Chapter 8
Blood Pressure and Cardiovascular Disease in the Elderly

Kei Asayama and Takayoshi Ohkubo

Abstract Even though Japan has the longest life expectancy in the world, blood pressure has not been adequately controlled, irrespective of age. More than half of Japanese individuals of ≥70 years of age had blood pressure levels of ≥140/≥90 mmHg. Though the impact of blood pressure on cardiovascular complications differs according to the age, blood pressure lowering treatment reduces cardiovascular risk across various baseline blood pressure levels and comorbidities. Meanwhile, antihypertensive treatment itself is a sort of marker of the chronicity and severity of blood pressure elevation as well as the subclinical disease burden. Clinicians who initiate antihypertensive drug therapy should therefore recognize that patients have an increased risk in general, e.g., they fail to make lifestyle modifications, not just only related to their blood pressure level. Furthermore, self-measured home blood pressure is more reliable prognostic factors than the conventional office blood pressure, and affordable and validated automated devices for the self-measurement of home blood pressure are readily available. The careful and intensive follow-up of elderly individuals with hypertension is essential, and active utilization of the self-measured home blood pressure is desirable.

Keywords Blood pressure · Elderly · Cardiovascular disease · Out-of-office blood pressure · Self-measured home blood pressure · Antihypertensive drug therapy · Epidemiology · Population science · Clinical trial

K. Asayama (✉) · T. Ohkubo
Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan

Tohoku Institute for Management of Blood Pressure, Sendai, Japan
e-mail: kei@asayama.org

M. Washio, C. Kiyohara (eds.), *Health Issues and Care System for the Elderly*, Current Topics in Environmental Health and Preventive Medicine,
https://doi.org/10.1007/978-981-13-1762-0_8

8.1 Introduction

The impact of blood pressure on cardiovascular complications differs according to the age of the individual [1, 2]. Systolic blood pressure levels increase with age, while diastolic blood pressure values peak at approximately 60 years of age [3]; thus, isolated systolic hypertension, systolic blood pressure ≥140 mmHg with diastolic blood pressure <90 mmHg, is dominant among elderly individuals [4], and systolic blood pressure is a main driver of the risk of cardiovascular disease. In this section, we provide an overview of the current blood pressure level and the impact of blood pressure on cardiovascular complications in relation to antihypertensive drug treatment and blood pressure information, i.e., conventional office and out-of-office home blood pressure.

8.2 Blood Pressure and Its Control in Relation to Aging

Over the long term, an affluent lifestyle can influence the progression of arteriosclerosis. Because both environmental and genetic factors affect the blood pressure trend with age, standardized epidemiological methods that integrate clinical, environmental, and genetic information are necessary to clarify the natural course of blood pressure changes that occur in relation to aging.

The systolic blood pressure level generally increases with age [3]; in Japan, however, the systolic blood pressure levels have gradually decrease since 1965 [5–7]. The spontaneous increase that is observed in the systolic blood pressure with aging is not observed in the diastolic blood pressure. According to the Fifth National Survey on Circulatory Disorders in Japan [8] and the collaborative meta-analysis of individual participant data Japan Arteriosclerosis Longitudinal Study (JALS) [3], the ceiling of diastolic blood pressure in individuals without antihypertensive drug treatment is observed before 60 years of age in men and before 70 years of age in women (Fig. 8.1). Among patients who receive antihypertensive drug medication, an obvious inverse association between age and diastolic blood pressure was found, regardless of sex [3].

Even though Japan has the longest life expectancy in the world [9], blood pressure has not been adequately controlled, irrespective of age [3]. Several studies have reported that more than half of Japanese individuals of ≥70 years of age had blood pressure levels of ≥140/≥90 mmHg [3, 10, 11]. Approximately 1 million US residents in the Practice Innovation and Clinical Excellence (PINNACLE) clinical registry (white, 85.4%; black, 11.9%; antihypertensive drug nonusers, 26.3%) were assessed between 2008 and 2012. Among the patients with hypertension, 66.9% of the patients who were ≥60 years of age without diabetes fulfilled the treatment goal of <140/<90 mmHg [12]. For the prevention of cardiovascular disease in elderly individuals, we should routinely consider reducing their blood pressure to the normotensive range [13].

