



Hypertension paradox in Japan: the road ahead

Shigeru Shibata¹

Keywords Hypertension paradox · Guideline · Real-world data · White-coat hypertension · Diabetes

Received: 24 July 2023 / Accepted: 28 July 2023 / Published online: 29 August 2023
© The Author(s), under exclusive licence to The Japanese Society of Hypertension 2023

More than 40 million people are estimated to have hypertension in Japan, constituting one of the principal factors that influence both total and healthy life expectancy [1]. Epidemiological studies involving Japanese individuals have demonstrated a positive association between blood pressure (BP) categories and the risk of cardiovascular diseases, with the relationship being more evident in younger age groups [2]. As one of the landmark clinical trials, the Systolic Blood Pressure Intervention Trial found that the primary outcome, composed of myocardial infarction, acute coronary syndrome, stroke, heart failure, and death from cardiovascular causes, occurred significantly less in the intensive target BP group than the standard target BP group with the hazard ratio of 0.75 (95% confidence interval, 0.64–0.89) [3], demonstrating the importance of tight BP control. Consistently, a meta-analysis of 19 studies enrolling 55,529 participants indicated that the intensive BP lowering (targeting <130/80 mmHg) was associated with reduced cardiovascular events [4]. Moreover, the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients study has also shown that the primary outcome (a composite of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, and death from cardiovascular causes) occurred less in the intensive treatment group (a target systolic BP of 110 to <130 mmHg) than the standard treatment group (a target systolic BP of 130 to <150) [5].

All the above data indicate that strict BP control contributes to the reduction in the future occurrence of cardiovascular diseases in hypertensive patients. Accordingly, the current guideline for the management of hypertension in

Japan (JSH 2019) sets the target levels of BP control at <130/80 mmHg, except in individuals with >75 years, having cerebrovascular disease with bilateral carotid artery stenosis and cerebral main artery occlusion, or having chronic kidney disease (CKD) without proteinuria [6]. However, tightening the BP control can be associated with unintended responses, such as electrolyte abnormalities, hypotension, and acute kidney injury, in a subpopulation of subjects [3, 5], which can potentially increase the difficulty of intensive BP lowering, resulting in a gap between guidelines and actual clinical practice.

The study by Kobayashi et al. [7] analyzed the current situation of BP management in hypertensive patients in Kanagawa Prefecture, Japan. The study was performed by the Kanagawa Physicians Association in collaboration with the Japan Medical Association Database of Clinical Medicine, which is the registry that includes nearly 20,000 patients with hypertension or diabetes mellitus (DM). In this study, the data of 835 patients in Kanagawa in 2021 were compared with the cross-sectional data obtained in 2011 and 2014 in the same region [8, 9]. The study found that the average office systolic BP levels in the study participants were 136.5 ± 17.4 mmHg, which was significantly higher than those in 2011 or 2014 survey even after adjustment with covariates. In contrast, home systolic BP was slightly lower (128.8 ± 8.1 mmHg) than in previous surveys, which indicates that the difference between home and office BP levels was increased. The subgroup analysis by the comorbid condition revealed that the difference between the two BP measurements was more pronounced in patients without DM (home systolic BP, 128.8 ± 11.4 mmHg; office systolic BP, 141.1 ± 18.3 mmHg) than those with DM (home systolic BP, 127.5 ± 9.3 mmHg; office systolic BP, 133.9 ± 16.4 mmHg) (Fig. 1).

Besides the changes in BP values, the authors also analyzed the achievement rates of target BPs. Overall, the achievement rate for the target home BP of <135/85 mmHg was 74.4% in the 2021 study, which was numerically higher

