Target Blood Pressure for Treatment of Isolated Systolic Hypertension in the Elderly
Valsartan in Elderly Isolated Systolic Hypertension Study

Toshio Ogihara, Takao Saruta, Hiromi Rakugi, Hiroaki Matsuoka, Kazuaki Shimamoto, Kazuyuki Shimada, Yutaka Imai, Kenjiro Kikuchi, Sadayoshi Ito, Tanenao Eto, Genjiro Kimura, Tsutomu Imaizumi, Shuichi Takishita, Hirotugu Ueshima, for the Valsartan in Elderly Isolated Systolic Hypertension Study Group

Abstract—In this prospective, randomized, open-label, blinded end point study, we aimed to establish whether strict blood pressure control (≤140 mm Hg) is superior to moderate blood pressure control (≥140 mm Hg to ≤150 mm Hg) in reducing cardiovascular mortality and morbidity in elderly patients with isolated systolic hypertension. We divided 3260 patients aged 70 to 84 years with isolated systolic hypertension (sitting blood pressure 160 to 199 mm Hg) into 2 groups, according to strict or moderate blood pressure treatment. A composite of cardiovascular events was evaluated for ≥2 years. The strict control (1545 patients) and moderate control (1534 patients) groups were well matched (mean age: 76.1 years; mean blood pressure: 169.5/81.5 mm Hg). Median follow-up was 3.07 years. At 3 years, blood pressure reached 136.6/74.8 mm Hg and 142.0/76.5 mm Hg, respectively. The blood pressure difference between the 2 groups was 5.4/1.7 mm Hg. The overall rate of the primary composite end point was 10.6 per 1000 patient-years in the strict control group and 12.0 per 1000 patient-years in the moderate control group (hazard ratio: 0.89; [95% CI: 0.60 to 1.34]; P=0.38). In summary, blood pressure targets of ≤140 mm Hg are safely achievable in relatively healthy patients ≥70 years of age with isolated systolic hypertension, although our trial was underpowered to definitively determine whether strict control was superior to less stringent blood pressure targets. (Hypertension. 2010;56:00-00.)

Key Words: isolated systolic hypertension ■ elderly ■ blood pressure ■ prognosis ■ valsartan

High blood pressure (BP) is well known to be a major risk factor for cardiovascular events, such as stroke and myocardial infarction, and linear relationships between cardiovascular risk and both systolic and diastolic BPs, unrelated to age, have also been reported based on a meta-analysis of large cohort studies conducted worldwide. In particular, systolic BP predominantly affects cardiovascular events in elderly people.

Numerous large clinical trials, such as the Systolic Hypertension in the Elderly Program, Swedish Trial in Old Patients, Medical Research Council, Systolic Hypertension in Europe, and Systolic Hypertension in China, have provided evidence of the benefits of reducing BP in the elderly. Meta-analysis of clinical trials showed that treatment of hypertension in older adults is as beneficial as that in younger adults. A recent study performed in hypertensive patients aged ≥80 years of age, the Hypertension in the Very Elderly Trial, showed that antihypertensive treatment is beneficial to reduce the risks of death from stroke, death from any cause, and heart failure. These observations indicate that antihypertensive treatment is beneficial even in very elderly patients.

To reduce cardiovascular risks, in general BP should be kept as low as possible based on evidence from numerous clinical trials and epidemiological data. On the other hand, several epidemiological studies in the elderly, such as Vantaa and Leiden 85-Plus, reported a poor prognosis in those with systolic BP <140 mm Hg. Furthermore, excessive BP lowering in the elderly may be harmful, because target organ perfusion is decreased and autoregulation impairment may occur, particularly in elderly patients with cardiovascular complications. The J-curve phenomenon associated with...
excessive diastolic BP reduction in elderly patients has been reported in the Practitioner’s Trial on the Efficacy of Anti-hypertensive Treatment in the Elderly\textsuperscript{15} and some post hoc analyses of large clinical studies, such as the Systolic Hypertension in the Elderly Program\textsuperscript{16} and Systolic Hypertension in Europe.\textsuperscript{17} In another post hoc analysis of the Systolic Hypertension in the Elderly Program, the greatest benefits in terms of lowering stroke risk were observed in patients with systolic BP $<150$ mm Hg rather than in those with systolic pressure $<140$ mm Hg.\textsuperscript{18}

