ORIGINAL ARTICLE

Determination of the optimal on-treatment diastolic blood pressure range using automated office measurements in patients without cardiovascular disease

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KEY WORDS

arterial hypertension, blood pressure lowering, diastolic blood pressure, primary prevention, treatment targets

ABSTRACT

INTRODUCTION Optimal diastolic blood pressure (DBP) during antihypertensive treatment in patients without a history of cardiovascular disease (CVD) remains unknown.

OBJECTIVES This post-hoc analysis of the SPRINT (Systolic Blood Pressure Intervention Trial) data aimed to determine the optimal DBP evaluated using automated office blood pressure measurements (AOBPM) in hypertensive patients without a history of CVD.

PATIENTS AND METHODS Data of 1470 patients with CVD and 7117 patients without CVD were used. Clinical composite endpoint (CE) was defined as the occurrence of myocardial infarction, acute coronary syndrome other than myocardial infarction, decompensation of heart failure, stroke, or cardiovascular death. Two different approaches based on the hazard ratio plot were used to identify the optimal DBP range. The first approach was to determine the 10 mm Hg–wide DBP range with the lowest risk for CE. In the second approach, it was assumed that the hazard ratio of CE at the boundary points of the optimal DBP range should be the same in patients with and without CVD.

RESULTS Two ranges of on-treatment DBP were proposed: 73.7 to 83.7 mm Hg (first approach) and 63.6 to 95.8 mm Hg (second approach). The risk for CE was increased by 3% and 20% at the boundary points of the range, respectively, depending on the method of DBP determination.

CONCLUSIONS Due to the fact that the range determined by the second method was wide and substantially different from the one recommended by the European Society of Cardiology (70–79 mm Hg), we have concluded that a DBP range of 73.7 to 83.7 mm Hg, measured using AOBPM, should be considered optimal in patients without CVD.

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INTRODUCTION Clinical trials that determine the target blood pressure (BP) range in patients with hypertension are mainly focused on the high-risk population.[1-5] However, the majority of patients with hypertension do not have any cardiovascular disease (CVD). Both European and American guidelines recommended target BP values based on office BP measurements[5,6]; however, search for the best method for BP measurement remains one of the most fundamental issues in hypertension. The most widely used methods are office, home, and 24-hour ambulatory BP measurements (ABPM). Each of them has its strengths and limitations.[7] Blood pressure values obtained by various methods cannot be simply recalculated, because of the differences between them.[8] The target BP values based on the automated office BP measurements (AOBPM) have not been established using data from randomized trials, although this method is recommended for diagnostic purposes.[9] The only randomized study (SPRINT [Systolic Blood Pressure Intervention Trial]) that determined BP values using AOBPM reported the outcomes of patients based on their systolic BP (SBP).[3] Data regarding the optimal on-treatment diastolic BP (DBP)

WHAT'S NEW?

Both high and low values of diastolic blood pressure (DBP) during antihypertensive treatment are recognized as harmful. On-treatment (DBP) in the range of 70 to 79 mm Hg is currently considered optimal; however, the evidence regarding patients without prior cardiovascular disease is lacking. In the present study, 2 different strategies of optimal DBP determination were evaluated. As a result, the optimal DBP on-treatment range of 73.7 to 83.7 mm Hg in patients without prior cardiovascular disease was proposed.

range using AOBPM are limited. According to the European Society of Cardiology (ESC) guidelines, the target DBP should range between 70 and 79 mm Hg in all patients; however, more studies are warranted to evaluate this recommendation.[6] Using the SPRINT data, we previously reported that in the subpopulation with CVD, the optimal DBP using AOBPM ranged between 68.6 and 78.6 mm Hg.[10] Both elevated and extremely low on-treatment DBP values were associated with unfavorable outcomes. This observation was previously reported in other studies, but mostly in patients with CVD. Data regarding the population at high cardiovascular risk, but without CVD, are limited. Thus, the SPRINT data were analyzed to establish the optimal treatment range for DBP based on AOBPM in a population at high cardiovascular risk and without prior CVD.

PATIENTS AND METHODS The SPRINT study evaluated the effects of intensive (target <120 mm Hg) as compared with standard (target <140 mm Hg) SBP reduction.[3] Patients at high cardiovascular risk, older than 50 years, and with SBP of 130 to 180 mm Hg were enrolled. High cardiovascular risk was defined as fulfilling one of the following criteria: clinical or subclinical CVD, chronic kidney disease, Framingham risk score greater than 15% for 10-year CVD risk, or age over 75 years. Patients with a history of diabetes or stroke were excluded. The definitions of clinical and subclinical CVD are presented in TABLE 1. In SPRINT a composite primary outcome event was defined as myocardial infarction (MI), acute coronary syndrome other than MI, exacerbation of heart failure, stroke, and cardiovascular death. The trial proved that intensive as compared with standard BP lowering was associated with reduced risk (hazard ratio [HR], 0.75; 95% CI, 0.64–0.89; P <0.001) for composite outcome occurrence.

