Blood Pressure Goal in Elderly Hypertensive Patients with Diabetes Mellitus: A Subanalysis of the CASE-J Trial

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On behalf of CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan) trial Group

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COI (Conflict of Interest)
Disclosure Information

Kenji Ueshima

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I have the following financial relationships to disclose.
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20.1 Elderly Patients

- Blood pressure goal is the same as in younger patients, i.e. <140/90 mmHg or below, if tolerated. Many elderly patients need two or more drugs to control blood pressure and reductions to <140 mmHg systolic may be difficult to obtain.

20.2 Diabetic Patients

- Goal blood pressure should be <130/80 mmHg and antihypertensive drug treatment may be started already when BP is in the high normal range.
Hypertension in the elderly

- Treatment sufficient to achieve the final target of blood pressure control should be performed in elderly patients. Prognosis is expected to improve by reducing blood pressure to <140/90mmHg at all ages. In patients that have been well treated before the age of 65 years, the same antihypertensive treatment should be continued after the age of 65 years.

Diabetes mellitus

- The target of blood pressure control in hypertension complicated with diabetes mellitus should be <130/80 mmHg.
Various guidelines for the management of hypertension recommend that blood pressure (BP) goal should be <140/90 mmHg in the elderly and <130/80 mmHg in patients with diabetes mellitus (DM), respectively.

However, BP goal in elderly patients with DM remains to be elucidated.
Purpose

✓ To examine the relationship between achieved BP level and cardiovascular (CV) risk to evaluate BP goal in elderly hypertensive patients (≥65 years old) with DM using database of CASE-J trial.

✓ CASE-J trial was a randomized clinical trial to compare the effects of the angiotensin II receptor blocker, candesartan and the calcium channel blocker, amlodipine on the incidence of CV events in high-risk Japanese hypertensive patients.
Outline of the CASE-J Trial

- Subjects: 4,728 High-risk Japanese hypertensive patients
- Randomization: 2,364 patients in Candesartan
  2,364 patients in Amlodipine
- Mean Follow-up period: 3.2 years
  (Follow-up rate: 97.1 %)
- Study design: Open Label Randomized Controlled Trial
- Evaluation: PROBE method
- Primary endpoint:
  Composite of CV morbidity and mortality
  Sudden death, Cerebrovascular events, Cardiac events,
  Renal events, and Vascular events
Result of Primary Endpoint

HR=1.01; 95% CI 0.79-1.28; P=0.969

Amlodipine 17.6 / 1000 patient-years
Candesartan 17.7 / 1000 patient-years
Methods in the Subanalysis

✓ As an observational cohort study irrespective of allocated drugs

✓ Subject: 2,377 patients aged 65 or older, who had at least one visit during the follow-up period.

✓ Groups: according to existence or absence of DM at baseline, they were divided into the two groups.

  With DM : n=1,031

  Without DM : n=1,346

Achieved BP: the last value of BP in patients who did not experience CV events, and the value of BP prior to CV events in those who experienced CV events.

✓ Hazard ratio (HR): calculated with the multiple Cox regression analysis adjusted for baseline characteristics.
# Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>With DM</th>
<th>Without DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>2377</td>
<td>1031</td>
<td>1346</td>
</tr>
<tr>
<td>Prior antihypertensive treatment</td>
<td>1794 (75.5)</td>
<td>784 (76.0)</td>
<td>1010 (75.0)</td>
</tr>
<tr>
<td>Drug, Candesartan</td>
<td>1181 (49.7)</td>
<td>501 (48.6)</td>
<td>680 (50.5)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>72.0 ± 5.0</td>
<td>71.3 ± 4.8</td>
<td>72.5 ± 5.1</td>
</tr>
<tr>
<td>Men</td>
<td>1144 (48.1)</td>
<td>513 (49.8)</td>
<td>631 (46.9)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>24.0 ± 3.4</td>
<td>24.5 ± 3.5</td>
<td>23.6 ± 3.3</td>
</tr>
<tr>
<td>SBP (mmHg)*</td>
<td>164.5 ± 13.3</td>
<td>161.9 ± 12.1</td>
<td>166.5 ± 13.8</td>
</tr>
<tr>
<td>DBP (mmHg)*</td>
<td>89.2 ± 10.9</td>
<td>86.3 ± 10.2</td>
<td>91.4 ± 10.8</td>
</tr>
<tr>
<td>HR (beats/min)*</td>
<td>71.9 ± 11.0</td>
<td>72.7 ± 11.2</td>
<td>71.3 ± 10.8</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1046 (44.0)</td>
<td>454 (43.4)</td>
<td>577 (43.4)</td>
</tr>
<tr>
<td>Cerebrovascular disease*</td>
<td>327 (13.8)</td>
<td>90 (8.7)</td>
<td>237 (17.6)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy*</td>
<td>771 (32.4)</td>
<td>231 (22.4)</td>
<td>540 (40.1)</td>
</tr>
<tr>
<td>Ishchemic heart disease*</td>
<td>387 (16.3)</td>
<td>139 (13.5)</td>
<td>248 (18.4)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>454 (19.1)</td>
<td>191 (18.5)</td>
<td>263 (19.5)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>247 (10.4)</td>
<td>120 (11.6)</td>
<td>127 (9.4)</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>38 (1.6)</td>
<td>25 (1.9)</td>
<td>13 (1.3)</td>
</tr>
</tbody>
</table>

