**Isolated Systolic Blood Pressure**

**On-Treatment Blood Pressure and Cardiovascular Outcomes in Older Adults With Isolated Systolic Hypertension**

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See Editorial Commentary, pp 200–201

**Abstract**—Our aim was to assess optimal on-treatment blood pressure (BP) at which cardiovascular disease (CVD) and all-cause mortality risks are minimized in Japanese older adults with isolated systolic hypertension. We used data from the VALISH study (Valsartan in Elderly Isolated Systolic Hypertension) that recruited older adults (n=3035; mean age, 76 years) with systolic BP (SBP) of ≥160 mm Hg and diastolic BP of <90 mm Hg. Patients were treated by valsartan. Patients were also categorized into 3 groups based on achieved on-treatment SBP of <130 mm Hg (n=317), 130 to <145 mm Hg (n=2025), or ≥145 mm Hg (n=693). The primary outcome was composite CVD (coronary heart disease, stroke, heart failure, cardiovascular deaths, other vascular diseases, and kidney diseases) with secondary outcome being all-cause mortality. Cox proportional hazards models were used to assess the CVD risk for each group. Over a median 3-year follow-up (8022 person-years), 93 CVD events and 52 deaths occurred. Using the on-treatment SBP of 130 to <145 mm Hg as reference stratum, the multivariable-adjusted hazard ratios and 95% confidence intervals of CVD and all-cause mortality risks for those with SBP<130 mm Hg were 2.08 (1.12–3.83) and 2.09 (0.93–4.71) and for those with SBP≥145 mm Hg were 2.29 (1.44–3.62) and 2.51 (1.35–4.66), respectively. On-treatment diastolic BP yielded no relationships with CVD or all-cause mortality risk. In conclusion, among Japanese older adults with isolated systolic hypertension, SBP in the range between 130 and 144 mm Hg was associated with minimal adverse outcomes and a reduction in CVD and all-cause mortality. The BP range will need to be confirmed in randomized controlled trials.

**Clinical Trial Registration**—URL: [https://www.clinicaltrials.gov](https://www.clinicaltrials.gov). Unique identifier: NCT00151229.

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**Key Words:** blood pressure ■ cardiovascular diseases ■ elderly ■ hypertension ■ mortality ■ U-shaped relationship

By 2050, older adults (aged ≥65 years) will number >1 billion worldwide, representing 15% of the global population.1 Despite the ubiquity of this aging phenomenon, there is often uncertainty in the clinical management of older adults, particularly with regard to intensity of therapy.2 Hypertension, defined as systolic BP (SBP) of ≥140 mm Hg or diastolic BP (DBP) of ≥90 mm Hg, is one such problem. The optimal BP goal for older adults continues to be debated and its determination is a pressing need.2,3

SBP tends to rise with age, and the prevalence of hypertension is 60% to 90% in older adults.4,5 More than 60% of older people with hypertension have isolated systolic hypertension (ISH)5,6; elevated SBP but normal or even low DBP, as a consequence of reduced elasticity and compliance of large arteries and atherosclerosis.6,7 Because ISH is associated with high risk for serious health problems, including coronary heart disease (CHD), stroke, heart failure, and kidney disease,6–10 the urgency is greater than ever to determine on-treatment BP levels at which cardiovascular risks are minimized in older adults with ISH.

Using data from the VALISH study (Valsartan in Elderly Isolated Systolic Hypertension), a randomized controlled trial designed to compare the effect of intensive (SBP target <140 mm Hg) versus moderate (≥140 and <150 mm Hg) SBP-lowering treatment on cardiovascular outcomes in older Japanese patients with ISH,11,12 we sought to assess the
associations between on-treatment BP levels and cardiovascular outcomes. The primary end points were similar between intensive and moderate BP-lowering treatment,\textsuperscript{1,12} and therefore analyses were conducted by merging all participant data.

**Methods**

**Study Design**

This is a post hoc, on-treatment analysis of the VALISH study, a multicenter, parallel-group, prospective, randomized, open-label, blinded end point, investigator-designed trial conducted in Japan.\textsuperscript{1,12} The study protocol was approved by all of the involved ethics committees, and all of the patients gave written informed consent. The patients were recruited between February 2004 and August 2005 and followed up until March 2008. The inclusion and exclusion criteria, study design details, and full results have been published previously.\textsuperscript{1,12} Briefly, patients aged 70 to 84 years with ISH (SBP≥160 mm Hg and DBP≥90 mm Hg) were enrolled in the study and randomly assigned as intensive versus moderate BP-lowering treatment. For patients who have been treated with 1 or 2 antihypertensive drugs other than valsartan, these drugs were switched to valsartan without using a washout period. Valsartan, 40 to 80 mg QD, was administered as the first-step treatment. If the target SBP in each group was not achieved within 1 to 2 months, the dose of valsartan was increased to 160 mg per day, followed by other antihypertensive classes except other angiotensin II type 1 receptor blockers (eg, diuretics and calcium channel blockers) until the target SBP was reached.

Patients visited the clinic every 3 months for at least 2 years, and investigators were asked to complete case report forms documenting adverse events, end points, withdrawals, and vital signs including BP. Clinic BP measurements were undertaken at each local medical institution according to the recommendations of the Japanese Guideline for Treatment of Hypertension,\textsuperscript{13} by medical staff using the standard sphygmomanometer or an automated device on the brachial artery after the patients had rested for 5 minutes in a seated position. On-treatment BP was calculated by mean BP level achieved by the treatment for each patient using all but the baseline BP measurements to describe the shape of the associations between absolute BP change from baseline to follow-up (ie, on-treatment BP minus the baseline BP) and cardiovascular outcomes. To avoid choosing a reference point that may increase the likelihood of getting significant results, we used different reference points when fitting the cubic spline curves. Then, we estimated the optimal BP associated with minimal cardiovascular risk, which was defined as a reference category when patients were categorized into 3 groups by their on-treatment BP. However, this may be an arbitrary classification. Therefore, in a sensitivity analysis, we divided study population into quartiles according to on-treatment BP and assessed their clinical consequences. We also drew a restricted cubic spline curve (knots at every 3 mm Hg in BP) to describe the shape of the associations between absolute BP change from baseline to follow-up (ie, on-treatment BP minus the baseline BP) and cardiovascular outcomes.