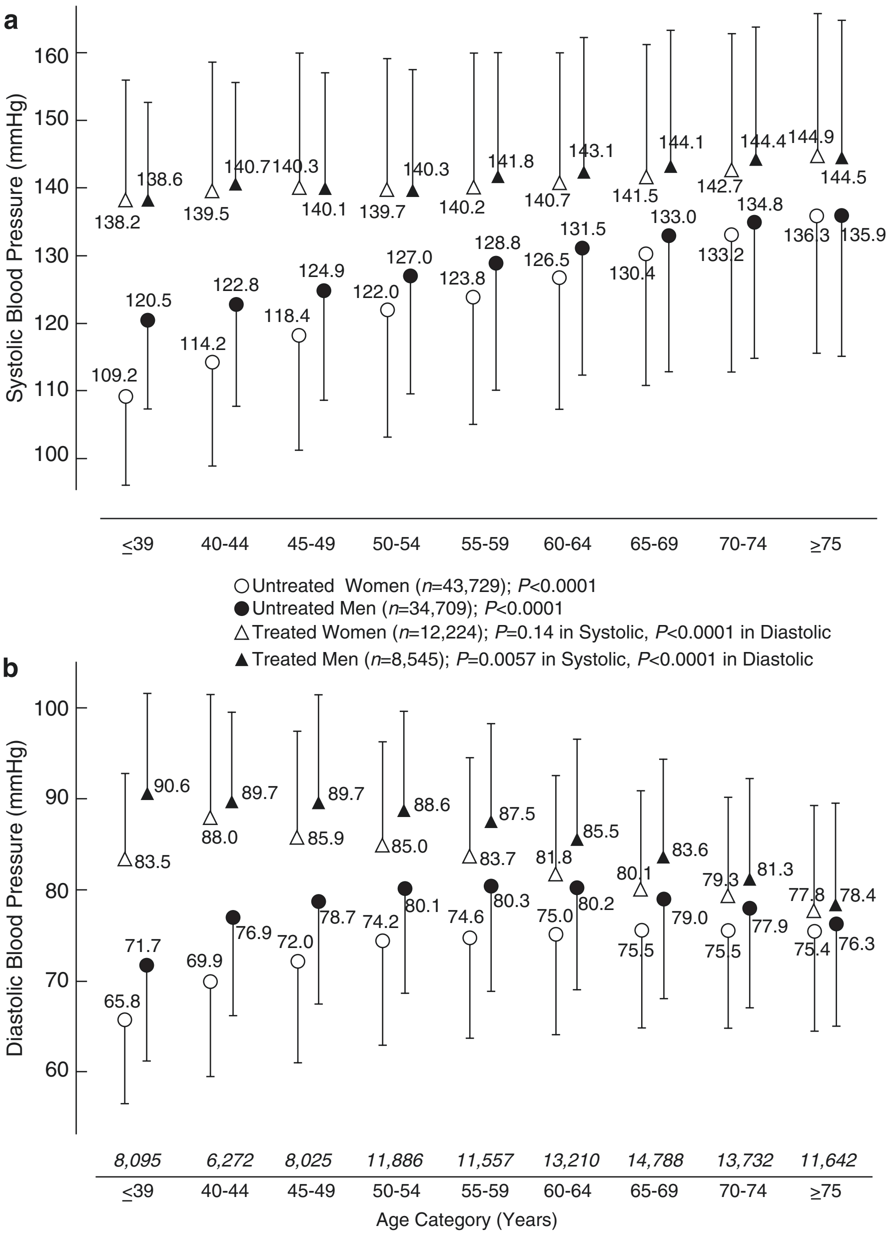

Fig. 8.1 The systolic (**a**) and diastolic (**b**) blood pressure according to age category and treatment status. Women and men without antihypertensive drug treatment at baseline are represented as open and filled circles, respectively. Those with treatment are represented as corresponding triangles. Vertical lines represent one side of the SD. Numbers on the horizontal axis indicate the number of participants in each age category. *P* values denote the linearity among age groups. Reproduced from Asayama and colleagues [3]

8.3 The Impact of Blood Pressure Reduction in Clinical Trials

Blood pressure lowering treatment reduces cardiovascular risk across various baseline blood pressure levels and comorbidities [13]. In a recent meta-analysis of 613,815 participants from 123 randomized trials, a 10-mmHg decrease in systolic blood pressure was associated with a significant 20% reduction (95% CI, 17–23%) in the incidence of major adverse cardiovascular events (MACE) [13]. However, there has not been a specific target blood pressure for treating hypertension in the elderly. In the Systolic Hypertension in the Elderly Program (SHEP) trial, which included patients of ≥60 years of age with systolic hypertension (systolic, ≥160 mmHg), antihypertensive drug treatment reduced the incidence of total stroke and MACE [14]. The Hypertension in the Very Elderly Trial (HYVET) demonstrated the benefit of active treatment in individuals of ≥80 years of age [15]. In contrast, the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) [16] and the Valsartan in Elderly Isolated Systolic Hypertension (VALISH) trial failed to identify any benefits of reducing the systolic blood pressure to <140 mmHg in elderly patients [16, 17]. This may be because these trials [16, 17] were underpowered; the observed event rate in VALISH was less than half the rate estimated in the protocol setting [17].

