



Step for breaking free from clinical inertia

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In August 2021, the main results of STEP, a comparison of blood pressure targets for older hypertensive patients between two groups, were published [1]. STEP is a Chinese version of the US SPRINT study [2], which showed the benefits of intensive treatment. However, STEP has a couple of significant differences compared to SPRINT. STEP included diabetic patients (19%), used standard office blood pressure measurements, not automated office blood pressure measurements, used combination with home blood pressure measurements, compared the influence of apps, which may affect practice behavior. Several organizations have published hypertension treatment guidelines since 2017 from the USA [3], Europe [4], Japan [5], the International Society of Hypertension [6], and WHO [7]. The STEP will have a significant impact on the future revision of the guidelines for the treatment of hypertension.

The STEP study compared the incidence of combined cardiovascular events in hypertensive patients aged 60–80 years (mean age 66.3 years) without previous stroke, divided into two groups: the 110–129 mmHg systolic blood pressure group (intensive treatment group) and the 130–149 mmHg systolic blood pressure group (standard treatment group). The study compared the incidence of combined cardiovascular events in the intensive treatment group and the standard treatment group. Cardiovascular events occurred in 3.5% of patients in the intensive treatment group with a significant risk reduction of 26% compared with 4.6% in the standard treatment group. STEP assessed the risk of excessive blood pressure reduction by symptoms and renal dysfunction, then confirmed the safety of intensive antihypertensive treatment.

These results of the STEP may require reconsidering their antihypertensive blood pressure targets or age categories. Since the STEP intensive treatment group achieved a

target blood pressure of 127.5 mmHg, the guidelines from Europe [4] may reconsider removing a lower range for target blood pressure of the recommendation of 130–139 mmHg in the 65–79 years. The guidelines from ISH [6] recommend <130 mmHg for <65 years and <140 mmHg for ≥65 years, but may reconsider the age of separation for older people from 65 to higher.

It is also important to note that the STEP subjects are up to 80 years of age, and no studies have yet demonstrated the benefit and safety of lowering blood pressure to less than 130 mmHg in hypertensive patients aged over 80 years. From a geriatric point of view, it is precisely after the age of late 70 years that the decline in various organ reserves and multimorbidity often occurs. Therefore it is necessary to consider blood pressure targets classified by age or alternative biological indicators rather than those without age classification.

A systematic review by the Japanese Society of Hypertension [8] conducted to examine antihypertensive targets for people aged 75 years, and over found that the mean age of subjects in each included study ranged from 76 to 80 years, about 10 years older than the 67.9 years in SPRINT and 66.2 years in STEP. In this systematic review, the authors selected six randomized controlled trials. They performed a meta-analysis of these trials to enable us to examine, whether a more intensive antihypertensive target than a systolic blood pressure of less than 150 mmHg should recommend for hypertensive patients aged 75 years or older (some aged 70 years or older). This meta-analysis showed that more intensive antihypertensive treatment is better for reducing cardiovascular and all-cause mortality, and that there is insufficient evidence to recommend less than 130 mmHg. Therefore, the Japanese guidelines recommended an antihypertensive target of less than 140 mmHg for hypertensive patients aged 75 years and over. In addition, the meta-analysis for the Japanese guidelines failed to show a benefit of active antihypertensive measures for the composite of cerebral-vascular and cardiovascular events ($P = 0.13$) [8]. We conducted a new meta-analysis by adding data from STEP in the 70–80 age group. As shown in Fig. 1, there were

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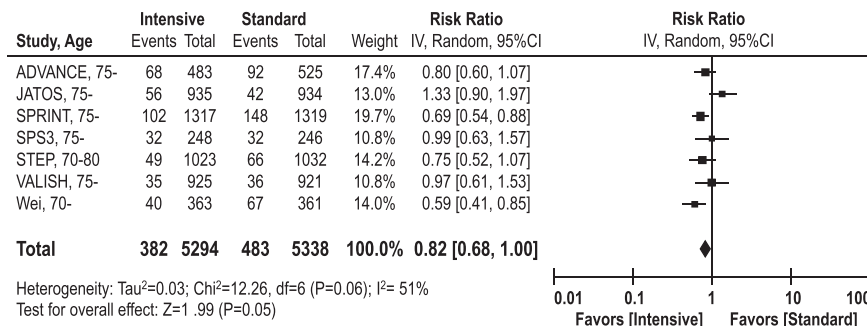