✉ Shigeru Shibata
shigeru.shibata@med.teikyo-u.ac.jp

¹ Division of Nephrology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan

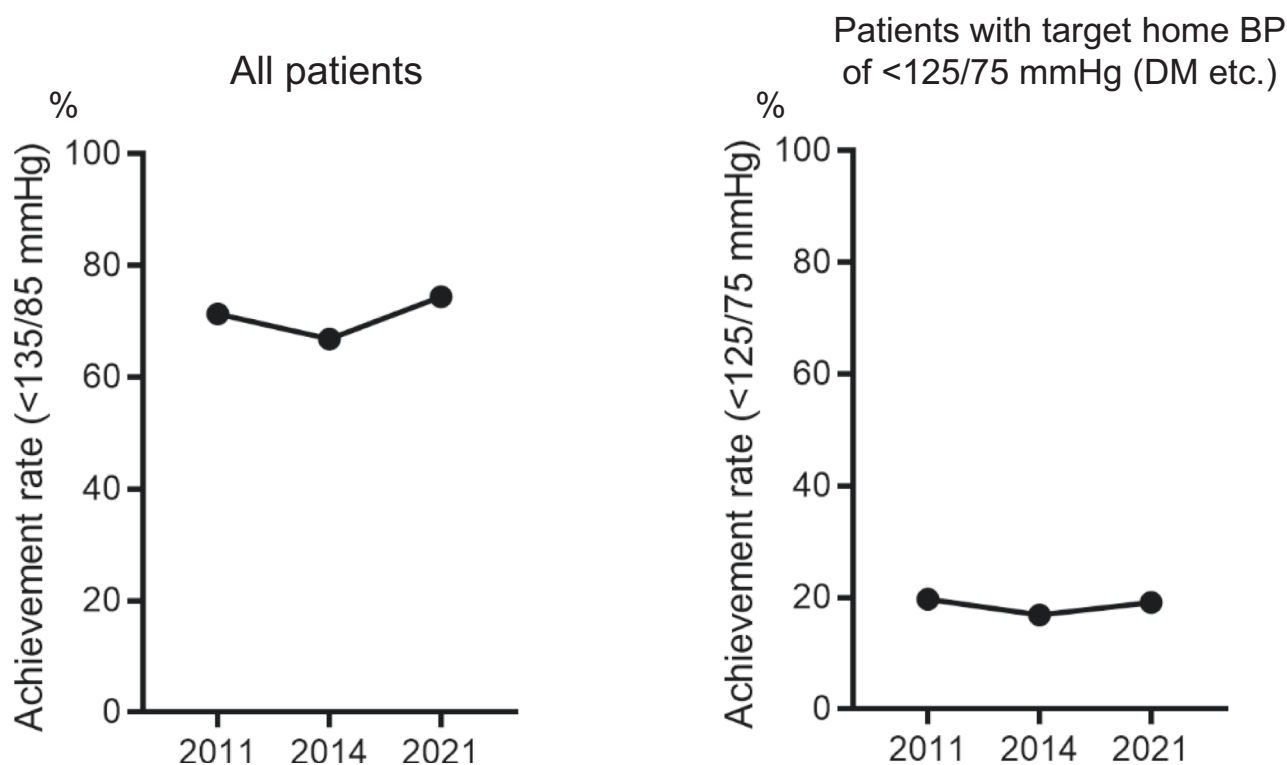


Fig. 1 Achievement rates of target home blood pressure in hypertensive patients. Adapted from Kobayashi et al. [7]

than the 2014 study (66.8%) and the 2011 study (71.3%). However, the achievement rate of target office BP of <140/90 mmHg was 59.8%, which was lower than that in the 2014 study (67.9%) and in the 2011 study (72.2%). In the subgroup analysis for those with DM, cardiovascular disease, CKD, or <75 years of age, the achievement rates of target home and office BP (<125/75 mmHg for home BP and <130/80 mmHg for office BP) were low at 19.1% and 30.4%, respectively, which was not improved from the previous surveys. For those with the target office BP values of <140/90 mmHg, the achievement rate decreased from 60~70% to 46.7% in the 2021 survey; however, more than 80% of patients had controlled home BP levels (<135/85 mmHg) in this population.

As correctly noted by the authors, the data in 2011, 2014, and 2021 were taken independently and the patient characteristics were considerably different, which constitutes a potential limitation of the study. For example, compared with the 2011 or 2014 surveys, the 2021 survey included a higher proportion of diabetic patients (64% as compared with 18 to 20%). Also, the number of patients with the target office BP value of <140/90 was relatively small in the 2021 survey compared with the previous surveys. Despite this, the data by Kobayashi et al. provide up-to-date information regarding BP control in real-world hypertensive patients and point to the presence of the evidence practice gap in this field. A clear message is that the achievement

rate of target BP control in hypertensive patients with DM continues to be low, which needs to be improved to prevent the occurrence of end-organ damage. With the advent of the sodium-glucose co-transporter 2 inhibitor and the non-steroidal mineralocorticoid receptor antagonist, there has been a marked improvement in the treatment of diabetic kidney disease patients [10–12]; nonetheless, the importance of the strict BP control in these patients should not be underestimated. In the FIDELIO-DKD cohort, there was a positive relationship between time-varying office systolic BP levels (ranging from 120 to 160 mmHg) and the risk of primary kidney composite outcome in both treatment groups [13]. Also, the target BP levels for a majority of hypertensive patients have been tightened with the revision of the Japanese guideline in 2019, which may need to be recognized more widely.

