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EDITORIAL

Utility of the "Strategy of Blood Pressure Intervention in Elderly Hypertensive Patients" for home blood pressure management in a real-world setting

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The Strategy of Blood Pressure Intervention in Elderly Hypertensive Patients (STEP) trial [1] that included mainly young-old (54% women, mean age 66 years old) and low-to-mild-risk hypertensive patients (94% already treated at baseline [2]) in China who had a smartphone and were able to use smartphone applications demonstrated that intensive reduction in the office systolic blood pressure (BP) to a target of 110 to <130 mmHg (intensive treatment) resulted in a significantly lower incidence of cardiovascular events than reduction to a target of 130 to <150 mmHg (standard treatment) during a median follow-up period of 3.34 years [1]. Primary-outcome events occurred in 147 patients (3.5%) in the intensive-treatment group, compared with 196 patients (4.6%) in the standard-treatment group (hazard ratio, 0.74; 95% confidence interval [CI], 0.60–0.92; $P = 0.007$). The relatively low event rates in the intensive-treatment group were broadly comparable to the between-group differences in achieved BP values (~9.2 and 2.8 mmHg for systolic and diastolic BP, respectively): the mean systolic BP was 126.7 mmHg in the intensive-treatment group and 135.9 mmHg in the standard-treatment group, whereas the mean diastolic BP was 76.4 and 79.2 mmHg, respectively. At 42 months, the mean number of antihypertensive medications administered per patient was 1.9 in the intensive-treatment group and 1.5 in the standard-treatment group, indicating that a between-group difference in the mean number of antihypertensive medications of 0.4. In the STEP trial, the mean number of antihypertensive medications alone was used to indicate the intensity of the antihypertensive treatment, whereas the dose of antihypertensive medications, which is another important factor representing the intensity of the antihypertensive treatment, was not herein described. Further analysis is warranted to clarify how the difference in the dose of antihypertensive medications may be attributable to the difference in the BP values and the incidence of primary-outcome events.

In the STEP trial [1, 2], all patients were required to obtain home BP readings at least 1 day per week during follow-up. Every patient was provided with a validated automated home BP monitor (Omron Healthcare Co. Ltd, Kyoto, Japan). The BP monitor was paired with a smartphone-based app with a Bluetooth function. The app was used to collect home BP readings obtained by the patient and then to upload the readings to a data-recording center. Patients were required to rest for at least 5 minutes in a seated position before the initial BP reading was obtained, and BP was measured three times at least 1 minute apart in the morning within 1 hour of waking after urination but before antihypertensive drugs intake and breakfast.

Although no information was provided on home BP values at baseline before the initiation of study treatment, the between-group differences in achieved home BP values at 2 years from randomization were ~8.0 and 3.5 mmHg for systolic and diastolic BP, respectively, which was comparable to the between-group differences in achieved office BP values mentioned above [1]. Figure 1B also showed seasonal variation in home BP values. However, the variation was strange in that differed from previous reports describing lower BP values during winter [3, 4], although no discussion was provided.

Furthermore, interestingly, home BP values increased by a few millimeters of mercury throughout the intervention period in the standard-treatment group (achieved average home systolic BP values: >135 mmHg, which exceeded the reference values for home systolic BP) and decreased by a few millimeters of mercury during the first 2 years in the

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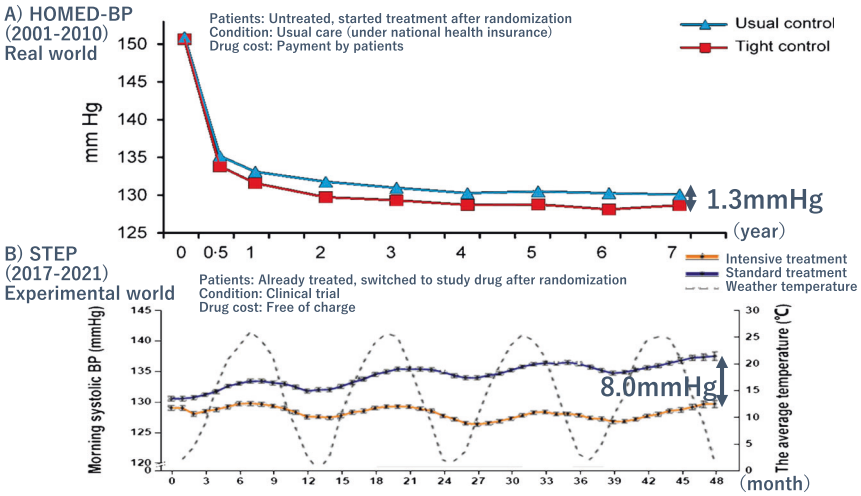