Clinical characteristics according to on-treatment SBP categories were compared using the ANOVA for continuous variables, and categorical parameters were compared with the $\chi^2$ test. Outcomes were assessed with Kaplan–Meier plots, and Cox proportional hazards models were assessed to estimate multivariate-adjusted hazard ratios and 95% confidence intervals of incident CVD risk associated with on-treatment SBP. The proportionality assumption for the Cox analyses was confirmed graphically and with the inclusion of a time by on-treatment SBP interaction. Follow-up time was censored on the date of last event ascertainment. Patients who did not experience any component of outcomes were censored at the last study visit. Our analyses were performed with sequential adjustments. In the first step, we performed unadjusted analyses (model 1). In the second step, we added demographic variables (age and sex) and treatment strategy (intensive versus moderate SBP-lowering treatment) as adjustment covariates (model 2). In the third step, we added clinical characteristics at baseline (smoking, prevalent diabetes mellitus, prevalence hyperlipidemia, hypertension medication use, and prevalent CVD) and baseline SBP level as covariates (model 3). These covariates were selected a priori because they are risk factors for incident CVD.\textsuperscript{16} In the last step, we further adjusted for on-treatment DBP (model 4) or absolute SBP change from baseline to follow-up (model 5). Next, analyses of the interaction between on-treatment SBP and sex, baseline age (<80 and ≥80 years), treatment strategy (intensive versus moderate SBP lowering), baseline antihypertensive medication use, and prevalent diabetes mellitus or CVD at baseline in association with incident CVD were performed with inclusion of multiplicative interaction terms. Subgroup analyses by these clinical characteristics were also conducted. Statistical significance was defined as a $P<0.05$ on 2-sided tests. All statistical analyses were performed with STATA version 12.1 (STATA Corp, College Station, TX).

**Outcomes Ascertainment**

Details have been described in the online-only Data Supplement.\textsuperscript{1,12}

**Statistical Analysis**

Descriptive statistics are presented as means and SD, and proportions where appropriate. Several investigations of BP and outcomes in older adults have demonstrated nonlinear associations, and thus we used a data-guided approach to assess the nature of the relationship between on-treatment BP and outcomes. To identify the point of lowest risk of events, we began by fitting restricted cubic spline models with knots at every 3 mm Hg of on-treatment BP and cardiovascular outcomes. To avoid choosing a reference point that may increase the likelihood of getting significant results, we used different reference points when fitting the cubic spline curves. Then, we estimated the optimal BP associated with minimal cardiovascular risk, which was defined as a reference category when patients were categorized into 3 groups by their on-treatment BP. However, this may be an arbitrary classification. Therefore, in a sensitivity analysis, we divided study population into quartiles according to on-treatment BP and assessed their clinical consequences. We also drew a restricted cubic spline curve (knots at every 3 mm Hg in BP) to describe the shape of the associations between absolute BP change from baseline to follow-up (ie, on-treatment BP minus the baseline BP) and cardiovascular outcomes.

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**Results**

Of the 3079 VALISH patients, we excluded 44 patients without any BP measurements during follow-up (7 patients experienced CVD events and 1 patient died before their first follow-up examination), leaving a sample of 3035 patients for analysis. Table 1 provides the demographic variables and clinical characteristics of the included patients.

During a median (interquartile range) follow-up of 3.0 years (2.3–3.3 years; 8022.13 person-years), 93 composite CVD events (11.9 per 1000 person-years), including 29 CHD events (3.6 per 1000 person-years) and 34 strokes (4.2 per 1000 person-years), and 52 deaths (6.5 per 1000 person-years) occurred. Figure 1 shows the hazard ratios of incident CVD risk associated with on-treatment SBP or DBP level. A U-shaped relationship was observed between on-treatment SBP and CVD risk. Until SBP reaches ≈140 mm Hg, lower on-treatment SBP was linearly associated with a reduced risk of CVD. We defined the lowest risk at SBP of 130 to <145 mm Hg on the basis of analyses in which we used different reference points when fitting the cubic spline curve (Figure S1 in the online-only Data Supplement). Conversely, on-treatment DBP yielded no relationship with CVD risk (Figure 1). The amount of absolute SBP change from baseline to follow-up yielded a U-shaped relationship with CVD risk (Figure S2). We defined the lowest risk at a SBP change between −40 and −30 mm Hg on the basis of analyses in which we used different reference points when fitting the cubic spline curve (Figure S3). When all-cause mortality was assessed as an outcome, results are similar (Figure S4).

Patients were stratified into 3 groups based on their achieved on-treatment SBP: those with SBP of <130 mm Hg (n=317), 130 to <145 mm Hg (n=2025), or ≥145 mm Hg (n=693). Their mean (SD) on-treatment SBP levels were 125 (5) mm Hg, 138 (4) mm Hg, and 151 (8) mm Hg, respectively (Table 1). The distribution of on-treatment SBP is shown in Figure S5. Among those with on-treatment SBP of <130 mm Hg, 70% were assigned to receive intensive BP-lowering
therapy. Baseline SBP and pulse pressure levels and the proportion of antihypertensive medication use were higher in those with on-treatment SBP of \( \geq 145 \) than in those with on-treatment SBP of 130 to <145 mm Hg or <130 mm Hg, whereas the proportion of prevalent CVD at baseline was highest in those with on-treatment SBP <130 mm Hg.