In the previous placebo-controlled comparative trials in elderly hypertensives, systolic and diastolic BPs at the final step of the study were 144 to 167 mm Hg and 68 to 87 mm Hg, respectively, in the active treatment groups of patients 66 to 76 years of age.\textsuperscript{18,19} No trial has achieved a systolic BP $<140$ mm Hg. Furthermore, in the Hypertension in the Very Elderly Trial, which showed clinical benefits of antihypertensive therapy, target BP was set at $<150/80$ mm Hg in the protocol, and the achieved BP was 144/78 mm Hg 2 years after the trial start.\textsuperscript{19} These results may be related to the fact that it is often difficult to achieve target BP $<140/90$ mm Hg in the elderly, although that level is generally recommended in the guidelines. Furthermore, it is reported that the optimal target BP in the elderly remains uncertain.\textsuperscript{20,21} Recently, the principal results of the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients were reported. The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients was performed to compare the 2-year cardiovascular incidences in elderly hypertensive patients between 2 systolic BP groups (a $<140$-mm Hg target group and a 140- to 159-mm Hg target group).\textsuperscript{21} Regrettably, however, the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients could not conclude which regimen is better because of a lack of statistical power.

In the present clinical trial, that is, the Valsartan in Elderly Isolated Systolic Hypertension (VALISH) Study, we compared the incidences of cardiovascular mortality and morbidity in elderly patients with isolated systolic hypertension between a strict control group (systolic BP $<140$ mm Hg) and a moderate control group (systolic BP 140 to 149 mm Hg). An angiotensin II type 1 receptor blocker, valsartan, was used as the initial antihypertensive regimen in this trial.

**Methods**

**Study Design**

The design of the study was described previously.\textsuperscript{22} The VALISH Study was a multicenter, parallel-group, prospective, randomized, open-label, blinded end point, 22 investigator-designed trial conducted in Japan. The purpose was to compare the occurrence of cardiovascular events between 2 target systolic BP levels, $<140$ mm Hg (strict control group) and $\geq 140$ mm Hg to $<150$ mm Hg (moderate control group), in elderly patients with isolated systolic hypertension. We estimated the incidence of cardiovascular events at 21.4% and 29.1% per 1000 patient-years in the strict and moderate control groups, respectively, based on the results of the Practitioner’s Trial on the Efficacy of Antihypertensive Treatment in the Elderly\textsuperscript{16} and the Japan Multicenter Investigation for Cardiovascular Diseases-B\textsuperscript{23} performed in Japan. On the basis of this estimation, 6685 person-years of follow-up was required to detect a risk reduction of 26% at the 2-sided $\alpha$ level of 5% and with a power (1-$\beta$) of 80%. We finally designed the study with follow-up of 3000 patients for $\geq$2 years. The study protocol was approved by all of the involved ethics committees, and all of the patients gave written informed consent.

**Population and Treatment**

The inclusion and exclusion criteria were described previously.\textsuperscript{22} Briefly, patients $\geq$70 and $<85$ years of age with isolated systolic hypertension (systolic BP $>160$ mm Hg and diastolic BP $<90$ mm Hg) were enrolled into the study. After obtaining written informed consent from all of the patients for the study, the patients were randomly assigned by the VALISH Data Center according to the following factors: sex, age ($<75$ or $\geq75$ years), systolic BP ($<175$ or $\geq175$ mm Hg), antihypertensive therapy, and institution (weighting coefficient: 2). Valsartan, 40 to 80 mg once daily, was administrated as the first-step therapy. If the target BP in each group was not achieved within 1 to 2 months, the dose of valsartan was increased $\pm$160 mg, and/or other antihypertensive agents except other angiotensin II type 1 receptor blockers were added, for example, low-dose diuretics, Ca antagonists, and so on to maintain the target BP.