Fig. 1 **A** Follow-up of 1759 patients randomized to the usual control and 1759 allocated to tight control for systolic home BP in the HOMED-BP study (2001–2010) [5], and **B** systolic home BP in relation to the outside temperature in the two treatment groups throughout the STEP trial (2017–2021) [1]

intensive-treatment group, remaining stable thereafter, irrespective of seasons. A further analysis to clarify the factors underlying this phenomenon with consideration of the effect of the change in intensity of antihypertensive treatment and change in lifestyles is warranted.

In the study protocol [2], the titration (increase or decrease) of antihypertensive treatment, which enabled the patients' BP to reach the randomized target BP levels, was based on the office BP. Therefore, study treatment was not increased in patients with masked uncontrolled hypertension (those with treated home BP ≥ 135/85 mmHg) when the office BP was within the protocol range in the standard-treatment group. This protocol might be the reason for the elevated event rates in the standard-treatment group.

Twenty years ago, we conducted the multicenter Hypertension Objective Treatment Based on Measurement by Electrical Devices of BP trial (HOMED-BP; 2001–2010), which involved 3518 low-to-mild-risk hypertensive patients (50% women; mean age 59.6 years old) with an untreated systolic/diastolic home BP of 135–179/85–119 mmHg [5]. Home BP was measured by a newly developed (at that time) automatic device, based on the cuff-oscillometric principle, which can memorize systolic/diastolic BP values and the date and time of each measurement (HEM-747IC-N; Omron). Registered patients are instructed how to use the device and then asked to take a BP reading in the sitting position once every morning within an hour of waking and after at least 2 minutes of rest. The home BP of an individual, defined as the average of the last five consecutive measurements before every visit, is used for the inclusion, randomization, and treatment. Patients were randomized to the usual control group (125–134/80–84 mmHg) and the tight control group (<125/<80 mmHg) of home BP. At the last follow-up (median 5.3 years), the tight control group used only slightly more antihypertensive drugs (1.82 vs. 1.74 defined daily doses) and had only slightly more home BP reduction (21.3/13.1 mmHg vs. 22.7/13.9 mmHg; between-group difference 1.4/0.8 mmHg) than the usual control group. The primary endpoint occurred in 25 in the usual control group and in 26 in the usual control group (hazard ratio, 1.02; 95% CI, 0.59–1.77; $P = 0.94$), suggesting that such small between-group differences in home BP values did not affect the incidence of events.

In the HOMED-BP study, conducted among untreated patients under real-world, usual health insurance conditions (Fig. 1A), doctors and patients were reluctant to start and up-titrate antihypertensive drug treatment in order to achieve the stringent BP targets outlined in the protocol and often overruled or did not adhere to the centrally generated treatment recommendations [5]. Because the HOMED-BP study was conducted under usual healthcare conditions, we included in the protocol that the final decision was up to doctors. Accordingly, the rate at which treatment recommendations were implemented during the first 2 years after randomization was below 30%. As a result, the home BP was only 1.3 (systolic) and 0.8 mmHg (diastolic) lower in patients randomized to tight control than in those with usual control. It is possible that the patients in the tight control group refused to increase the number of drugs they were taking since these patients were concerned about drug prices as the patients had to pay for the drugs according to the Japanese National Health Insurance program from the moment that the patients were included in the HOMED-BP study. This might therefore be associated with the lack of any substantial difference in the home BP values between the tight control group and the usual control group.

The STEP trial [1, 2], similar to the Systolic BP Intervention Trial [6], was an experimental clinical trial (Fig. 1B), and the doctors and patients were essentially obligated to follow the protocol. Furthermore, most patients were already being treated [2] with antihypertensive drugs

paid for by themselves. After randomization, the previous antihypertensive drugs were stopped, and new study drugs were provided to patients free of charge, allowing the study patients to save money on medication. These may be reasons why the patients in the intensive-treatment group agreed to add drugs even though their home or office BP values were on average lower than the usually recommended target BP levels (office BP of 140/90 mmHg and home BP of 135/85 mmHg). In addition, the patients were limited to those who were reasonably digitally savvy with a smartphone and able to use smartphone applications. However, such situations are less common in the real world. Further investigations are needed to clarify whether or not this strategy is effective in real-world settings.

Compliance with ethical standards

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