* P<0.05 vs. Without DM
Blood Pressure Change

**Baseline**

**With DM**

- DM: 161.9 ± 12.1
- Non-DM: 166.5 ± 13.8

**Without DM**

- DM: 137.1 ± 12.8
- Non-DM: 135.4 ± 11.7

**DM: 86.3 ± 10.2**

**Non-DM: 91.4 ± 10.8**

**DM: 74.5 ± 9.4**

**Non-DM: 75.5 ± 8.7**

* P<0.05 vs. Without DM
Cumulative Incidence of CV Events

Adjusted HR: 2.18, 95%CI: 1.65-2.88, P<0.001
Crude Incidence Rate of CV Events at Each Achieved BP Level

Achieved SBP

Achieved DBP

Incidence rate (per 1000 patient-year)
Relations between Achieved SBP Level and the Risk of CV Events after Adjustment

HR of an achieved SBP <130 mmHg category without DM was assigned a reference value of 1.0.
* P<0.05 vs SBP <130 mmHg in Without DM
Relations between Achieved DBP Level and the Risk of CV Events after Adjustment

HR of an achieved DBP 75-<80 mmHg category without DM was assigned a reference value of 1.0.

* P<0.05. vs DBP 75-<80 mmHg in Without DM
Relations between Achieved DBP Level and the Risk of Cerebrovascular Events after Adjustment

HR of an achieved DBP 75-<80 mmHg category without DM was assigned a reference value of 1.0.

* P<0.05. vs DBP 75-<80 mmHg in Without DM
Relations between Achieved DBP Level and the Risk of Cardiac Events after Adjustment

![Graph showing the relationship between achieved DBP level and the risk of cardiac events. The graph compares the risk with and without DM, with interaction P=0.192. HR of an achieved DBP 75-<80 mmHg category without DM was assigned a reference value of 1.0. * P<0.05 vs DBP 75-<80 mmHg in Without DM.]
Summary

✓ In the relations between achieved SBP and the risk of CV events, lower achieved SBP was associated with the reduced risk in both elderly patients with or without DM.

✓ However, the SBP lowering effect was attenuated in patients with DM compared with those without DM. A risk reduction was observed down to the level of achieved SBP <140 mmHg in patients without DM and <130 mmHg in DM patients.

✓ For DBP, a risk reduction was observed down to the level of achieved DBP <85 mmHg in both groups.

✓ A J-shaped relationship between achieved DBP level and CV events (especially, cardiac events) was observed at achieved DBP <75 mmHg in elderly patients with DM.
Limitations

✓ The CASE-J trial was not originally designed to examine the optimal BP levels in hypertensive patients.

✓ This subanalysis was post hoc analysis. The number of CV events may not be enough and the mean follow-up period (3.2 years) may not be enough long to analyze the relationship between achieved BP level and CV events in these patients.
Conclusion

✓ The present subanalysis suggests that reduction of BP down to <130/85 mmHg is beneficial for elderly hypertensive patients with DM according to the recommendation for not the elderly but rather diabetics.

✓ Excessive DBP lowering <75 mmHg in patients with DM may increase the CV risk, especially cardiac events.
Treatment Protocol of the CASE-J Trial

1 month

- Add diuretics, β-blockers etc.
- Titrate Candesartan (up to 12 mg/day)

Candesartan 4 ~ 8 mg/day

Amlodipine 2.5 ~ 5 mg/day

- Titrate Amlodipine (up to 10 mg/day)
- Add diuretics, β-blockers etc.