The incidence rate of CVD events was lower in those with on-treatment SBP of 130 to <145 mm Hg (7.8/1000 person-years) than in those with on-treatment SBP of <130 mm Hg (16.5/1000 person-years) and with on-treatment SBP of \( \geq 145 \) mm Hg (21.6/1000 person-years; Table S1). Figure 2 shows the Kaplan–Meier cumulative probability of remaining free of a CVD event, stratified by on-treatment SBP categories. The probability was highest in those with on-treatment SBP of 130 to <145 mm Hg.

Results from Cox models suggested that patients with on-treatment SBP of <130 mm Hg or \( \geq 145 \) mm Hg had an increased risk of composite CVD compared with those with on-treatment SBP of 130 to <145 mm Hg (Table 2, model 1). Adjustments for demographic variables (model 2), baseline clinical characteristics (model 3), and on-treatment DBP (model 4) did not change the results. With further adjustment for absolute SBP change from baseline to follow-up, which was used as a categorical variable (<−40 versus −40 to −30 versus >−30 mm Hg) because it showed a U-shaped relationship with CVD risk (Figure S2), CVD and all-cause mortality risks of on-treatment SBP of <130 mm Hg were attenuated, whereas those of on-treatment SBP of \( \geq 145 \) mm Hg retained statistical significance (model 5). When we assessed hard CVD events (n=60) as an outcome, results were similar (Table S2).

Repeating Cox analyses including on-treatment SBP categories and all covariates, with the inclusion of an interaction term, suggested that there were no significant interactions between on-treatment SBP categories and sex, baseline age

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**Table 1. Patient Characteristics According to On-Treatment SBP Categories (n=3035)**

<table>
<thead>
<tr>
<th>Descriptive Variable at Baseline</th>
<th>Total (n=3035)</th>
<th>On-Treatment SBP</th>
<th>( \text{BP} &lt; 130 \text{ mm Hg} ) (n=317)</th>
<th>( \text{BP} \geq 130 \text{ mm Hg} ) (n=2,025)</th>
<th>( \text{SBP} \geq 145 \text{ mm Hg} ) (n=693)</th>
<th>( P ) Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>76.1±4.1</td>
<td>76.0±4.0</td>
<td>76.2±4.1</td>
<td>0.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>1141 (37.6)</td>
<td>119 (37.5)</td>
<td>759 (37.5)</td>
<td>263 (38.0)</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.5±3.4</td>
<td>22.7±3.5</td>
<td>23.5±3.4</td>
<td>23.6±3.5</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>446 (14.7)</td>
<td>45 (14.2)</td>
<td>306 (15.1)</td>
<td>95 (13.7)</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>169.2±8.7</td>
<td>167.3±9.2</td>
<td>169.2±8.3</td>
<td>170.2±9.4</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>81.7±6.4</td>
<td>81.4±6.9</td>
<td>82.0±6.0</td>
<td>80.8±7.2</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>87.5±10.0</td>
<td>85.9±10.2</td>
<td>87.2±9.7</td>
<td>89.4±10.8</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Baseline antihypertensive medication use,* n (%)</td>
<td>1507 (49.7)</td>
<td>155 (48.9)</td>
<td>930 (45.9)</td>
<td>422 (60.9)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Calcium-channel blockers, n (%)</td>
<td>981 (32.3)</td>
<td>99 (31.2)</td>
<td>584 (28.8)</td>
<td>298 (43.0)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>ACE inhibitors, n (%)</td>
<td>241 (7.9)</td>
<td>18 (5.7)</td>
<td>150 (7.4)</td>
<td>73 (10.5)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Angiotensin receptor blockers, n (%)</td>
<td>388 (12.8)</td>
<td>44 (13.9)</td>
<td>230 (11.4)</td>
<td>114 (16.5)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>131 (4.3)</td>
<td>13 (4.1)</td>
<td>79 (3.9)</td>
<td>39 (5.6)</td>
<td>0.15</td>
<td></td>
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<tr>
<td>β-Blockers, n (%)</td>
<td>125 (4.1)</td>
<td>17 (5.3)</td>
<td>67 (3.3)</td>
<td>41 (5.9)</td>
<td>0.01</td>
<td></td>
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<tr>
<td>Prevalent hyperlipidemia, n (%)</td>
<td>630 (20.8)</td>
<td>63 (19.9)</td>
<td>410 (20.2)</td>
<td>157 (22.7)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Prevalent diabetes mellitus, n (%)</td>
<td>393 (12.9)</td>
<td>32 (10.1)</td>
<td>229 (11.3)</td>
<td>132 (19.0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Prevalent CVD, n (%)</td>
<td>356 (11.7)</td>
<td>63 (19.9)</td>
<td>200 (9.9)</td>
<td>93 (13.4)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Prevalent CHD, n (%)</td>
<td>148 (4.9)</td>
<td>31 (8.8)</td>
<td>81 (4.0)</td>
<td>36 (5.2)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Prevalent stroke, n (%)</td>
<td>190 (6.3)</td>
<td>29 (9.2)</td>
<td>109 (5.4)</td>
<td>52 (7.5)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Assigned as intensive BP-lowering therapy, n (%)</td>
<td>1526 (50.3)</td>
<td>217 (68.5)</td>
<td>1051 (51.9)</td>
<td>258 (37.2)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ±SD or percentage. Prevalent CVD includes coronary heart disease, stroke, and heart failure. ACE indicates angiotensin-converting enzyme; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*The proportion of antihypertensive medication use when patients were randomized is shown. Statistical significance was defined as \( P < 0.05 \).
(≤80 and ≥80 years), treatment strategy (intensive versus moderate SBP lowering), and prevalent diabetes mellitus or CVD at baseline in association with CVD risk (all P≥0.07). The results obtained from subgroup analyses by these clinical characteristics were similar to those in the main analyses (Figure S6).