Among 9361 SPRINT participants, 1877 had a history of CVD (1562 had clinical CVD and 493 had a history of subclinical CVD) and a total of 7484 patients had no history of CVD. According to the SPRINT protocol, participants achieved a stable BP after 6 months. For the purposes of our analysis, we excluded the patients with unavailable data after the sixth month from enrolment until the end of the study and those with subclinical CVD. Therefore, among 7484 SPRINT participants without a history of CVD, 7117 with available data in the time period after 6 months from enrolment until the end of the study were included. Out of 1877 patients with CVD, the data of 1470 with clinical CVD were used as a basis to determine risk thresholds for selecting the optimal DBP values (FIGURE 1).

The limited SPRINT data, obtained from the National Heart, Lung and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Centre, were used to perform the analysis;[11] however, the manuscript does not necessarily reflect the opinions or views of the SPRINT Research Group or the NHLBI. Our analysis was approved by the Ethics Committee of the Medical University of Warsaw (no. AKBE/5/2018) and by the NHLBI.

All participants provided written consent for their participation in SPRINT; nevertheless, the requirements for written consent to perform the current analysis were waived because the data were anonymized.

Data availability statement The data supporting the findings of this study can be obtained from the NHLBI, but restrictions apply regarding their availability. Since these data are under the license for the current study, they are not publicly obtainable. The data are available from the NHLBI upon reasonable request. The authors have no right to share the data.

Blood pressure measurement Omron Healthcare Model 907 (Kyoto, Japan) was used for AOBPM in SPRINT.[3] Blood pressure was measured 3 times per visit with a 1-minute interval after 5 minutes of rest. The mean of the 3 measurements was computed. In the intensive treatment arm, BP was lowered to achieve SBP of less than 120 mm Hg; in the standard treatment arm, the BP value was lowered to achieve SBP of less than 140 mm Hg and hypotensive treatment was down-titrated when SBP was lower than 130 mm Hg at a single visit or lower than 135 mm Hg at 2 consecutive visits. No DBP target was established in both intensive and standard treatment arms; however, after meeting the SBP goal, the participants were treated to achieve DBP of less than 90 mm Hg. In our study, on-treatment BP values were computed as means of each participant's SBP and DBP values during the analyzed period (since the sixth month from enrolment to the end of the study).

Clinical endpoint The clinical composite endpoint (CE) analyzed in our study was defined in the same way as the primary composite outcome in original SPRINT and included MI, acute coronary syndrome other than MI, decompensation of heart failure, stroke, or cardiovascular death.[3]

Statistical analysis We performed a post-hoc analysis of the SPRINT subset data. All continuous variables were expressed as mean (SD) or median and interquartile range, depending on the distribution. All discrete variables were expressed as number and percentage. Restricted

TABLE 1 The definitions of clinical and subclinical cardiovascular disease according to the original SPRINT (Systolic Blood Pressure Intervention Trial) study protocol

Clinical cardiovascular disease
• Previous myocardial infarction, percutaneous coronary artery intervention, coronary artery bypass grafting, carotid endarterectomy, carotid stenting
• Peripheral artery disease with revascularization
• Acute coronary syndrome with or without change on resting electrocardiogram, electrocardiogram changes on a graded exercise test, or positive cardiac imaging study
• At least 50% stenosis of the diameter of the coronary, carotid, or lower extremity artery
• Abdominal aortic aneurysm ≥5 cm with or without repair
Subclinical cardiovascular disease
• Coronary artery calcium score ≥400 within the past 2 years
• Ankle brachial index ≤0.9 within the past 2 years
• Left ventricular hypertrophy on electrocardiogram (based on computer reading), echocardiogram, or another cardiac imaging procedure report within the past 2 years