Patients visited the clinic every 3 months at a minimum for 2 years, and investigators were asked to complete case report forms documenting adverse events, end points, withdrawals, vital signs including BP and heart rate, and so on. At completion of the study, the VALISH Data Center asked all of the investigators about the outcomes of all of the patients enrolled as a part of maintenance of patient follow-up quality.

The primary end point of this study was a composite of cardiovascular events: sudden death, fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, death because of heart failure, other cardiovascular death, unplanned hospitalization for cardiovascular disease, and renal dysfunction (doubling of serum creatinine to a level $>2.0$ mg per 100 mL or introduction of dialysis). Secondary end points were each components of the primary end point, total mortality, and new onset or exacerbation of angina pectoris. Cardiovascular death, fatal or nonfatal myocardial infarction, and fatal or nonfatal stroke excluding transient ischemic attacks were evaluated as hard end points. End points and adverse events were blindly evaluated according to the prospective, randomized, open-label, blinded end point design\textsuperscript{20} by the endpoint committee and the safety committee, respectively.

**Statistical Analysis**

Statistical analysis was performed by Shin Nippon Biomedical Laboratories, Ltd according to the statistical analysis plan approved by the statistics committee (see Appendix). All of the registered study patients assigned to treatment were analyzed on an intention-to-treat basis. In addition, a per-protocol analysis was performed. Event rates in the 2 target BP groups were compared by log-rank test and the Kaplan-Meier method. The adjusted odds ratio for background factors was tested for proportional hazards and determined by the Cox proportional hazards model. Among background factors, the following factors were used as covariates: sex, age, body mass index (BMI), smoking, dyslipidemia, diabetes mellitus, and antihypertensive agents used before enrollment. Relative frequencies of end points were compared using a $\chi^2$ test, and the changes in each test parameter were evaluated by ANCOVA and ANOVA models. Consistency of treatment effects in prespecified subgroups was explored by the Cox regression model, with tests for interaction. These analyses were performed using the SAS system (release 9.1, SAS Institute Inc).

**Results**

In total, 3260 patients from 461 centers in Japan were registered from February 2004 to August 2005 and then randomly assigned to either the strict control group or the moderate control group. Because 181 patients were lost to
follow-up, 3079 were followed up until March 2008 or for ≥2.5 years (Figure 1). The mean follow-up period was 2.85 years, and the median was 3.07 years. The fifth to 95th percentile interval of the follow-up period was 0.50 to 3.82 years. The study accumulated 8765.3 person-years of follow-up (4436.6 person-years in the strict control group and 4338.7 person-years in the moderate control group), which was 1.31 times expectation. The baseline characteristics of both groups (1545 in the strict control group and 1534 in the moderate control group) and cardiovascular medications, including antihypertensives being taken at randomization, are listed in Table 1. There were no differences between the 2 groups except for the smoker ratio and ratios of cardiovascular complication, that is, stroke, ischemic heart disease, heart failure, and renal dysfunction, were <10% in both groups.

All of the patients were started on valsartan as the base regimen. At the end of follow-up, the mean dose of valsartan was 91.2±36.9 mg/d in the strict control group and 88.1±36.8 mg/d in the moderate control group (P=0.02), and 56.1% of patients received only valsartan monotherapy in the strict control group and 57.6% in the moderate control group (Table 2). Patients whose treatment required the addition of other antihypertensive drugs accounted for 43.9% of the strict control group and 42.4% of the moderate control group. These drugs were mostly Ca antagonists in both groups. At the end of follow-up, the mean number of antihypertensive drugs used, including valsartan, was 1.6±0.9 in the strict control group and 1.6±0.9 in the moderate control group (P=0.56).