Finally, the study showed that there was a significant increase in the proportion of white-coat hypertension in the 2021 survey. It is likely that this finding reflects the fact that the home BP values were given priority to guide treatment in the JSH 2019. Although there is no definitive evidence that white-coat hypertension is the risk factor for the occurrence of cardiovascular diseases, a careful follow-up is recommended since a subpopulation of patients can develop sustained hypertension and cardiac hypertrophy [14, 15]. In one study, there was a positive association of the white-coat effect with BP response to stress, and also with the left

ventricular mass in male untreated hypertensive patients [16]. These patients also showed high ambulatory BP, suggesting that influential factors for the out-of-office BP, such as work stress, can be involved in the latter association. The advancement in wearable monitoring devices that enable the collection of acute BP changes in daily life will greatly facilitate the research to further clarify the clinical significance of BP variations in different situations [17]. In summary, the data by Kobayashi et al. [7] describe the remaining challenges to conquer the hypertension paradox [18] and to reduce the number of patients with uncontrolled hypertension in Japan.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Sakaue S, Kanai M, Karjalainen J, Akiyama M, Kurki M, Matoba N, et al. Trans-biobank analysis with 676,000 individuals elucidates the association of polygenic risk scores of complex traits with human lifespan. *Nat Med.* 2020;26:542–8.
2. Fujiyoshi A, Ohkubo T, Miura K, Murakami Y, Nagasawa SY, Okamura T, et al. Blood pressure categories and long-term risk of cardiovascular disease according to age group in Japanese men and women. *Hypertens Res.* 2012;35:947–53.
3. Group SR, Wright JT Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med.* 2015;373:2103–16.
4. Sakima A, Satonaka H, Nishida N, Yatsu K, Arima H. Optimal blood pressure targets for patients with hypertension: a systematic review and meta-analysis. *Hypertens Res.* 2019;42:483–95.
5. Zhang W, Zhang S, Deng Y, Wu S, Ren J, Sun G, et al. Trial of intensive blood-pressure control in older patients with hypertension. *N Engl J Med.* 2021;385:1268–79.
6. Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019). *Hypertens Res.* 2019;42:1235–481.
7. Kobayashi K, Chin K, Hatori N, Furuki T, Sakai H, Miyakawa M, et al. Cross-sectional survey of hypertension management in clinical practice in Japan: the Kanagawa Hypertension Study 2021 conducted in collaboration with Japan Medical Association Database of Clinical Medicine. *Hypertens Res.* 2023. <https://doi.org/10.1038/s41440-023-01366-z>.
8. Hatori N, Sakai H, Sato K, Mitani K, Miyajima M, Yuasa S, et al. Changes in blood-pressure control among patients with hypertension from 2008 through 2011: surveys of actual clinical practice. *J Nippon Med Sch.* 2014;81:258–63.
9. Hatori N, Sakai H, Sato K, Miyajima M, Yuasa S, Kuboshima S, et al. A survey of actual clinical practice concerning blood pressure control among patients with hypertension in Kanagawa 2014. *J Nippon Med Sch.* 2016;83:188–95.
10. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med.* 2020;383:2219–29.
11. Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet.* 2022;400:1788–801.
12. Fujii W, Shibata S. Mineralocorticoid receptor antagonists for preventing chronic kidney disease progression: current evidence and future challenges. *Int J Mol Sci.* 2023;24:7719.
13. Ruilope LM, Agarwal R, Anker SD, Filippatos G, Pitt B, Rossing P, et al. Blood pressure and cardiorenal outcomes with finerenone in chronic kidney disease in type 2 diabetes. *Hypertension.* 2022;79:2685–95.
14. Munakata M. Clinical significance of stress-related increase in blood pressure: current evidence in office and out-of-office settings. *Hypertens Res.* 2018;41:553–69.
15. Mancia G, Facchetti R, Grassi G, Bombelli M. Adverse prognostic value of persistent office blood pressure elevation in white coat hypertension. *Hypertension.* 2015;66:437–44.
16. Munakata M, Saito Y, Nunokawa T, Ito N, Fukudo S, Yoshinaga K. Clinical significance of blood pressure response triggered by a doctor's visit in patients with essential hypertension. *Hypertens Res.* 2002;25:343–9.
17. Kario K, Tomitani N, Morimoto T, Kanegae H, Lacy P, Williams B. Relationship between blood pressure repeatedly measured by a wrist-cuff oscillometric wearable blood pressure monitoring device and left ventricular mass index in working hypertensive patients. *Hypertens Res.* 2022;45:87–96.
18. Chobanian AV. Shattuck Lecture. The hypertension paradox--more uncontrolled disease despite improved therapy. *N Engl J Med.* 2009;361:878–87.