Fig. 1 Effect of intensive BP lowering on risk of composite cardiovascular events in older patients Boxes and horizontal lines represent RR and 95% CI for each trial. The size of boxes is proportional to the weight of that trial result. Diamonds represent the 95% CI for pooled

estimates of effect and are centered on pooled RR. Diamonds represent the 95% CI for pooled estimates of effect and are centered on pooled RR

fewer events in the intensive treatment group with a risk ratio of 0.82 (95% CI 0.68–1.00, $P = 0.05$). After additional validation, we should reconsider the age categories set for JSH2019 when detailed data on the STEP 70–80 age group are published. We should emphasize that four of the seven studies, including STEP, were conducted in Asia and represent 61% of the total population, making this analysis important in terms of the Asian guiding principles.

Another critical aspect of STEP includes 19% of patients with diabetes, whereas SPRINT did not include. As shown in the STEP Supplementary Appendix, the trend towards fewer events in the intensive treatment group remained unchanged, with hazard ratios (95% CI) of 0.74 (0.57–0.94) and 0.77 (0.50–1.17), respectively. Regarding the previous stroke excluded in either SPRINT or STEP, a meta-analysis including the results of RESPECT, a Japanese trial of antihypertensive targets, has confirmed the importance of intensive lowering of blood pressure to <130 mmHg [9]. These recent reports during the past few years, including the STEP results, provide strong evidence of the superiority of intensive blood pressure reduction in patients with high cardiovascular risk.

The low control rate of hypertensive patients is a problem throughout the world, including in Japan [10]. As the definition of control rate means the proportion of treated patients who are <140/90 mmHg, the proportion of patients <130 mmHg is even lower. A significant reason for the low rate of blood pressure control is the presence of clinical inertia. We should use the publication of the STEP results as an opportunity to actively deliver information and evidence on the importance of active antihypertensive treatment to practitioners and to break away from clinical inertia. It is time for the Japanese Society of Hypertension and all related organizations concerned with hypertension to launch a global awareness campaign to strengthen antihypertensive treatment.

Another significant aspect of STEP is measuring home blood pressure with a validated automated monitor and

uploading it to the data-recording center. Although it is not a comparative study of blood pressure target set using home blood pressure as an index, we expect to obtain much information about the index of home blood pressure for intensive antihypertensive treatment. After 1 year of the STEP, the blood pressure visually measured from the graph was 127.5/76.3 mmHg in the office and 127.2/78.5 mmHg in the home in the intensive treatment group, and 135.3/79.0 mmHg and 131.8/80.3 mmHg at home in the standard treatment group [1]. The Japanese guidelines recommend a target for home blood pressure that is 5 mmHg lower than the target for office blood pressure within the range of antihypertensive targets [5]. As the association between the office and home blood pressure in STEP was not simply a difference of 5 mmHg, the guidelines may need to reconsider the setting of home blood pressure targets in conjunction with other studies.

Finally, we should note with great respect that the changes in blood pressure over time reveal the hard work of the investigators in conducting the study. In the standard treatment group, the office blood pressure has remained almost the same level, and the home blood pressure has risen rather than fallen; in the intensive treatment group, the office blood pressure has continued to fall, and the home blood pressure has remained the same or fallen slightly over time. If the differences in blood pressure between the two groups were too small, the study would not examine the difference in event occurrence. Efforts to devise a study protocol and alert physicians during the study are presumed to have resulted in the crucial findings of STEP. We express our sincere respect to all those involved in the study.

Compliance with ethical standards

Conflict of interest HR has received lecture fees from Daiichi Sankyo, MSD, Novartis Pharma, Takeda Pharmaceutical, and research grants from Astellas Pharma, Bayer Yakuhin, Daiichi Sankyo, Dainippon Sumitomo Pharma, Kyowa Hakko Kirin, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, MSD, Nippon Boehringer Ingelheim, Novartis Pharma, Sanofi, and Takeda Pharmaceutical.

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