The Systolic Blood Pressure Intervention Trial (SPRINT) is a landmark study of the treatment of hypertension in both the general [18] and elderly [19] populations. The trial randomized 9631 patients of ≥50 years of age with moderate cardiovascular risk and a systolic blood pressure of 130–180 mmHg [18]. Patients with diabetes and those with history of a prior stroke were excluded because the same study group reported that intensive blood pressure reduction among such patients did not significantly reduce the rate of MACE, although a marginal reduction was observed (HR 0.88; 95% CI, 0.73–1.06) [20]. The research group compared a systolic blood pressure goal of <140 mmHg with a goal of <120 mmHg among 2636 hypertensive patients of ≥75 years of age in SPRINT. In comparison to the former standard treatment group, the latter intensive treatment group demonstrated a significantly greater reduction of MACE by 34% (95% CI, 15–49%), and a 33% (95% CI, 9–51%) reduction of all-cause mortality [19]. The absolute cardiovascular event rates in the subgroup of the approximately 30% of the patients who exhibited frailty were also lower in the intensive treatment group [19].

Different from SPRINT, among men of ≥55 years and women of ≥65 years who were classified as intermediate risk in the Heart Outcomes Prevention Evaluation (HOPE)-3 trial (n = 12,705), therapy with candesartan (16 mg/day) plus hydrochlorothiazide (12.5 mg/day) failed to reduce the incidence of MACE in comparison to a placebo (relative risk reduction, 7%; 95% CI, −10% to 21%) [21]. Besides advanced age, many possible reasons for the findings of SPRINT and HOPE-3, as well as other trials, were discussed [22, 23], including antihypertensive drug agents; for instance, chlorthalidone, which was used in SPRINT, has a greater preventive effect against cardiovascular complications than hydrochlorothiazide [22]. We should note that eligible patients who were allocated to the intensive treatment group in SPRINT showed a 14.8/7.6 mmHg reduction in blood pressure [18, 23]. In HOPE-3, participants in the active treatment group with a systolic blood pressure that was in the upper third (>143.5 mmHg; mean, 154.1 ± 8.9 mmHg) had nominally significantly lower rates of MACE in comparison to those in the placebo group (HR, 0.73; 95% CI, 0.56–0.94) [21, 23]. Based on the SPRINT findings [19] as well as the findings in this HOPE-3 subgroup [21], intensive blood pressure lowering treatment appears to be less harmful, at least among elderly patients with hypertension and moderate cardiovascular risk.

8.4 Recent Findings from the EPOCH-JAPAN Observational Study

The early introduction of antihypertensive medication has a long-term beneficial effect with regard to cardiovascular events [24]. However, people using antihypertensive medication were found to have a higher cardiovascular risk in comparison to those without treatment for a given level of baseline blood pressure after adjustment for major confounding factors [25–27]. Antihypertensive treatment itself is a sort of marker of the chronicity and severity of blood pressure elevation as well as the subclinical disease burden in observational studies [25–28]. The most important explanation for treated hypertensive patients who still have a high cardiovascular risk is lack of control of blood pressure and of other risk factors [28]. Not just related to the blood pressure level alone, clinicians who initiate antihypertensive drug therapy should recognize that patients have an increased risk in general, e.g., they fail to make lifestyle modifications [29].

To clarify the impact of antihypertensive drug treatment on the blood pressure level and the residual cardiovascular risk in elderly population, an individual-level meta-analysis was conducted among 26,133 participants of 60–89 years of age who were recruited from 1980 to 1995 from seven general population cohorts and who were enrolled in the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) [30]. Participants were cross-classified by age category, 60–74 years (young-old) versus 75–89 years (old-old), and by the usage of antihypertensive medication at baseline. Individual blood pressure levels were categorized into six categories according to the recent hypertension guidelines [31, 32]. Among the 4150 old-old participants, 32.2% received antihypertensive medication at baseline. The blood pressures of the treated participants, in reference to the risk for the untreated population, were 12.3 (95% CI, 11.7–12.9)/5.5 (5.2–5.9) mmHg higher among the young-old and 7.6 (6.2–9.1)/2.4 (1.6–3.2) mmHg higher among the old-old. The risk of cardiovascular mortality among the treated participants compared with the untreated population was consistently higher in the young-old (HR, 1.30; 95% CI, 1.16–1.46) and old-old participants (HR, 1.35; 95% CI, 1.16–1.56).