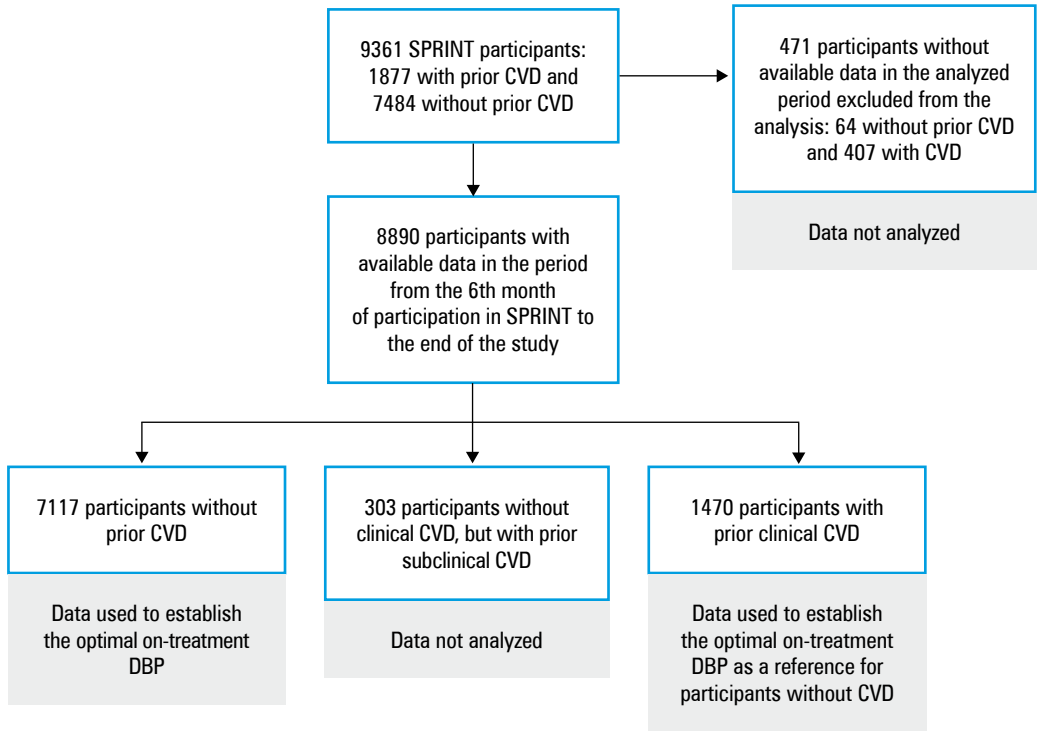

FIGURE 1 Flowchart presenting the process of SPRINT (Systolic Blood Pressure Intervention Trial) participant selection for the current analysis
Abbreviations: CVD, cardiovascular disease

cubic splines were used to present the nonlinear relationship between DBP and HR on the plot. The optimal range of DBP was selected using the HR plot.

All computations were performed in the R 3.4.0 environment for statistical programming (R Foundation for Statistical Computing, Vienna, Austria) using standard, survival, and rms packages.

Selecting the optimal on-treatment diastolic blood pressure range There is no statement or position paper outlining how the optimal BP range should be determined. The concept of an "optimal" range of BP entered the clinical practice for the first time after the publication of the ESC guidelines.[6] Nevertheless, the authors of that document did not provide the rationale of the strategy for selecting the optimal DBP range. For this reason, we proposed 2 approaches which were considered and applied to estimate the optimal on-treatment DBP range. Both of them are based on the plot showing the relationship between HR and on-treatment DBP. Hazard ratio was computed and plotted using the on-treatment DBP value with the minimum of HR as a reference (HR at minimum: 1).

In the first approach (the 10 mm Hg–wide optimal DBP range approach), in accordance with the current ESC guidelines, the optimal on-treatment DBP range should be 10 mm Hg wide. Such approach was successfully applied previously in the group of SPRINT participants with CVD.[10]

In the second approach (the equal HR approach), the data of patients with CVD were used to plot HR against DBP. Then, the HRs at the

TABLE 2 Clinical characteristics and outcomes in patients with and without cardiovascular disease