When we used on-treatment SBP quartiles to test the association between on-treatment SBP and CVD risk, the third quartile group was defined as the lowest risk on the basis of analyses in which we set the reference group separately (Figure S7). A U-shaped relationship was observed between on-treatment SBP and CVD risk, with the lowest risk at the third quartile (on-treatment SBP: 139–144 mm Hg; Figure 3).

Using a reference of on-treatment SBP of 130 to <145 mm Hg and absolute SBP change from baseline to follow-up of −40 to −30 mm Hg (ie, a reduction in SBP during follow-up was 30–40 mm Hg), at which the risk of CVD event was minimized (Figure 1; Figure S2), CVD risk associated with on-treatment SBP<130 mm Hg was significant when a reduction in SBP was >40 mm Hg. Whereas CVD risk associated with on-treatment SBP of ≥145 mm Hg was significant when a reduction in SBP was <30 mm Hg (Table 3).

Discussion

Our study, based on results from observational and secondary analyses in the VALISH study, demonstrated that among older Japanese adults with ISH and SBP of ≥160 mm Hg at baseline, the on-treatment SBP level at which the risks of CVD events and all-cause mortality were minimized was 130 to <145 mm Hg. On-treatment SBP of <130 or ≥145 mm Hg were associated with increased risks of CVD events and all-cause mortality (ie, a U-shaped relationship), which was held in each of the randomized treatment groups in the VALISH study. With adjustment for absolute SBP change from baseline to follow-up, the CVD risk of on-treatment SBP <130 mm Hg was attenuated, whereas that of on-treatment SBP of ≥145 mm Hg retained statistical significance. On-treatment DBP was not associated with the risk of CVD events or all-cause mortality.

Findings in Context

Three major outcome studies of ISH have been conducted in the United States, Europe, and China. The SHEP (Systolic Hypertension in the Elderly Program)17 and the Syst-Eur trial (Systolic Hypertension in Europe) demonstrated that lowering SBP in older (≥60 years) adults with ISH reduced adverse cardiovascular outcomes.18 The Syst-China trial (Systolic
Hypertension in China) also demonstrated that antihypertensive treatment prevents stroke and all-cause mortality. The SBP achieved by treatment was 143 to 144 mm Hg, which was the basis for the Joint National Committee 8 panel’s selection of 150 mm Hg as a treatment target for older adults. We observed that lowering SBP, until reaching \( \approx 140 \) mm Hg, was linearly associated with reduced risks of CVD events and all-cause mortality. This is consistent with the recent meta-analysis demonstrating the efficacy of SBP lowering <140 mm Hg in high-risk patients. Baseline SBP and pulse pressure levels and the proportion of antihypertensive medication use were higher in those with on-treatment SBP of \( \geq 145 \) than in those with on-treatment SBP of 130 to <145 mm Hg or <130 mm Hg. The CVD risk of on-treatment SBP of \( \geq 145 \) mm Hg was significant in those with a reduction in SBP from baseline to follow-up of <−30 mm Hg. These findings suggest that CVD risk of on-treatment SBP of \( \geq 145 \) mm Hg may be attributable to insufficient BP reduction in high-risk patients. Although the BP lowering in our patients seemed to be primarily derived from medication, this conclusion was only observational in nature, and thus our results cannot be used as evidence against the Joint National Committee 8 panel’s decision.

Caution is required in interpreting the results on the range of optimal on-treatment SBP in older Japanese adults with ISH. Because of a lack of consensus on the optimal on-treatment SBP level in older adults with ISH, we used a data-guided approach (ie, restricted cubic spline curve) to assess the relationship between on-treatment BP and outcomes. The optimal on-treatment BP group (ie, on-treatment SBP of 130 to <145 mm Hg) in this study encompassed a wide BP range and included 67% of the study population, and thus it may be an arbitrary classification. Although the analyses by on-treatment SBP quartiles showed a similar U-shaped relationship between on-treatment SBP and CVD risk, the selection of the reference group may also be somewhat arbitrary. To adjudicate whether an on-treatment SBP of 130 to <145 mm Hg is an optimal treatment target for older adults with

### Table 2. Unadjusted and Multivariable-Adjusted Hazard Ratios (95% Confidence Intervals) for Risks of Composite CVD and All-Cause Mortality by On-Treatment SBP Categories

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>On-Treatment SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP&lt;130 mm Hg (n=317)</td>
</tr>
<tr>
<td>Composite CVD events</td>
<td>Model 1 (unadjusted)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Model 2 (unadjusted)</td>
</tr>
<tr>
<td></td>
<td>Model 3 (unadjusted)</td>
</tr>
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<td></td>
<td>Model 4 (unadjusted)</td>
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</table>

Unadjusted and adjusted hazard ratios (95% confidence intervals) for risks of composite CVD events and all-cause mortality among each on-treatment SBP category are shown. As adjustment factors, model 2 includes demographic variables (age at baseline, sex, treatment strategy: intensive vs moderate BP-lowering treatment), model 3 includes demographic variables plus clinical characteristics at baseline (smoking status, prevalent diabetes mellitus, prevalence hyperlipidemia, SBP level, hypertension medication use, and prevalent CVD), Model 4 includes demographic variables plus clinical characteristics at baseline plus on-treatment diastolic blood pressure, and model 5 includes demographic variables plus clinical characteristics at baseline plus SBP change from baseline to follow-up (<−40 vs −40 to −30 vs >−30 mm Hg). CVD indicates cardiovascular disease; and SBP, systolic blood pressure.