Changes in BP during follow-up are shown in Figure 2. Both systolic and diastolic BPs significantly reduced after 3 months in both groups. BPs reached 136.6±13.3/74.8±8.8 mm Hg and 142±12.5/76.5±8.9 mm Hg at 36 months of follow-up in the strict and moderate control groups, respectively. The BP differences between the 2 groups were 5.6 mm Hg in systolic BP and 1.7 mm Hg in diastolic BP at 36 months of follow-up (P<0.001 for both systolic and diastolic BPs). Heart rates did not differ significantly between the 2 groups during the course of the study.

Figure 3A shows the Kaplan-Meier curves for the primary composite end point with intention-to-treat analysis. The overall rate of the primary composite end point was 10.6 per 1000 patient-years in the strict control group and 12.0 per 1000 patient-years in the moderate control group (P=0.38).

These incidences were less than a half of the estimated values. Figure 3B shows the Kaplan-Meier curves for the primary composite end point with per-protocol analysis. Data were collected from patients in whom the average BP for the last 2 visits was within the targeted range in each group (1043 patients of the strict control group and 733 patients of the moderate control group). The incidences of the primary

<table>
<thead>
<tr>
<th>Cardiovascular history, n (%)</th>
<th>Women, n (%)</th>
<th>Age, y</th>
<th>BMI, kg/m²</th>
<th>SBP, mm Hg</th>
<th>DBP, mm Hg</th>
<th>Heart rate, bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>99 (6.4)</td>
<td>76.1 ±4.1</td>
<td>23.5 ±3.4</td>
<td>169.5 ±7.9</td>
<td>81.7 ±6.6</td>
<td>72.4 ±9.8</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>81 (5.2)</td>
<td>72.4 ±4.7</td>
<td>23.4 ±3.4</td>
<td>169.6 ±7.9</td>
<td>81.2 ±6.8</td>
<td>71.9 ±9.5</td>
</tr>
<tr>
<td>Heart failure</td>
<td>25 (1.6)</td>
<td>72.4 ±4.7</td>
<td>23.4 ±3.4</td>
<td>169.6 ±7.9</td>
<td>81.2 ±6.8</td>
<td>72.4 ±9.8</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>19 (1.2)</td>
<td>72.4 ±4.7</td>
<td>23.4 ±3.4</td>
<td>169.6 ±7.9</td>
<td>81.2 ±6.8</td>
<td>72.4 ±9.8</td>
</tr>
<tr>
<td>Cardiovascular risk factors, n (%)</td>
<td>325 (21.0)</td>
<td>267 (17.4)</td>
<td>779 (52.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>211 (13.7)</td>
<td>188 (12.3)</td>
<td>756 (49.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>595 (38.5)</td>
<td>561 (36.6)</td>
<td>758 (49.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensives, n (%)</td>
<td>480 (31.7)</td>
<td>511 (33.3)</td>
<td>758 (49.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca antagonists</td>
<td>191 (12.4)</td>
<td>200 (13.0)</td>
<td>758 (49.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>121 (7.8)</td>
<td>123 (8.0)</td>
<td>758 (49.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>61 (3.9)</td>
<td>72 (4.7)</td>
<td>758 (49.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>36 (2.3)</td>
<td>35 (2.3)</td>
<td>758 (49.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>34 (2.2)</td>
<td>29 (1.9)</td>
<td>758 (49.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other drugs, n (%)</td>
<td>345 (22.9)</td>
<td>442 (28.8)</td>
<td>758 (49.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SBP indicates systolic BP; DBP, diastolic BP; ARB, angiotensin receptor blockers; ACE, angiotensin-converting enzyme. Data are mean±SD unless otherwise specified.
composite end point were 2.4% (8.2 per 1000 patient-years) in the strict control group and 2.3% (7.8 per 1000 patient-years) in the moderate control group (hazard ratio: 1.04 [95% CI: 0.56 to 1.93]; \( P = 0.89 \)).

Figure 4 shows the primary composite end point and individual end points. There were no significant differences in any end point between the strict and moderate control groups. The relative risk of the primary end point in each prespecified subgroup by baseline variables is shown in Figure 5. No significant heterogeneity of variance for possible interactions between treatment and baseline variables was detected in any of the variables.