Parameter	Participants without CVD (n = 7117)	Participants with CVD (n = 1470)	*P* value
Age, y	66 (60–75)	70 (63–78)	<0.001
Allocation to the intensive treatment arm	3561 (50)	737 (50.1)	0.984
Female sex	2661 (37.4)	354 (24.1)	<0.001
Black race	2343 (32.9)	284 (19.3)	<0.001
BMI, kg/m^2, mean (SD)	30 (5.8)	29.2 (5.4)	<0.001
Prior subclinical CVD	0	166 (11.3)	<0.001
Prior CKD	1889 (26.5)	518 (35.2)	<0.001
Creatinine, mg/dl, mean (SD)	1.06 (0.33)	1.1 (0.3)	<0.001
eGFR, ml/min/1.73 m^2, mean (SD)	72.6 (20.5)	68.3 (19.9)	<0.001
Current smoker	924 (13)	208 (14.1)	0.236
Former smoker	2916 (41)	760 (51.7)	<0.001
Never smoker	3271 (46)	501 (34.1)	<0.001
On aspirin	3203 (45.1)	1204 (82.1)	<0.001
On statin	2644 (37.4)	1116 (76.3)	<0.001
Total cholesterol, mg/dl	191 (167–218)	161 (142–190)	<0.001
Non-HDL cholesterol, mg/dl	137 (114–163)	112 (92–138)	<0.001
HDL cholesterol, mg/dl, mean (SD)	53.5 (14.7)	49.8 (12.8)	<0.001
Triglycerides, mg/dl	107 (77–151)	108 (77–148)	0.978
Glucose, mg/dl	97 (90–105)	98 (92–106)	<0.001
Baseline DBP, mm Hg, mean (SD)	79 (11.7)	74.2 (12.1)	<0.001
Baseline SBP, mm Hg, mean (SD)	139.9 (15.5)	138.1 (15.8)	<0.001
On-treatment DBP, mm Hg, mean (SD)	72 (9.4)	68.3 (9.4)	<0.001
On-treatment SBP, mm Hg, mean (SD)	128.2 (10.7)	127.9 (10.7)	0.439
Clinical composite endpoint	293 (4.1)	159 (10.8)	<0.001
MI	110 (1.5)	62 (4.2)	<0.001
Acute coronary syndrome other than MI	29 (0.4)	35 (2.4)	<0.001
Acute exacerbation of heart failure	82 (1.2)	40 (2.7)	<0.001
Stroke	74 (1)	33 (2.2)	<0.001
Cardiovascular death	44 (0.6)	33 (2.2)	<0.001
All-cause death	188 (2.6)	91 (6.2)	<0.001

Data are presented as number (percentage) of patients or median (interquartile range) unless otherwise indicated.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease equation; HDL, high-density lipoprotein; MI, myocardial infarction; SBP, systolic blood pressure; others, see FIGURE 1

boundary points of the optimal on-treatment DBP range (which was previously found to be 68.6–78.6 mm Hg) were calculated. Assuming that HRs at the boundary points of the optimal on-treatment DBP range should be similar in patients with and without CVD, we determined the DBP values with the HR values corresponding to the HR values at the boundary points of the optimal range (68.6–78.6 mm Hg) in individuals with CVD. The DBP values obtained using this approach were considered to determine the optimal DBP range in patients without CVD.

The strategies for optimal DBP determination proposed above are not supported by research, they only remain our proposal. The 10 mm Hg–wide range strategy is justified by the ESC recommendations and the human preference for round numbers. The equal HR approach is based on the selection of a relative risk value from which we consider the risk to be increased. The threshold value indicating unacceptable risk has not been established. In our analysis, we assumed that this value should be the same for people with and without CVD. As will be shown later, this threshold risk value corresponded with a 20% increase in risk, which one may find truly significant. Nevertheless, in light of the corresponding analysis in the group of people with CVD and the wide acceptance of the ESC recommendations, there is no reason to reject this threshold value or the approach.

RESULTS The data of 7117 participants (women, 37.4%) without CVD were analyzed. The mean (SD) on-treatment DBP and SBP values were 72 (9.4) mm Hg and 128.2 (10.7) mm Hg, respectively. A total of 3745 participants (52.6%) were older than 65 years, and 1649 (23.2%) were aged over 75 years. The baseline characteristics and outcomes of the investigated subpopulation and patients with CVD are listed in TABLE 2.

In the study population, 44 patients (0.6%) had DBP <50 mm Hg; 698 (9.8%) had DBP ≥50 and <60 mm Hg; 2210 (31.1%) had DBP ≥60 and <70 mm Hg; 2705 (38%) had DBP ≥70 and <80 mm Hg, and 1460 (20.5%) had DBP ≥80 mm Hg.

During the study period, CE occurred in 293 patients (4.1%), including 110 (1.5%) with MI, 29 (0.4%) with acute coronary syndrome other than MI, 82 (1.2%) with acute exacerbations of heart failure, 74 (1%) with stroke, and 44 (0.6%) with cardiovascular death. The histogram of on-treatment DBP and percentage of CE events at each level of on-treatment DBP are shown in FIGURE 2.