In the EPOCH-JAPAN database, the risks of cardiovascular mortality in the six blood pressure categories according to the treatment status are shown in Fig. 8.2. Irrespective of the antihypertensive medication status, the increase in the risk of total cardiovascular mortality that occurred with the elevation of blood pressure was significant among the young-old ($P \leq 0.0008$), but not significant among old-old

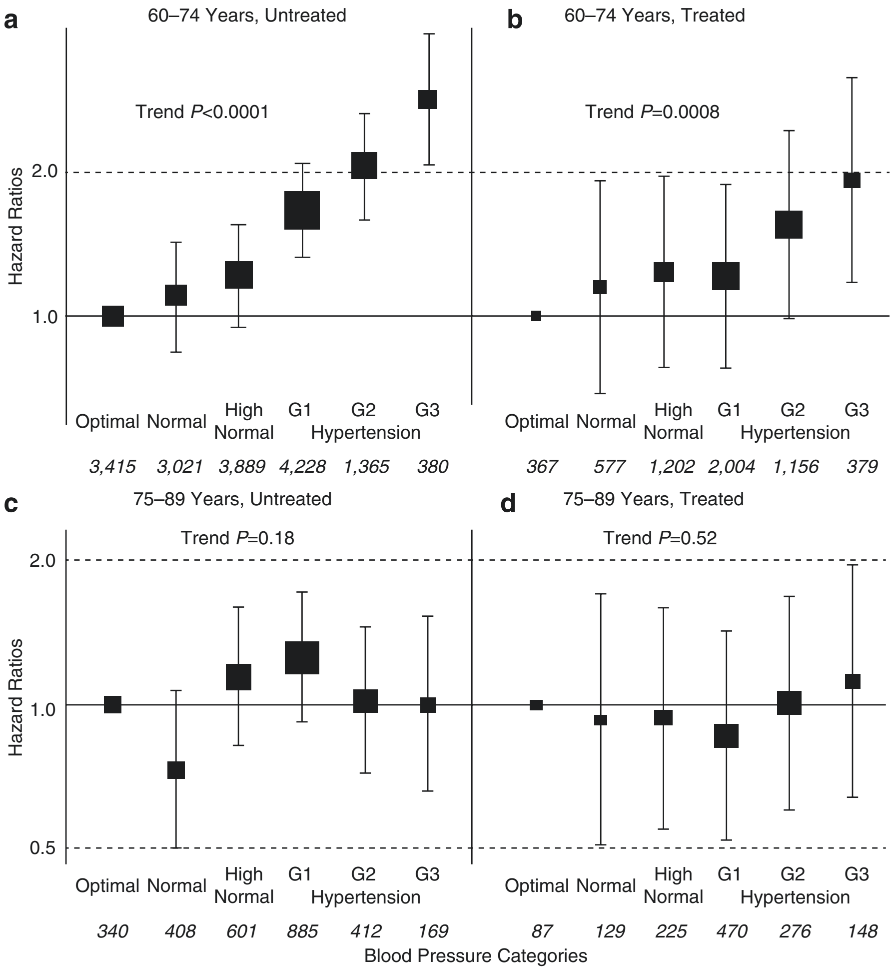

Fig. 8.2 The risk of total cardiovascular mortality among six blood pressure levels in untreated (**a**, **c**) and treated (**b**, **d**) participants of 60–74 years of age (**a**, **b**) and 75–89 years of age (**c**, **d**). Filled squares represent the hazard ratios in comparison to an optimal blood pressure level and are sized in proportion to the number of total cardiovascular deaths observed. Vertical bars indicate the 95% confidence intervals at each level. Blood pressure levels are defined as optimal (<120/<80 mmHg), normal (120–129/80–84 mmHg), high normal (130–139/85–89 mmHg), grade 1 (G1) hypertension (140–159/90–99 mmHg), grade 2 (G2) hypertension (160–179/100–109 mmHg), and grade 3 (G3) hypertension (≥180/≥110 mmHg). Trend *P* values denote the linearity among the six blood pressure levels. Adjustment was performed for sex, age, body mass index, history of cardiovascular disease, total cholesterol, lipid-lowering medication, diabetes mellitus, smoking, habitual drinking, and cohort. Reproduced from Asayama and colleagues [25]

participants ($P \geq 0.18$). The importance of blood pressure control in the elderly should not be underestimated [14, 19, 33, 34]; however, the precautions related to antihypertensive drug therapy in the elderly population vary. Chronological age alone is not sufficient for making useful judgments in relation to therapy [35], and the application of antihypertensive drug therapy should be based on factors that reflect the individual's condition, e.g., frailty and the cognitive function. Because the impact of blood pressure and the benefit of treatment are expected to be lower in older individuals [36], the early detection of hypertension and prompt intervention, including lifestyle modifications [37], is crucial to the long-term approach. Furthermore, we should be vigilant to detect residual cardiovascular risks in treated elderly hypertensive patients [26, 28], despite the fact that these risks are not well specified.

8.5 Out-of-Office Blood Pressure: Self-Measurement at Home

Out-of-office blood pressure, the self-measured home blood pressure and ambulatory blood pressure monitoring, is more reliable prognostic factors than the conventional office blood pressure, which is measured in an outpatient clinic or a health check center [38]. The superiority of out-of-office blood pressure over conventional blood pressure for the prediction of cardiovascular events also applies to older patients in general practice [39]. In the Systolic Hypertension in Europe (Syst-Eur) trial, the ambulatory systolic blood pressure was found to be a significant predictor of the cardiovascular risk among untreated elderly with isolated systolic hypertension and was superior to the conventional blood pressure in this regard [40]. The exclusive use of conventional blood pressure would result in failure to recognize white-coat, which should be carefully monitored [41–43], and masked hypertension, which should be considered to be associated with a similar degree of risk to sustained hypertension [42].

