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COMMENT

Time in therapeutic range in context of blood pressure management

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Blood pressure (BP) to target levels is associated with a significant risk reduction of cardiovascular (CV) diseases, and advances in pharmacotherapy have allowed meticulous BP maintenance in individuals with hypertension [1–3]. Recent large-scale meta-analyses have shown that a 5-mmHg decrease in the systolic blood pressure (SBP) is associated with a 10% risk reduction for major CV events, irrespective of CV comorbidities, age of the patient, history of diabetes mellitus, and even at normal or high-normal BP levels [4–6]. Thus, BP control is one of the most beneficial healthcare strategies. The NCD Risk Factor Collaboration examined trends in hypertension awareness, treatment, and control among 526,336 participants aged 40–79 years in 12 high-income countries using 123 nationally representative surveys [7]. In addition, the hypertension guidelines also indicate that hypertension remains a critical healthcare problem globally [1–3, 7]. Of the 12 countries, Japan was reported to have the lowest hypertension control [7]; of the 43 million individuals with hypertension in Japan, approximately 31 million had uncontrolled hypertension (≥140/90 mmHg) [1].

BP is a dynamic parameter that varies from minute to minute, day to day, visit to visit, and seasonally even in the absence of lifestyle and antihypertensive drug modifications. Moreover, BP variability is a known independent predictor of CV events. Therefore, identifying a therapeutic range for BP in addition to a specific threshold as the target BP for antihypertensive therapy would be a more practical and clinically relevant approach [8]. In 2017, Doumas et al. first advocated for time in therapeutic range (TTR) for BP measurements [9]. TTR expresses the percentage of BP measurements recorded within a given BP window. TTR for BP includes both the mean BP value and the degree of BP variability during the follow-up period for each individual, reflecting BP variation over time (within and outside of the target range). Doumas et al. examined the impact of TTR for office SBP (between 120 and 140 mmHg) on all-cause mortality in 689 051 individuals from the US Veterans Administration Medical Centers over 10 years [9]. They categorized TTR for office SBP (120–140 mm Hg) into within, above, or below quartiles, and related it to all-cause mortality. Among patients with established hypertension at baseline, the TTR in the highest controlled quartile (>75% of measurements within 120–140 mmHg) was associated with the lowest all-cause mortality rate of (6.5%) over the follow-up period, whereas TTR in the lowest controlled quartile (0–25% of measurements) was associated with the highest all-cause mortality rates (23.5%). The authors concluded that TTR for office SBP was a strong predictor of all-cause mortality in clinical practice [9]. Several recent post hoc analyses of randomized controlled trials have corroborated the role of TTR for BP as a significant predictor of clinical outcomes, such as risk of death, cardiovascular events, and renal events [10, 11]. In a post hoc analysis of SPRINT (Systolic Blood Pressure Intervention Trial) data, TTR for office SBP was defined as 110–130 mmHg and 120–140 mmHg during the 0–3 month-period for the intensive and standard arms of the trial, respectively [10]. Participants were divided into quartiles of TTR for office SBP (0%– < 25%, 25%– < 50%, 50%– < 75%, and 70–100%, respectively). The mean office SBP was 140 mmHg in the lowest controlled quartile and 124 mmHg in the highest controlled quartile. Additionally, a higher TTR for office SBP was associated with a lower risk of CV events, regardless of the difference in target BP for the intensive and standard arms. Notably, the TTR for office SBP predicted CV events even after fully adjusted models, including mean office SBP, and BP variability, were used [10]. Based on the available evidence, Fig. 1

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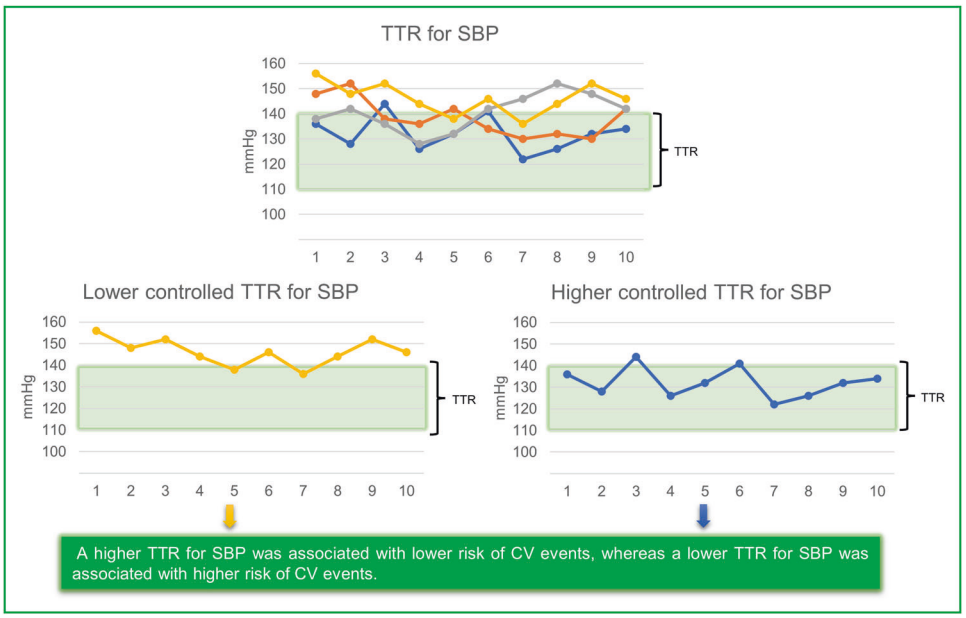

Fig. 1 Time in therapeutic range for systolic blood pressure as a predictor of cardiovascular events. This figure shows the relationship between TTR category for SBP and risk of CV events. Therapeutic ranges vary from study to study, but most use either an office SBP of 110 mmHg to 130 mmHg or 120 mmHg to 140 mmHg. A higher TTR for SBP is associated with a lower risk of CV events. CV cardiovascular, SBP systolic blood pressure, TTR time in therapeutic range

illustrates the relationship between the TTR for SBP and the risk of CV events.