Follow-up period: 3 years or more

BP recording

Informed consent
BP recording
Enrollment

Candesartan cilexetil
: 4 ~ 8 mg/day. If necessary, the dose was increased up to 12 mg/day.

Amlodipine besylate
: 2.5 ~ 5 mg/day. If necessary, the dose was increased up to 10 mg/day.

If the response was insufficient, diuretics or β-blockers etc were added to the regimen in both groups.
Treatment plan for hypertension complicated by diabetes mellitus.

Blood pressure to start treatment >=130/80 mmHg

Drug therapy with lifestyle modifications and glycemia control*

Primary drug: ACE inhibitor, ARB

Insufficient effect

- Increase in dose
- Concomitant use of Ca antagonist or diuretic

Insufficient effect

Combinations of 3 drugs: ARB or ACE inhibitor, Ca antagonist, diuretic

Target level <130/80 mmHg

*If the blood pressure is 130–139/80–89mmHg, and the target of blood pressure control is expected to be achieved through lifestyle modifications, blood pressure control by such modifications may be attempted over a period not exceeding 3 months.
Hypertension in the elderly

Treatment algorithm for elderly patients with hypertension

**Step 1**
(Antihypertensive drugs may be changed if the antihypertensive effect is insufficient or the drug is poorly tolerated.)

- Ca antagonist
- ARB/ACE inhibitor
- Low-dose diuretic

**Step 2**
Combination of 2 drugs

- Ca antagonist + ARB/ACE inhibitor
- Ca antagonist + Low-dose diuretic
- ARB/ACE inhibitor + Low-dose diuretic

**Step 3**
(β- or α-blockers may be used depending on patients.)

Ca antagonist + ARB/ACE inhibitor + Low-dose diuretic

Antihypertensive drug treatment should be started generally at half the regular dose, and the dose should be increased at an interval of 4 weeks to 3 months. The final target of blood pressure is <140/90mmHg. In patients aged ≥75 years with grade II or III hypertension (≥160mmHg), blood pressure should be reduced carefully by setting an intermediate target of <150/90mmHg.
Relations between achieved SBP level and the risk of cerebrovascular events

HR of an achieved SBP <130 mmHg category without DM was assigned a reference value of 1.0.

* P<0.05. vs SBP <130 mmHg in Without DM
Relations between achieved SBP level and the risk of cardiac events

HR of an achieved SBP <130 mmHg category without DM was assigned a reference value of 1.0.

* P<0.05. vs SBP <130 mmHg in Without DM
<table>
<thead>
<tr>
<th></th>
<th>登録時DMなし</th>
<th>DBP&lt;75</th>
<th>登録時DMあり</th>
<th>DBP&lt;75</th>
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<tbody>
<tr>
<td></td>
<td>65歳未満</td>
<td>65歳以上</td>
<td>65歳未満</td>
<td>65歳以上</td>
</tr>
<tr>
<td>突然死 (%)</td>
<td>22.2</td>
<td>20.0</td>
<td>5.3</td>
<td>11.4</td>
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<tr>
<td>脳イベント (%)</td>
<td>22.2</td>
<td>40.0</td>
<td>10.5</td>
<td>34.1</td>
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<td>心イベント (%)</td>
<td>44.4</td>
<td>15.0</td>
<td>52.6</td>
<td>38.6</td>
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<tr>
<td>腎イベント (%)</td>
<td>11.1</td>
<td>10.0</td>
<td>21.1</td>
<td>15.9</td>
</tr>
<tr>
<td>その他 (%)</td>
<td>0.0</td>
<td>15.0</td>
<td>10.5</td>
<td>0.0</td>
</tr>
<tr>
<td>全体(N)</td>
<td>9</td>
<td>20</td>
<td>19</td>
<td>44</td>
</tr>
</tbody>
</table>
Relations between achieved SBP level and the risk of cerebrovascular events

HR of an achieved SBP <130 mmHg category without DM was assigned a reference value of 1.0.

* P<0.05. vs SBP <130 mmHg in **Without DM**
Relations between achieved SBP level and the risk of cardiac events

Without DM
With DM

Interaction P=0.157

* P<0.05. vs SBP <130 mmHg in Without DM

HR of an achieved SBP <130 mmHg category without DM was assigned a reference value of 1.0.