Statistical significance was defined as \( P<0.05 \). * \( P<0.05 \), † \( P<0.001 \), ‡ \( P<0.01 \).

Figure 3: Adjusted hazard ratios (HRs) for risk of composite cardiovascular disease (CVD) events by on-treatment systolic blood pressure (SBP) quartiles. Bars represent adjusted HRs (95% confidence intervals [CIs]) of composite CVD risk by on-treatment SBP quartiles. The third quartile group was defined as reference. As adjustment factors, age, sex, treatment strategy (intensive vs moderate SBP lowering), clinical characteristics at baseline (smoking, prevalent diabetes mellitus, prevalence hyperlipidemia, SBP level, use of antihypertensive drugs, and prevalent CVD) were used.
ISH, randomized controlled clinical trials with the objective of investigating optimal BP targets are needed to make more definitive conclusions.

We found higher CVD events and mortality if SBP was lowered <130 mmHg compared with an on-treatment SBP of 130 to <145 mmHg. Seventy percent of those with an on-treatment SBP of <130 mmHg were assigned to receive intensive BP-lowering therapy. The CVD risk of on-treatment SBP <130 mmHg was significant only in those with a reduction in SBP from baseline to follow-up of >40 mmHg. Although the results require careful interpretation because of the small event number, they may suggest that CVD risk associated with on-treatment SBP of <130 mmHg is attributable to excess reduction in SBP during follow-up. However, it cannot be known in our cases whether antihypertensive treatment caused the adverse effects, or whether these effects were simply the result of subclinical disease that was unmasked by treatment.

The SPRINT investigators (Systolic Blood Pressure Intervention Trial) observed that, among hypertensive patients without diabetes mellitus, lowering SBP to a target goal of <120 mmHg, as compared with <140 mmHg, reduced CVD events and all-cause mortality even in those aged >75 years.22,23 However, the results need to be considered in the context that patients with diabetes mellitus and stroke were excluded from SPRINT, and the recruited older patients were not exclusively patients with ISH. In addition, the baseline SBP in older adults of SPRINT was much lower than our patients (142/72 versus 169/82 mmHg), whereas attained SBP was similar between the intensive treatment group in SPRINT and on-treatment SBP of <130 mmHg group in VALISH (123/62 versus 125/70 mmHg). This raises the question about whether it is the SBP change or the achieved level that matters in older adults. Other differences include the way BP was measured in SPRINT and the speed of BP change between VALISH and SPRINT, which older adults with ISH may not tolerate rapid BP change because of their stiffened arteries. BP measurement in SPRINT used automated office BP that yields BPs as much as 10 mmHg systolic lower than routine office measurement.24 The current study highlights the need to carefully evaluate the effect of intensive SBP lowering in high-risk older adults, such as those with ISH and comorbidity, particularly the amount of SBP reduction by treatment.

Whether BP treatment targets in older adults should consider factors such as frailty or functional status (eg, slow gait speed, poor grip strength, and unexplained weight loss) has been the topic of considerable debate.1 In exploratory analyses from SPRINT,23 the cardiovascular benefit of lowering SBP to a target goal of <120 mmHg, as compared with <140 mmHg, was consistent regardless of the degree of individual frailty status or gait speed. Conversely, observational studies in older adults illustrate that the relationship between on-treatment BP and outcomes differs by frailty.1 SPRINT excluded patients with 1-minute standing SBP of <110 mmHg, unintentional weight loss of >10% in the last 6 months, and living in nursing homes.25 Therefore, the SPRINT results may have a limited transferability to very frail older adults. Whether the degree of frailty helps guide treatment targets in older adults cannot be determined and is beyond the scope of this study and will require further investigation.

DBP lowering is an inevitable consequence when physicians treat older patients with ISH, which raises a concern that low DBP may have an adverse effect on coronary circulation because the heart is perfused during diastole. In the SHEP study, CVD risk increased in treated patients whose DBP was lowered <70 mmHg.26 The Syst-Eur trial found that in those with CHD at baseline, on-treatment DBP of <70 mmHg was associated with CVD risk.27 Conversely, we found no relationship between CVD risk and on-treatment DBP. These studies vary in several respects, including the populations, baseline comorbidities, and treatment regimens, which might have contributed to the inconsistent results. The proportion of incident CHD to total events was lower in the VALISH study than in

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### Table 3. Incidence Rates of Composite CVD and Multivariable-Adjusted Hazard Ratios for Risk of Composite CVD Events Among Each Group Stratified by On-Treatment SBP Level and the Amount of Absolute SBP Change From Baseline to Follow-Up

<table>
<thead>
<tr>
<th>SBP Reduction &gt;40 mmHg</th>
<th>SBP Reduction of 40–30 mmHg</th>
<th>SBP Reduction &lt;30 mmHg</th>
</tr>
</thead>
</table>
| **The frequency of CVD events (total number) and corresponding incidence rates (per 1000 person-years)** | **The incidence rates of composite CVD and multivariable-adjusted hazard ratios for risk of composite CVD among each group stratified by on-treatment SBP level and SBP reduction from baseline to follow-up are shown. CI indicates confidence interval; CVD, cardiovascular disease; HR, hazard ratio; and SBP, systolic blood pressure.**

<table>
<thead>
<tr>
<th>On-treatment SBP &lt;130 mmHg</th>
<th>10/169 (22.42; 12.06 to 41.66)</th>
<th>4/139 (10.88; 4.09 to 29.00)</th>
<th>0/9</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-treatment SBP of 130 to &lt;145 mmHg</td>
<td>6/329 (6.53; 2.93 to 14.53)</td>
<td>17/1,513 (8.75; 5.44 to 14.08)</td>
<td>20/543 (7.55; 4.87 to 11.71)</td>
</tr>
<tr>
<td>On-treatment SBP ≥145 mmHg</td>
<td>1/23 (14.86; 2.09 to 105.52)</td>
<td>1/142 (5.24; 0.74 to 37.18)</td>
<td>34/528 (24.20; 17.29 to 33.86)</td>
</tr>
</tbody>
</table>