As hypertension guidelines recommend the use of out-of-office BP monitoring (both ambulatory and home BP) to facilitate the diagnosis, monitoring, and treatment [1–3], TTR for out-of-office BP is a viable and more advantageous option for improving the quality of hypertension management. However, most of the currently available investigations dealing with TTR for BP and clinical outcomes have used office BP measurements [9–11]. The only study investigating the impact of TTR for BP (including both office and 24-hour ambulatory SBP) on CV risk reduction was evaluated in a post hoc analysis of the Global SYMPLICITY Registry, which was designed to assess the safety and efficacy of renal denervation in patients with uncontrolled hypertension [12]. The authors reported that a 10% increase in TTR for both office and ambulatory SBP was associated with significant risk reduction for major CV events, CV death, all-cause death, myocardial infarction, and stroke.

In this issue of the *Hypertension Research*, Kario et al. add new data on the impact of TTR for home BP on risk reduction of CV events [13]. Using extended data from the J-HOP (Japan Morning Surge-Home Blood Pressure) study, a prospective observational study evaluating the effect of home BP monitoring on the prediction of CV events in Japanese outpatients with hypertension and at least one CV risk factor, the investigators examined the association between TTR for home SBP and the occurrence of CV events in this population. The morning-evening mean home SBP was determined for each participant using baseline home SBP readings taken over 13 days, and TTR for home SBP was defined as the proportion of time spent with this average home SBP value in the range of 100–135 mmHg [13]. Participants ($n = 4\,070$) were divided into quartiles of TTR for home SBP (<15.3%, 15.3%–<66.6%, 66.6%–<100%, and 100%, respectively). The mean morning-evening home SBP noted in the study was 152.9 mmHg in the lowest controlled quartile and 120.1 mmHg in the highest controlled quartile; lower TTR for home SBP was associated with a higher adjusted risk of both total CV events and stroke. Also, a 10% decrease in TTR for home SBP was a significant predictor of total CV events and stroke. The authors concluded that TTR for home SBP reflects both achievement of target average home BP and diurnal variability and proposed a threshold value of ≥67% TTR for home SBP to reduce cardiovascular risk. The study used a large sample from 25 out of 47 prefectures in Japan, provided real-world data using standardized measurement of home BP, and had a sufficient follow-up rate of participants and data collection during the observation periods [13]. However, the study included only a short time window for defining TTR (13 days at baseline), lacked follow-up data on TTR for home BP, and did not sufficiently adjust for potential confounders, such as medication adherence, salt intake, and physical activity. Nevertheless, this study provides useful information for hypertension management to improve quality of BP control in clinical practice.

Major initiatives in the management of hypertension are targeted not only at improving the attainment rates for target BP levels but also at sustaining BP control over time in patients with hypertension to achieve primary and secondary prevention of CV events [8]. However, current clinical decision-making is based on the assessment of BP control at a specific single time point around the globe. Evidence-

based guidelines recommend lowering BP to target levels [1–3], but practical application of the assessment of long-term BP control with treatment are inadequate. Previous studies and this study provide a thorough overview of the evidence supporting TTR as an intuitive metric of BP control and predictor of CV events [9–13], and clinicians and healthcare providers may consider using TTR for BP as a metric of the quality of BP control. So how should clinicians, researchers, and policymakers develop strategies to implement TTR for BP in patients with hypertension? Guidelines for management of hypertension recommend multidisciplinary team-based care involving physicians, pharmacists, nurses, dietitians, and other healthcare providers for the management of hypertension [1–3] to promote better medication adherence and BP control. Dixon et al. showed that a pharmacist-physician collaborative model group had a higher TTR for office SBP, higher medication adherence, and lower clinical inertia than usual care [14]. In addition, digital technology may have a promising role in improving TTR for BP. Kario et al. reported the results of the HERB Digital Hypertension 1 pivotal trial, a Japanese multicenter, prospective, open label, randomized controlled trial of a digital therapeutic application for essential hypertension [15]. Compared with the control group (lifestyle modification alone), the digital therapeutics group (HERB system plus lifestyle modification) exhibited greater reductions in body weight and 24-hour ambulatory, home, and office SBP, as well as improvements in lifestyle. Therefore, the impact of digital technology on TTR for BP must be determined in future studies.

In summary, TTR for BP is expected to improve the quality of hypertension management. However, the available evidence on TTR for BP and CV outcomes is from retrospectiv analyses. We need more evidence on long-term periods of TTR for BP on the quality of hypertension management through prospective studies.

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Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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