The relationship between on-treatment DBP and HR is presented in FIGURE 3A (patients with CVD) and FIGURE 3B (patients without CVD). Hazard ratios were adjusted for age, sex, current smoking status, on-treatment SBP, body mass index (BMI), and a history of chronic kidney disease. In patients without a history of CVD according to the HR plot, we found the minimum HR value for on-treatment DBP of 78.3 mm Hg. In accordance with the first approach (10 mm Hg–wide optimal DBP range), the calculation of the DBP range was based on the 10 mm Hg width of the range, as proposed in the ESC guidelines,[6] which indicated the DBP range of 73.7 to 83.7 mm Hg. At the boundary points of the interval (considering DBP of 78.3 mm Hg as the value with the lowest risk), HRs were 1.035 (95% CI, 0.92–1.17) and 1.033 (95% CI, 0.86–1.24), respectively (FIGURE 3B). Almost one-third (2227 [31.3%]) of the SPRINT study participants without a history of CVD had on-treatment DBP in the specified range. Most of the SPRINT study participants without prior CVD

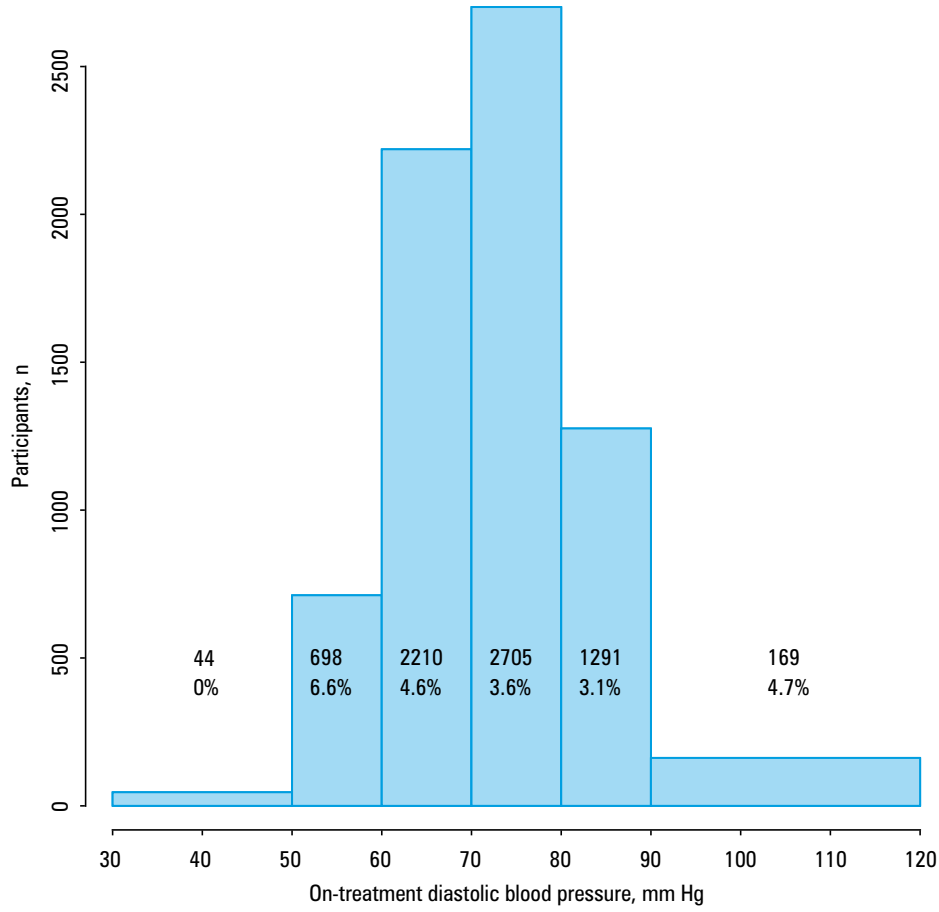

FIGURE 2 Histogram of on-treatment diastolic blood pressure with the number of participants and percentage of clinical composite endpoints in each diastolic blood pressure interval

had DBP lower than 73.7 mm Hg (4085 [57.4%]). Only 805 (11.3%) had on-treatment DBP higher than 83.7 mm Hg. There were 80 cases of CE (rate of 3.6%) in patients who had on-treatment DBP within the range of 73.7 to 83.7 mm Hg, while in others, 213 cases of CE (rate of 4.36%) were noted. After the adjustment for age, sex, smoking status, on-treatment SBP, BMI, and a history of chronic kidney disease, on-treatment DBP in the range of 73.7 to 83.7 mm Hg was associated with a 5.5% higher risk for CE in comparison with on-treatment DBP outside this range (HR, 1.06; 95% CI, 0.8–1.39).