**Multivariable-adjusted HRs (95% CIs) for risks of composite CVD**

<table>
<thead>
<tr>
<th>On-treatment SBP &lt;130 mmHg</th>
<th>2.61 (1.19–5.73)†</th>
<th>1.20 (0.39–3.69)</th>
<th>…</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-treatment SBP of 130 to &lt;145 mmHg</td>
<td>0.80 (0.29–2.21)</td>
<td>1 (reference)</td>
<td>0.81 (0.41–1.64)</td>
</tr>
<tr>
<td>On-treatment SBP ≥145 mmHg</td>
<td>2.04 (0.23–17.64)</td>
<td>0.66 (0.84–5.20)</td>
<td>2.64 (1.44–4.83)†</td>
</tr>
</tbody>
</table>

The incidence rates of composite CVD and multivariable-adjusted hazard ratios for risk of composite CVD among each group stratified by on-treatment SBP level and SBP reduction from baseline to follow-up are shown. CI indicates confidence interval; CVD, cardiovascular disease; HR, hazard ratio; and SBP, systolic blood pressure.

*As adjustment factors, age at baseline, sex, treatment strategy (intensive vs moderate BP-lowering treatment), and baseline SBP level were included. Statistical significance was defined as P<0.05. †P<0.05, ‡P<0.01.
the SHEP and Syst-Eur trials (30% versus 40%–45%). The baseline prevalence of CHD was also lower in our study than in the SHEP and Syst-Eur trials (5 versus 5%–14%). Although subclinical CHD was not evaluated, an Agatston coronary artery calcium (CAC) score of ≥100 is more common in older whites than in Japanese (60% versus 30%). Taken together, these facts suggest that target organ heterogeneity may exist, ie, the optimal treatment BP may differ by organs (the heart, the brain, and the kidney). This possibility, however, could not be tested because of the low number of events in this study.

The strengths of our study include the recruitment of well-characterized patients, adjudication of suspected cardiovascular outcomes by a panel of physicians using detailed evaluation criteria, and high retention. However, there are also some limitations. First, this is a post hoc analysis from a randomized trial, and thus its nature is almost equivalent to that of an observational study. Although the achieved BP was primarily from treatment, there remains the possibility of residual confounding in the associations between achieved BP and CVD event. Indeed, the patients with on-treatment SBP of <130 mm Hg had the highest proportion of prevalent CVD at baseline. Recent post hoc analyses from the SPS3 (Secondary Prevention of Small Subcortical Strokes) trial revealed a J-shaped relationship between on-treatment SBP and recurrent stroke events among patients with lacunar infarcts. However, our models were adjusted for prevalent CVD at baseline, and we found no evidence for effect modification in the stratified analyses. Second, out-of-office BP and orthostatic BP change were not assessed. The impacts of overtreatment for the white-coat effect or orthostatic hypotension on outcomes remain uncertain. Finally, our results may not be generalizable to older adults without ISH or other race/ethnic groups.

Perspectives
In older adults with ISH, lowering of SBP was associated with reduced risks of CVD events and all-cause mortality, irrespective of on-treatment DBP. However, on-treatment SBP of <130 mm Hg may deserve careful attention, and probably excess reduction in SBP by treatment (eg, SBP reduction of >40 mm Hg from baseline) should be avoided. High BP in older adults is a complex and heterogeneous pathological condition, and thus one size may not fit all in the clinical management. Determining which patients would be most likely to benefit from lowering SBP to a target goal of <130 (or 120) mm Hg and those who should avoid such treatment (eg, those with vascular stiffness) may help to prevent CVD, reduce unnecessary medical expenditures, and increase treatment efficiency in older adults with hypertension.

Acknowledgments
We gratefully acknowledge the contribution of the VALISH study group (Valsartan in Elderly Isolated Systolic Hypertension), the members of which are listed in the Appendix of original article by Ogihara et al.

Sources of Funding
This study was funded by a grant from the Japan Cardiovascular Research Foundation and supported by the Japanese Society of Hypertension. Dr Yano was supported by the AHA Strategically Focused Research Network Fellow Grant.

Disclosures

References

What Is New?

• Among older Japanese adults with isolated systolic hypertension, the on-treatment systolic blood pressure (SBP) level at which the risks of cardiovascular disease events and all-cause mortality were minimized was 130 to <145 mmHg. On-treatment SBP of <130 mmHg or ≥145 mmHg were associated with increased risks of cardiovascular disease events and all-cause mortality (ie, a U-shaped relationship).

What Is Relevant?

• The current study highlights the need to carefully evaluate the effect of intensive SBP-lowering in high-risk older adults, such as those with isolated systolic hypertension, particularly the amount of SBP reduction by treatment.