Only a few studies have assessed the risk in relation to home blood pressure in octogenarians. The Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population Study (PARTAGE) [44, 45] included 1127 frail nursing home residents. Among these residents, 227 took ≥2 antihypertensive drugs with a systolic home blood pressure of <130 mmHg (averaged 119/65 mmHg). The mortality rates in these residents and the other 900 residents (averaged 142/75 mmHg) were 32.2% and 19.7%, respectively, and the adjusted HR for cardiovascular events associated with a low blood pressure with combination drug treatment was 1.28 (95% CI, 0.99–1.65) [44]. Moreover, in another analysis of the same cohort, the patients with a lower home diastolic blood pressure (49.3–68.5 mmHg) lived 2 years less than those with higher blood pressure ($P = 0.021$) [45]. These findings raise a cautionary note regarding the safety of combination drug therapy in frail elderly patients with a low systolic home blood pressure [46].

The International Database of HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO) is a collaborating research project. In this project, an individual participant-level database was constructed and maintained at the Studies Coordinating Centre in Leuven, Belgium [47]. Three-hundred seventy-five octogenarians were enrolled in the IDHOCO [48]. A multivariable-adjusted Cox model revealed that among 202 untreated octogenarians, the risk of systolic home blood pressure reached statistical significance in the top fifth (≥152.4 mmHg) for cardiovascular mortality (HR, 2.19; 95% CI, 1.04–4.64) and for all fatal plus nonfatal cardiovascular events combined (HR, 2.09; 95% CI, 1.11–3.91). In contrast, the HRs in the lower fifth (≤65.1 mmHg) were significantly high ($P \leq 0.022$) while that in the upper fifth was significantly low for cardiovascular mortality ($P = 0.034$). The 5-year risk of a cardiovascular event showed an opposite trend between systolic and diastolic home blood pressure (Fig. 8.3). Whereas, among the other 173 octogenarians who were treated with antihypertensive medication at baseline, the relationship between cardiovascular events and the systolic blood pressure was curvilinear, independent of the diastolic blood pressure level, with a nadir at ≈150 mmHg, as shown in Fig. 8.4. Notwithstanding the potential limitations, the IDHOCO findings [48] have a number of implications for clinical practice: (1) a home diastolic blood pressure of <65 mmHg was associated with a worse cardiovascular prognosis, while values above ≈80 mmHg predicted a better outcome in untreated individuals, and (2) a systolic home blood pressure of <126.9 mmHg was associated with increased total mortality with the lowest risk at 148.6 mmHg in treated patients.

Recently, day-to-day home blood pressure variability is considered to be a risk factor for the development of dementia [49] (see Chap. 6) and cognitive decline [50].

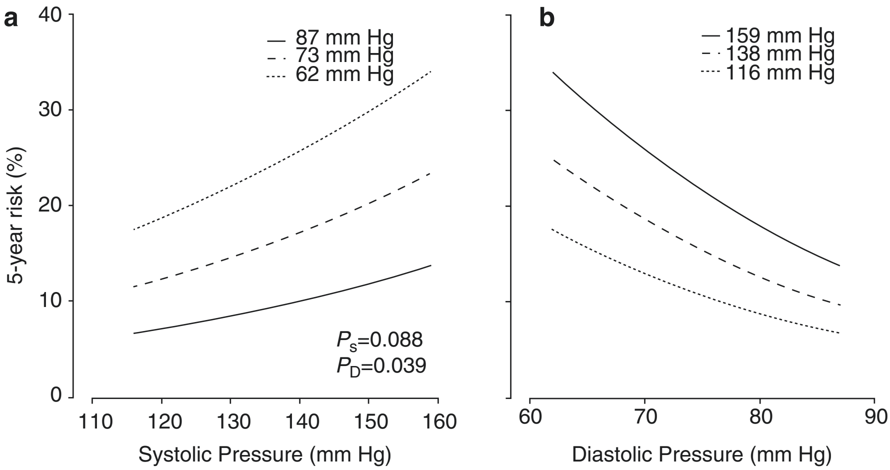

Fig. 8.3 The 5-year risk of a cardiovascular event associated with systolic (**a**) or diastolic (**b**) home blood pressure analyzed as continuous variables and across percentiles (10th, 50th, and 90th) of the alternative component of blood pressure in 202 untreated octogenarians. The risk was standardized according to the distribution (ratio or mean) in the whole untreated population of cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, and history of cardiovascular disease and diabetes mellitus. P_S and P_D indicate the significance of the association with systolic and diastolic home blood pressure, respectively. Reproduced from Aparicio and colleagues [48]