In the second approach (equal HR), we considered the DBP range of 68.6 to 78.6 mm Hg, previously established for patients with CVD (FIGURE 3B).[10] The HR of risk for CE at the BP point of 68.6 mm Hg in comparison with the risk at the BP point of 74 mm Hg (DBP with the lowest risk) was 1.2 (95% CI, 0.92–1.56). The HR of risk at the DBP of 78.6 mm Hg in comparison with the risk at the DBP of 74 mm Hg was 1.21 (95% CI, 0.92–1.59). We used these calculated HRs to establish the optimal DBP range in patients without CVD. With the HR of 1.2, the lower boundary point of DBP range was 63.6 mm Hg (HR, 1.2; 95% CI, 0.84–1.72) and the higher boundary point was 95.8 mm Hg (HR, 1.2; 95% CI, 0.57–2.56). Therefore, according to the second approach, the optimal on-treatment DBP in patients without CVD was 63.6 to 95.8 mm Hg (FIGURE 3B). Four-fifths (5733 [80.5%]) of the SPRINT study participants without CVD had on-treatment DBP in this range. On-treatment DBP lower than 63.6 mm Hg was present in 1357 (19.1%) participants, while only in 27 (0.4%) on-treatment DBP was higher than 95.8 mm Hg.

There were 215 cases of CE (rate of 3.8%) in patients who had on-treatment DBP within the range of 63.6 to 95.8 mm Hg and 78 cases (rate of 5.6%). in those with DBP outside this range. After the adjustment for age, sex, smoking status, on-treatment SBP, BMI, and a history of chronic kidney disease, on-treatment DBP higher than 95.8 mm Hg or lower than 63.6 mm Hg was related to a 18.9% higher risk for CE in comparison with on-treatment DBP in the range of 63.6 to 95.8 mm Hg (HR, 1.19; 95% CI, 0.89–1.59).

DISCUSSION In the current study, we proposed 2 optimal DBP ranges based on AOBPM for patients without CVD. The use of both proposed DBP ranges should be commented in view of their advantages and limitations.

The range of 73.7 to 83.7 mm Hg, which was calculated using the 10 mm Hg–wide range approach seems to be in line with the current guidelines. However, this DBP range was associated with only a 3% increase of risk at the boundary points of the DBP interval. Diastolic BP outside the range was associated with a 5.5% higher risk than DBP within the range of 73.7 to 83.7 mm Hg. Therefore, it should be considered whether such a small increase of risk has any clinical significance in a population with a 4.1% rate of CE during the trial. On the other hand, the wide DBP range of 63.6 to