Summary

Among Japanese older adults with isolated systolic hypertension, SBP in the range between 130 and 144 mmHg was associated with minimal adverse outcomes and a reduction in cardiovascular disease and all-cause mortality. The BP range will need to be confirmed in randomized controlled trials.
On-Treatment Blood Pressure and Cardiovascular Outcomes in Older Adults With Isolated Systolic Hypertension

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Supplementary Material

On-treatment Blood Pressure and Cardiovascular Outcomes in Older Adults with Isolated Systolic Hypertension

Subtitle: Optimal On-treatment BP in Older Adults with ISH

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Outcomes Ascertainment

The prespecified primary outcome was composite cardiovascular disease (CVD), including coronary heart disease (sudden death, fatal or nonfatal myocardial infarction, and new onset or exacerbation of angina pectoris), fatal or nonfatal stroke, death from heart failure, other cardiovascular deaths, unplanned hospitalization for CVD, and kidney diseases (doubling of serum creatinine to a level >2.0 mg per 100 mL or introduction of dialysis).\textsuperscript{1,2} Hard CVD, including sudden death, myocardial infarction, stroke, and heart failure death was evaluated separately. Secondary endpoint was all-cause mortality. These outcomes were blindly evaluated by the endpoint committee and the safety committee, respectively.\textsuperscript{1,2}

### Supplementary Table

<table>
<thead>
<tr>
<th>On-treatment SBP categories</th>
<th>Composite CVD events, No. (per 1,000 person-years; 95% CIs)</th>
<th>All-cause mortality, No. (per 1,000 person-years; 95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=3,035)</td>
<td>93 (11.59; 9.46 to 14.21)</td>
<td>52 (6.47; 4.93 to 8.49)</td>
</tr>
<tr>
<td>On treatment SBP&lt;130 mmHg (n=317)</td>
<td>14 (16.48; 9.76 to 27.82)</td>
<td>8 (9.42; 4.71 to 18.84)</td>
</tr>
<tr>
<td>On-treatment SBP of 130 to &lt;145 mmHg (n=2,025)</td>
<td>43 (7.81; 5.79 to 10.52)</td>
<td>24 (4.35; 2.92 to 6.49)</td>
</tr>
<tr>
<td>On-treatment SBP&gt;145mmHg (n=693)</td>
<td>36 (21.64; 15.61 to 30.00)</td>
<td>20 (11.97; 7.73 to 18.56)</td>
</tr>
</tbody>
</table>

The incidence rates of composite CVD and all-cause mortality by on-treatment SBP categories are shown. Composite CVD includes CHD, fatal or nonfatal stroke, death from heart failure, other cardiovascular death, unplanned hospitalization for cardiovascular disease, and kidney diseases (doubling of serum creatinine to a level >2.0 mg per 100 mL or introduction of dialysis). SBP indicates systolic blood pressure; CVD, cardiovascular disease; No, number; CI, confidence interval.
Supplementary Table S2. Unadjusted and multivariable-adjusted HRs (95% CIs) for risk of hard CVD events according to on-treatment SBP categories

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>On-treatment SBP level</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP&lt;130 mmHg (n=317)</td>
<td>SBP of 130 to &lt;145 mmHg (n=2,025)</td>
<td>SBP≥145mmHg (n=693)</td>
</tr>
<tr>
<td>Hard CVD events (n=60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1 (unadjusted)</td>
<td>1.99 (0.899-4.39)</td>
<td>1 (reference)</td>
<td>3.32 (1.93-5.72)‡</td>
</tr>
<tr>
<td>Model 2</td>
<td>2.03 (0.92-4.51)</td>
<td>1 (reference)</td>
<td>3.25 (1.87-5.64)‡</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.94 (0.87-4.33)</td>
<td>1 (reference)</td>
<td>2.77 (1.58-4.88)‡</td>
</tr>
<tr>
<td>Model 4</td>
<td>2.30 (0.999-5.28)</td>
<td>1 (reference)</td>
<td>2.57 (1.44-4.56)†</td>
</tr>
<tr>
<td>Model 5</td>
<td>1.61 (0.60-4.29)</td>
<td>1 (reference)</td>
<td>2.81 (1.50-5.26)†</td>
</tr>
</tbody>
</table>

Hard CVD included sudden death, myocardial infarction, stroke, and heart failure death. Unadjusted and adjusted HRs (95% CI) for risk of hard CVD events among each on-treatment SBP category are shown. As adjustment factors, Model 2 includes demographic variables (age at baseline, sex, treatment strategy: intensive vs. moderate BP lowering treatment), Model 3 includes demographic variables + clinical characteristics at baseline (smoking status, prevalent diabetes, prevalence hyperlipidemia, SBP level, hypertension medication use, and prevalent CVD), Model 4 includes demographic variables + clinical characteristics at baseline + on-treatment DBP, and Model 5 includes demographic variables + clinical characteristics at baseline + on-treatment DBP, and Model 5 includes demographic variables + clinical characteristics at baseline + SBP change from baseline to follow-up (< -40 mmHg vs. -40 to -30 mmHg vs. > -30 mmHg). Statistical significance was defined as *P < 0.05; †P < 0.01; ‡P < 0.001.
Supplementary Figure

Supplementary Figure S1

Figure S1: On-treatment SBP and composite CVD events

The figures show adjusted HRs (95% CIs) of composite CVD risk associated with on-treatment SBP. The black solid lines are the restricted cubic spline fit, and the black dotted lines are the 95% confidence intervals. As adjustment factors, age, sex, treatment strategy (intensive vs. moderate SBP lowering), clinical characteristics at baseline (smoking, prevalent diabetes, prevalence hyperlipidemia, SBP level, use of antihypertensive drugs, and prevalent CVD) were used. Reference points were set differently in each figure (blue lines). The red lines are indicative of HRs of one.