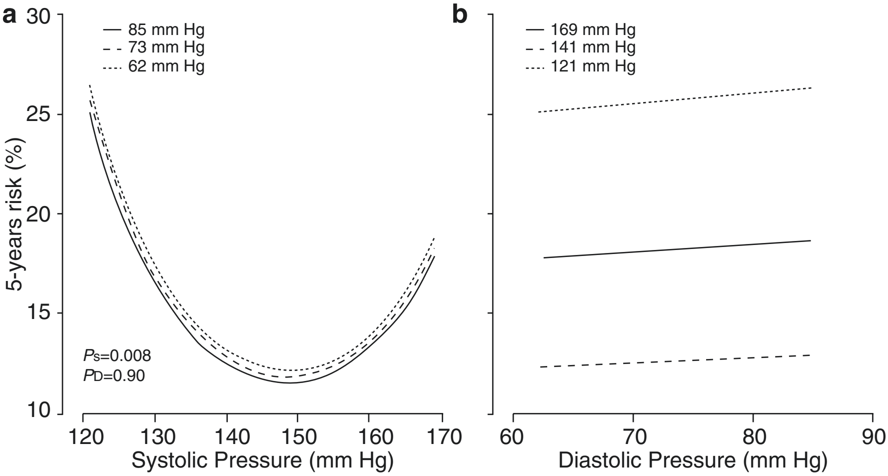

Fig. 8.4 The 5-year risk of a cardiovascular event associated with systolic (**a**) or diastolic (**b**) home blood pressure analyzed as continuous variables and across percentiles (10th, 50th, and 90th) of the alternative component of blood pressure in 173 treated octogenarians. The risk was standardized according to the distribution (ratio or mean) in the whole treated population of cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, and history of cardiovascular disease and diabetes mellitus. P_S and P_D indicate the significance of the association with systolic and diastolic home blood pressure, respectively. The relationship with systolic blood pressure was U-shaped with a nadir at 148.6 mmHg. Reproduced from Aparicio and colleagues [48]

Among residents who participated in the Ohasama study, the home systolic blood pressure at baseline was significantly associated with cognitive decline after a median 7.8 years of follow-up (odds ratio per 1-SD increase, 1.48; $P = 0.03$); however, the conventional systolic blood pressure was not (odds ratio, 1.24; $P = 0.2$) [50]. Furthermore, the day-to-day variability in systolic blood pressure, represented as the SD, showed a significant association with cognitive decline after adjustment for the home systolic blood pressure level (odds ratio, 1.51; $P = 0.02$) [50]. Although the impact of the blood pressure level on cardiovascular complications is attenuated in old-old individuals in comparison to young-old and younger individuals [25, 30], we should pay careful attention to the other outcomes in these populations, and home blood pressure variability as well as the home blood pressure level may be a useful predictor of worse outcomes in the elderly population; however, it should be noted that home blood pressure variability would be difficult to be modified by drug treatment [51].

8.6 Perspectives

SPRINT demonstrated that antihypertensive drug treatment has a beneficial effect with regard to reducing cardiovascular complications in elderly patients with hypertension [52]. The optimal systolic blood pressure goal of <140 mmHg seems reasonable [4], and a more intensive treatment goal, e.g., <130/<80 mmHg for moderate- to high-risk old-old patients, can be recommended [52, 53]. Nevertheless, we should be cautious about the fact that patients on antihypertensive drug treatment had a 1.2–1.5-fold higher risk of cardiovascular mortality in comparison to untreated individuals [30] and that the impact of the blood pressure level decreases with age [30]. Patients with frequent falls, advanced cognitive impairment, and multiple comorbidities may be at risk of adverse outcomes with intensive blood pressure lowering, particularly under combination drug therapy [46], because such residents typically reside in nursing homes, require assistance for their daily living, and are never represented in modern randomized trials [53]. Once a patient starts antihypertensive drug treatment, the self-measurement of the home blood pressure should be performed for the long-term management of hypertension because the recording of the daily home measurements enables us to safely and conveniently monitor adverse effects. Home blood pressure measurement is feasible and can be largely diffused to the elderly individuals in the general population [54]. Furthermore, affordable and validated automated devices for the self-measurement of home blood pressure are readily available. The careful and intensive follow-up of elderly individuals with hypertension is essential [30], and active utilization of the self-measured home blood pressure is desirable.

Acknowledgments We gratefully acknowledge the secretary of the Department of Hygiene and Public Health, Teikyo University School of Medicine for their valuable support.

Sources of Funding None.

Conflict of Interests K. Asayama and T. Ohkubo are consultants for Omron Healthcare Co., Ltd (Kyoto, Japan).