The rates of adverse events were similar in the 2 groups (18.2% in the strict control group and 17.9% in the moderate control group; \( P = 0.851 \)), and most were gastrointestinal or respiratory symptoms. Those of serious adverse events (5.6% versus 5.2%; \( P = 0.61 \)) and those related to and with suspected relation to valsartan (5.6% versus 4.4%; \( P = 0.126 \)) were also similar between the strict and moderate control groups. The rates of discontinuation because of adverse events, whether definitely or only suspected to be related to valsartan, were 1.9% in the strict control group and 1.2% in the moderate control group (\( P = 0.11 \)).

### Discussion

The present VALISH Study found no difference in the primary end point rate between the 2 BP targets, that is, \(< 140 \) mm Hg and between 140 to 149 mm Hg. This finding was confirmed with both intention-to-treat and per-protocol analyses. Furthermore, the secondary end points, including the definitive end point, and all causes of death had similar rates in the 2 target groups. The subanalysis of the prespecified subgroups based on sex, age, BMI, and complications similarly revealed no difference in the primary end point rate between the 2 target groups.

In general, cardiovascular risk reduction by antihypertensive treatment is related to the magnitude of the BP decrease. On the basis of a meta-analysis conducted by Staessen et al on the magnitude of BP lowering by antihypertensive drugs and the degree of cardiovascular hazard risk reduction, a BP reduction of 5 mm Hg will lead to an \( \approx 20\% \) reduction in total cardiovascular risk, a 30% reduction in stroke, and a 25% reduction in myocardial infarction. The present study, VALISH, resulted in no difference in the primary end point rate between the moderate and strict control groups, although the difference in achieved systolic BP between 2 groups was 5.6 mm Hg. Therefore, we simply assume that moderate control of BP, for example, \(< 150 \) mm Hg, as in this study, may be sufficient to reduce cardiovascular events in elderly hypertensive patients.

In a subanalysis of the Candesartan Antihypertensive Survival Evaluation in Japan, 24 the cardiovascular risk hazard ratio in patients over age 65 years began to rise when systolic BP exceeded 140 mm Hg, whereas the hazard ratio in patients over age 75 years began to rise.
significantly when systolic BP exceeded 150 mm Hg, thus supporting the view reported by Port et al.\(^{25}\) that the threshold of the cardiovascular risk hazard ratio shifts to the right with advancing age.

As a limitation of our study, statistical power was insufficient to evaluate whether strict control is superior to moderate control in preventing cardiovascular events in elderly patients. The observed incidence of primary end points in the VALISH Study was less than half of the values estimated in the protocol setting although we followed 1.3-times person-years of our protocol setting. The major reason for such a small number of incidents may be that the enrolled patients in our study were relatively healthy compared with those in Japan Multicenter Investigation for Cardiovascular Diseases-B,\(^{23}\) which was referred to in the VALISH protocol. Although patients in the VALISH Study were >10 years older than those in the Japan Multicenter Investigation for Cardiovascular Diseases-B, the prevalence of prior history of coronary artery diseases was 5% in the VALISH Study and 100% in the Japan Multicenter Investigation for Cardiovascular Diseases-B. It is desirable to follow a larger number of patients for a longer period of time to determine an appropriate target BP to be achieved for relatively healthy elderly patients with hypertension.

Figure 3. Kaplan-Meier estimates of the primary end point. The primary end point is a composite of sudden death, fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, heart failure death, other cardiovascular death, unplanned hospitalization because of cardiovascular diseases, and renal dysfunction. The hazard ratio was adjusted for the following covariates: sex, age, BMI, smoking, dyslipidemia, diabetes mellitus, and antihypertensive agents used before enrollment. A, Intention-to-treat analysis; B, per-protocol analysis.