In Figures A and E (reference points: on-treatment SBP of 125 or 145 mmHg), we
observed lower hazard ratios for composite CVD events (i.e., hazard ratios and 95% confidence intervals <1) for on-treatment SBP around 140 mmHg (green arrows). Such a relationship was not observed in Figures B, C, and D when the reference points were 130, 135, and 140 mmHg, respectively. Therefore, we concluded that on-treatment SBP of 130 to < 145 mmHg would be an optimal range for minimizing the risk of CVD events in older Japanese adults with ISH.
Supplementary Figure S2

Figure S2: The amount of SBP change from baseline to follow-up and composite CVD events

The figures show adjusted HRs (95% CIs) of composite CVD risk associated with the amount of BP change from baseline to follow-up. The solid blue lines are the restricted cubic spline fit, and the dotted lines are 95% confidence intervals. As adjustment factors, age, sex, treatment strategy (intensive vs. moderate SBP lowering), clinical characteristics at baseline (smoking, prevalent diabetes, prevalence hyperlipidemia, use of antihypertensive drugs, and prevalent CVD) were used. Reference point was set as -30 mmHg.
**Supplementary Figure S3**

**Figure S3: The amount of SBP change from baseline to follow-up and composite CVD events**

The figures show adjusted HRs (95% CIs) of composite CVD risk associated with the amount of BP change from baseline to follow-up. The black solid lines are the restricted cubic spline fit, and the black dotted lines are the 95% confidence interval. As adjustment factors, age, sex, treatment strategy (intensive vs. moderate SBP lowering), clinical characteristics at baseline (smoking, prevalent diabetes, prevalence hyperlipidemia, use of antihypertensive drugs, and prevalent CVD) were used. Reference points were set differently in each figure (blue lines). The red lines are indicative of HRs of one.

In Figures A and E (reference points: SBP reduction from baseline [defined by on-treatment SBP minus baseline SBP] of 25 or 45 mmHg), we observed lower hazard ratios for composite CVD events (i.e., hazard ratios and its 95% confidence intervals <1) for a...
SBR reduction of 30 to <40 mmHg (green arrows). Such a relationship was not observed in Figures B, C, and D when the reference points were 30, 35, and 40 mmHg, respectively. Therefore, we concluded that an SBP reduction of 30 to < 40 mmHg would be optimal for minimizing the risk of CVD events in older Japanese adults with ISH.
Supplementary Figure S4

**Figure S4: On-treatment SBP, DBP, and all-cause mortality**

The figures show adjusted HRs (95% CIs) of all-cause mortality risk associated with on-treatment SBP (left) and DBP (right). The blue solid lines are the restricted cubic spline fit, and the dotted lines are 95% confidence intervals. As adjustment factors, age, sex, treatment strategy (intensive vs. moderate SBP lowering), clinical characteristics at baseline (smoking, prevalent diabetes, prevalence hyperlipidemia, SBP level [DBP level in the right figure], use of antihypertensive drugs, and prevalent CVD) were used. Reference points were set as SBP 135 mmHg and DBP 70 mmHg, respectively.
Supplementary Figure S5

Figure S5: Histogram of on-treatment SBP in the VALISH Study.
Supplementary Figure S6

Adjusted HRs for composite CVD events

On-treatment SBP categories
(event/total number)

Low SBP (4/73)
Reference (18/483)
High SBP (9/173)

Low SBP (10/244)
Reference (25/1,542)
High SBP (27/520)

Low SBP (5/119)
Reference (20/759)
High SBP (16/263)

Low SBP (9/198)
Reference (23/1,266)
High SBP (20/430)

Low SBP (10/217)
Reference (18/1,051)
High SBP (16/258)

Low SBP (4/100)
Reference (25/974)
High SBP (20/435)
Adjusted HRs for composite CVD events

On-treatment SBP categories
(event/total number)

Prevalent diabetes at baseline (-)
Low SBP (11/285)
Reference (31/1,796)
High SBP (21/561)

Prevalent diabetes at baseline (+)
Low SBP (3/32)
Reference (12/229)
High SBP (15/132)

Prevalent CVD at baseline (-)
Low SBP (9/254)
Reference (32/1,825)
High SBP (28/600)

Prevalent CVD at baseline (+)
Low SBP (5/63)
Reference (11/200)
High SBP (8/93)

Hypertensive drug use at baseline (-)
Low SBP (6/162)
Reference (19/1,095)
High SBP (12/271)

Hypertensive drug use at baseline (+)
Low SBP (8/155)
Reference (24/930)
High SBP (24/422)
Figure S6: Adjusted HRs by on-treatment SBP categories: clinical characteristics-specific analyses

Bars represent adjusted HRs (95% CIs) of composite CVD risk by on-treatment SBP categories. Low SBP indicates on-treatment SBP < 130 mmHg; reference, on-treatment SBP of 130 to < 145 mmHg; and high SBP, on-treatment SBP ≥ 145 mmHg. As adjustment factors, age (not included in age 80-specific analyses), sex (not included in sex-specific analyses), treatment strategy (intensive vs. moderate SBP lowering; not included in treatment strategy-specific analyses), smoking status at baseline, prevalent diabetes at baseline (not included if diabetes-specific analyses), prevalence hyperlipidemia at baseline, SBP level at baseline, use of antihypertensive drugs at baseline (not included in antihypertensive medication use-specific analyses), and prevalent CVD at baseline (not included in prevalent CVD-specific analyses) were used.

HR indicates hazard ratio; CI, confidence interval; SBP, systolic blood pressure; CVD, cardiovascular disease. Statistical significance was defined as \( P < 0.05 \). *\( P < 0.05 \); †\( P < 0.01 \); ‡\( P < 0.001 \).
Figure S7: Adjusted HRs for risk of composite CVD events by on-treatment SBP quartiles

Bars represent adjusted HRs (95% CIs) of composite CVD risk by on-treatment SBP quartiles. The reference group was set differently in each figure (red square). As adjustment factors, age, sex, treatment strategy (intensive vs. moderate SBP lowering), clinical characteristics...
at baseline (smoking, prevalent diabetes, prevalence hyperlipidemia, SBP level, use of antihypertensive drugs, and prevalent CVD) were used.

The first quartile included on-treatment SBP around 130 mmHg, which may be why it yielded non-significant risk compared with the second or third quartile groups. The results suggest that CVD risk was lowest in the third quartile group, which would support the approach taken in Figure 3 (i.e., use of the third quartile group as the reference group).