Hg) to those measured by AOBP in the less intensely treated group of SPRINT,15 but daytime systolic ABP values were more than 10 mm Hg lower (126–128 mm Hg in ONTARGET versus 139 mm Hg in SPRINT).

That the BP values measured in the less intense treatment arm of SPRINT indicate poorly controlled BP is also shown by a recent study by Wohlfahrt et al32 in a population sample of Brno (Czech Republic) in which the hypertension threshold of 140/90 mm Hg with conventional measurements corresponds to 131/85 mm Hg with AOBP values. Therefore, if the SPRINT results are translated in the common language of all other BP-lowering trials, SPRINT seems to have shown the benefits of lowering a poorly controlled clinic SBP of ≈147 to 152 mm Hg and a poorly controlled 24-hour ambulatory SBP of 134 mm Hg (estimated), down to values of ≈127 to 132 mm Hg for conventional clinic SBP and of 123 mm Hg for 24-hour ambulatory SBP, thus confirming what shown by many previous trials of BP lowering.6

An additional question is what do the AOBP values mean? Do they represent a valuable approximation to mean values obtained through 24-hour ABP monitoring? The answer is
not, because SPRINT shows that AOBP values are generally lower, and often markedly lower, than ABP values. Such low BP levels remind of BP research of over 70 years ago, when Sir Horace Smith suggested to measure what he called basal BP in absence of all emotional stimuli and showed that basal BP was 7 to 8 mm Hg lower than casual BP even in normotensive individuals. At those old times, no ambulatory BP monitoring was possible for comparison, and certainly, the basal BP measurements by Smith were a much more complicated procedure than the unattended automated readings on which the SPRINT was designed. Indeed, it is not unreasonable to hypothesize that many of the procedures used by Smith to have his patients relaxed would have been useless if AOBP were available at those times, because it might have been enough to have the patient alone in a quiet room with an automatically functioning BP device to achieve basal BP levels.

Moreover, do the SPRINT data encourage widening the use of AOBP measurements? AOBP is certainly not a substitute of ABP: apart from the unique possibility by ABP monitoring of evaluating BP during both daytime and nighttime and measuring 24-hour variability, the SPRINT data published by Drawz et al show that not only AOBP values are generally lower than ABP but also correlation of AOBP with ABP is rather poor. Of course, AOBP may represent a better standardized and reproducible method to measure BP than conventional clinic BP, and it cannot be excluded that AOBP values, as Smith thought of basal BP, better correlate with hypertension-related events. However, in absence of strong evidence supporting the prognostic value of AOBP, resuscitating a technique abandoned over 70 years ago, and using it as a standard for BP clinic measurement would require developing new outcome-based standards for definition of hypertension and BP treatment goals in order to substitute all what we have learnt during the past century by using a probably imperfect, but nonetheless profitable, method such as conventional BP measurement.

If this time-honored method is going to be abandoned in the future, it may rather be in favor of a more widely informative method, such as ABP monitoring, provided that its practical advantages, now acknowledged in many clinical guidelines, are definitely demonstrated. Finally, the data reported by Drawz et al suggest a more general conclusion, that is, the importance of a clear definition of the type of BP measurement technique adopted, when identifying BP thresholds and targets in clinical trials. Indeed, the discussions raised by SPRINT data emphasize the need of achieving standardization of the methodology for BP measurement in clinical trials, to make their results not only better comparable but also easier to be translated into messages for everyday practice.

Disclosures
None.

References


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