References

1. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903–13.
2. Lawes CM, Rodgers A, Bennett DA, Parag V, Suh I, Ueshima H, et al. Blood pressure and cardiovascular disease in the Asia Pacific region. J Hypertens. 2003;21(4):707–16.
3. Asayama K, Hozawa A, Taguri M, Ohkubo T, Tabara Y, Suzuki K, et al. Blood pressure, heart rate, and double product in a pooled cohort: the Japan arteriosclerosis longitudinal study. J Hypertens. 2017;35(9):1808–15.
4. Bavishi C, Goel S, Messerli FH. Isolated systolic hypertension: an update after SPRINT. Am J Med. 2016;129(12):1251–8.
5. Miura K, Nagai M, Ohkubo T. Epidemiology of hypertension in Japan. Circ J. 2013; 77(9):2226–31.
6. Ueshima H. Explanation for the Japanese paradox: prevention of increase in coronary heart disease and reduction in stroke. J Atheroscler Thromb. 2007;14(6):278–86.
7. Ueshima H, Tatara K, Asakura S, Okamoto M. Declining trends in blood pressure level and the prevalence of hypertension, and changes in related factors in Japan, 1956–1980. J Chronic Dis. 1987;40(2):137–47.

8. Ministry of Health, Labor and Welfare. National survey on circulatory disease, 2000. Tokyo: Ministry of Health, Labor and Welfare; 2002.
9. World Health Organization. World Health Statistics 2016: Monitoring health for the SDGs. 2016. http://www.who.int/gho/publications/world_health_statistics/2016/en/.
10. Hozawa A, Ohkubo T, Kikuya M, Yamaguchi J, Ohmori K, Fujiwara T, et al. Blood pressure control assessed by home, ambulatory and conventional blood pressure measurements in the Japanese general population: the Ohasama study. Hypertens Res. 2002;25(1):57–63.
11. Ohkubo T, Obara T, Funahashi J, Kikuya M, Asayama K, Metoki H, et al. Control of blood pressure as measured at home and office, and comparison with physicians' assessment of control among treated hypertensive patients in Japan: first report of the Japan Home versus Office Blood Pressure Measurement Evaluation (J-HOME) study. Hypertens Res. 2004;27(10):755–63.
12. Borden WB, Maddox TM, Tang F, Rumsfeld JS, Oetgen WJ, Mullen JB, et al. Impact of the 2014 expert panel recommendations for management of high blood pressure on contemporary cardiovascular practice: insights from the NCDR PINNACLE registry. J Am Coll Cardiol. 2014;64(21):2196–203.
13. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957–67.
14. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA. 1991;265(24):3255–64.
15. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358(18):1887–98.
16. JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). Hypertens Res. 2008;31(12):2115–27.
17. Ogihara T, Saruta T, Rakugi H, Matsuoka H, Shimamoto K, Shimada K, et al. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. Hypertension. 2010;56(2):196–202.
18. SPRINT Research Group, 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(22):2103–16.
19. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged >/=75 years: a randomized clinical trial. JAMA. 2016;315(24):2673–82.
20. Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1575–85.
21. Lonn EM, Bosch J, Lopez-Jaramillo P, Zhu J, Liu L, Pais P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016;374(21):2009–20.
22. Whelton PK, Reboussin DM, Fine LJ. Comparing the SPRINT and the HOPE-3 blood pressure trial. JAMA Cardiol. 2016;1(8):855–6.
23. Yusuf S, Lonn E. The SPRINT and the HOPE-3 trial in the context of other blood pressure-lowering trials. JAMA Cardiol. 2016;1(8):857–8.
24. Bosch J, Lonn E, Pogue J, Arnold JM, Dagenais GR, Yusuf S, et al. Long-term effects of ramipril on cardiovascular events and on diabetes: results of the HOPE study extension. Circulation. 2005;112(9):1339–46.
25. Asayama K, Satoh M, Murakami Y, Ohkubo T, Nagasawa SY, Tsuji I, et al. Cardiovascular risk with and without antihypertensive drug treatment in the Japanese general population: participant-level meta-analysis. Hypertension. 2014;63(6):1189–97.
26. Asayama K, Ohkubo T, Yoshida S, Suzuki K, Metoki H, Harada A, et al. Stroke risk and antihypertensive drug treatment in the general population: the Japan arteriosclerosis longitudinal study. J Hypertens. 2009;27(2):357–64.