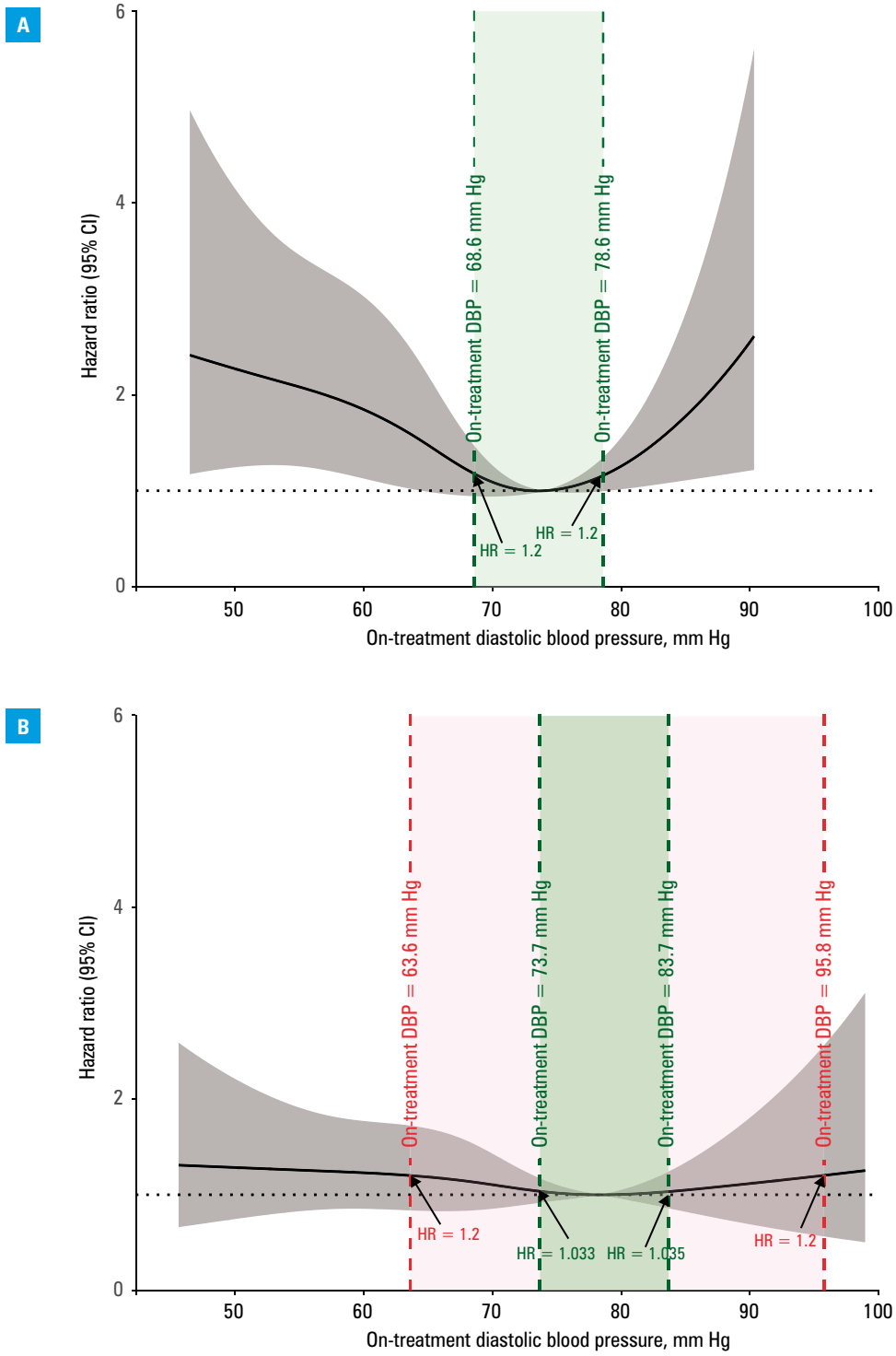

FIGURE 3 Hazard ratio (HR) plots according to on-treatment diastolic blood pressure (DBP) in patients with (**A**) and without (**B**) cardiovascular disease; the hazard ratio was computed using the DBP value with the minimum risk as a reference. **A** – 10 mm Hg–wide interval of DBP showing optimal DBP in patients with cardiovascular disease; **B** – 2 intervals of DBP considered optimal in patients without cardiovascular disease: 63.6 to 95.8 mm Hg (the 10 mm Hg–wide optimal DBP range approach; red) and 73.7 to 83.7 mm Hg (the equal HR approach; green)

95.8 mm Hg, based on the equal HR strategy, may not be applicable in clinical practice. Almost all patients reaching the SBP goals would have DBP values within such a broad range. Consequently, this would lead to a situation when there is no target DBP value during the treatment and the increase in risk within the optimal range is acceptable.

The strategies for determination of an optimal DBP range proposed herein are the first attempt to solve this problem in a quantitative manner. There is limited evidence supporting the ESC recommendation of a DBP range of 70 to 79 mm Hg in patients without CVD. This recommendation is based mainly on studies conducted in patients

with CVD. Until prospective studies are conducted, an indirect analysis is warranted to determine optimal DBP in hypertensive patients without CVD. Thus, we decided to present both of the above approaches. In our opinion the first approach (the 10 mm Hg–wide range strategy) delivers DBP values that are more applicable in clinical conditions than the second method (the equal HR approach). The currently presented DBP range of 73.7 to 83.7 mm Hg is not identical to the one recommended by the ESC (70–79 mm Hg); however, the differences between AOBPM and office BP measurement should be taken into consideration.

The difference in the width of DBP ranges is due to different assumptions taken for the calculation of the optimal on-treatment DBP range in populations with and without a history of CVD. It is also tempting to speculate that the increased risk of CE associated with too high and too low on-treatment DBP is less potent in patients without CVD compared with those with prior CVD. Considering this hypothesis and bearing in mind that most SPRINT participants had no history of CVD, the results of our analysis and other studies showing no increase in risk for low DBP are not surprising.[12,13]