Figure 4. Comparisons of hazard ratios and 95% CIs for the primary end point and secondary end point. Hazard ratio was adjusted for the following covariates: sex, age, BMI, smoking, dyslipidemia, diabetes mellitus, and antihypertensive agents used before enrollment. 1Data include sudden death, fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, heart failure death, other cardiovascular death, unplanned hospitalization because of cardiovascular diseases, renal dysfunction (doubling of serum creatinine and creatinine, to >2.0 mg per 100 mL, or introduction of dialysis). 2Data include cardiovascular death, nonfatal stroke (exclude transient ischemic attack), and nonfatal myocardial infarction.
Regarding the optimal levels of target BP in the elderly, we should discuss the effects of more strict control than <140 mm Hg on the cardiovascular incidence. The recently reported Italian Study on the Cardiovascular Effects of Systolic Blood Pressure Control showed that a tight-control treatment (<130 mm Hg) reduced a composite cardiovascular end point by 50% compared with the usual-control treatment (<140 mm Hg).26 The reduced end points in the tight-control group, however, were composed mainly of coronary revascularization and new-onset atrial fibrillation, which were not assigned as the end point in the VALISH Study. Because the average age of study subjects of Italian Study on the Cardiovascular Effects of Systolic Blood Pressure Control was 67 years, whether the target BP would be <140 mm Hg or <150 mm Hg is still an important and unresolved issue, at least in elderly hypertensive patients.

The incidence of drug-related adverse events necessitating discontinuation of the trial did not differ significantly between the moderate (1.9%) and strict (1.2%) control groups. Thus, the risk for adverse events did not rise even in the strict control group. The incidence of adverse events was low in both groups, indicating that valsartan-based antihypertensive treatment is safe and well tolerated in elderly patients.

In conclusion, the recommended BP target of <140 mm Hg is safely achieved in relatively healthy patients ≥70 years of age with isolated systolic hypertension. However, strict BP control may not enhance the clinical benefit in the prevention of cardiovascular events as compared with that of moderate BP control.

**Perspectives**
The difference in composite cardiovascular rate between the strict and the moderate BP control groups was not significant in relatively healthy elderly patients with isolated systolic hypertension. Even if this difference was significant, with an increased study population and an extended follow-up period the number needed to treat, estimated from the results of intention-to-treat analysis, looks to be very large (≈700 per year). However, considering the huge population of elderly people with hypertension (>10 million at 70 to 84 years of age in Japan), whether moderate BP control, such as <150 mm Hg, is adequate or strict BP control is absolutely required for elderly hypertensive patients is still an important issue to be addressed. Furthermore, this issue should be discussed from the viewpoints of cost benefit and risks involved with excess BP reduction. Additional studies and meta-analyses are expected to address these questions in elderly hypertensive patients.

### Appendix

**VALISH Study Committees**
The steering committee includes Takao Saruta (chair), Toshio Ogihara (chair), Yutaka Imai, Kazuyuki Shimada, Kazuaki Shimamoto, Kenjiro Kikuchi, Toshio Fujita, and Hiroaki Matsuoka. The protocol committee includes Hiroaki Matsuoka (chair), Toshio Ogihara, Kazuaki Shimamoto, and Toshio Fujita. The safety committee includes Kazuaki Shimamoto (chair), Sadayoshi Ito, Tanemo Eto, and Kenjiro Kikuchi. The end point committee includes Kazuyuki Shimada (chair), Tsutomu Imaizumi, Genjiro Kimura, and Shiuchi Takishita. The statistical committee includes Yutaka Imai (Chair) and Hirotsugu Ueshima. The study secretary is Hiromi Nakajima. The list of investigators of the VALISH Study is available in the online Data Supplement at http://hyper.ahajournals.org.

**Acknowledgments**
We gratefully acknowledge the contribution of the VALISH Study Group, the members of which are listed in the Appendix. We also thank Dr Tomomi Fujisawa (Osaka University Graduate School of
Disclosures
All of the authors report receiving lecture fees from various pharmaceutical companies in Japan, including Novartis Pharma Japan.

References
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ONLINE SUPPLEMENT

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Short title: Target BP for Treatment of Elderly Hypertension
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