27. Lieb W, Enserro DM, Sullivan LM, Vasan RS. Residual cardiovascular risk in individuals on blood pressure-lowering treatment. J Am Heart Assoc. 2015;4(11):e002155.
28. Ibsen H. Antihypertensive treatment and risk of cardiovascular complications: is the cure worse than the disease? J Hypertens. 2009;27(2):221–3.
29. Kjeldsen SE, Jamerson KA, Bakris GL, Pitt B, Dahlof B, Velazquez EJ, et al. Predictors of blood pressure response to intensified and fixed combination treatment of hypertension: the ACCOMPLISH study. Blood Press. 2008;17(1):7–17.
30. Asayama K, Ohkubo T, Satoh A, Tanaka S, Higashiyama A, Murakami Y, et al. Cardiovascular risk and blood pressure lowering treatment among elderly individuals: evidence for cardiovascular prevention from observational cohorts in Japan. J Hypertens. 2018;36:410–8.
31. Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, et al. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2009). Hypertens Res. 2009;32(1):3–107.
32. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159–219.
33. Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet. 2001;358(9290):1305–15.
34. Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet. 2003;362(9395):1527–35.
35. Materson BJ, Garcia-Estrada M, Preston RA. Hypertension in the frail elderly. J Am Soc Hypertens. 2016;10(6):536–41.
36. Staessen JA, Fagard R, Thijs L, Celis H, Birkenhager WH, Bulpitt CJ, et al. Subgroup and per-protocol analysis of the randomized European Trial on Isolated Systolic Hypertension in the Elderly. Arch Intern Med. 1998;158(15):1681–91.
37. Shimamoto K, Ando K, Fujita T, Hasebe N, Higaki J, Horiuchi M, et al. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2014). Hypertens Res. 2014;37(4):253–390.
38. Asayama K, Brguljan-Hitij J, Imai Y. Out-of-office blood pressure improves risk stratification in normotension and prehypertension people. Curr Hypertens Rep. 2014;16(10):478.
39. Fagard RH, Van Den Broeke C, De Cort P. Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice. J Hum Hypertens. 2005;19(10):801–7.
40. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. JAMA. 1999;282(6):539–46.
41. Franklin SS, Thijs L, Hansen TW, Li Y, Boggia J, Kikuya M, et al. Significance of white-coat hypertension in older persons with isolated systolic hypertension: a meta-analysis using the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes population. Hypertension. 2012;59(3):564–71.
42. Asayama K, Thijs L, Li Y, Gu YM, Hara A, Liu YP, et al. Setting thresholds to varying blood pressure monitoring intervals differentially affects risk estimates associated with white-coat and masked hypertension in the population. Hypertension. 2014;64(5):935–42.
43. Ugajin T, Hozawa A, Ohkubo T, Asayama K, Kikuya M, Obara T, et al. White-coat hypertension as a risk factor for the development of home hypertension: the Ohasama study. Arch Intern Med. 2005;165(13):1541–6.
44. Benetos A, Labat C, Rossignol P, Fay R, Rolland Y, Valbusa F, et al. Treatment with multiple blood pressure medications, achieved blood pressure, and mortality in older nursing home residents: the PARTAGE study. JAMA Intern Med. 2015;175(6):989–95.

45. Benetos A, Gautier S, Labat C, Salvi P, Valbusa F, Marino F, et al. Mortality and cardiovascular events are best predicted by low central/peripheral pulse pressure amplification but not by high blood pressure levels in elderly nursing home subjects: the PARTAGE (predictive values of blood pressure and arterial stiffness in institutionalized very aged population) study. J Am Coll Cardiol. 2012;60(16):1503–11.
46. Aronow WS. Multiple blood pressure medications and mortality among elderly individuals. JAMA. 2015;313(13):1362–3.
47. Niiranen TJ, Thijs L, Asayama K, Johansson JK, Ohkubo T, Kikuya M, et al. The International Database of HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO): moving from baseline characteristics to research perspectives. Hypertens Res. 2012;35(11):1072–9.
48. Aparicio LS, Thijs L, Boggia J, Jacobs L, Barochiner J, Odili AN, et al. Defining thresholds for home blood pressure monitoring in octogenarians. Hypertension. 2015;66(4):865–73.
49. Oishi E, Ohara T, Sakata S, Fukuhara M, Hata J, Yoshida D, et al. Day-to-day blood pressure variability and risk of dementia in a general Japanese Elderly Population: the Hisayama study. Circulation. 2017;136(6):516–25.
50. Matsumoto A, Satoh M, Kikuya M, Ohkubo T, Hirano M, Inoue R, et al. Day-to-day variability in home blood pressure is associated with cognitive decline: the Ohasama study. Hypertension. 2014;63(6):1333–8.
51. Asayama K, Ohkubo T, Hanazawa T, Watabe D, Hosaka M, Satoh M, et al. Does antihypertensive drug class affect day-to-day variability of self-measured home blood pressure? The HOMED-BP study. J Am Heart Assoc. 2016;5(3):e002995.
52. Rochlani Y, Khan MH, Aronow WS. Managing hypertension in patients aged 75 years and older. Curr Hypertens Rep. 2017;19(11):88.
53. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):e13–e115..
54. Cacciolati C, Tzourio C, Dufouil C, Alperovitch A, Hanon O. Feasibility of home blood pressure measurement in elderly individuals: cross-sectional analysis of a population-based sample. Am J Hypertens. 2012;25(12):1279–85.