A difference was observed between the optimal on-treatment DBP range proposed herein and the one recommended in the guidelines for patients with hypertension, without a distinction based on the presence of previous CVD.[6] The reason behind this discrepancy remains unclear, but 2 possibilities have been considered. First, AOBPM delivers different BP values than other methods of BP measurement that were used to establish the optimal DBP range recommended in the guidelines.[6] To date, only small differences were found between AOBPM and other methods of BP measurement, which does not justify the difference between the width of DBP range and its values. Tang et al[14] showed that DBP values based on AOBPM were higher by 3.8 mm Hg than those obtained using research-grade methods. In a previous study that compared AOBPM and office or research-grade measurements, small differences in DBP values (–3 and –2.4 mm Hg) were found.[15] Similarly, Filipovský et al[16] showed a moderate correlation between the automated and auscultatory or home BP measurements, with large limits of agreement. Corresponding results were found when DBP based on AOBPM was compared with values obtained from ABPM.[17] On the contrary, the SPRINT Ambulatory Blood Pressure Study showed lack of agreement between SBP derived from AOBPM and daytime ABPM, based on the Bland–Altman plots.[18] Comparing the DBP values, Myers et al[19] showed that DBP of 80 mm Hg based on AOBPM corresponded with the mean awake ABPM of DBP at 81.5 mm Hg. In a recent meta-analysis, Roerecke et al[20] showed that the AOBPM values were similar to the ABPM values. Our previous analysis[10] suggested that the optimal DBP of 68.6 to 78.6 mm Hg is similar to the DBP range recommended by the ESC.[6] Thus, the difference between various methods of BP measurement does not explain the discrepancy in the currently calculated optimal on-treatment DBP range in patients without CVD and the DBP range recommended by the ESC.[6] Another possible explanation for this difference is that the range proposed by the ESC is the same, regardless of the presence or absence of CVD. Probably, the optimal on-treatment DBP in patients without CVD is different from that in individuals with prior CVD. Such a hypothesis can be supported by the fact that patients without CVD have better preserved blood flow autoregulation mechanisms than those with a history of CVD. This was confirmed by the observation of a less potent risk increase towards lower or higher DBP in patients without CVD in comparison with those with CVD (**FIGURE 3A** and **3B**).

So far, none of the randomized studies aimed to establish the optimal DBP values which are currently achieved during intensive SBP lowering; hence, the available evidence regarding the optimal DBP in patients with no history of CVD is limited. In an analysis by Lonn et al,[21] patients at intermediate cardiovascular risk who were actively treated did not benefit from the study intervention despite the reduction in SBP (by a mean [SD] value of 6 [3] mm Hg) and DBP (by a mean [SD] value of 3 [8] mm Hg). In SPRINT, patients who achieved a mean SBP of 121.4 mm Hg after 1 year of participation had a mean DBP of 68.7 mm Hg.[3] The participants of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial also achieved lower DBP values (intensive BP reduction group: mean, 64.4 mm Hg; standard BP reduction group: mean, 70.5 mm Hg).[1] In the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) and TRASCEND (Telmisartan Randomised Assessment of Study in ACE and Intolerant Participants with Cardiovascular Disease) trials, every fifth person who achieved the SBP therapeutic goal of 120 to 130 mm Hg had DBP lower than 70 mm Hg.[22] The DBP targets recommended by the ESC were based on several meta-analyses and post-hoc analyses of large trials.[6] However, there was limited evidence supporting the recommendation of DBP between 70 and 79 mm Hg in patients without CVD. Thomopoulos et al[23] revealed that lowering DBP to less than 80 mm Hg is more beneficial than maintaining DBP of 80 mm Hg or higher. Nevertheless, the lower values were not determined. In contrast, Ettehad et al[24] did not focus on determining the optimal DBP target. A study by Xie et al[25] did not provide the optimal DBP target, since it was focused on intensive BP lowering and the direct targets were not defined. An analysis of the ONTARGET and TRASCEND trials showing an optimal DBP range of 70 to 80 mm Hg was performed in a population with CVD.[22] Similarly to our study, a post-hoc analysis of the VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) trial did not show any evidence of the J-shaped curve in patients without CVD.[26]

Limitations Our study had some limitations. First, the post-hoc design could lead to potential bias and the results should be interpreted carefully. Second, the number of participants with DBP higher than 90 mm Hg was relatively small, which led to a small number of events in this group of patients. This limitation could have had an impact on the accuracy of determining the higher boundary point of the optimal DBP range. The premature termination of SPRINT was related to the limited number of events that could be analyzed. The AOBPM method in SPRINT was not properly implemented in the majority of measurements; only 50% of measurements were unattended. Patients with diabetes and those who experienced stroke were excluded from SPRINT; therefore, caution should be used when generalizing our results to other populations. It should also be underlined that patients younger than 50 years were not included in SPRINT.

Conclusions In summary, our analysis, which focused on patients without a history of CVD, suggested that the optimal on-treatment DBP range is different from the one currently recommended for all individuals with hypertension.[8] From the perspective of everyday clinical practice, the optimal on-treatment DBP range of 73.7 to 83.7 mm Hg based on AOBPM should be considered in patients without CVD and those older than 50 years.

ARTICLE INFORMATION

NOTE Online identifiers were assigned to PS (ORCiD ID, https://orcid.org/0000-0003-0662-8678), JL (ORCiD ID, https://orcid.org/0000-0003-3780-8073), and MS (ORCiD ID, https://orcid.org/0000-0001-8548-9762).

CONTRIBUTION STATEMENT JL, MS, and PS contributed to the concept of the study. PS performed the statistical analysis. All authors interpreted the results of the study. PS and MS prepared a draft version of the manuscript. JL revised and corrected the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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